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Time-dependent response of ionic polymer networks to pH and ionic strength changes

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Summary

Changes of ionic strength or pH of a swelling medium may lead to expansion or contraction of ionic polymer networks or charged hydrogels which have been immersed in this swelling medium. This phenomenon is analyzed by using a Boltzmann superposition equation which relates the strain to the applied ionic strength or pH. A material property, the ionic mechanochemical compliance, $L(t-\tau)$, is introduced which describes the viscoelastic response of a gel to the swelling environment. Experiment results of swelling of anionically charged hydrogels are presented and analyzed.

Introduction

In recent years, there have been significant developments in the field of drug delivery devices which utilize intelligent hydrogels, i.e. swollen crosslinked polymeric networks which respond to their physiological environment (Kou et al., 1988; Siegel and Firestone, 1988; Siegel et al., 1988; Brannon-Peppas and Peppas, 1989; Brannon-Peppas and Harland, 1990). Such hydrogels usually contain anionic or cationic groups and respond relatively fast to changes of the pH or ionic strength (Katayama, 1986; Siegel et al., 1988; Prange et al., 1989). Most studies reporting pH-sensitive swelling behavior have been with copolymeric hydrogels of hydroxylated derivatives of various methacrylates.

Possible applications of such hydrogel carriers will be in controlled release systems which allow release over specific time intervals, triggered by changes in the physiological pH or ionic strength. These will be particularly beneficial in gastrointestinal systems, especially in conjunction with bioadhesive delivery (Lenaerts and Gurny, 1990).

Several models are available now to describe the equilibrium behavior of such systems as a function of temperature, pH or ionic strength (Hoffman et al., 1986; Brannon-Peppas and Peppas, 1988; Siegel and Firestone, 1988; Peppas and Brannon-Peppas, 1990). Yet, there have not been models to describe the dynamic behavior of such systems. Therefore, the purpose of this study was to develop a new model to describe changes in the swelling ratio of pH-sensitive hydrogels as a func-

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tion of the pH or ionic strength of the swelling medium.

Model Development

We consider a thin film or a long cylinder of a polymeric hydrogel, produced by the crosslinking reaction of a hydrophilic polymer in the presence of water at constant temperature and pH. Let this hydrogel be placed in successive aqueous solutions of ionic strengths I_1, I_2, I_3, etc. at times τ_1, τ_2, τ_3, etc., respectively.

Since the network of the polymeric material is ionic, the successive change of swelling solutions will lead to corresponding changes of its (swollen) volume, or, for one-dimensional diffusion, to corresponding changes of its length. Defining by l_0 the original length of the sample and by l its length at any time during the swelling process, we may define the strain, ϵ, of the sample due to swelling as:

$$\epsilon = \frac{l - l_0}{l_0} = \frac{\Delta l}{l_0} \tag{1}$$

The overall behavior of the hydrogel as a result of the ionic strength changes is shown in Fig. 1. Upon application of I_1 at time τ_1, the strain increases exponentially up to a new asymptotic value. Application of a higher ionic strength, I_2, at τ_2 leads to further increase of the strain.

The change in hydrogel sample dimensions due to changes in ionic strength are characterized by two properties:

(i) the responses (strains) to the inputs (ionic strengths) during the successive change of solutions are additive; and

(ii) the responses observed (strains) are independent of the specific time the inputs (ionic strengths) were applied.

With these properties of the system in consideration, the Boltzmann superposition principle can be invoked (Aklonis and MacKnight, 1983) and applied

$$\epsilon(t) = \int_0^t L(t-\tau)\frac{\partial I(\tau)}{\partial \tau}\,d\tau \tag{2}$$

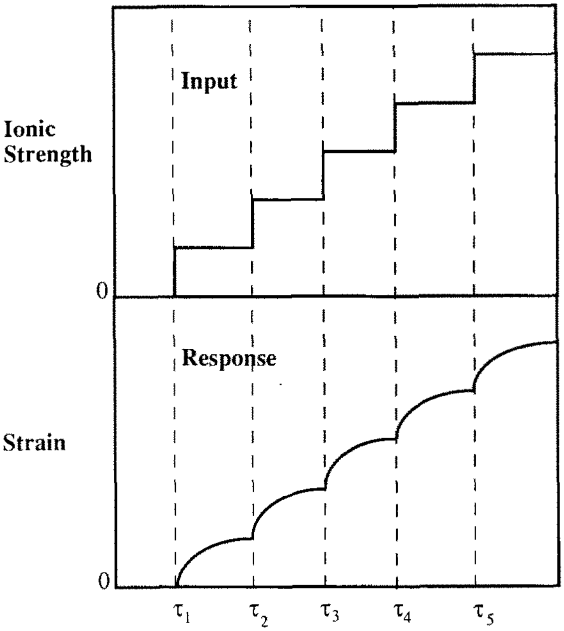

Fig. 1. The response (strain) of a charged swollen network to a change of the input (ionic strength) applied over different time intervals, τ_1, τ_2, τ_3, etc.

Here $\epsilon(t)$ is the time-dependent strain of the pH or ionic strength sensitive gel, I is the ionic strength of the swelling solution, τ is a dummy variable and $L(t-\tau)$ is a property of the polymer gel.

Eqn 1 indicates that the strain of the sample is a weighted integral of the ionic strength gradient over the time. The time intervals are from the beginning of the experiment ($t = 0$), rather than from $t = -\infty$ as it is common to write for mechanical property analysis, since it is assumed that the gel has not been exposed to other ionic solutions before the experiment.

The parameter $L(t-\tau)$ is a material property characteristic of the ionic network in consideration. For an abrupt (elastic) response of just one ionic strength step function, this parameter may be expressed as:

$$L = \frac{\epsilon}{I} \tag{3}$$

Since ionic strength is usually expressed in mol/kg, the units of $L(t-\tau)$ are kg/mol. The parameter $L(t-\tau)$ will be henceforth called the *ionic mechanochemical compliance*.

Further analysis of this model can be provided by assuming that the hydrogel sample is isotropic and by expressing the time-dependent swelling ratio, $Q(t)$, according to Eqn 4

$$Q(t)=\frac{V_g(t)}{V_d}=\frac{l^3}{l_0^3}=\frac{(l_0+\Delta l)^3}{l_0^3}=[1+\epsilon(t)]^3 \tag{4}$$

Then, from Eqns 2 and 4 we obtain:

$$Q(t)=\left[1+\int_0^t L(t-\tau)\frac{\partial I(\tau)}{\partial\tau}\mathrm{d}\tau\right]^3 \tag{5}$$

Thus, the volume swelling ratio is a function of time and depends only on the mode of application of the external physiological solution and the elastic behavior of the gel.

Experimental

Hydrogel samples were prepared in 6 ml cylindrical polypropylene vials. Each sample contained vacuum distilled and purified co-monomers, 0.5 wt% benzoyl peroxide as an initiator and 0.5 mol% ethylene glycol dimethacrylate (EGDMA) as a crosslinking agent. In addition to the pure homopolymer poly(2-hydroxyethyl methacrylate) (PHEMA), the following copolymers were made by adding the designated comonomer quantities (where HEMA is expressed as molar fraction, f_1, in the feed): poly(2-hydroxyethyl methacrylate-co-methacrylic acid) [P(HEMA-co-MAA)] containing $f_1 = 0.80$ and $f_1 = 0.90$; poly(2-hydroxyethyl methacrylate-co-maleic anhydride) [P(HEMA-co-MAH)] containing $f_1 = 0.80$; and poly(2-hydroxyethyl methacrylate-co-isopropyl acrylamide) [P(HEMA-co-IPAc] containing $f_1 = 0.60$.

The comonomers, crosslinking agent and initiator were mixed at room temperature and then immersed in a water bath whose temperature was gradually increased according to the following program: 1 h at 40 °C, 2 h at 50 °C, 3 h at 60 °C, 11 h at 65 °C, 11 h at 70 °C, 11 h at 75 °C and 10 h at 80 °C. This reaction temperature change is preferred to achieve *uniform* and bubble-free samples. For the preparation of P(HEMA-co-MAA) samples, 25 vol% distilled water was added to facilitate good mixing.

The glassy cylinders produced were annealed at 80 °C for 2 days (sub-T_g annealing to relieve the stresses) and cut into this disc (thickness of 0.5–1 mm, diameter 12.7 mm).

All samples were swollen in buffered solutions at 25 °C and their weights were measured as a function of time. They were first placed in a buffered aqueous solution of pH = 10 (containing 0.0524 M $Na_2CO_3 \cdot H_2O$ and 0.0417 M $NaHCO_3$, with an ionic strength of $I_0 = 0.2353$ eq./l) for 335 min. They were then transferred to a buffered aqueous solution of pH = 2 (containing 0.0546 M tartaric acid and 0.0088 M potassium biphthalate) for 105 min. Finally, they were returned to pH = 10 ($I_2 = 0.2353$ eq./l) for 160 min.

Results and Discussion

Eqn 5 presents the volume equilibrium swelling ratio as a function of time. The general relation is a simple monotonically increasing function of time. It should be noted that the step function $\partial I(\tau)/\partial\tau$ can be positive or negative. In the first case, the strain $\epsilon(t)$ according to Eqn 2 or the swelling ratio $Q(t)$ according to Eqn 5 increase, whereas in the second case they decrease. Therefore, these equations can describe any change of ionic strength and its effect on sample size.

The property $L(t-\tau)$ is characteristic of the polymer/swelling agent system. For purely elastic gels (e.g. highly swollen gels) this property becomes independent of time. If the ionic strength change is known as a function of time, one can calculate the exact dependence of swelling ratio on time. For example, when

$$I(\tau)=\alpha+\beta\tau+\gamma\tau^2 \tag{6}$$

then Eqn 5 becomes

$$Q(t)=\left\{1+L\left[\alpha\tau+\frac{\beta\tau^2}{2}+\frac{\gamma\tau^3}{3}\right]_0^t\right\}^3 \tag{7}$$

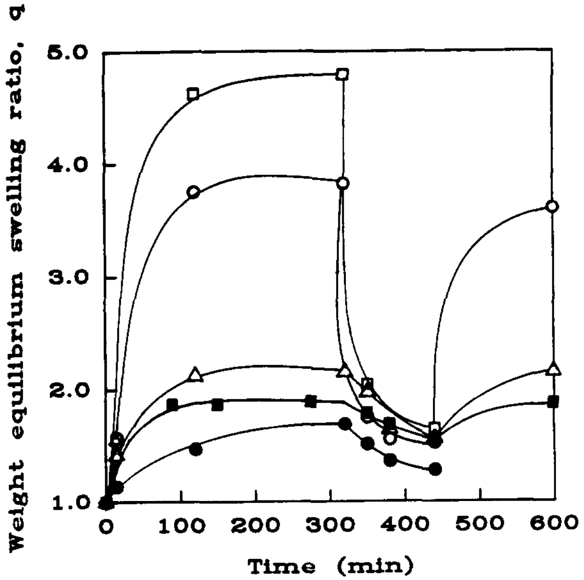

Fig. 2. Dynamic swelling of dry, crosslinked polymer samples placed in a pH = 10.0 buffered solution at $t = 0$ min, pH = 2.0 at $t = 335$ min and again into a pH = 10.0 buffered solution at $t = 440$ min at 25 °C. Data are presented for P(HEMA-co-MAA) containing 10 mol% MAA (○), or 20 mol% MAA (□), for P(HEMA-co-IPAc) with 40 mol% IPAc (△), for P(HEMA-co-MAH) with 20 mol% MAH (●) and finally for a pure homopolymer PHEMA (□).

The swelling response of the hydrogels tested as a result of the abrupt changes in pH is shown in Fig. 2. First, data for the basic homopolymer PHEMA are presented which indicate that a slight change of the weight swelling ratio is observed as the pH changed from 10, to 2 and back to 10. The equilibrium weight swelling ratio at pH = 10 was the same after the first cycle indicating a relatively elastic response of the network.

The experimentally determined weight swelling ratio, q, is related to the volume swelling ratio by the simple Eqn 8, where ρ_w and ρ_p are the densities of water and dry copolymer, respectively

$$q = 1 + \frac{\rho_w}{\rho_p}(Q - 1) \tag{8}$$

These data are compared to the swelling behavior of two P(HEMA-co-MAA) hydrogels, where the swelling change is the most noticeable. The same figure includes data from two other hydrogels that show a somewhat lower dependence of their swelling behavior on pH. The curves are the best fits of the experimental data.

It must be noted that in the analysis of the cyclic swelling behavior using Eqn 2 or 4, the ionic mechanochemical compliance may be constant only if the chains show an immediate response to the change of ionic strength. Otherwise, this parameter is truly time-dependent, and chain relaxation becomes a controlling mechanism of the swelling process.

We may further express the ionic mechanochemical compliance, $L(t)$, in terms of the relaxation time, θ, by writing:

$$L(t) = \int_0^{\infty} L(\theta)[1 - e^{-t/\theta}]\mathrm{d}\theta \tag{9}$$

Written by analogy to similar mechanical equations for the elastic modulus, Eqn 6 indicates that the mechanochemical compliance can be expressed as a decaying function of the time. This equation can be further simplified to give

$$L(t) = \int_0^{\infty} \theta L(\theta)[1 - e^{-t/\theta}]\frac{\mathrm{d}\theta}{\theta} \tag{10}$$

By combining Eqns 5 and 9 or 10 we can determine the relaxation time. However, an approximate calculation of the relaxation time, θ, for the time-dependent phenomenon can be performed by analyzing the initial slope of the swelling curve, by plotting the ln $Q^{1/3}$ as a function of time. Then, the slope will give the reciprocal of an average relaxation time, $\bar{\theta}$. Since all of the polymers studied here had reached a volume near their equilibrium-swelling volume by the 150 min reading, the 15 min reading was used for calculations to approximate the relaxation time for each sample. The results of these calculations are given in Table 1. It is stressed that this calculation is only approximate and can be done for gels which respond relatively fast to changes in physiological conditions. It can be seen that P(HEMA-co-MAH) which has the slowest ‘approach’ to equilibrium as seen in Fig. 2, has the slowest relaxation time of 500 min. The fast swelling, MAA-containing hy-

TABLE 1

Swelling characteristics and relaxation behavior of ionic gels

Gel and HEMA mol fraction	Weight swelling ratio q	Volume swelling ratio Q	Average relaxation time $\bar{\theta}$ (min)
P(HEMA-co-MAA) [$f_1 = 0.90$]	1.55	1.44	123
P(HEMA-co-MAA) [$f_1 = 0.80$]	1.70	1.56	101
P(HEMA-co-IPAc) [$f_1 = 0.60$]	1.41	1.32	161
P(HEMA-co-MAH) [$f_1 = 0.80$]	1.12	1.095	500
PHEMA	1.32	1.255	198

drogels exhibited relaxation times of the order of 100–125 min.

Conclusions

We have developed a new mathematical expression to describe changes in swelling characteristics of ionic polymeric gels as the external conditions change. This expression is based on a mechanochemical analysis and uses the Boltzmann superposition.

Acknowledgments

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