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Mechanisms of solute and drug transport in relaxing, swellable, hydrophilic glassy polymers

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Abstract

Water and solute or drug transport in crosslinked polymeric materials was investigated to determine the effects of polymer morphology, composition and solute properties on transport behavior. Two crosslinked polymer systems, poly(2-hydroxyethyl methacrylate-*co*-methyl methacrylate) (P(HEMA-*co*-MMA)) and poly(vinyl alcohol) (PVA), were used in water transport and solute release experiments. Structural parameters of the polymers investigated in this work included the initial polymer molecular weight, the nominal crosslinking ratio, and the copolymer composition. Swelling rates, water diffusion coefficients and the diffusional Deborah number, *De*, were used to characterize the water uptake process. Swelling rates correlated well with the polymer network mesh sizes; the slowest rate of water uptake was observed in P(HEMA-*co*-MMA) samples containing large quantities of methyl methacrylate. Initial crosslinking ratios had a sizable effect on water uptake in crosslinked PVA samples but not in the P(HEMA-*co*-MMA) polymers. Drug release rates, drug diffusion coefficients and the swelling interface number, *Sw*, were used to characterize solute transport. Release experiments were conducted using eight solutes: theophylline, triamterene, oxprenolol HCl, buflomedil HCl, vitamin B_{12}, dextran, inulin and myoglobin. Release rates decreased with increasing solute molecular weight. A molecular weight cut-off, beyond which drug release was greatly hindered by the hydrogel mesh size, was established for each polymer tested.

Keywords: Crosslinking; Hydrogel; Relaxation

1. Introduction

1.1. Solute release from swellable systems

Controlled delivery of bioactive agents has been a major field of research over the last 30 years. A variety of methods have been used to target biologically active molecules to specific sites and extend their therapeutic lifetimes once inside the body. Polymeric drug carrier systems have several advantages in optimizing patient treatment regimes. In particular, swelling-controlled release systems [1] are capable of delivering drugs at constant rates over an extended period of time. In these systems, the rate of drug delivery is controlled by the balance between drug (solute) diffusion across a concentration gradient, the polymer relaxation occurring as the crosslinked polymer imbibes water, and the osmotic pressure occurring during the swelling process [2,3]. This osmotic pressure is related to the high drug concentration inside the network. Swelling-controlled release systems are particularly valuable [1,3], due to possibilities of achieving zero-order release. This is done by modification of the transport properties of the device, and by engineering specific polymer carriers.

An important goal of drug delivery is to obtain a constant release rate for a prolonged time. Therefore, Case II transport, in which transport rates are independent of time, has been investigated by many researchers [2–4] in attempts to create long-term drug delivery devices. Several efforts to achieve zero-order drug delivery have been made, including creative device geometries, front synchronization [5,6] and parabolic initial drug concentration profiles [7]. Swelling-controlled hydrogels and membrane reservoir devices have so far shown the most promise.

Penetrant uptake behavior into crosslinked polymers has been investigated over the past several decades, with notable contributions made to the understanding of deviations from classical Fickian diffusion [8–11]. This general behavior, known as anomalous transport, is bound by pure Fickian diffusion and Case II transport which have been

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observed in several polymer/penetrant systems [11]. Transport in all of these physical situations can generally be reduced to three types of driving forces: a penetrant concentration gradient, a polymer stress gradient, and osmotic forces.

Swelling-controlled release systems are based on the above principles, where a polymeric carrier can counterbalance normal Fickian diffusion by hindering the release of an imbedded solute or drug, leading to an extended period of drug delivery under zero-order release conditions [12]. In addition, the presence of a polymer network surrounding a drug or protein molecule has also been shown to act as a stabilizer [13], maintaining biological activity until the solute is released.

1.2. Structural and compositional factors in swellable polymer systems

Many experimental variables can affect water uptake in glassy polymers. The effects of sample geometry on water uptake as described by the power law model presented in Eq. (1) have been investigated previously [14,15]. Here, M_t/M_∞ is the fractional drug released from the polymer at time, t, and n is a diffusional exponent that determines the release mechanism.

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

The effects of crosslinking density [16], drug loading [4], and copolymer composition [13] on swelling kinetics have also been determined experimentally for specific systems. Recently, Colombo et al. [17] determined that there is a strong correlation between swelling front motion, or the sharp barrier between glassy and swollen regions in the polymer, and drug release kinetics, with Case II drug release resulting when water diffusional and polymer dissolution fronts are synchronized. However, Eq. (1) may be less applicable to polymers releasing high-molecular-weight drugs.

1.3. Application of swellable polymer systems to controlled drug delivery

Swellable hydrophilic polymers have been used for the purpose of prolonged drug delivery and drug targeting [3]. Delivery systems based on relaxing hydrogels are capable of slow release of an imbedded drug, with release controlled by the rate of swelling and relaxation of the polymer [1,18].

One of the first observations of non-Fickian transport in a matrix device was made by Roseman and Higuchi [19], who studied the release of drugs from silicone matrices. Although these were not swellable systems, experimental findings showed that drug interactions with the polymer caused deviations from Fickian diffusion. The effects of polymer/drug interactions and loading concentration on drug release profiles can be very pronounced as shown by Pham and Lee [20] who investigated the front behavior in three grades of hydroxypropylmethyl cellulose loaded with fluorescein as a model drug. Similarly, Brown et al. [21] studied the effects of osmotic pressure on sodium salicylate release from non-swellable matrices. Super Case II transport was observed due to a large increase in osmotic pressure driving forces at the time when solvent fronts met.

In our research group, there has been much work on controlled release from swellable systems. For example, we have shown [8,9,22] that solute size and polymer composition had profound effects on release profiles. We also developed [23] a model to predict solute diffusion in polymers. In this model, the presence of the polymer network could retard solute diffusion, through three primary variables: the molecular weight between crosslinks, the equilibrium volume swelling ration, and the solute radius.

Swelling and relaxational behavior of poly(2-hydroxyethyl methacrylate-*co*-methyl methacrylate) (P(HEMA-*co*-MMA)) polymers were observed by Davidson and Peppas [4] who determined polymer relaxation times by mechanical stress relaxation experiments and used them to calculate the diffusional Deborah number (*De*), a dimensionless parameter relating solvent uptake to macromolecular relaxation. Korsmeyer et al. [9] investigated significant dimensional changes during swelling, monitored these swelling fronts using polarized light, and studied the effect of polymer composition on drug release. They were also able to estimate diffusion coefficients through pulsed gradient spin echo nuclear magnetic resonance (PGSE-NMR) spectroscopy.

Franson and Peppas [13] observed the swelling front motion using polarized light to view stressed regions in P(HEMA-*co*-MMA) and related gels when exposed to water. They noted the importance of gel history on the swelling behavior. After a dry sample was swollen to equilibrium, some macromolecular chains could be disentangled to yield a different structure and different swelling kinetics upon subsequent swelling processes. They also correlated the diffusional exponent, n, of Eq. (1) to polymer composition. They introduced the swelling interface number, *Sw*, as an important dimensionless parameter to characterize water transport in comparison to solute release. They showed that *Sw* values correlated with the order of release, n, in an inverse logarithmic fashion. Finally, Ritger and Peppas [15] studied various sample geometries, and determined appropriate values of n for spherical, cylindrical and planar devices. In addition, they used the aspect ratio to determined the appropriate exponent for a system varying from 0.5 for slab geometries to 0.43 for cylinders, to 0.45 for spheres.

Despite the extensive pharmaceutically-relevant literature that shows unequivocally that anomalous and Case-II transport of water has been observed in many systems, it is disheartening to read the disorientation applied by certain researchers in the pharmaceutical field [24] who claim that relaxation has never been observed in water/polymer systems! The present work is one more proof of the failure

of such sweeping statements in the pharmaceutical literature.

2. Experimental

2.1. Polymer sample synthesis

Three crosslinked polymer systems were investigated, including poly(vinyl alcohol) (PVA) and hydrophobic copolymers of poly(2-hydroxyethyl methacrylate) (PHEMA). The properties of PVA were varied by changing the linear molecular weight and degree of acetate group hydrolysis. Comonomers reacted with HEMA included methyl methacrylate (MMA), a hydrophobic modifier, and *N*-vinyl-2-pyrrolidone (NVP), a hydrophilic modifier.

The PVA grades used (Elvanol, duPont, Wilmington, DE, USA) had molecular weights of $\overline{M}_n = 48\,237$ (polydispersity index, PI = 2.15), $\overline{M}_n = 35\,740$ (PI = 2.16), and $\overline{M}_n =$ 15,752 (PI = 2.7). PVA was first dissolved in deionized water by heating 5, 10 or 15 wt% PVA solutions at 90°C for 6 h, then chemically crosslinked using glutaraldehyde. A 2:1:2:3 volume ratio of 50 vol% methanol (solvent), 10 vol% acetic acid (buffering agent), 25 wt% glutaraldehyde (crosslinking agent), and 10 vol% sulfuric acid (catalyst) was sequentially added to the PVA solution according to the desired crosslinking ratio (from 1 to 10 mol% of glutaraldehyde per vinyl alcohol repeating unit). PVA solutions were then cast onto large glass Petri dishes and the reaction was carried out at 37°C for 24 h. Disc-shaped and dumbbell-shaped samples were cut using a cork borer and an ASTM die. The samples were washed in deionized water until no trace of unreacted components could be detected by UV spectrophotometry.

For the synthesis of the P(HEMA-*co*-MMA) and poly-(hydroxy ethyl methacrylate-*co*-*N*-vinyl-2-pyrrolidone) (P(HEMA-*co*-NVP)) samples, HEMA (Aldrich, Milwaukee, WI, USA) was purified by passing it through a column filled with De-hibit resin (Polysciences, Warrington, PA, USA), whereas MMA and NVP were vacuum distilled to remove the inhibitor. All other chemicals were used as received. Crosslinked P(HEMA-*co*-MMA) and P(HEMA-*co*-NVP) samples were prepared by free radical polymerization in the presence of ethylene glycol dimethacrylate (EGDMA) as a crosslinking agent. Appropriate molar quantities of the monomers were mixed with 0.1, 1 or 2 mol% EGDMA in a 40 vol% solvent (methanol for MMA, or water for NVP-containing copolymers).

For thermally-initiated polymerizations we used 1 wt% azobis(isobutyronitrile) (AIBN), while 1 wt% each of sodium metabisulfite and ammonium persulfate were used for redox-initiated reactions. After bubbling nitrogen through the reaction mixture for 5 min to remove dissolved oxygen, thermally-initiated polymerizations were carried out at 50°C for 48 h, while redox-initiated reactions were completed at 37°C for 48 h. Disc- and dumbbell-shaped samples were again cut from the resulting films. All samples were washed in deionized water to remove unreacted monomers until less than 1 ppm monomer was detected in the wash solution. Finally, the samples were dried to constant weight at ambient temperature under vacuum.

2.2. Dynamic and equilibrium swelling studies

Water swelling experiments were conducted at 37°C using of P(HEMA-*co*-MMA), P(HEMA-*co*-NVP) and PVA samples with nominal crosslinking ratios at 0.001 to 0.010 mol mol^{-1}. The weights of samples were recorded by periodically removing them from the swelling media, blotting with absorbent tissue and weighing. When the samples reached equilibrium penetrant uptake, weight measurements were taken again, employing a buoyancy technique. The weight swelling ratios, or the equivalent water uptakes, were plotted as functions of time.

2.3. Solute properties and loading techniques

Eight solutes were selected for loading and release studies. As shown in Table 1, the solutes varied in molecular weight from 200 to 70 000. All drugs and proteins were

Table 1
Properties of solutes used in this work

Drug	Molecular weight	Experimental diffusion coefficient (10^7 cm^2 s^{-1})	Hydrod. radius r_h (Å)	Water solubility (g l^{-1})
Theophylline	180	117.6	3.7	8.3
Proxyphylline	238.2	74.9	3.53	1000
Triamterene	253.3	68.7	3.43	> 0.1
Oxprenolol HCl	302	67.6	3.92	> 2
Buflomedil HCl	343.8	51.7	4.05	650
Diltiazem	451	51.7	4.24	∞
Vitamin B_{12}	1355	44.3	8.5	12.5
FITC-Dextran	4400	15.4	16.5	–
	16 000	7.7	25.1	–
	150 000	0.8	280	–
Inulin	5200	16.7	11.1	Slightly soluble

obtained from Sigma (St. Louis, MO, USA). The molecular characteristics of the various solutes used in diffusion experiments are summarized in Table 1. Molecular sizes and shapes were important in determining how drugs would diffuse through the mesh space of the hydrogel. The diffusion coefficient of each solute in water is also listed as taken from cited literature sources or estimated by extrapolation from data given by Lustig and Peppas [25]. The listed values have been corrected to 37°C, unless otherwise noted. Hydrodynamic radii, r_h, defined as the radii of equivalent spheres of the same molecular weight are also listed. Water solubility data are also included since the limits of solubility can influence the diffusive processes.

Molecular dispersion of the model drugs in crosslinked polymer samples were accomplished by two loading techniques: equilibrium partitioning and copolymerization/crosslinking in the presence of the drug. Using the equilibrium partitioning technique, crosslinked polymer samples were swollen in a concentrated drug solution, allowing enough time for the drug to diffuse to the center of the gel and lead to samples with uniformly distributed drug. After imbibition, the samples were removed from the drug solutions, rinsed briefly with deionized water to remove surface-adsorbed drug, and dried to constant weight under vacuum.

Model solutes were also loaded during copolymerization and crosslinking reactions. For crosslinked PVA samples, 1 to 10 wt% drug was added to aqueous PVA solutions and mixed thoroughly prior to crosslinking and casting to form samples with uniformly dispersed solutes. To prepare drug-loaded P(HEMA-*co*-MMA) samples, bioactive agents were added to the comonomer mixture. Drug-loaded samples prepared by this method were rinsed only briefly to remove surface-bound drugs while maintaining the drug imbedded in the carriers, and dried to constant weight under vacuum.

2.4. Drug release studies

Drug release experiments were conducted with the swelling-controlled release systems prepared. Standard 1-l United States Pharmacopoeia (USP) dissolution cells (type II, Hanson Research, Chatsworth, CA, USA) were maintained at 37°C and the stirring rate was kept to 100 rpm. Aliquots (3 ml) were removed periodically from the release solution, and absorbance was measured using a UV/vis spectrophotometer. Care was taken to ensure that drug concentrations in the release media were small enough to maintain the assumption of perfect sink conditions.

3. Results and discussion

3.1. Effect of polymer composition on swelling of P(HEMA-co-MMA) hydrogels

The influence of the overall hydrophilicity of PHEMA copolymers on water transport through them was determined by varying the copolymer hydrophilicity by copolymerization of MMA and NVP as comonomers. An

Table 2
Initial water uptake rates in redox- and thermally-initiated free radical solution polymerized samples of P(HEMA-*co*-MMA) and P(HEMA-*co*-NVP) crosslinked by EGDMA

Hydrogel sample	HEMA content (mol%)	Crosslinking ratio, X (mol mol^{-1})	Initial uptake rate ($g_w\ g_p^{-1}\ h^{-1}$)	Standard deviation ($g_w\ g_p^{-1}\ h^{-1}$)
Redox-initiated P(HEMA-co-MMA) samples				
RXHM100-1	100	0.01	1.356	0.420
RXHM100-2	100	0.02	1.272	0.276
RXHM75-1	75	0.01	0.504	0.072
RXHM75-2	75	0.02	0.552	0.246
Thermally-initiated P(HEMA-co-NVP) samples				
THN75-1	75	0.01	2.084	–
THN25-1	25	0.01	3.501	–
Thermally-initiated P(HEMA-co-MMA) samples				
THM100-0.1	100	0.001	1.050	0.234
THM100-1	100	0.010	2.154	0.606
THM100-2	100	0.020	1.362	0.156
THM75-0.1	75	0.001	0.624	0.096
THM75-1	75	0.010	0.594	0.138
THM75-2	75	0.020	0.456	0.072
THM60-0.1	60	0.001	0.498	0.096
THM60-1	60	0.010	0.270	0.060
THM60-2	60	0.020	0.318	0.096
THM50-1	50	0.010	0.320	–
THM25-1	25	0.010	0.095	–
THM0-1	0	0.010	0.011	–

Values are the average of three or more experiments.

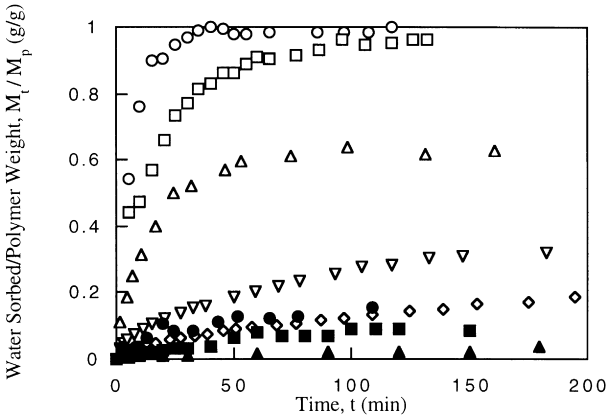

Fig. 1. Effect of copolymer composition on water uptake into crosslinked P(HEMA-*co*-NVP) polymers containing 75 (○) and 25 (□) mol% NVP, crosslinked PHEMA (△) and crosslinked P(HEMA-*co*-MMA) containing 25 (▽), 40 (◇), 50 (●), 75 (■) and 100 (▲) mol% MMA at 37°C. Crosslinked samples were prepared by thermally-initiated, free radical solution copolymerization in the presence of 1 mol% EGDMA as a crosslinking agent.

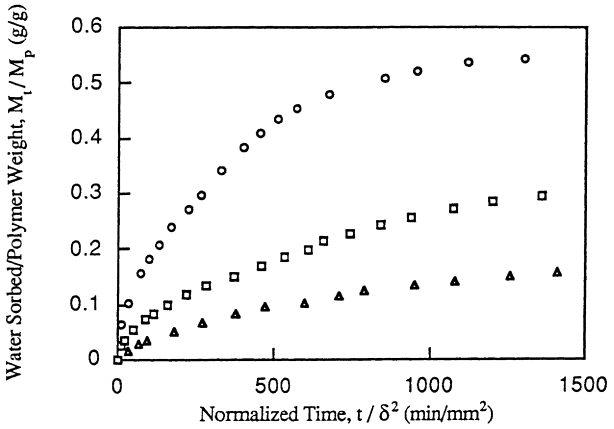

Fig. 2. Effect of copolymer composition on water uptake into crosslinked P(HEMA-*co*-MMA) polymers containing 100 (○), 75 (□), and 60 (△) mol% HEMA with a nominal crosslinking ratio of 0.01 at 37°C. Crosslinked samples were prepared by thermally-initiated, free radical solution copolymerization in the presence of 2 mol% EGDMA as a crosslinking agent. Samples were tested in triplicate.

increase in the amount of MMA incorporated in the copolymer decreased the overall hydrophilicity of the polymers, whereas an increase in NVP increased the swelling ratio and the rate of water uptake relative to pure PHEMA gels as shown in Fig. 1. These results present the swelling behavior of eight copolymers of progressively decreasing hydrophilicity. From these studies, the initial water uptake was calculated as shown in Table 2. Initial uptake rates were 2.08 and 3.50 $g_w\, g_p^{-1}\, h^{-1}$ for P(HEMA-*co*-NVP) samples containing 75 or 25 mol% HEMA, respectively, while the uptake rates were somewhat smaller for crosslinked PHEMA and P(HEMA-*co*-MMA) samples.

The copolymer composition and initial crosslinking ratio influenced the rate of water uptake. Because the main interest of the present work was the identification polymers which could expand slowly to allow prolonged solute release, all further work with acrylate-based polymers was conducted using crosslinked PHEMA, and its hydrophobically-modified P(HEMA-*co*-MMA) copolymers.

The effect of comonomer feed concentrations on swelling behavior in P(HEMA-*co*-MMA) gels is shown in the data in Fig. 2. The amount of water absorbed by the copolymer samples was normalized in each plot with respect to the dry polymer weight, while the time was normalized by dividing by the square of the sample thickness, δ^2, to account for differences in sample thicknesses when comparing water uptake data from multiple samples. PHEMA samples absorbed 50 to 60% of their dry weight in water, while the P(HEMA-*co*-MMA) samples with 75 mol% HEMA absorbed 25 to 35% of their dry weight in water, and samples with 60 mol% HEMA absorbed less than 20%. Moreover, with the addition of hydrophobic moieties on the polymer backbone with increasing MMA content, the time required for the polymer to reach equilibrium swelling conditions increased. The initial sorption rates observed for the different polymer compositions (Table 2) indicated that an increase in MMA content of the P(HEMA-*co*-MMA) networks caused a significant drop in the water sorption rate, decreasing from greater than 1 $g_w\, g_p^{-1}\, h^{-1}$ for crosslinked PHEMA to 0.01 $g_w\, g_p^{-1}\, h^{-1}$ for crosslinked PMMA.

3.2. Effect of crosslinking ratio on swelling of P(HEMA-co-MMA) hydrogels

The effect of the crosslinking ratio on the swelling behavior of P(HEMA-*co*-MMA) samples was not as significant as the polymer composition, as seen from the data of Fig. 3. Swelling was limited by the overall hydrophilicity of the samples, and not by the presence of crosslinks. In general, the uptake rates decreased with increasing nominal crosslinking ratios; for example, the thermally-initiated P(HEMA-*co*-MMA) networks containing 75 mol% HEMA had average initial sorption rates of 0.624, 0.594, and

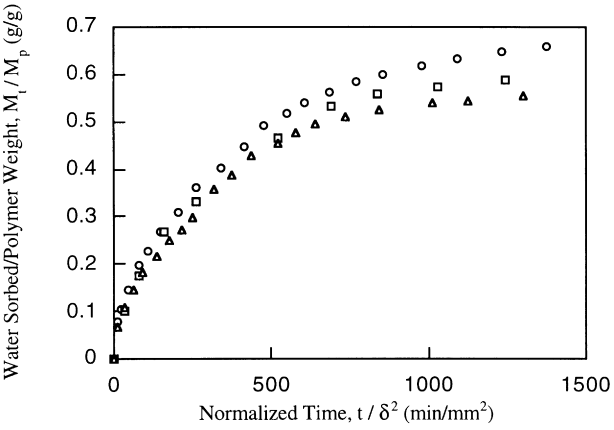

Fig. 3. Effect of nominal crosslinking ratio on water uptake into crosslinked PHEMA polymers at 37°C. Crosslinked samples were prepared by thermally-initiated free radical solution copolymerization in the presence of 0.1 (○), 1 (□), and 2 (△) mol% EGDMA as a crosslinking agent. Samples were tested in triplicate; representative data are shown here.

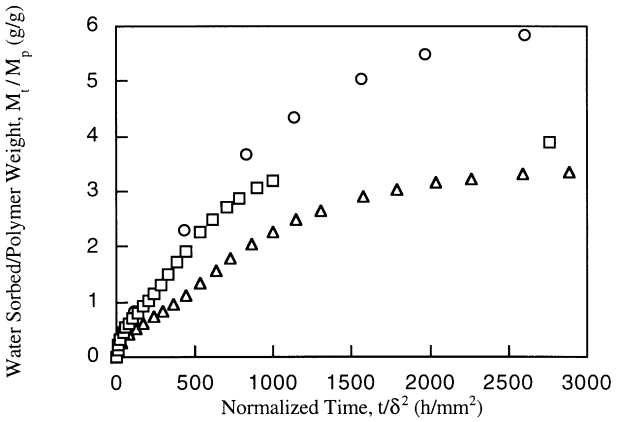

Fig. 4. Effect of PVA molecular weight prior to crosslinking and degree of hydrolysis on water uptake at 37°C into crosslinked PVA samples prepared from 15 wt% aqueous PVA solutions with, glutaraldehyde. Initial linear PVA number-average molecular weights, $\overline{M}_n$, degrees of PVA hydrolysis and nominal crosslinking ratios, X, used included: 15 800, 85% hydrolysis, $X = 0.01$ (○); 48 200, 99% hydrolysis, $X = 0.01$ (□); and 35 700, 99% hydrolysis, $X = 0.01$ (△). Samples were tested in triplicate; representative data are shown here.

0.456 $g_w\ g_p^{-1}\ h^{-1}$ for nominal crosslinking ratios of 0.001, 0.01, and 0.02 mol mol^{-1}. Although these values show a decreasing trend with crosslinking ratio, the standard deviations in the experimental data did not allow these conclusions to be fully justified. Moreover, the differences in water uptake were influenced much more by the polymer composition and the crosslinking ratio was not an important factor for water transport in PHEMA and P(HEMA-*co*-MMA) gels. This conclusion deviated from a previous observation by Franson and Peppas [13].

3.3. Effect of molecular weight and degree of hydrolysis on swelling of PVA gels

Water sorption experiments were also carried out on crosslinked PVA samples. The linear molecular weight of PVA before crosslinking and the degree of hydrolysis of poly(vinyl acetate), the precursor of PVA, were both important factors in determining the overall structure of the gel and its swelling behavior. As shown in Fig. 4, the initial molecular weight of PVA had a significant effect on the swelling behavior. The initial water uptake rates in the polymer samples were generally higher for samples formed from lower-molecular-weight PVA (in Table 3, compare water sorption rates for samples A15-1, A10-1, A05-1 and A10-10 to the polymer samples formed from the same PVA concentration and with the same crosslinking ratio, namely samples B15-1, B10-1, B05-1 and B10-10, respectively). In samples A formed from the higher-molecular-weight PVA, a greater number of intramolecular bonds was formed leading to a more open network structure. Intramolecular polymer interactions are somewhat more favored in high-molecular-weight PVA chains in solution, A, than in lower molecular weight chains, B. Therefore, networks formed from PVA samples with $\overline{M}_n = 48\,200$ swelled more quickly and to a higher degree than similar gels prepared from PVA chains with initial $\overline{M}_n = 35\,700$ at the same concentration.

The degree of hydrolysis had a significant effect on the swelling behavior of PVA hydrogels. In general, water sorption is faster in partially hydrolysed PVA samples, as these materials are more hydrophilic than fully hydrolysed PVA. In addition, the crosslink bridges formed by glutaraldehyde require two neighboring hydrolysed groups on the PVA backbone and cannot successfully connect PVA chains when a significant amount of pendent acetate groups exists. This results in a structure that is less fully crosslinked than a similar network formed from completely hydrolysed PVA. The initial sorption rates in the 85% hydrolysed PVA networks (samples C15-1, C10-1 and C05-1) ranged from 2.5 to 4.0 $g_w\ g_p^{-1}\ h^{-1}$, compared with rates less than 1.0 $g_w\ g_p^{-1}\ h^{-1}$ in the 99% hydrolysed samples (Table 3).

Table 3
Initial sorption rates in crosslinked PVA samples

Hydrogel sample	PVA molecular weight, $\overline{M}_n$ (% hydrolysis)	Initial PVA solution conc. (wt%)	Crosslinking ratio, X (mol mol^{-1})	Initial uptake rate ($g_w\ g_p^{-1}\ h^{-1}$)	Standard deviation ($g_w\ g_p^{-1}\ h^{-1}$)
A15-1	48 200 (99)	15	0.01	0.908	0.107
A10-1	48 200 (99)	10	0.01	0.744	0.546
A05-1	48 200 (99)	5	0.01	3.70	0.13
A10-10	48 200 (99)	10	0.10	0.210	0.032
B15-1	35 700 (99)	15	0.01	0.953	0.140
B10-1	35 700 (99)	10	0.01	0.830	0.026
B05-1	35 700 (99)	5	0.01	12.8	3.03
B05-10	35 700 (99)	5	0.10	0.506	–
B10-10	35 700 (99)	10	0.10	0.421	–
C05-1	15 800 (85)	5	0.01	3.97	–
C10-1	15 800 (85)	10	0.01	2.53	–
C15-1	15 800 (85)	15	0.01	2.69	1.96
C15-10	15 800 (85)	15	0.10	0.311	0.107

Where standard deviations are listed, values are the average of three or more experiments.

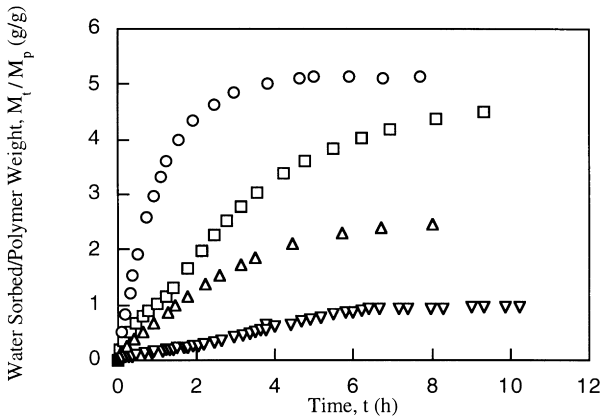

Fig. 5. Effect of PVA concentration and nominal crosslinking ratio on water uptake at 37°C into crosslinked PVA samples with $\overline{M}_n = 48\,200$, Prepared from 5 wt% ($X = 0.01$) (○), 10 wt% ($X = 0.01$) (□), 15 wt% ($X = 0.01$) (△), and 10 wt% ($X = 0.10$) (▽). Aqueous PVA solutions with a 99% degree of hydrolysis were used in the presence of glutaraldehyde. Samples were tested in triplicate; representative data are shown here.

3.4. Effect of PVA concentration and degree of hydrolysis on swelling of PVA samples

The effect of the initial concentrations of aqueous PVA and glutaraldehyde solutions used in the crosslinking reaction on the swelling behavior of the ensuing crosslinked PVA samples is shown in Fig. 5. The results follow expected trends: hydrogels crosslinked from 5 wt% solutions swelled faster and to higher swelling ratios than those formed from 10 or 15 wt% solutions. This was attributed to a difference in the ratio of inter- to intramolecular crosslinks which could form in each case. For each of the PVA molecular weight grades, higher PVA concentration in the crosslinking solution caused more intermolecular bonds to be formed, leading to a more rigid structure, lowering the equilibrium water uptake, and decreasing the observed water sorption rates as shown in the data of Table 4. When the PVA concentration increased from 5 to 15 wt% at a constant nominal crosslinking ratio of 0.01 mol mol^{-1},

Table 4
Water diffusion coefficients in redox- and thermally-initiated free radical solution polymerized samples of P(HEMA-*co*-MMA) crosslinked by EGDMA, and in crosslinked PVA samples

P(HEMA-*co*-MMA) samples				
Hydrogel sample	HEMA content (mol%)	Crosslinking ratio, X (mol mol^{-1})	Water diffusion coefficient, D ($\times 10^7$ cm^2 s^{-1})	Diffusional exponent, n
Redox-initiated				
RXHM100-1	100	0.01	7.59 ± 1.94	0.503 ± 0.007
RXHM100-2	100	0.02	9.01 ± 0.12	0.55l ± 0.005
RXHM75-1	75	0.01	5.55 ± 0.14	0.483 ± 0.004
RXHM75-2	75	0.02	4.10 ± 2.09	0.533 ± 0.006
Thermally-initiated				
THM100-0.1	100	0.001	4.81 ± 0.37	0.504 ± 0.005
THM100-1	100	0.010	4.23 ± 0.95	0.512 ± 0.040
THM100-2	100	0.020	4.74 ± 1.31	0.514 ± 0.020
THM75-0.1	75	0.001	3.03 ± 0.38	0.531 ± 0.013
THM75-1	75	0.010	2.90 ± 0.82	0.534 ± 0.057
THM75-2	75	0.020	2.91 ± 0.99	0.518 ± 0.037
THM60-0.1	60	0.001	2.50 ± 0.49	0.495 ± 0.041
THM60-1	60	0.010	1.78 ± 1.24	0.540 ± 0.033
THM60-2	60	0.020	1.98 ± 0.61	0.600 ± 0.012

PVA samples					
Hydrogel sample	PVA molecular weight, $\overline{M}_n$ (% hydrolysis)	Initial PVA solution conc. (wt%)	Crosslinking ratio, X (mol mol^{-1})	Water diffusion coefficient, D ($\times 10^7$ cm^2 s^{-1})	Diffusional exponent, n
A15-1	48 200 (99%)	15	0.01	2.36 ± 1.33	0.720 ± 0.034
A10-1	48 200 (99%)	10	0.01	1.40 ± 0.58	0.762 ± 0.067
A05-1	48 200 (99%)	5	0.01	2.50 ± 0.51	0.776 ± 0.024
A10-10	48 200 (99%)	10	0.10	0.60 ± 0.22	0.904 ± 0.138
B15-1	35 700 (99%)	15	0.01	0.94 ± 0.27	0.767 ± 0.083
B10-1	35 700 (99%)	10	0.01	1.08 ± 1.13	0.830 ± 0.069
B05-1	35 700 (99%)	5	0.01	1.47 ± 0.54	0.649 ± 0.055
B05-10	35 700 (99%)	5	0.01	–	0.773
B10-10	35 700 (99%)	10	0.10	–	0.863 ± 0.232
C05-1	15 800 (85%)	5	0.01	1.36 + 0.84	0.706 ± 0.021
C15-1	15 800 (85%)	15	0.01	3.84 ± 3.69	0.691 ± 0.056
C15-10	15 800 (85%)	15	0.10	0.20 ± 0.06	1.259 ± 0.185

Determined by early-time approximation using Eq. (6) and Eq. (1). Values listed are the average of three or more experiments.

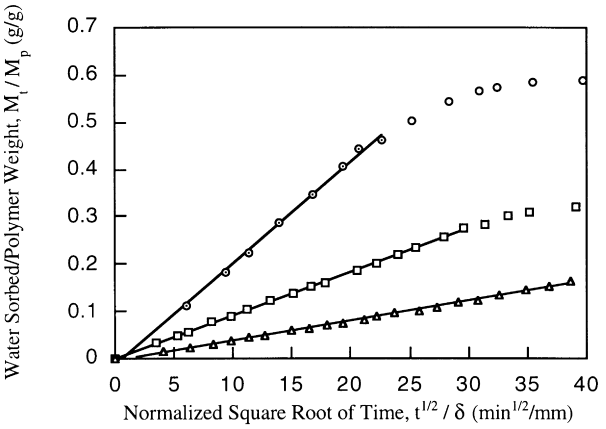

Fig. 6. Water uptake in P(HEMA-*co*-MMA) samples at 37°C plotted versus a normalized square root of time. Crosslinked P(HEMA-*co*-MMA) samples were prepared by thermally-initiated free radical solution polymerization with 100 (○), 75 (□), and 60 (△) mol% HEMA at 37°C in the presence of 1 mol% EGDMA as a crosslinking agent. Samples were tested in triplicate; representative data are shown here.

sorption rates in the corresponding samples dropped from 3.70 to 0.91 $g_w\, g_p^{-1}\, h^{-1}$ for PVA polymer A ($\overline{M}_n = 48\,200$), from 12.8 to 0.953 $g_w\, g_p^{-1}\, h^{-1}$ for PVA polymer B ($\overline{M}_n = 35\,700$) and from 3.97 to 2.69 $g_w\, g_p^{-1}\, h^{-1}$ for polymer C ($\overline{M}_n = 15\,800$). Sorption rates also decreased from 0.506 to 0.421 $g_w\, g_p^{-1}\, h^{-1}$ for samples with nominal crosslinking ratios of 0.10 in polymer B ($\overline{M}_n = 35\,700$), when the initial PVA solution concentration was increased from 5 to 10 wt%.

An increase in the crosslinking ratio from 1 to 10 mol% had a predictable effect on the swelling behavior. With such a large degree of physical restriction in the hydrogel network, water uptake decreased markedly, and the swelling rate decreased as well.

3.5. Analysis of Fickian swelling behavior in P(HEMA-co-MMA) samples

To further analyze the water transport in swellable polymers, the water sorption data in thermally-initiated crosslinked P(HEMA-*co*-MAA) samples with compositions of 60, 75 and 100 mol% HEMA were replotted against the normalized square root of time as shown in Fig. 6. A linear fit of the data was obtained for all samples, with diffusional exponents, *n*, near 0.50. According to Eq. (1), this indicates a Fickian water transport mechanism.

3.6. Mathematical analysis of water uptake studies

Analysis of the swelling behavior of PVA and P(HEMA-*co*-MMA) hydrogels was carried out using the one-dimensional water diffusion equation. The Fickian diffusion equation for one-dimensional water transport may be solved under initial and boundary conditions equivalent to the conditions of testing here, to give Eq. (2).

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp\left\{\frac{-D(2n+1)^2\pi^2 t}{\delta^2}\right\} \quad (2)$$

Here, the initial and boundary conditions are written as:

$$t = 0 \;\; -\delta/2 < x < \delta/2 \;\; c_1 = 0 \quad (3)$$

$$t > 0 \;\; x = 0 \;\; \frac{\partial c_1}{\partial x} = 0 \quad (4)$$

$$t > 0 \;\; x = \pm\, \delta/2 \;\; c_1 = c_{1e} \quad (5)$$

Here, D is the water diffusion coefficient in the polymer. The early-time approximation of Eq. (2) can be written as:

$$\frac{M_t}{M_\infty} \cong 4\left(\frac{Dt}{\pi\delta^2}\right)^{0.5} \quad (6)$$

Thus, the water diffusion coefficient would be easily calculated. Diffusion coefficients were also calculated from the late-time approximation of Eq. (2), written as:

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2} \exp\left(\frac{-\pi^2 Dt}{\delta^2}\right) \quad (7)$$

Early-time approximations of the water diffusion coefficients, D, as determined by Eq. (6), are listed in Table 4. Values were averaged over three or more samples and standard deviations were reported.

For redox-initiated P(HEMA-*co*-MMA) hydrogels, the diffusion coefficients ranged from 4×10^{-7} to $9 \times 10^{-7}\, cm^2\, s^{-1}$, with higher diffusion coefficients in gels of pure PHEMA. Diffusion coefficients dropped by almost a factor of two when the composition of the hydrogel was changed from 100 to 75 mol% HEMA. Diffusion coefficients were higher in the 75 mol% HEMA gel with a nominal crosslinking ratio of 0.01 than in the same composition gel with $X = 0.02$ mol mol^{-1}, as expected, but the opposite trend was observed for networks containing pure PHEMA.

Water diffusion coefficients during sorption into thermally-initiated P(HEMA-*co*-MMA) gels showed a similar decreasing trend as the composition was hydrophobically-modified with the addition of MMA as shown in Table 4. From these data, it was also concluded that the crosslinking ratio (in the range of 0.1 to 2 mol%) had no consistent effect on water transport in these copolymers.

Water diffusion coefficients in uncrosslinked P(HEMA-*co*-MMA) samples were also reported by Davidson and Peppas [4] as estimated by an early-time approximation. Water diffusion coefficients decreased with decreasing HEMA content, with values decreasing from 1.7×10^{-7} to $0.4 \times 10^{-7}\, cm^2\, s^{-1}$ as the copolymer composition decreased from 100 to 50 mol% HEMA. These values were on the same order of magnitude as the results shown in Table 4, though somewhat smaller. This difference was attributed to differences in reaction procedures, as well as the difference in crosslinking concentration.

In general, water diffusion coefficients in PVA hydrogels increased with a decrease in the PVA concentration during crosslinking (Table 4). As before, this was attributed to the ratio of inter- to intramolecular crosslinks which formed from the 5, 10 and 15 wt% PVA solutions. The diffusion coefficients determined from the early-time approximation were on the same order as values for P(HEMA-*co*-MMA) gels. Two samples with 10 mol% crosslinking exhibited diffusion coefficients below 1×10^{-7} cm^2 s^{-1}, significantly lower than those observed for the 1 mol% crosslinked PVA networks. Late-time approximations of water diffusion coefficients were calculated from the last 50% of the water uptake data using Eq. (7). For P(HEMA-*co*-MMA) hydrogels, there was again a much greater effect of polymer composition on the diffusion coefficient than the crosslinking ratio. However, the late-time approximations of diffusion coefficients decreased as expected with an increase in crosslinking ratio. For PVA hydrogels, the water diffusion coefficients calculated from the late-time approximation of Eq. (7) were the lowest in gels crosslinked with 10 mol% glutaraldehyde, with values of approximately 2×10^{-7} cm^2 s^{-1}, compared with $(2.5–3.9) \times 10^{-7}$ cm^2 s^{-1} for 1 mol% crosslinked PVA samples.

Data from water sorption experiments were also fit to the power law Eq. (1) and the diffusional exponents, n, are listed in Table 4. Values of n near 0.5 indicated a Fickian transport process, as is the case with most polymethacrylate hydrogels. However, P(HEMA-*co*-MMA) hydrogels containing 60 mol% HEMA, with $X = 0.02$ mol mol^{-1}, displayed some deviation from normal Fickian behavior, as indicated by diffusional exponents of 0.60. In general, water transport in PVA samples displayed significant deviations from Fickian behavior because of stress-induced polymer relaxation, which led to anomalous transport behavior in all of the PVA samples studied. One important trend was the increase of the diffusional exponent with increasing crosslinking ratios, a conclusion already made in the unpublished work of Chadwell [26]. These studies, and the data of Table 4, show once more that the allegations of Fickian diffusion of water in glassy hydrophilic polymers [24] are unfounded.

The power law exponent was greater than one for the swelling of sample C15-10, denoting Super Case II transport behavior. However, there was no noticeable trend in the diffusional exponent values with the PVA concentration during crosslinking, molecular weight, or degree of hydrolysis. The anomalous transport behavior observed in PVA hydrogels made these materials particularly interesting for further study.

3.7. Molecular weight between crosslinks and mesh size

In the case of swelling-controlled release systems and hydrogels used for drug delivery, it is important not only that swelling increases progressively with time, but also that the mesh size of the hydrogel is able to molecularly accommodate the drug. Therefore, the mesh size of the network, ξ, is an important parameter for prediction of hydrogel permeability. From the gravimetric sorption data, volume swelling ratios under equilibrium conditions could be determined. Subsequently, these results were useful in determination of the structure of the polymeric samples through calculation of hydrogel mesh space detailed elsewhere [18].

Mesh sizes calculated for each of the polymer systems are listed in Table 5. P(HEMA-*co*-MMA) hydrogels with a crosslinking ratio of 1 mol% had mesh sizes varying from 3.5 to 17.7 Å. PVA networks were more open, with the largest mesh size (109.1 Å) observed in the C15-1 sample crosslinked with 1 mol% glutaraldehyde from 15 wt% PVA solutions with initial $\overline{M}_n = 15\,800$, and having an 85% degree of hydrolysis. This was consistent with the previous crosslinking analysis indicating that reactions were less efficient in the PVA solutions due to the propensity for intramolecular crosslinking in lower-molecular-weight PVA and the presence of acetate groups on the backbone hindering formation of the glutaraldehyde bridge structure. Other PVA networks formed from 15 wt% solutions of PVA with 1 mol% glutaraldehyde had mesh sizes near 100 Å. Finally, PVA gels crosslinked with 10 mol% glutaraldehyde had much smaller mesh sizes, with an average of 15.3 Å for gel C15-10.

Table 5
Mesh sizes of P(HEMA-*co*-MMA) and PVA hydrogels used in drug release studies

Thermally-initiated P(HEMA-*co*-MMA) samples			
Hydrogel sample	HEMA content (mol%)	Crosslinking ratio, X (mol mol^{-1})	Mesh size (Å)
THM100-1	100	0.01	17.7
THM75-1	75	0.02	3.5
PVA hydrogels			
Hydrogel sample	PVA molecular weight, $\overline{M}_n$ (% hydrolysis)	Crosslinking ratio, X (mol mol^{-1})	Mesh size (Å)
A15-1	48 200 (99%)	0.01	98.0
B15-1	35 700 (99%)	0.01	86.4
C15-1	15 800 (85%)	0.01	109.1
C15-10	15 800 (85%)	0.10	15.3

Table 6
Percentage of drug loaded (wt%) by equilibrium partitioning in redox-initiated free radical solution polymerized samples of P(HEMA-*co*-MMA) crosslinked by EGDMA

Loading into crosslinked P(HEMA-*co*-MMA) samples from aqueous solutions			
Drug	Sample identification		
	THM60-1	THM75-1	THM100-1
Theophylline	0.077 ± 0.016	0.079 ± 0.028	0.071 ± 0.010
Triamterene	0.140 ± 0.061	0.499 ± 0.017	0.639 ± 0.038
Oxprenolol HCl	–	0.701 ± 0.494	–

Loading into crosslinked P(HEMA-*co*-MMA) samples from ethanolic solution		
Drug	Sample identification	
	THM75-1	THM100-1
Theophylline	6.48 ± 2.76	4.33 ± 0.30
Triamterene	0.37 ± 0.27	0.54 ± 0.27
Oxprenolol HCl	57.4 ± 0.5	–
Buflomedil HCl	3.65 ± 0.87	4.02 ± 0.35
Vitamin B_{12}	0.15 ± 0.06	14.8 ± 1.4
FITC-Dextran 4400	0.69 ± 0.14	8.82 ± 1.96

Drug	Sample identification			
	JA15-1	JB15-1	JC15-1	JC15-10
Theophylline	7.90 ± 1.01	7.96 ± 0.52	7.97 ± 2.69	3.70 ± 0.50
Triamterene	0.72 ± 0.20	1.02 ± 0.52	3.98 ± 2.14	1.53 ± 0.14
Oxprenolol HCl	–	34.1 ± 1.4	35.2 ± 4.2	–
Buflomedil HCl	–	60.4 ± 32.8	89.3 ± 74.0	–
Vitamin B_{12}	10.6 ± 0.2	1.49 ± 0.37	7.58 ± 0.20	1.86 ± 0.42
FITC-Dextran 4400	6.14 ± 2.16	75.8 ± 21.3	8.57 ± 5.95	
Myoglobin	7.32 ± 6.03	6.34 ± 2.64	22.6 ± 18.5	2.62 ± 1.13

Loading solutions were concentrated drug in water or ethanol, as noted. Crosslinked polymer systems included P(HEMA-*co*-MMA) samples formed by thermal initiation in the presence of 1 mol% EGDMA as a crosslinking agent. The HEMA content was 60 mol% (THM60-1), 75 mol% (THM75-1) or 100 mol% (THM100-1). Values are the average of three or more experiments.

3.8. Drug loading by equilibrium partitioning

Analysis of drug release behavior requires an understanding of the factors influencing the drug loading into each sample, as the drug concentration is an important factor in the observed release rates. Water was chosen as a dissolution medium for drug imbibition into PVA hydrogels, while ethanol was the optimal solvent for loading drugs into P(HEMA-*co*-MMA) networks, allowing higher degrees of swelling and therefore greater amounts of drug imbibed than loading from aqueous solutions. Table 6 lists the drug loading concentrations achieved for P(HEMA-*co*-MMA) samples loaded with drug from aqueous and ethanolic solutions. Depending upon the specific polymer–drug system, loading efficiencies were up to two orders of magnitude higher when using ethanol solutions than with aqueous solutions.

The amount of drug loaded into each crosslinked polymer sample was a function of the partition coefficient between the drug in free solution and the gel. Therefore, drugs which were more soluble in the loading solutions were loaded to higher concentration into polymer samples, as was the case with theophylline, oxprenolol HCl and buflomedil HCl loading into P(HEMA-*co*-MMA) samples (Table 6). More hydrophobic drugs, such as vitamin B_{12} and FITC-dextran 4400, were excluded more effectively by hydrophobically-modified P(HEMA-*co*-MMA) samples. The loading of oxprenolol HCl into pure PHEMA gels was so high that the presence of the low-molecular-weight solute significantly lowered the glass transition temperature of the crosslinked PHEMA samples, making those samples rubbery at 37°C.

Drug loading in crosslinked PVA samples was also carried out by imbibition. In most cases, loading by equilibrium partitioning produced hydrogel samples with nearly equal amounts of drug incorporated, as indicated by small standard deviations. Similar to the observed trends in the P(HEMA-*co*-MMA) sample loading, more hydrophilic drugs were readily loaded into crosslinked PVA samples, while hydrophobic drugs, such as triamterene and higher-molecular-weight solutes, had reduced loading concentrations.

3.9. Effect of polymer composition and structure on drug release behavior

Release studies were conducted using theophylline, oxprenolol HCl, triamterene, buflomedil HCl, vitamin B_{12},

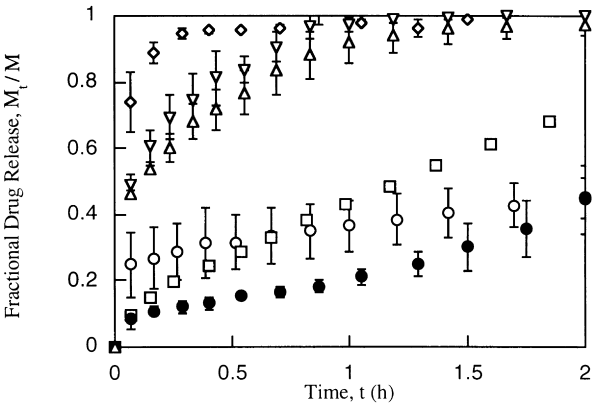

Fig. 7. Effect of polymer structure and composition on theophylline release from crosslinked P(HEMA-*co*-MMA) and PVA samples at 37°C, plotted for short release times. Release was conducted from P(HEMA-*co*-MMA) samples of 75 mol% (○) and 100 mol% (□) HEMA composition, crosslinked with 1 mol% EGDMA, and from glutaraldehyde-crosslinked PVA samples formed from 15 wt% aqueous solutions of linear PVA with initial $\overline{M}_n = 48\,200$, $X = 0.01$, with 99% hydrolysis (△), $\overline{M}_n = 35\,700$, $X = 0.01$, with 99% hydrolysis (▽), $\overline{M}_n = 15{,}800$, $X = 0.01$, with 85% hydrolysis (◇), and $\overline{M}_n = 15\,800$, $X = 0.10$, with 85% hydrolysis (●). Drugs were loaded by equilibrium partitioning from saturated drug solutions in ethanol for HEMA-containing hydrogels, and saturated aqueous drug solutions for PVA gels. Error bars represent standard deviations for three experiments; where not shown, only one experiment was conducted.

FITC-dextran 4400, inulin and myoglobin as model solutes. Typical release studies are presented in Figs. 7–13. In most cases, three experiments were conducted for each polymer/drug system; thus, data represent averages, with error bars representing standard deviations.

Average initial release rates were calculated for all drug release experiments, using the first few data points after any initial burst effect, and are tabulated in Table 8.

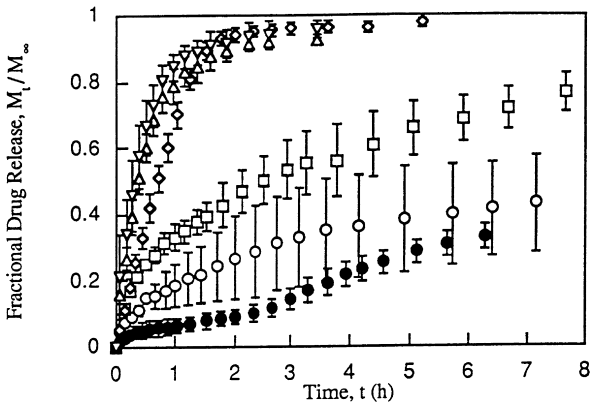

Fig. 8. Effect of polymer structure and composition on theophylline release from crosslinked P(HEMA-*co*-MMA) and PVA samples at 37°C, plotted for long release times. Release was conducted from P(HEMA-*co*-MMA) samples of 75 mol% (○) and 100 mol% (□) HEMA composition, crosslinked with 1 mol% EGDMA, and from glutaraldehyde-crosslinked PVA samples formed from 15 wt% aqueous solutions of linear PVA with initial $\overline{M}_n = 15\,800$, $X = 0.10$, with 85% hydrolysis (△). Drugs were loaded by equilibrium partitioning from saturated drug solutions in ethanol for HEMA-containing hydrogels, and saturated aqueous drug solutions for PVA gels. Error bars represent standard deviations for three experiments; where not shown, only one experiment was conducted.

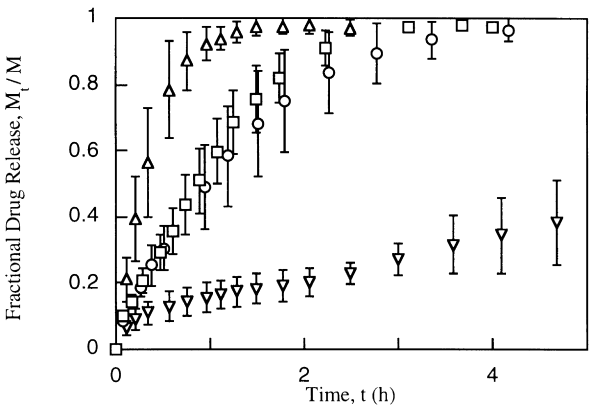

Fig. 9. Effect of polymer structure and composition on vitamin B_{12} release from crosslinked PVA samples at 37°C. Release was conducted from glutaraldehyde-crosslinked PVA samples formed from 15 wt% aqueous solutions of linear PVA with initial $\overline{M}_n = 48\,200$, $X = 0.01$, with 99% hydrolysis (○), $\overline{M}_n = 35\,700$, $X = 0.01$, with 99% hydrolysis (□), $\overline{M}_n = 15\,800$, $X = 0.01$, with 85% hydrolysis (△), and $\overline{M}_n = 15\,800$, $X = 0.10$, with 85% hydrolysis (▽). Drugs were loaded by equilibrium partitioning for 14 days from saturated aqueous drug solutions. Error bars represent standard deviations for three experiments.

Fractional theophylline release from P(HEMA-*co*-MMA) and PVA hydrogels is plotted as a function of time in Fig. 7. The release profiles followed expected trends, in that the release was most rapid from hydrogels having the largest mesh sizes, namely the three PVA hydrogels with nominal crosslinking ratio of $X = 0.01$. The highest initial release rate was observed with the gel crosslinked from PVA with the lowest initial molecular weight, $\overline{M}_n = 15\,800$, before crosslinking. In these systems all of the drug was released from the system in less than 1 h. Theophylline release rates

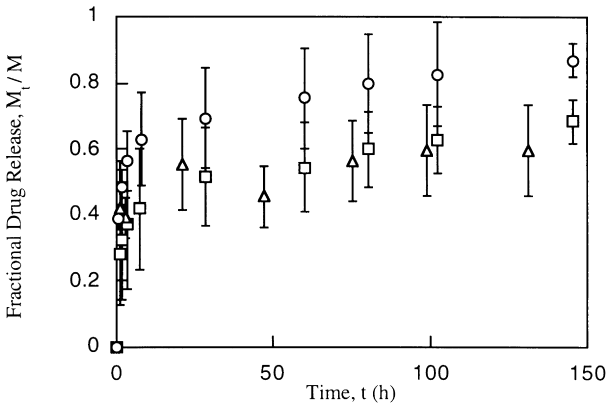

Fig. 10. Effect of polymer structure and composition on FITC-Dextran 4400 release from crosslinked PVA samples at 37°C. Release was conducted from glutaraldehyde-crosslinked PVA samples formed from 15 wt% aqueous solutions of linear PVA with initial $\overline{M}_n = 48\,200$, $X = 0.01$, with 99% hydrolysis (○), $\overline{M}_n = 35\,700$, $X = 0.01$, with 99% hydrolysis (□), and $\overline{M}_n = 15\,800$, $X = 0.01$, with 85% hydrolysis (△). Drugs were loaded by equilibrium partitioning from saturated drug solutions in ethanol for HEMA-containing hydrogels, and saturated aqueous drug solutions for PVA gels. Error bars represent standard deviations for three experiments.

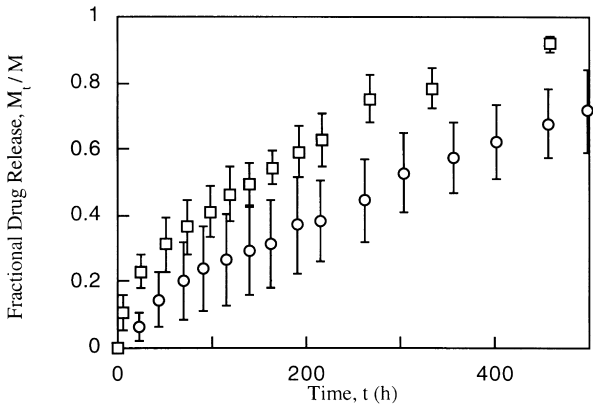

Fig. 11. Effect of polymer structure and composition on FITC-Dextran 4400 release from crosslinked P(HEMA-*co*-MMA) samples at 37°C. Release was conducted from P(HEMA-*co*-MMA) samples of 75 mol% (○) and 100 mol% (□) HEMA composition, crosslinked with 1 mol% EGDMA. Drugs were loaded by equilibrium partitioning from saturated drug solutions in ethanol. Error bars represent standard deviations for three experiments.

decreased slightly for higher-molecular-weight crosslinked PVA samples.

Compared to the crosslinked PVA networks with $X = 0.01$, the polymeric carriers composed of crosslinked P(HEMA-*co*-MMA) and PVA networks with $X = 0.10$ displayed prolonged release of theophylline (see Figs 7–9). Theophylline release from the PVA networks showed Case II kinetics, mirroring the water uptake profile of this polymer as evidenced by the release profile at 1 h (Fig. 7). This indicated that the molecular structure of this polymer had a great influence on the drug diffusion coefficient, as expected when comparing the mesh size of the tested hydrogel (15.3 Å) to the molecular diameter of theophylline (6.1 Å).

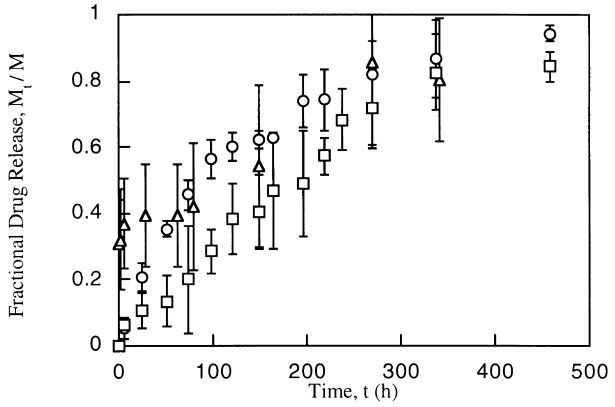

Fig. 12. Effect of polymer structure and composition on insulin release from crosslinked P(HEMA-*co*-MMA) and PVA samples at 37°C. Release was conducted from P(HEMA-*co*-MMA) samples of 75 mol% (○) and 100 mol% (□) HEMA composition, crosslinked with 1 mol% EGDMA, and from glutaraldehyde-crosslinked PVA samples formed from 15 wt% aqueous solutions of linear PVA with initial $\overline{M}_n = 35\,700$, $X = 0.01$, with 99% hydrolysis (△). Drugs were loaded by equilibrium partitioning for 14 days from saturated drug solutions in ethanol for HEMA-containing hydrogels, and saturated aqueous drug solutions for PVA gels. Error bars represent standard deviations for three experiments.

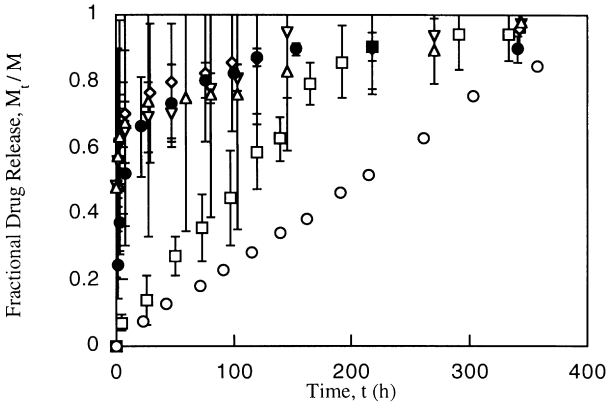

Fig. 13. Effect of polymer structure and composition on myoglobin release from crosslinked P(HEMA-*co*-MAA) and PVA samples at 37°C. Release was conducted from P(HEMA-*co*-MAA) samples of 75 mol% (○) and 100 mol% (□) HEMA composition, crosslinked with 1 mol% EGDMA, and from glutaraldehyde-crosslinked PVA samples formed from 15 wt% aqueous solutions of linear PVA with initial $\overline{M}_n = 48\,200$, $X = 0.01$, with 99% hydrolysis (△), $\overline{M}_n = 35\,700$, $X = 0.01$, with 99% hydrolysis (▽), $\overline{M}_n = 15\,800$, $X = 0.01$, with 85% hydrolysis (◇), and $\overline{M}_n = 15\,800$, $X = 0.10$, with 85% hydrolysis (●). Drugs were loaded by equilibrium partitioning for 14 days from saturated drug solutions in ethanol for HEMA-containing hydrogels, and saturated aqueous drug solutions for PVA gels. Error bars represent standard deviations for three experiments; where not shown, only one experiment was conducted.

Oxprenolol HCl release was investigated using three polymer systems (Table 8). Similar to the results of theophylline release experiments, oxprenolol HCl release was most rapid in PVA hydrogels formed from low-molecular-weight ($\overline{M}_n = 15\,800$) samples. Release decreased somewhat in P(HEMA-*co*-MMA) hydrogels with 75% HEMA, but release rates were still extremely high.

Triamterene was the least hydrophilic of the low-molecular-weight drugs investigated. This lower hydrophilicity greatly affected the total amount of triamterene loaded into hydrogels as shown in Table 7. Solute hydrophilicity had a large influence on drug release characteristics as well. Compared with release of similar molecular weight compounds, such as buflomedil HCl or theophylline, which had initial release rates exceeding 1000 mg h^{-1} in some polymer networks, initial triamterene release rates were below 100 mg h^{-1}. Triamterene release was most rapid from the 99% hydrolysed crosslinked PVA samples, while release from crosslinked PVA samples with 85% degree of hydrolysis had slower release kinetics as shown in Fig. 8. This slower release was due to an increased affinity (or partitioning) of triamterene for the poly(vinyl acetate) moieties in the hydrogel structure.

Buflomedil HCl was another low-molecular-weight drug used in the release studies. Release of buflomedil HCl from two PVA samples was nearly as rapid as for oxprenolol HCl (Table 8). The dominant factor in release was the front velocity, as the presence of water dissolving the imbedded solute was the rate-limiting step. Release of buflomedil HCl from crosslinked P(HEMA-*co*-MMA) samples was

Table 7
Initial normalized drug release rates (mg h^{-1}) from crosslinked P(HEMA-*co*-MMA) and PVA swelling-controlled release systems at 37°C

Drug	MW	Polymer					
		THM75-1	TH100-1	A15-1	B15-1	C15-1	C15-10
Theophylline	180	206	249	1780	676	168	74
Triamterene	253.3	19	20	38	79	10	3
Oxprenolol	302	10 700	–	–	3500	3730	–
Buflomedil	343.8	57	262	–	5950	5130	–
Vitamin B_{12}	1355	0.05	19	395	53	352	53
FITC Dextran	4400	0.32	4.9	19	162	2.0	–
Myoglobin	17 200	0.51	4.9	30	17	22	23

Drug loaded by equilibrium partitioning. Crosslinked samples included P(HEMA-*co*-MMA) with compositions of 75 mol% HEMA (THM75-1) and 100 mol% HEMA (TH100-1), each crosslinked by 1 mol% EGDMA, and PVA samples formed by crosslinking linear PVA from 15 wt% aqueous solutions with glutaraldehyde. Linear PVA molecular weights investigated, with degrees of hydrolysis and nominal crosslinking ratios were: $\overline{M}_n = 48\,200$, hydrolysis = 99%, $X = 0.01$ (A15-1); $\overline{M}_n = 35\,700$, hydrolysis = 99%, $X = 0.01$ (B15-1); $\overline{M}_n = 15\,800$, hydrolysis = 85%, $X = 0.01$ (C15-1); and $\overline{M}_n = 15\,800$, hydrolysis = 85%, $X = 0.10$ (C15-10). Rates were the average of three experiments.

somewhat slower as the mesh space was smaller and the swelling rate was also slower.

Vitamin B_{12} release studies were conducted and analyzed using Eq. (1). Fig. 9 shows typical curves of release from PVA films. Anomalous and Case II release was observed with constant release over most of the release period. Initial release rates decreased with smaller hydrogel mesh sizes and slower swelling kinetics (see also Table 8).

Release studies of FITC-dextran 4400 from crosslinked PVA and P(HEMA-*co*-MAA) systems are summarized in Figs 10 and 11. In crosslinked PVA samples, there was a significant burst effect followed by slow release. FITC-dextran 4400 release from P(HEMA-*co*-MMA) hydrogels showed slow release patterns indicative of the very small mesh size of these networks (Fig. 11).

Inulin release was significantly hindered by even the PVA hydrogel with a mesh size of 86.4 Å (Fig. 12 and Table 8). After an initial burst of inulin from this sample, the release rates were nearly as low as observed in the crosslinked P(HEMA-*co*-MMA) samples.

Release of myoglobin from crosslinked PVA samples (Fig. 13) showed a significant burst effect, followed by slow release, while P(HEMA-*co*-MMA) samples allowed nearly zero-order myoglobin release, over 200 h.

In summary, the polymer structure and composition were shown to greatly influence drug diffusion. The primary factors influencing drug release profiles were directly related to the polymer swelling behavior: mesh size, polymer hydrophilicity, crosslinking ratio, and composition.

3.10. Effect of drug characteristics on release from polymer carriers

As the hydrophilicity and size of each drug compound had a significant effect on drug release behavior, they were investigated more thoroughly. Drug release data were plotted as a function of time for all drugs tested on the same polymer.

Release profiles of high-molecular-weight solutes from the pure PHEMA networks are shown in Fig. 14. The release of each of these drugs occurred over a time-scale much longer than observed for theophylline, buflomedil HCl and triamterene. Release profiles for five low-molecular-weight drugs from crosslinked PVA samples

Table 8
Drug diffusion coefficients (D, $\times 10^8$ cm^2 s^{-1}) at 37°C as estimated by the late-time approximation (Eq. (7)) for drug release from crosslinked P(HEMA-*co*-MMA) and PVA samples[a]

Drug	MW	THM75-1	TH100-1	A15-1	B15-1	C15-1	C15-10
Theophylline	180	2.68 ± 1.07	11.6 ± 1.0	96.3 ± 11.8	90.5 ± 40.6	31.5 ± 3.5	11.2 ± 4.5
Triamterene	253.3	5.34 ± 3.52	2.81 ± 1.22	22.2 ± 4.0	96.2 ± 50.2	30.6 ± 13.5	2.13 ± 0.39
Oxprenolol	302	22.9 ± 3.2	–	–	90.9 ± 52.5	119 ± 28	–
Buflomedil	343.8	–	4.92 ± 2.32	–	121 ± 12	108 ± 40	–
Vitamin B_{12}	1355	0.027 ± 0.009	0.729 ± 0.363	50.0 ± 11.3	28.2 ± 11.6	47.2 ± 15.9	5.42 ± 6.32
FITC-Dextran	4400	0.043 ± 0.038	0.067 ± 0.020	–	0.388 ± 0.152	0.623 ± 0.487	–
Inulin	5200	0.091 ± 0.045	0.048 ± 0.01	–	0.414	–	–
Myoglobin	17 200	0.0823	0.205 ± 0.084	0.454	0.547 ± 0.089	8.66 ± 7.74	3.13 ± 3.62

[a] Hydrogels of P(HEMA-*co*-MMA) of compositions 75 mol% HEMA (THM75-1) and 100 mol% HEMA (TH100-1) were crosslinked by 1 mol% EGDMA, and PVA samples were formed by crosslinking linear PVA from 15 wt% aqueous solutions with glutaraldehyde. Linear PVA molecular weights investigated, with degrees of hydrolysis and nominal crosslinking ratio were: $\overline{M}_n = 48\,200$, hydrolysis = 99%, $X = 0.01$ (A15-1); $\overline{M}_n = 35\,700$, hydrolysis = 99%, $X = 0.01$ (B15-1); $\overline{M}_n = 15\,800$, hydrolysis = 85%, $X = 0.01$ (C15-1); and $\overline{M}_n = 15\,800$, hydrolysis = 85%, $X = 0.10$ (C15-10). Standard deviations represent the average of three trials. Where blank, experiments were not performed.

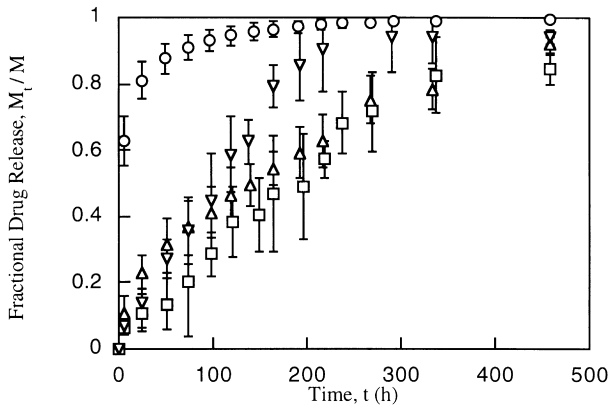

Fig. 14. Effect of solute size on drug release characteristics from crosslinked PHEMA samples at 37°C, plotted for high-molecular-weight drugs. Release of vitamin B_{12} (○), inulin (□), FITC-dextran 4400 (△), and myoglobin (▽) from PHEMA samples. Drugs were loaded by equilibrium partitioning from concentrated drug solutions in ethanol for 14 days. PHEMA hydrogels were formed by crosslinking during thermally-initiated free radical polymerization from monomers with 1 mol% EGDMA as a crosslinking agent. Error bars represent standard deviations for three experiments.

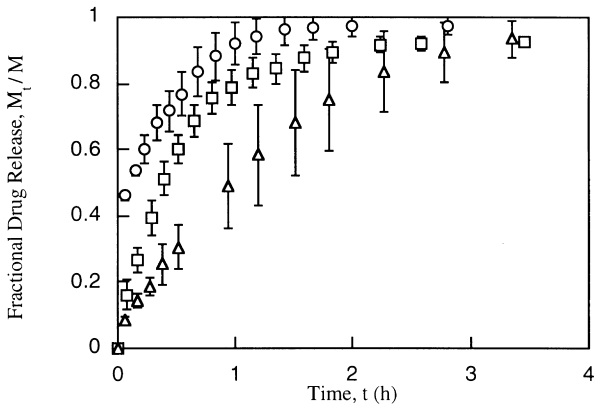

Fig. 15. Effect of solute size on drug release characteristics from crosslinked PVA samples (A15-1) at 37°C, plotted theophylline (○), triamterene (□), and vitamin B_{12} (△). Drugs were loaded by equilibrium partitioning from concentrated aqueous drug solutions for 14 days. PVA hydrogels were formed by crosslinking PVA chains with initial $\overline{M}_n$ = 48 200 and 99% degree of hydrolysis, with 1 mol% glutaraldehyde from 15 wt% aqueous PVA solutions. Error bars represent standard deviations for three experiments.

are shown in Fig. 15. Theophylline, buflomedil HCl, oxprenolol HCl and triamterene were all released rapidly from these hydrogels.

Drug diffusion coefficients were estimated from these results using the early-time (Eq. (6)) and late-time (Eq. (7)) approximations of the release equations. The diffusional exponents, *n*, were also determined by fitting the data to the power law model (Eq. (1)). Analysis of the drug release behavior of high-molecular-weight drugs with Eq. (6) may give misleading data. Thus, Eq. (7) may be more appropriate.

Late-time approximations of the drug diffusion coefficients are presented in Table 9. For the lower-molecular-weight drugs, ranging from theophylline to buflomedil HCl, the drug diffusion coefficients were on the order of 10^{-8} to 10^{-6} $cm^2\,s^{-1}$, with carrier mesh size and hydrophilicity significantly affecting the diffusion coefficient.

The drug diffusion coefficients determined from the late-time release approximations were normalized with respect to the drug diffusion coefficient in water for each drug at 37°C and the results are shown in Table 10.

The relative importance of Fickian and relaxation processes on the mechanism of drug release were compared using the diffusional exponent values determined for each of the swelling-controlled release systems as shown in Tables 11–13. For those experiments where *n* values could be determined, the values ranged from 0.45 to greater than 1, indicating a wide variance in drug transport characteristics. The drug transport ranged from Fickian diffusion, which was observed primarily for the release of hydrophilic, low-molecular-weight drugs from P(HEMA-*co*-MMA) samples, to anomalous and Case II (zero-order release) transport, which was more notable for release of high-molecular-weight drugs from P(HEMA-*co*-MMA) samples, and the release of all of the model drugs from PVA gels. In

Table 9
Comparison (%) of drug diffusion coefficients as estimated by the late-time approximation (Eq. (7)) for release at 37°C from crosslinked P(HEMA-*co*-MMA) and PVA samples with free diffusion coefficients in water at 37°C[a]

Drug	MW	THM75-1	TH100-1	A15-1	B15-1	C15-1	C15-10
Theophylline	180	0.228 ± 0.091	0.986 ± 0.086	9.19 ± 1.00	7.69 ± 3.46	2.68 ± 0.29	0.950 ± 0.384
Triamterene	253.3	0.777 ± 0.513	0.409 ± 0.177	3.23 ± 0.49	14.0 ± 7.3	4.46 ± 1.97	0.310 ± 0.056
Oxprenolol	302	3.39 ± 0.47	–	–	13.5 ± 7.8	17.6 ± 4.1	–
Buflomedil	343.8	–	0.952 ± 0.448	–	23.5 ± 2.4	21.0 ± 7.8	–
Vitamin B_{12}	1355	0.007 ± 0.001	0.192 ± 0.096	13.2 ± 2.9	7.43 ± 3.06	12.5 ± 4.2	1.43 ± 1.67
FITC-Dextran	4400	0.027 ± 0.024	0.043 ± 0.013	–	0.252 ± 0.099	0.405 ± 0.316	–
Inulin	5200	0.054 ± 0.027	0.029 ± 0.010	–	0.248	–	–
Myoglobin	17 200	0.0619	0.154 ± 0.063	0.341	0.411 ± 0.067	6.51 ± 5.82	2.35 ± 2.72

[a] Hydrogels of P(HEMA-*co*-MMA) of compositions 75 mol% HEMA (THM75-1) and 100 mol% HEMA (TH100-1) were crosslinked by 1 mol% EGDMA, and PVA samples were formed by crosslinking linear PVA from 15 wt% aqueous solutions with glutaraldehyde. Linear PVA molecular weights investigated, with degrees of hydrolysis and nominal crosslinking ratio were: $\overline{M}_n$ = 48 200, hydrolysis = 99%, X = 0.01 (A15-1); $\overline{M}_n$ = 35 700, hydrolysis = 99%, X = 0.01 (B15-1); $\overline{M}_n$ = 15 800, hydrolysis = 85%, X = 0.01 (C15-1); and $\overline{M}_n$ = 15 800, hydrolysis = 85%, X = 0.10 (C15-10). Standard deviations represent the average of three trials. Where blank, experiments were not performed.

Table 10
Drug diffusion coefficients in crosslinked PVA samples at 37°C

Drug	Molecular weight	Drug diffusion coefficient ($\times 10^8$ cm^2 s^{-1})	Drug diffusion coefficient relative to free solution
Theophylline	180	58.4	0.050
Oxprenolol HCl	302	5.07 ± 3.39	0.751
Oxprenolol HCl	302	37.4	0.055
Oxprenolol HCl	302	37.0 ± 12.3	0.055
Triamterene	253.3	20.0 ± 1.0	0.029

Drug diffusion coefficients were determined by the late time approximation. Polymers were formed from aqueous PVA solutions with an initial $\overline{M}_n$ and having an 85% degree of hydrolysis, in the presence of 1 mol% glutaraldehyde as a crosslinking agent and a known amount of drug. Where standard deviations are listed, data represent the averages and of three experiments.

Table 11
Diffusional exponents, *n*, for drug release in water at 37°C from crosslinked P(HEMA-*co*-MMA) and PVA swelling-controlled release samples

Drug	MW	THM75-1	TH100-1	A15-1	B15-1	C15-1	C15-10
Theophylline	180	0.491	0.768	x	0.449	x	0.853
Triamterene	253.3	x	0.448	0.704	0.978	0.922	0.698
Oxprenolol HCl	302	0.721	–	–	0.981	x	–
Buflomedil HCl	343.8	0.536	0.598	–	0.854	0.770	–
Vitamin B_{12}	1355	x	x	0.855	1.07	0.844	0.609
FITC-Dextran	4400	0.811	0.588	x	x	x	–
Inulin	5200	x	x	–	x	–	–
Myoglobin	17 200	0.717	1.31	x	x	x	x

Drug loaded by equilibrium partitioning. Hydrogels of P(HEMA-*co*-MMA) with compositions 75 mol% HEMA (THM75-1) and 100 mol% HEMA (TH100-1) were crosslinked by 1 mol% EGDMA, and PVA hydrogels were formed by crosslinking linear PVA from 15 wt% aqueous solutions with glutaraldehyde. Linear PVA molecular weights investigated, with degrees of hydrolysis and crosslinking ratio were: $\overline{M}_n = 48\,200$, $X = 0.01$, hydrolysis = 99% (A15-1); $\overline{M}_n = 35\,700$, $X = 0.01$, hydrolysis = 99% (B15-1); $\overline{M}_n = 15\,800$, $X = 0.01$, hydrolysis = 85% (C15-1); and $\overline{M}_n = 15\,800$, $X = 0.10$, hydrolysis = 85% (C15-10). Standard deviations represent the average of three experiments. Blank spaces indicate experiments were not conducted, while an x in the table represents experiments which were conducted, but not enough data were collected in the early portion of the release period to yield accurate *n* values.

general, the diffusional exponents increased with drug molecular weight. In fact, in higher-molecular-weight solute transport, diffusion was hindered by the presence of the polymer mesh. Thus, release of vitamin B_{12}, FITC dextran, inulin and myoglobin followed non-Fickian behavior. For drug release from P(HEMA-*co*-MMA) samples, there was a large difference in diffusional exponents with small increases in drug molecular weight. This was due to the small mesh size of these networks. However, once a critical molecular weight was reached, the diffusional exponent leveled off for release of FITC dextran and myoglobin, the drugs with high molecular weights. A less drastic increase in the drug release diffusional exponent was observed for release from PHEMA gels.

4. Conclusions

It has been demonstrated that solute transport in swellable hydrophilic polymers is affected by a variety of structural and physical characteristics of the crosslinked polymers and by the nature of the solutes used. Water swelling

Table 12
Diffusional exponents, *n*, for drug release in water at 37°C from crosslinked P(HEMA-*co*-MMA) samples[a]

Drug	Molecular weight	Total drug released (wt%)	Power law diffusional exponent, *n*
Oxprenolol HCl	302	12.5	0.488
Buflomedil HCl	343.8	6.05	0.517
Vitamin B_{12}	1355	1.47	0.465

[a] Drugs loaded during polymerization. Polymers were formed by thermal initiation of a 75 mol% HEMA/25 mol% MMA solution in the presence of 1 mol% EGDMA as a crosslinking agent, and 5 wt% drug. Data represent the averages and standard deviations of three experiments.

Table 13
Drug release power law diffusional exponents, *n*, for drug release in water at 37°C from crosslinked PVA samples[a]

Drug	Molecular weight	Power law diffusional exponent, *n*
Theophylline	180	0.567
Oxprenolol HCl	302	0.638
Oxprenolol HCl	302	0.569
Triamterene	253.3	1.044

[a] Drugs loaded during polymerization. Polymers were formed from aqueous PVA solutions with an initial and having an 85% degree of hydrolysis, in the presence of 1 mol% glutaraldehyde as a crosslinking agent and a known amount of drug. Data represent the averages of three experiments.

experiments using hydrogels showed the effects of cross-linking ratio and polymer composition and molecular weight. The mechanism of drug release was Fickian, anomalous or Case II transport depending on the size of the diffusing drug molecule and the size exclusion characteristics of the polymer carrier.

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