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Research Article

Composite Poly(vinyl alcohol) Beads for Controlled Drug Delivery

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A new method of preparing composite poly(vinyl alcohol) (PVA) beads with a double-layer structure has been developed, which involves a stepwise saponification of suspension polymerized poly(vinyl acetate) (PVAc) beads and subsequent stepwise cross-linking of the PVA core and shell with glutaraldehyde. This process results in PVA beads with thin, highly cross-linked outer shells and lightly cross-linked inner cores of different degrees of cross-linking. In addition to structural characterization of the polymer based on equilibrium swelling measurements, the kinetics of water swelling and drug release from these beads were studied at 37°C using acetaminophen and proxyphylline as model drugs. The results show that the outer shell functions as a rate-controlling membrane upon increasing its cross-linking ratio, X, above 0.47. This aspect is reflected in the observed diffusional time lags and constant-rate regions during swelling and drug release. Based on observed time lags, the diffusion coefficient of water through the outer PVA shell with a high cross-linking ratio of $X = 0.5$ is estimated to be at least six times higher than that of acetaminophen and proxyphylline. In addition, drug diffusion coefficients in the lightly cross-linked PVA core appear to be at least 10 times larger than that in the highly cross-linked outer shell. At lower shell cross-linking ratios ($X < 0.4$), the diffusional time lags appear to be absent and the diffusion profiles are apparently first-order (Fickian) in nature.

KEY WORDS: poly(vinyl alcohol); glutaraldehyde cross-linking; hydrogels; composite beads; drug release; swelling kinetics.

INTRODUCTION

Hydrogels are gaining increasing popularity in the area of controlled-release drug delivery (1–3). These polymers are generally glassy in the dehydrated state but swell to become an elastic gel upon water penetration. The entrapped drug within the swelling matrix concomitantly dissolves and diffuses through the swollen network into the surrounding aqueous environment. A slow macromolecular relaxation process at the swelling front often provides another mechanism in addition to diffusion to alter the release kinetics from an inherent first-order behavior. Frequently, the rate of drug release from hydrogels is further regulated by controlling the cross-linking density and the extent of water swelling (4–6).

Poly(vinyl alcohol) (PVA) hydrogels have been studied extensively as controlled-release drug carriers in the form of either a single-unit compressed tablet or a multiparticulate dose containing granules or particles (7–9). In order to prolong the drug release from such an inherently hydrophilic polymer network, PVA is often modified by cross-linking to reduce the macromolecular mesh size available for drug diffusion. The cross-linking can be carried out either before or after the drug loading. Obviously, the former process is preferred since it avoids possible side reactions between the drug and the cross-linking agent. It has been well documented that an increase in PVA cross-linking density results in a decrease in both the volume swelling and the rate of drug release. This can be attributed to the decrease in diffusion coefficients of both the drug and the solvent by the reduction of molecular weight between cross-links and the associated macromolecular mesh size (5).

Depending on the rate of water swelling of a dehydrated PVA hydrogel, the contribution of the slow macromolecular relaxation process at the swelling front may become important in determining the overall drug release kinetics. However, despite the growing interest in utilizing glassy PVA hydrogels as swelling-controlled delivery systems, the kinetics of swelling of cross-linked PVA hydrogels during drug release has not been studied in necessary detail. This is attributed primarily to the limitation of available sample geometry. The commonly employed planar geometry and granular particles are limited in their usefulness in obtaining reliable solvent penetration and volume swelling data in glassy polymers due to the edge effect, the anisotropic swelling behavior in thickness versus area, and technical difficulties in the direct observation of swelling boundaries. In contrast, spherical geometry eliminates these drawbacks and therefore permits accurate measurement of the swelling front penetration and transient dimensional changes during drug release. This aspect has been demonstrated by Lee (10) using glassy poly (2-hydroxyethyl methacrylate) (PHEMA) beads. Furthermore, from a practical standpoint, spherical beads

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are generally more preferred than the planar and cylindrical geometries, especially for applications involving multiparticulate dosage forms.

In this article, we report a new method of preparation of large spherical PVA beads having a double-layer structure from suspension polymerized poly(vinyl acetate) (PVAc) and the characterization of such beads with respect to the effect of cross-linking on swelling and drug release behavior. These PVA hydrogel beads are sufficiently large (up to 1.5-mm diameter) that they are potentially suitable for oral drug delivery applications.

EXPERIMENTAL

Synthesis of PVAc Beads

Spherical PVAc beads were prepared by free radical suspension polymerization of vacuum distilled vinyl acetate (Aldrich Chemical) in an aqueous medium containing 0.5–2% of fully hydrolyzed PVA (MW 106,000–110,000; Aldrich Chemical) as suspending agent and 0.5% of 2,2′-azobisisobutyronitrile (AIBN) as initiator. The relative amount of vinyl acetate to water in the polymerization mixture was 1:5 by weight. The polymerization was carried out in a 2-liter reaction flask at 60–65°C and 150 rpm for 5–6 hr. The PVAc beads so prepared were filtered, washed with hot water to remove residual suspending agent, and extracted with methanol/water mixtures for 3 days before being dried.

Preparation of PVA Beads

Double-layered PVA beads consisting of a highly cross-linked outer shell and a lightly cross-linked inner core were prepared from suspension polymerized PVAc beads by a process involving stepwise saponification with subsequent stepwise cross-linking. This is a modification of the process reported by Hirayama *et al.* (11) for preparing micron-size PVA particles as column packing materials in gel permeation chromatography. Specifically, intermediate gel beads (designated PVA I) with a thin cross-linked PVA shell and an uncross-linked PVA core were prepared by first partially saponifying the PVAc beads in a 35% aqueous solution of $NaOH/Na_2SO_4$/methanol (2:1:1, by weight). The hydrolysis reaction took place from the surface of the PVAc beads and the clear saponified region expanded via a moving front separating it from the opaque PVAc core. The reaction time was controlled such that the thickness of the saponified surface layer was about 10% of the original radius. These beads were then treated in an aqueous solution containing 2% of glutaraldehyde, 5% of acetic acid/methanol (1:2, by weight), and 0.04% of H_2SO_4 as catalyst for 2 hr at 60°C to cross-link the swollen PVA surface layer. Subsequent saponification in the alkaline methanolic solution described above converts the remaining PVAc core into PVA (uncross-linked).

The resulting PVA I beads were then subjected to additional cross-linking in the above-described acidic methanolic solution of glutaraldehyde to produce PVA beads (designated as PVA II) having highly cross-linked outer shells and lightly cross-linked inner cores. A range of cross-linking density was obtained by varying the initial concentration of glutaraldehyde to achieve the calculated cross-linking ratio X, defined as the number of moles of glutaraldehyde per mole of repeating vinyl alcohol units in PVA. The resulting PVA II beads were soaked in water for 3 days to remove any extractables before being dried and fractionated for further study. The values of X referred in the following are the cross-linking ratios of the PVA core unless otherwise noted.

Swelling and Drug Release Experiments

Acetaminophen and proxyphylline were selected as model drugs for swelling and drug release experiments because they cover a large range of water solubilities (approx. 1.4% for acetaminophen and 50% for proxyphylline). Different acetaminophen and proxyphylline loading levels in PVA I and PVA II were achieved by equilibriating PVA beads in concentrated aqueous drug solutions at 37°C for 4 days. After filtering, rinsing, and drying, the drug-loaded beads of an average diameter of 0.9–1 mm were used for subsequent swelling and drug release studies in distilled/deionized water. The amount of drug loading was determined spectrophotometrically after a complete extraction of drug-loaded beads in water. The swelling experiments were performed in a water-jacketted cuvette maintained at 37°C with a circulating water bath. The swelling front movement was observed with a WILD M420 stereomicroscope equipped with camera attachments. The *in vitro* drug release at 37°C under perfect sink diffusion condition was monitored continuously in a stirred cuvette on a Hewlett–Packard 8452A diode-array UV-vis spectrophotometer equipped with a water-jacketted cuvette holder and a built-in magnetic stirrer, at 280 nm for acetaminophen and 260 nm for proxyphylline.

RESULTS AND DISCUSSION

Preparation of PVAc and PVA Beads

Suspension polymerized PVAc beads synthesized in the present study were smooth and spherical. Beads of diameter up to 1.5 mm have been prepared by varying polymerization conditions such as the concentration of suspending agent and the rate of agitation. Figure 1 shows a typical particle size distribution of PVAc beads prepared in this study. Ordinarily, PVA is obtained directly from PVAc by alkali or acid hydrolysis in an alcohol solution (12). However, in order to preserve the spherical shape of PVA, it was not feasible to use this direct process due to the lack of structural rigidity and the gradual dissolution of converted PVA in the aqueous saponification medium. Therefore, a stepwise saponification process, as described under Experimental, was

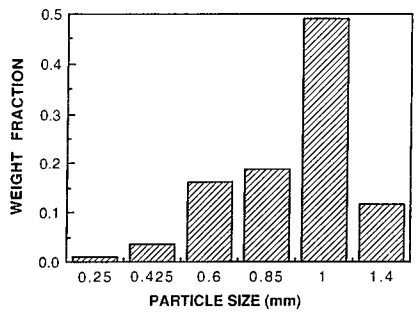

Fig. 1. A typical particle size distribution of suspension polymerized PVAc beads prepared in this study.

employed. In the first step, PVAc beads were only saponified on the surface up to about 10% penetration of the original radius. At this stage, the rigidity of these beads was provided by the nonswelling PVAc core and the swollen PVA surface layer was prevented from dissolving by a high concentration of Na_2SO_4 in the saponification medium. During the subsequent glutaraldehyde cross-linking, a reduction in thickness of the swollen PVA shell to about 5% of the radius was observed.

The cross-linked PVA shell, so formed, provides structural support for the PVA gel core in PVA I, which was subsequently formed by saponifying the remaining PVAc core. Figure 2 shows a typical batch of partially saponified PVAc beads observed during the last step of conversion into PVA I, where the opaque PVAc core is separated from the thin, cross-linked PVA shell on the outer surface by a clear intermediate region of uncross-linked PVA gel.

PVA II beads consisting of a highly cross-linked outer shell and a lightly cross-linked inner core were prepared by further cross-linking of PVA I. The already cross-linked outer shell was further tightened by additional cross-linking throughout the bead. A reduction of the outer shell thickness was observed during such cross-linking process, resulting in an average swollen shell thickness of about 21 μm in PVA II. Since the original shell cross-linking ratio in PVA I beads was estimated from the swelling data to be $X \approx 0.3$, the cross-linking ratio of the inner core of PVA II beads should remain less than that of the outer shell by a constant factor of $X \approx 0.3$, provided that glutaraldehyde can partition to the same extent in both the shell and the core during the conversion of PVA I to PVA II. For the present system, such additivity of cross-linking ratios has been assumed. This seems to be a reasonable assumption in view of the small difference in polymer volume fraction observed between the PVA beads with and those without a shell (Table I). However, this may not be the case when there is a significant difference in solvent swelling between the shell and the core.

Polymer Characterization

Table I summarizes the swelling and structure characteristics of PVA II beads at 37°C as a function of the core cross-linking ratio, where the equilibrium volume swelling ratio Q, defined as the ratio of swollen to dry PVA volume, is equivalent to the reciprocal of the polymer volume fraction v_2. The number average molecular weight between cross-links $\overline{M}_c$ was calculated from a Flory–Rehner-type equation developed by Lucht and Peppas (13) for highly cross-linked networks:

$$\frac{1}{\overline{M}_c} = \frac{2}{\overline{M}_n} - \frac{\bar{v}[\ln(1 - v_2) + v_2 + \chi v_2^2](1 - v_2^{2/3}/N)^3}{V_1(v_2^{1/3} - v_2/2)(1 + v_2^{1/3}/N)^2} \quad (1)$$

The $\overline{M}_n$ is the number average molecular weight of uncross-linked polymer, χ the Flory thermodynamic interaction parameter for the PVA–water system, $\bar{v}$ the specific volume of PVA (=0.788 cm^3/g), and V_1 the molar volume of the swelling agent (=18 cm^3/mol). The parameter N is the number of links of the chain given by

$$N = 2\overline{M}_c/M_r \quad (2)$$

where M_r is the molecular weight of the vinyl alcohol repeating unit (=44). It must be noted that since the Flory interaction parameter χ is a function of temperature, composition, and polymer volume fraction, a sufficiently accurate χ value based on literature data for the *same* range of polymer volume fractions utilized is generally required to arrive at a meaningful estimate of network parameters such as $\overline{M}_c$ and ξ. Therefore, an average value of 0.7 was selected for the interaction parameter χ of the PVA–water system in the present range of polymer volume fractions (0.426–0.599) at 37°C. This is consistent with χ values of 0.7–0.8 reported by Yano (14) based on vapor phase absorption data at 30°C for the same range of PVA polymer volume fractions. Extrapolation to the present range of polymer volume fractions of results reported by Peppas and Merrill (15) for low PVA polymer volume fractions ($v_2 < 0.12$) gives a corresponding χ value at 30°C ranging from 0.57 to 0.62. Therefore, the choice of $\chi = 0.7$ at the higher temperature of 37°C for the present analysis seems quite reasonable in view of the results of Yano (14) and Peppas and Merrill (15). Equation (1) and its extensions have been successfully applied by Peppas *et al.* (16) to the structural analysis of highly cross-linked PHEMA hydrogels. They have shown that when $\overline{M}_n$ exceeds 10,000, the effect of $\overline{M}_n$ on $\overline{M}_c$ is minimal. A similar approach is adopted here for the present PVA gel beads by assuming that $\overline{M}_n$ is sufficiently large that the term $2/\overline{M}_n$ in Eq. (1) may be neglected. This seems to be a reasonable

Table I. Swelling and Structural Characteristics of Composite PVA Hydrogel Beads at 37°C

Cross-linking ratio, X (mol/mol)	Eq. polym. vol. fraction, v_2[a]	Eq. vol. swelling ratio, Q	Av. MW, $\overline{M}_c$	Mesh size ξ (Å)
0.05	0.426 ± 0.012	2.349	5940	100
0.10	0.492 ± 0.016	2.032	860	36
0.17	0.567 ± 0.007	1.863	350	22
0.20[b]	0.575 ± 0.011	1.740	320	21
0.20	0.599 ± 0.026	1.669	270	19

[a] Mean ± SD (n = 3).
[b] Without shell.

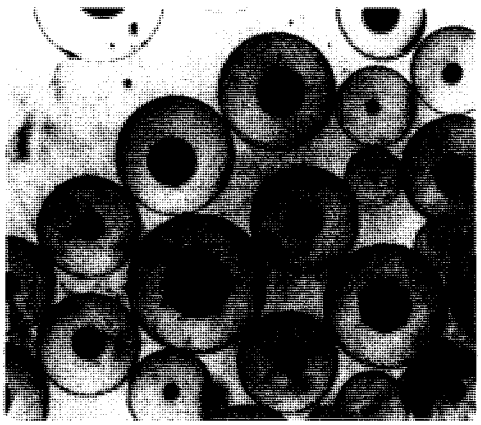

Fig. 2. Photograph showing a typical batch of partially saponified PVAc beads observed during the last step of conversion into composite PVA beads.

assumption in view of the results of Hirayama *et al.* (11) on the molecular weight of suspension polymerized PVAc. In this study Eq. (1) has been solved iteratively using $\overline{M}_c$ value for $N \rightarrow \infty$ as the initial estimate. Also reported in Table I is the mesh size ξ, which represents the maximum size of solute that can pass through the polymer network and, therefore, is an indication of the screening effect of the network on solute diffusion. It is determined from the following equation:

$$\xi = v_2^{-1/3}\, l\, N^{1/2} C_n^{1/2} \qquad (3)$$

where $l = 1.54$ Å is the C–C bond length, N the number of links defined by Eq. (2), and C_n the Flory characteristic ratio or rigidity factor (=8.9 for PVA) (5,6).

It is clear from Table I that, as the PVA cross-linking ratio X increases from 0.05 to 0.2, the molecular weight between cross-links $\overline{M}_c$ decreases from 5940 to 270, equivalent to from 135 to 6 repeating units, and the mesh size ξ reduces from 100 to 19 Å. These are consistent with data on glutaraldehyde-cross-linked PVA reported by Canal and Peppas (6) and by Gander *et al.* (8,9). Also included in Table I are data from a PVA core of $X = 0.2$ without the outer shell. The shell was carefully removed from the PVA II bead in the swollen state by first puncturing the shell with the edge of a razor, followed by peeling the shell slowly to separate it from the core. A comparison of results on PVA beads (core $X = 0.2$) with and without the outer shell suggests that the thin shell (about 21 μm) affects very little of the measured polymer volume fraction, the calculated molecular weight between cross-links and mesh size of the bulk PVA core (about 950-μm diameter). Only a small underestimation is expected when one evaluates structural characteristics of bulk PVA using swelling data of the present composite PVA beads. Since the solute transport through cross-linked PVA is directly affected by the network structure, the results of swelling and structural characterization presented here provide a useful frame of reference for the interpretation of diffusional drug release behavior from the present composite PVA beads.

Dynamic Swelling Properties

The dynamic swelling behavior of dehydrated PVA I and PVA II beads was studied by measuring the transient dimensional changes and solvent front penetrations. A typical swelling front penetration in PVA II beads is illustrated in Fig. 3. The effect of cross-linking ratio on the transient dimensional changes is shown in Fig. 4. An increase in PVA cross-linking ratio is seen to result in a lower water swelling capacity and slower approach to swelling equilibrium, both expressed in changes in bead diameter. Results given in Fig. 5 show that the penetrating solvent front (glassy/rubbery front) moves slower with increasing cross-linking ratios; some Fickian components are evident from the slight nonlinearity at the initial stage of the solvent penetration. These are followed by a linear (or constant-rate) penetration region and, eventually, an accelerated penetration near the center. The apparent acceleration of solvent front penetration near the center of a glassy polymer bead has been shown to be a natural result of the spherical geometry during solvent penetration in polymers (17), and not, as suggested by some

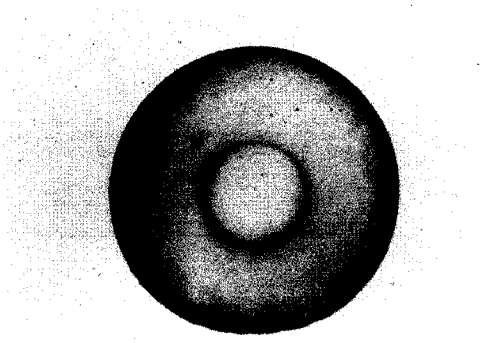

Fig. 3. Photograph showing a typical swelling front penetration in PVA II beads.

authors (18), a super-Case II transport behavior. Also shown in Fig. 5 is the appearance of an initial time lag in the solvent front penetration at a high cross-linking ratio of $X = 0.5$ in the shell. The absence of observable time lags at the lower cross-linking ratios suggests that the diffusion coefficient of water through the outer PVA shell was not significantly affected by the small degrees of cross-linking. However, the transport resistance of water through PVA shells with higher cross-linking ratios, or equivalently, smaller reduced network mesh sizes, was sufficiently large to produce a measurable time lag and prolongation of the approach toward swelling equilibrium.

Effect of Cross-Linking Ratio on the Kinetics of Drug Release

Figures 6a and 6b illustrate the effect of cross-linking ratio on the release kinetics of acetaminophen and proxyphylline, respectively. Similar to results on swelling front penetration, the effect of cross-linking ratio on the release of acetaminophen and proxyphylline was minimal at lower shell cross-linking ratios ($X < 0.35$), with drug release generally completed within 1–2 hr. The associated release profiles are first order in nature due to the spherical geometry. On the other hand, at a shell cross-linking ratio of $X = 0.5$ and a corresponding core cross-linking ratio of $X = 0.2$, the cumulative release profiles for both drugs show an initial time lag of up to 15 min, followed by a constant-rate region of 2–3 hr before tailing off in a first-order fashion. The over-

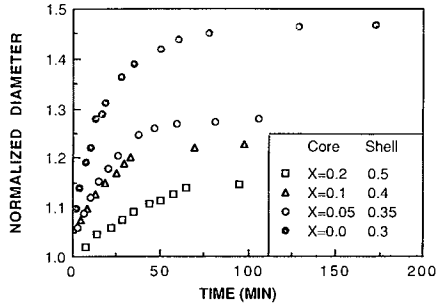

Fig. 4. Effect of cross-linking ratio on the transient dimensional swelling in composite PVA beads without drug at 37°C.

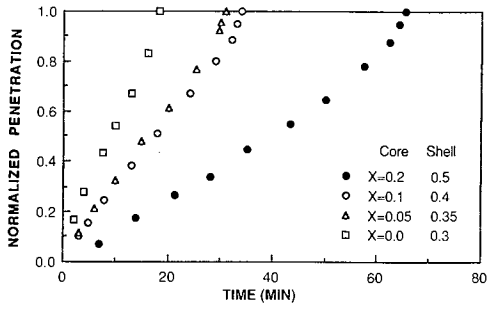

Fig. 5. Effect of cross-linking ratio on the transient swelling front position in composite PVA beads without drug at 37°C.

all duration of drug release in this case is extended to more than 10 hr. It is evident that at higher cross-linking ratios ($X > 0.47$), the outer shell initially acts as a rate-controlling membrane which gives rise to a diffusional time lag characteristic of membrane-reservoir systems. As drug release proceeds, the diffusional distance and, therefore, the transport resistance through the core PVA matrix increase steadily and eventually exceed the transport resistance through the outer shell. This results in the observed first-order decline in the release rate during the latter part of the drug release. It is interesting to note that the observed diffusional time-lag for PVA beads with a shell cross-linking ratio of $X = 0.5$ is longer (≈15 min) for the release of acetaminophen and proxyphylline than that for the solvent front penetration (≈2 min). Assuming that the initial drug diffusion from such a composite system can be described by the analysis of a membrane-reservoir system, at least approximately, the diffusion coefficient of water in the outer PVA shell with a high cross-linking ratio of $X = 0.5$ is estimated from the time-lag results to be at least six times higher than that of acetaminophen and proxyphylline, where the time lag is inversely proportional to the diffusion coefficient D for a given membrane thickness. Since it takes more than an hour for water penetration to complete in PVA II beads with a shell cross-linking ratio of $X = 0.5$ (Fig. 5) and less than 10% of the drug has been released during this period (Figs. 6a and b), it is reasonable to assume that the loaded drug is at or near saturation within the PVA core during most of the initial swelling phase. This permits an approximate analysis of the initial drug diffusion by solutions to a membrane-reservoir problem.

The effect of a highly cross-linked outer shell on the drug diffusion is further demonstrated in Fig. 7, where the releases of proxyphylline from PVA II beads (core $X = 0.2$, shell $X = 0.5$) with and without an outer shell are compared at similar drug loadings. The fact that a release time lag of about 15 min is present in beads with a shell but apparently absent in beads without a shell clearly suggests the role of the outer shell as a rate-controlling membrane at higher shell cross-linking ratios. It has to be noted that the release curves beyond the lag time portion appear to become parallel in Fig. 7. Apart from the possibility of incomplete removal of the outer shell from the specific PVA II bead studied here, the release behavior in Fig. 7 may also be the result of a shift from a membrane-controlled drug release to a matrix-controlled process soon after the initial time lag. To prolong the effect of such a membrane-controlled drug release, a thicker shell layer and/or a higher shell cross-linking ratio would have to be introduced during the formation of PVA I beads. Utilizing the time-lag relationship for spherical geometry (19), the apparent diffusion coefficient of proxyphylline in the outer PVA shell at $X = 0.5$ is estimated to be $D_{SL} = 0.82 \times 10^{-9}$ cm²/sec. Since the diffusional resistance through the PVA core matrix eventually exceeds that in the shell during the latter part of the drug release, the apparent proxyphylline diffusion coefficient in the PVA core at $X = 0.2$ is calculated from the final portion of the release curve to be $D_{CE} = 1.13 \times 10^{-8}$ cm²/sec using a large-time approximation to the solution of Fickian diffusion equation for spheres. These and additional diffusion coefficients in the PVA shell and core calculated from results in Figs. 6a and b are summarized in Table II. Evidently, the higher cross-linking ratio gives rise to smaller drug diffusion coefficients in the outer PVA shell by a factor of at least 10, comparing with that in the lightly cross-linked core. Such a significant decrease in drug diffusion coefficient in the outer PVA shell with a higher cross-linking ratio can be interpreted as a result

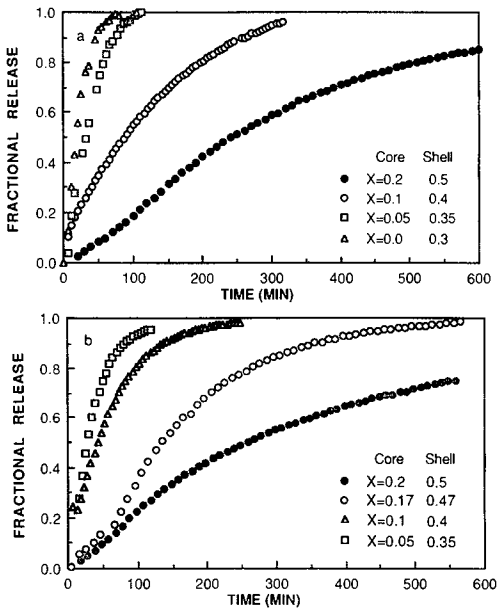

Fig. 6. Effect of cross-linking ratio on drug release from composite PVA beads at 37°C: (a) 4.9% acetaminophen loading; (b) 9.7% proxyphylline loading.

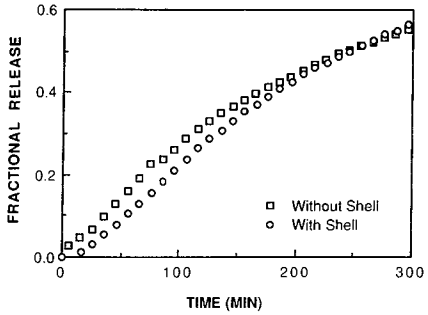

Fig. 7. Effect of rate-controlling shell on the proxyphylline release from composite PVA beads (core $X = 0.2$, shell $X = 0.5$) at 37°C. Drug loading: 9.7% with shell; 7.5% without shell.

Table II. Apparent Diffusion Coefficients[a] of Proxyphylline and Acetaminophen in Composite PVA Hydrogel Beads at 37°C

Cross-linking ratio, X (mol/mol)	Drug	$D_{SL} \times 10^9$ (cm²/sec)	$D_{CE} \times 10^9$ (cm²/sec)
0.17	Proxyphylline	2.46	44.5
0.2	Proxyphylline	0.82	11.3
0.2	Acetaminophen	1.02	29.1

[a] D_{SL}, drug diffusion coefficient in the PVA shell; D_{CE}, drug diffusion coefficient in the PVA core.

of the corresponding decreases in the molecular weight between cross-links and the associated network mesh size; the latter provides an indication of the screening effect of the PVA network on drug diffusion. Similarly, the larger molecular size of proxyphylline results in a smaller diffusion coefficient than that of acetaminophen at the same PVA cross-linking ratio (or the same mesh size).

Effect of Loading on Drug Release and Transient Dimensional Changes

Figure 8 shows the effect of drug loading on the fractional drug release of proxyphylline from PVA II beads with $X = 0.17$ in the core and $X = 0.47$ in the shell. As expected, the release rate increases with increasing drug loading. However, the release time lag appears to be less affected by the drug loading. Again, a thicker outer shell and/or a higher shell cross-linking ratio should prolong the time-lag effect and provide more membrane-controlled release characteristics. The transient dimensional changes during the simultaneous water penetration and proxyphylline release from such PVA II beads at 25.8% proxyphylline loading are shown in Fig. 9. Similar to our previous findings on PHEMA hydrogel beads (10,20), the diameter of a swelling PVA II bead is seen to go through a maximum followed by a gradual approach to an equilibrium value during proxyphylline release (Fig. 9a), where the bead diameter has been normalized to the initial dry diameter. It is interesting to note that the normalized bead diameter peaks at about 50 min, when the cumulative drug release is still less than 30% (Fig. 9b). This contrasts with the observed 70–80% cumulative drug release at swelling maxima during the release of very water-soluble drugs (solubility >50%), such as thiamine HCl and oxprenolol HCl, from monolithic PHEMA hydrogel beads. Although proxyphylline is also very water soluble (>50%), the presence of a rate-controlling outer shell in PVA II which permits rapid water transport while retarding drug diffusion appears to be responsible for the reduced extent of drug release at the swelling maximum. The general schemes of observed swelling and dimensional changes in hydrogel beads during drug release have recently been investigated in detail as a function of drug solubilities (20). It is believed that the presence of a homogeneously dissolved or dispersed drug in the hydrogel generates an additional osmotic driving force which alters both the total swelling pressure and the associated time-dependent relaxation of the hydrogel network during the simultaneous sorption of water and desorption of drug. Since the swelling by water tends to increase, whereas the release of drug tends to decrease, the dimension of a hydrogel bead, a combination of these two competing processes in appropriate proportion results in the observed maximum in the transient dimensional changes.

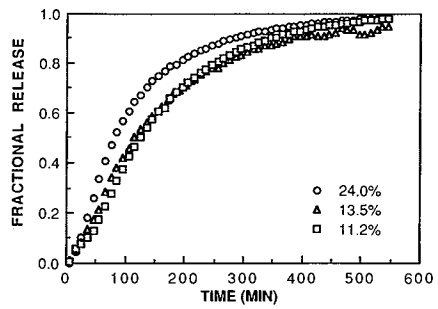

Fig. 8. Effect of drug loading on the fractional release of proxyphylline from composite PVA beads (core $X = 0.17$, shell $X = 0.47$) at 37°C.

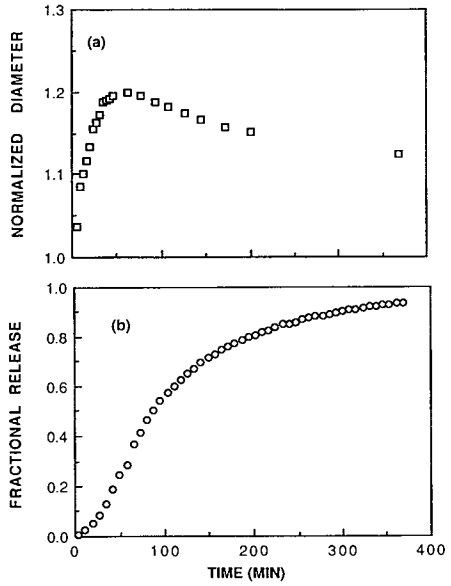

Fig. 9. Transient dimensional changes (a) during proxyphylline release (b) from composite PVA beads (core $X = 0.17$, shell $X = 0.47$) with 25.8% drug loading at 37°C.

CONCLUSION

A new method of preparing spherical PVA beads with a double-layer structure has been developed, which involves a stepwise saponification of suspension polymerized PVAc beads and stepwise cross-linking of the PVA core and shell to different degrees with glutaraldehyde. The structural characterization as well as the kinetics of swelling and drug release was studied as a function of PVA cross-linking ratio. The results demonstrate that the outer shell becomes a rate-controlling membrane upon increasing the shell cross-linking ratio above $X = 0.47$. This is reflected from the observed diffusional time lags and constant-rate regions during swelling and drug release. Although a matrix-controlled drug release behavior eventually will dominate the overall rate process, its contribution can be made smaller and the duration of constant-rate drug release can be further extended by increasing the outer PVA shell thickness and/or its cross-

linking density. The composite PVA beads so formed are potentially useful for drug delivery applications and ideally suited as matrices for the elucidation of swelling and drug release mechanisms devoid of drawbacks associated with other geometries.

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