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Review

Hydrogels: Swelling, Drug Loading, and Release

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Hydrogels have been used by many investigators in controlled-release drug delivery systems because of their good tissue compatibility and easy manipulation of swelling level and, thereby, solute permeability. The desired kinetics, duration, and rate of solute release from hydrogels are limited to specific conditions, such as hydrogel properties, amount of incorporated drug, drug solubility, and drug–polymer interactions. This review summarizes the compositional and structural effects of polymers on swelling, loading, and release and approaches to characterize solute release behavior in a dynamic state. A new approach is introduced to compensate drug effects (solubility and loading) with the release kinetics by varying the structure of heterogeneous polymers. Modulated or pulsatile drug delivery using functional hydrogels is a recent trend in hydrogel drug delivery.

KEY WORDS: hydrogels; swelling; loading; release kinetics; functional polymers.

INTRODUCTION

Hydrogels are polymers which have the ability to swell in water or aqueous solvent systems. The polymer structure is able to retain the solvents forming a swollen gel phase and, in cross-linked systems, will not dissolve regardless of the solvent.

Hydrogels suitable for diverse applications often involve hydroxyalkyl methacrylates. When used as implants, the rubbery nature of the hydrated hydrogels has been found to minimize mechanical irritation to surrounding tissue. The low interfacial tension between the hydrogel surface and the aqueous solution has been found to minimize protein adsorption and cell adhesion.

The monomer composition of a copolymer can be manipulated to influence the permeation and diffusion characteristics of the hydrogel, and through this manipulation, hydrogels can be synthesized to accommodate a variety of drugs loaded into the matrix. These include hydrophobic and hydrophilic substances, charged or neutral small molecules, and macromolecules. This avenue of controlled drug release has been pursued in recent years (1,2), but as yet no products have reached the market.

There are two general methods for loading of hydrogels as drug carriers. In one method, the hydrogel monomer is mixed with drug, an initiator, with or without a cross-linker, and allowed to polymerize, trapping the drug within the matrix (3). In the second approach, a preformed hydrogel is allowed to swell to equilibrium in a suitable drug solution. The drug-loaded hydrogel is dried and the device is obtained. The latter method has some advantages over the first method because polymerization conditions may have deleterious effects on drug properties and the difficulties in device purification after loading and polymerization often remain. The degree of swelling can be estimated by conventional Flory–Huggins swelling theory (4) and is determined by the polymer–solvent interaction parameter, cross-linking density of the polymer network, and polymerization conditions. The presence of drug in the solvent can also influence the degree of swelling.

Drug loading range per unit mass of a polymer can be estimated from the following relationships:

Lower limit (swollen phase only) =

$$(V_s/W_p) \times C_o \tag{1}$$

Upper limit (swollen and polymer phases) =

$$[(V_s + KV_p)/W_p] \times C_o \tag{2}$$

where V_s and V_p are the absorbed solvent and dried polymer volume respectively, W_p is the dried polymer weight, K is the partition coefficient between polymer chains and drug loading solution, and C_o is the drug concentration in solution. The calculation is based on the assumption that the absorbed solvent is in equilibrium with the loading solution and the drug concentration within the device is the same as that of the loading solution.

The release of drugs from these hydrogels (initially dried) involves the absorption of water into the matrix and simultaneous desorption of drugs via diffusion, as governed by Fick's law. The process can be modeled using a free-volume approach or a swelling-controlled release mechanism.

A free-volume approach can be applied to determine the diffusion coefficient (D_m) of a solute in a hydrated polymer. The fundamental experimental variables are the extent of hydration of the polymer and the molecular size of the permeating species:

$$\ln(D_m/D_o) \propto -(B_{q2}/V_f)(1/H - 1) \tag{3}$$

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where B_{q2} is proportional to the solute cross-sectional area (πr^2), V_f is the molar free volume, H the equilibrium hydration of the hydrogel, D_o the diffusion coefficient of the solute in water, and r the radius of the solute. Experimentally, plots of $\ln(D_m/D_o)$ versus r^2 of the solute are linear when hydrogels of equilibrium hydration are used (5). As hydration decreases, the fluctuating pore size and available free volume decrease, resulting in lower diffusion of large molecules. Hydrophylic solutes in the molecular weight range of 20 to 500 show linear plots, indicating a decreasing D_m with increasing solute size (6).

In this manuscript, we discuss the swelling, drug loading, and release of model drugs with Biomer (a segmented copolymer) and several newly synthesized hydrogels. The design concept of hydrogel drug delivery systems is presented schematically in Fig. 1.

SEGMENTED COPOLYMER

.Biomer, a polyurethane, not a hydrogel per se, consists of polyether (soft segment) and urethane urea (hard segment). The polyurethane could be considered as a water-swellable gel if a hydrophilic component, such as polyethylene oxide, were incorporated into the soft segment. The use of a selected solvent system allows the soft segment of the polymer to swell. The unswellable hard segment acts in a manner similar to physical cross-linking.

Drugs can be loaded into polyurethane using either of two methods (7). In the first method, the drug is loaded by swelling only the soft segment domain in the drug/ethanol solution. The use of a good solvent for only one segment allows high swelling of this segment, with subsequent selective drug loading into this segment. Alternatively, the drug can be mixed with a Biomer/dimethylacetate (DMAc) solution, followed by drying. Figures 2a and b are schematic representations of prednisolone-loaded Biomer by the above two methods. Table I represents the drug loading percentage and release rate. The maximum loading of prednisolone was 3% from a 0.028-g/ml ethanol solution. The calculated value was 3.4%, based upon a fraction of 0.6 of soft segment in the Biomer and no drug partitioning in hard segment chains. FTIR studies found that prednisolone loaded by ethanol swelling was associated with the soft segment, and no molecular interaction was observed. However, prednisolone loaded by DMAc solution casting was dispersed in both the hard segment and the soft segment. In addition, there was strong carbonyl hydrogen bonding observed due to the interaction between the drug and the hard segment. This is supported by the slower release kinetics of prednisolone observed from the solution method compared to the swelling procedure. Although a relatively low drug loading was observed with Biomer, this method could be applicable to drug delivery devices specifically requiring low-dose administration.

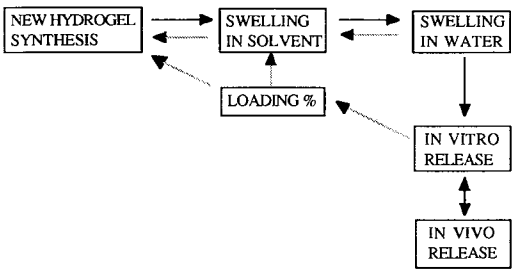

Fig. 1. The concept of hydrogel synthesis, drug loading by swelling, and release.

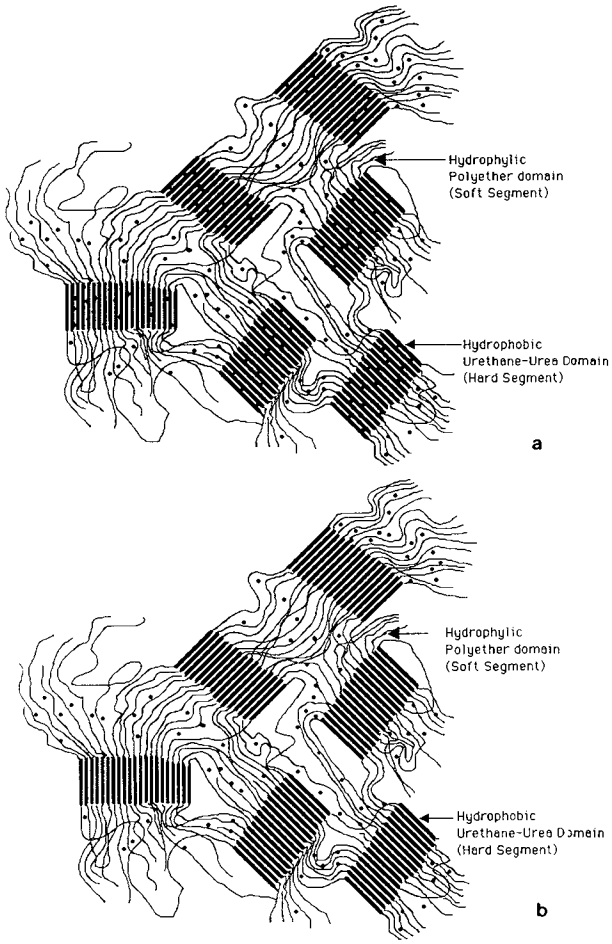

Fig. 2. (a) Drug-loaded Biomer by DMAc solution. (b) Drug-loaded Biomer by swelling in ethanol.

POLY(HEMA) AND ITS COPOLYMERS

Good and Mueller (8) synthesized a two-component hydrogel network by polymerizing HEMA (2-hydroxyethylmethacrylate) in the presence of poly(tetramethylene

Table I. Prednisoline Load (in EtOH) and Release (in Water)

Drug load (%, w/w)	1.6	2.2	2.3	2.4	3.0[a]
Slope (M_t/A vs $t^{1/2}$)	0.359	0.569	0.570	0.607	0.769

[a] Experimentally determined maximum loading (7).

Estimated maximum loading by calculation: 1.6 (g/g) × 0.6 × (1cm^3/0.79 g) × 0.028 (g/cm^3) × 100 = 3.4%; $(W_s/W_p) \times f_s \times (1/\rho_s) \times C_0 \times 100$ = maximum loading. W_s, absorbed solvent weight; W_p, dried polymer weight; f_s, soft segment fraction; ρ_s, solvent density; C_0, drug solubility in solvent.

oxide) (PTMO; isocyanate terminated) as a cross-linker. The variations in PTMO molecular weight and composition provided hydrogels with a range of equilibrium hydrations. Figure 3 represents the structure of poly(HEMA-PTMO). The loading of drug into these hydrogels is dependent on the ability of the network to swell in appropriate solvents. Swelling of the polymer system, varying the PTMO content, was measured in binary mixtures of ethanol and water and showed a maximum swelling with a solubility parameter of about 17 $(cal/ml)^{1/2}$ for all compositions. The gel with 10 wt% of PTMO (M_n 2450) showed higher swelling than poly(HEMA) in most of the solubility parameter range. Increases in PTMO molecular weight in hydrogels of 35 wt% PTMO composition produced an increased degree of swelling. The maximum degree of swelling was obtained in an 80% solution of ethanol in water. Constant cross-link density networks with increasing PTMO molecular weight caused decreases in the apparent solubility parameter of the polymers. Solutions of phenformin-HCl were sorbed into the polymer systems. The initial loading increased with increased maximum hydrogel swelling. Release patterns of drugs from loaded networks in 37°C water were fit to a mathematical model and appropriate diffusion parameters were determined.

Good (9) developed a mathematical model for the diffusion of water soluble drugs from hydrogels. This model accounted for the case of drug release from dehydrated polymer and a moving solvent front dissolving and extracting drug. Based on Fick's second law of diffusion, a solution was developed utilizing a time-dependent diffusion coefficient, which is based on the degree of swelling as a function of time. *In vitro* release of tripelennamine-HCl from cross-linked poly(HEMA) was fit to the mathematical model. Drug loading was achieved by swelling the hydrogel in a tripelennamine-HCl solution of an EtOH–H_2O mixture and allowing it to equilibrate. Fractional release rate increased slightly with increased initial loading content, and increased hydrogel film thickness caused a slower fractional release of drug. Diffusion coefficients determined by data fit to the mathematical model demonstrated that increased tripelennamine-HCl loading increases the diffusion coefficient.

Lee (10) applied a refined integral method to the problem of a moving solvent front (boundary) for erodible and nonerodible polymer matrices producing approximate analytical solutions to analyze release kinetics under perfect sink conditions. Lee's approximate solutions fit exact solutions for concentration profiles and for release of solute dispersed in a planar polymer matrix better than the pseudo-steady-state analysis of the equation:

$$M_t/A = (2DC_sC_o t)^{1/2} \quad \text{for} \quad C_o \gg C_s \tag{4}$$

where M_t is the amount of drug released during time t, A is the surface area of the polymer slab, C_s is the solubility of drug in polymer, and C_o is the initial drug concentration in polymer. This equation was applicable until no drug remained dispersed within the matrix. A plot of M_t/A versus $t^{1/2}$ gave a straight line with a slope yielding a diffusion constant. The approximate solutions were dependent upon the ratio of C_o to C_s for a good fit. For a C_o/C_s greater than 4.5, Lee's approximate solution deviated from the exact solution by less than 0.1%, and at a C_o/C_s of 1.04, the deviation was within 1%. For use of Eq. (2), within 1% error, a C_o/C_s greater than 10 was required. The solution for nonerodible spherical matrices produced similar results.

Attempts have been made to interpret kinetics of swelling and drug release from poly(HEMA) and its copolymers utilizing the concept that sorption of water into glassy hydrogels generally exhibits anomalous behavior ranging from Fickian to Case II diffusion. Variations have been found to be dependent upon the experimental conditions in relation to T_g and the thermodynamic parameters between the solvent and the hydrogels (11). Fickian or non-Fickian behavior of drug release depends on the rate of polymer relaxation at the glassy–rubbery transition at the swelling interface. For a polymer slab, Fickian diffusion is proportional to the square root of time, while Case II diffusion, which is determined by the rate of polymer relaxation and diffusional rate, exhibits a linear time dependence of solute release.

Three phenomenological equations were introduced to characterize types of solute diffusion in polymers. A common equation,

$$M/M_\infty = kt^n \tag{5}$$

represents the fraction of released drug and is a function of time, t. For $n > 0.5$, non-Fickian diffusion is observed, while $n = 0.5$ represents a Fickian diffusion mechanism. The case of $n = 1$ provides Case II transport mechanism in which drug release from hydrogel having slab geometry will be zero order. For predicting whether diffusion in a hydrogel is a relaxation-controlled diffusion process, the Debora number was defined as (12)

$$\mathrm{De} = \lambda_m/\theta_D \tag{6}$$

where λ_m is the mean relaxation time of the hydrogel/solvent system and θ_D is defined by L^2/D_s, with L the sample thickness and D_s the solvent diffusion coefficient. When De $\gg$ 1 or De $\ll$ 1, Fickian diffusion in either glassy or rubbery states occurs. If De $\approx$ 1, non-Fickian diffusion, including Case II transport, is anticipated. Korsmeyer and Peppas (13) defined the swelling interface number, S_w, which determines the mechanism of drug release from hydrogel given, as

$$S_w = V\delta(t)/D \tag{7}$$

where V is the velocity of the penetrating swelling front, $\delta(t)$ the time-dependent thickness of the swollen phase, and D the drug diffusion coefficient in the swollen phase. For the case of $S_w \ll 1$, drug diffusion through the swollen phase is

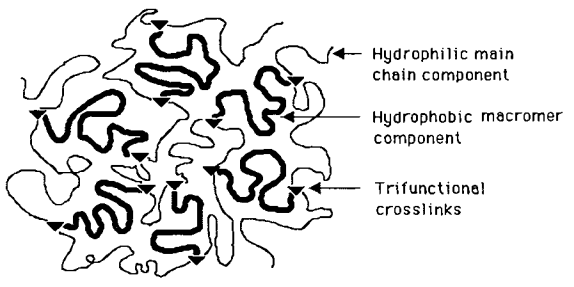

Fig. 3. Schematic representations of a poly(HEMA-PTMO) structure (8).

expected to be much faster than the rate at which the glassy-rubbery front advances and zero-order drug release is shown. Fickian release is observed in the case of $S_w \gg 1$ since the swelling front advances faster than drug release. For values of $S_w \approx 1$, non-Fickian drug release is anticipated. The characteristics for drug diffusion in hydrogels are summarized in Table II.

Korsmeyer and Peppas (14) synthesized glassy copolymers of HEMA and NVP (*N*-vinylpyrrolidone). The swelling mechanism was observed to be non-Fickian. Theophylline release from dehydrated gels gave a pseudo-zero-order release, depending on the copolymer composition and the thickness of the sample. The amount of drug loaded by soaking in aqueous solution was 5.86 to 6.12% (w/w) of the dried hydrogel. Equilibrium swelling of poly(HEMA-co-NVP) is tabulated in Table III. Fraction of released drug vs unitless time $\tau = Dt/L^2$ (D = solute diffusivity in a swollen matrix, t = time, and L = matrix thickness) was plotted and showed that poly(HEMA-co-NVP) hydrogels provide pseudo-zero-order release of theophylline following the swelling-controlled release mechanism discussed previously.

An important aspect in the use of hydrogels is the effect of drug loading level and dimensional changes of devices on the rate of drug release. Lee completed an investigation of dimensional changes in a cross-linked poly(HEMA) spherical matrix during solvent permeation and solute dissolution and diffusion in hydrogel beads (11). Thiamine-HCl was loaded into poly(HEMA) beads by swelling the polymer in aqueous or ethanolic solutions of various thiamine-HCl concentrations. Loadings were produced in the range of 3.8 to 25.1%. *In vitro* evaluation of release patterns showed a more rapid fractional release of drug with increased initial loading levels. The larger the initial load, the faster the solvent front penetrated the poly(HEMA) beads. With loading in excess of 18.8% the beads became opaque, while beads of loads below 18.8% remained clear after the solvent was removed by evaporation. Fickian diffusion ($t^{1/2}$ dependence) predominates in loadings above 18.8%, while anomalous diffusion patterns were seen in hydrogels loaded with less than 18.8% (a $t^{0.7}$ dependency). The dimensional ratio of swollen radius to dry radius increased fastest with the highest initial thiamine-HCl load, peaking within the first 0.5 h, then decreasing as drug was released. Poly(HEMA) without thiamine-HCl produced a gradual increase in the radius, reaching equilibrium hydration within 2 hr. The swelling ratios of loaded devices were not as large as that of unloaded poly(HEMA), while the ratios of dry radius of the loaded hydrogels to dry radius of pure poly(HEMA) increased significantly with increased loading. The loaded polymer bead already has extended chains and thus sorption of solvent and release of drug produce a smaller chain extension than in the nonloaded hydrogel. Following complete release of drug, the equilibrium hydrations of the poly(HEMA) beads were constant.

Table II. Summary of the Characteristics for Drug Diffusion in Hydrogels

Type	M/M_∞	De	Sw
Fickian diffusion	n = 0.5	$\ll 1$ or $\gg 1$	$\gg 1$
Non-Fickian diffusion (anormolus)	n > 0.5	~1	~1
Case II diffusion	n = 1	~1	$\ll 1$

Table III. Equilibrium Swelling of Poly(HEMA-co-NVP) Copolymers at 37°C (14)

HEMA mole fraction	Weight fraction of polymer	Weight gain (W_{H_2O}/W_p)	Radial expansion (d/d_0)	Axial expansion (L/L_0)
0.707	0.664	0.505	1.17	1.19
0.446	0.427	1.34	1.33	1.32
0.211	0.150	5.57	1.92	1.83

The transient dimensional changes during the simultaneous solvent penetration and thiamine-HCl levels were discussed. The spherical geometry has the advantage of eliminating the anisotropy and the edge effects normally associated with dimensional measurements in glassy polymer sheets. The radius of an unloaded bead increases monotonically toward the equilibrium radius, whereas that of a loaded bead goes through a maximum corresponding to about 70 to 80% total thiamine release before reaching the final equilibrium value. The continuous increase in the radius after the penetrating fronts have met is believed to be primarily the result of the solvent concentration gradient. The presence of homogeneously dissolved or dispersed thiamine-HCl in poly(HEMA) beads provides an additional osmotic driving force which alters both the total swelling osmotic pressure and the associated time-dependent relaxation of the hydrogel network during simultaneous sorption of water and desorption of drug.

Recently, Kou *et al.* (15) applied Eq. (3) to a dynamically swelling gel system to explain the release behavior of phenylpropanolamine from poly(HEMA-co-methacrylic acid). Since the swelling process of these ionizable polymers is relatively slow, even in the absence of a glassy core when transferred from drug loading solution (pH 1) to a release medium (pH 7), the release kinetics could not be interpreted by a swelling-controlled mechanism. They determined spacially averaged hydration as a function of only time, which was then coupled to a diffusion mechanism through a free-volume relationship. The theoretical prediction agreed well with the experimental results.

Zero-order release of drug from a monolithic device, if essential for a certain therapeutic application, can be designed, in practice, by creating rate-controlling barriers on hydrogel device surfaces. In principle, it should be possible to maintain constant concentration gradients via the introduction of a rate-limiting barrier to solute diffusion at the surface of the device. Poly(HEMA) monolithic devices were soaked in an ethanol solution of ethylene glycol dimethacrylate (EGDMA) followed by exposure to UV light to create a cross-linked surface layer at the outer edge. The cross-linked zone has a much lower permeability to solutes than the central region of the device and therefore serves as a rate-limiting barrier. Progesterone release studies demonstrate zero-order release from devices with a cross-linked outer layer. Drug release rates were dependent upon the UV treatment time, the EGDMA concentration, and the device soaking time in EGDMA solution (16). In an investigation of the

release of drugs from monolithic devices, Roseman and Higuchi (17) developed an equation which describes the release pattern for cylindrical monolithic devices, including the effects of an aqueous boundary layer. This equation would be applicable to the devices developed here with the assumption that the characteristics of the aqueous boundary layer of the Roseman–Higuchi model are applicable to the cross-linked barrier layer of our devices. The appropriate equation is

$$\frac{dm}{dt} = \frac{2\pi h r_o C_B D_B}{C_s L} \times \frac{D_m C_s L}{-0.5 D_B k r_o \ln(1 - F) + D_m L} \quad (8)$$

where

$$K = C_B/C_s \text{ and } F = (r_o^2 - r^2)/r_o^2$$

dm/dt is the drug release rate, F the fraction of drug released, K the partition coefficient between the cross-linked barrier layer and the core layer, D_B the diffusion coefficient in the barrier layer, D_m the diffusion coefficient in the core layer, C_s the drug solubility in the core layer, r_o the radius of the core layer, r the distance from the center of the cylinder to the receding drug boundary, h the height of the cylinder, and L the thickness of the barrier layer. If $D_B \ll D_m$, Eq. (6) reduces to

$$dm/dt = 2h\pi r_o C_B D_B/L \quad (9)$$

Thus in the limit $D_B \ll D_m$, the drug release rate should be dependent only upon the permeation characteristics of the barrier layer. In this limit the release rate should be zero order.

N-ACRYLOYL PYRROLIDINE–STYRENE COPOLYMERS

A major drawback for the use of swelling hydrogels as drug carriers is their limited swelling degree, which is not satisfactory for the loading of a high drug dose. This limitation is evident when two-component hydrogels are used since their maximum swelling in a water–ethanol mixture is only about 1.8 of W_s/W_p (W_s is the absorbed solvent weight).

In the case of poly(HEMA-co-NVP) both compositions are hydrophilic, presenting high swelling in water (up to $W_s/W_p = 6$). Fast drug release in the aqueous environment is expected due to high water swelling. With 5 to 6% theophylline loading (W_d/W_p), it was shown that drug release was complete within only several hours with 1-mm-thick gel (14). Poor mechanical properties are also expected with poly(HEMA-co-NVP) gel, unless a high concentration of cross-linking agent is used. New hydrogels based on the hydrophylic/hydrophobic balanced components have been synthesized. The synthesized gel of *N*-acryloyl pyrrolidine (APy, Japan Patent 58-103348) and styrene (St) shows high swelling in water–ethanol mixtures and relatively low swelling in water, depending on the styrene composition. The structure is shown in Fig. 4. Detailed synthesis is described elsewhere (18). APy monomer is patented (Japan patent 58-103348, U.S.A. patent pending). Figure 5 represents degree of swelling (W_s/W_p) vs ethanol content as the styrene content increases in the copolymer composition. Poly(HEMA) shows a maximum of $W_s/W_p = 2$ and $W_s/W_p = 7$ for homopolymer poly(APy). Poly(HEMA) and poly(APy) show their maximum swelling at 50 to 60% ethanol. The highest swelling was obtained with a 10% composition of styrene ($W_s/W_p = 8$).

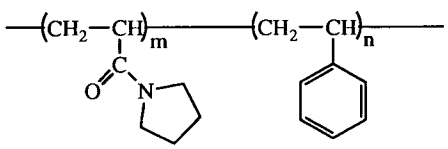

Fig. 4. The structure of poly(APy-co-St).

Drug loading levels in poly(HEMA-PTMO), poly(HEMA), and poly(APy-co-St) are listed in Table IV. For water-soluble drugs, the lowest loading is 0.3 [(poly(HEMA) with 1 mol% EGDMA] and the highest is 1.99 [with poly(APy-co-St), 70:30]. For the less hydrophilic drug, theophylline release could be maintained up to 36 hr in phosphate-buffered saline (PBS), as shown in Fig. 6. Release characteristics in simulated gastric fluid (SGF) were very similar to the release in PBS, demonstrating their pH-independent nature. The summary of theophylline release studies is listed in Table V. It is interesting to note that, although theophylline loading in water–ethanol mixtures did not vary much, the release rate of theophylline was very dependent on the equilibrium swelling of the hydrogel in water. This indicates that theophylline release rates in an aqueous environment can be controlled by controlling the equilibrium hydration of the hydrogels (Table V).

As the hydration (H) rate doubles, the relative diffusion rate increases 10 times, as estimated from Eq. (1). From the results, drug release in the aqueous environment evidently depends on the drug loading percentage and the drug diffusion rate. It follows that if the loading percentage can be fixed (controlled by the swelling medium used), then the release rate of drug will depend on the hydrogel swelling.

IPNs OF PTMO AND POLY(*N*,*N*-DIMETHYLACRYLAMIDE(DMAAm)-co-St)

The kinetics of water-soluble drug release from simple

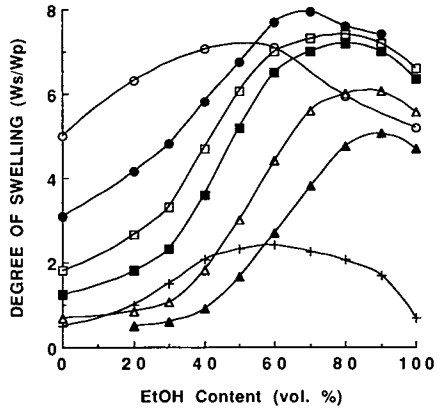

Fig. 5. Swelling of cross-linked poly(APy-co-St) in an ethanol/water mixture: (○), 0 mol% St; (●) 10 mol% St; (□) 15 mol% St; (■) 20 mol% St; (△) 30 mol% St; (▲) 40 mol% St; (+) poly(HEMA) cross-linked with 0.5 mol% EGDMA.

Table IV. Water-Soluble Drug Loading

	W_s/W_p	W_{H_2O}/W_p	W_D/W_p[a]		
			Tripelennamine-HCl	Phenformin-HCl	Theophylline
Poly(HEMA/PTMO)					
90:10	1.78	0.49	0.36–0.56	0.36–0.56 (0.27)[b]	0.036–0.056
80:20	1.33	0.37	0.27–0.47	0.27–0.47 (0.33)[b]	0.027–0.047
70:30	1.02	0.27	0.20–0.40	0.20–0.40 (0.22)[b]	0.020–0.040
60:40	0.89	0.19	0.18–0.38	0.18–0.38 (0.16)[b]	0.018–0.038
Poly(HEMA)					
0.5% EGDMA	2.20	0.60	0.44–0.64	0.44–0.64	0.044–0.064
1.0% EGDMA	1.51	0.56	0.30–0.56 (0.55)[b]	0.30–0.56	0.030–0.056
Poly(APy-co-St)					
90:10	8.95	1.65	1.8–2.0	1.8–2.0	0.18–0.20 (0.19)[b]
80:20	8.40	1.13	1.7–1.9	1.7–1.9	0.17–0.19 (0.19)[b]
70:30	8.05	0.72	1.6–1.8	1.6–1.8	0.16–0.18 (0.18)[b]
60:40	5.60	0.32	1.1–1.3	1.1–1.3	0.11–0.13

[a] Calculated values from a 20% drug solution for tripelennamine-HCl and phenformin-HCl and a 2% solution for theophylline.
[b] Experimental values of Good (9) for tripelennamine-HCl and phenformin-HCl and of our laboratory for theophylline.

monolithic devices range from first to pseudo-zero order. To obtain pseudo-zero-order release by Case II diffusion, it is necessary to minimize the loaded drug effect on the velocity of the moving solvent front and the osmotic pressure gradient. This restricts the applications of the polymeric system to a high dose of water-soluble drug, and if the polymeric matrix or drug properties are altered, the system response will not be predictable.

To use polymeric monolithic hydrogel devices for a wide range of drug solubility and loading content and to manipulate release kinetics, a new polymeric system was developed. The polymer system was composed of two chemically independent networks [interpenetrating polymer networks (IPN)]; one network is cross-linked PTMO, and the other network DMAAm/St (hydrophylic/hydrophobic) balanced copolymer (19). The ratio of the two networks, the cross-linking density of the PTMO network, and the copolymer composition of the vinyl network can be altered to compensate for the effects of water solubility of loaded drug and loading content on release kinetics and to obtain the desired release kinetics. After drug loading by the solvent sorption technique with drug solution in water/ethanol mixture, the release kinetics vary from first order to abnormally accelerated release rates, resulting in a sigmoidal release curve in the plotting of cumulative amount released versus time. This system can also generate zero-order release as presented in Fig. 7. We hypothesized that the net force between the osmotic pressure generated by dissolved drug inside the matrix and that generated by the swelling force of the hydrophilic component and elastic contraction force of the nonswelling PTMO network affects the release behavior of highly water-soluble drugs. For a moderately soluble drug, the morphology of the polymer matrix may also influence the release kinetics.

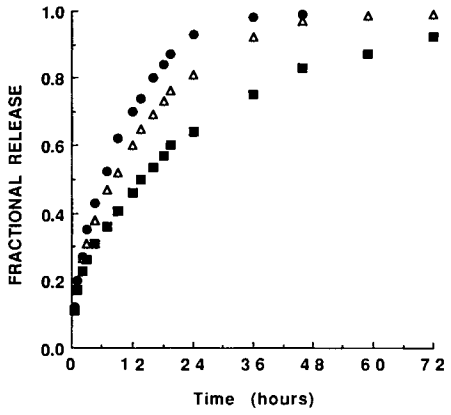

Fig. 6. Theophylline release from cross-linked poly(APy-co-St) in PBS, pH 7.4, 37°C: (●) 10 mol% St; (△) 15 mol% St; (□) 20 mol% St.

POLY(*N*-ISOPROPYLACRYLAMIDE) AND ITS COPOLYMERS

When it is necessary to load and release labile drugs, including peptide or protein drugs from hydrogels, water–ethanol mixtures are not suitable for such drugs because proteins easily undergo denaturation, even in benign solvents. This is a drawback of the previously discussed hydrogel or polymer systems. One method for loading protein drugs into the hydrogels is to utilize stimulus-sensitive hydrogels where swelling is sensitive to stimuli such as pH and temperature (20). The most stable condition for *in vitro* treatment of proteins is at a low temperature and a neutral pH. Thus, a hydrogel system demonstrating swelling high enough for protein drug loading at a low temperature and a lower degree of swelling at body temperature to control the release rate could be used for such labile drugs.

N-Alkyl-derivatized acrylamides, especially poly(*N*-isopropylacrylamide) (NiPAAm) and its copolymers, have demonstrated thermosensitive swelling characteristics. Aqueous solutions of poly(NiPAAm) are known to have a lower critical solution temperature (LCST), about 32°C. Below this temperature the solution is transparent, while the polymer precipitates above this temperature. This solubility transition converts to swelling transition in cross-linked hy-

Table V. The Relationship of Hydration and Theophilline Release Rate from Poly(APy-co-St)

Poly(APy-co-St)	W_D (mg)[a] in 265 mg W_p	W_{H_2O}/W_p	H (%)	Relative H	Relative D[b]
90:10	46	1.65	62	2.08	10.0
85:15	45.9	1.13	53	1.77	5.9
80:20	45.4	0.75	42	1.39	2.5
70:30	45	0.4	30	1	1

[a] Theophilline loaded in a 2% ethanol/water solution.
[b] Relative diffusion calculated by log D/D_0 vs H. Release experiments in PBS.

drogels. The swelling transition temperature, degrees of swelling before and after transition, and transition behavior around its LCST can be controlled by the chemical structure of comonomers and their content in copolymer composition. Drug release behaviors from such a polymer matrix are shown to have two mechanisms: squeezing the loaded drug by bulk deswelling (21) and on–off release by rigid skin formation on the surface resulting from rapid surface layer deswelling (22). The patterned release of chemicals may have an advantage over fixed release rates because it can mimic chronobiological release of some regulatory agents such as hormones (22).

In summary, drug loading by a swelling method can be performed based on the selection of the drug for therapeutic efficacy and hydrogel swelling data in the selected solvent (to provide a suitable load percentage). The drug loading content is controlled by the polymer composition and can be estimated from the swelling level in the loading solvent. Hydrogel swelling influences the release kinetics via a swelling-controlled mechanism or the free-volume theory. The free-volume theory can be utilized even for a dynamically swelling system through a swelling-dependent diffusion coefficient as a function of time. Additional factors which affect the drug release mechanism are the local partition coefficient when a phase-separated matrix us used, the overall hydrophilic/hydrophobic balance of the system, the osmotic effects of dissolved drug inside the matrix, and the polymer chain elasticity. The synthesis of a hydrogel matrix for a specific drug carrier should be tailored considering the physical properties of drugs, loading level, and desired release kinetics. The present trend in hydrogel technology in drug delivery is to develop functionalized matrices which respond to the environment in terms of swelling or drug release rate.

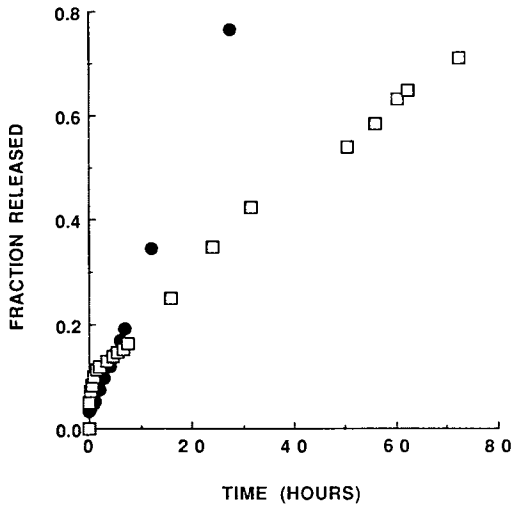

Fig. 7. Pseudo zero-order release from IPN matrices: pseudoephedrine-HCl (17.6 wt% loading. ●) and theophylline (9.0 wt% loading; □) release from an IPN composed of 50% PTMO, 30% DMAAm, and 20% St, by weight.

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