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G. V. N. Rathna[a]; D. V. Mohan Rao[a]; P. R. Chatterji[a]
[a] Organic Coatings and Polymers Division Indian Institute of Chemical Technology, Hyderabad, India

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HYDROGELS OF GELATIN–SODIUM CARBOXYMETHYL CELLULOSE: SYNTHESIS AND SWELLING KINETICS†

G. V. N. RATHNA, D. V. MOHAN RAO, and
P. R. CHATTERJI*

Organic Coatings and Polymers Division
Indian Institute of Chemical Technology
Hyderabad 500007, India

ABSTRACT

Hydrogels of gelatin crosslinked with glutaraldehyde and sodium carboxymethyl cellulose (NaCMC) of several compositions were prepared. The swelling kinetics as a function of composition, temperature, pH, and ionic strength was studied. The rate of swelling and equilibrium swelling were found to depend on the NaCMC content in all cases. The equilibrium swelling increased with the temperature. The gels, which were weakly acidic, registered increased swelling at higher pH. Swelling was suppressed in aqueous salt solutions. In agreement with predictions of the Donnan theory, swelling in monovalent salt solutions is greater than in divalent salt solutions.

INTRODUCTION

Hydrogels are three-dimensional networks which can take up enormous amounts of water [1, 2]. In the swollen state they are soft and rubbery, resembling a living tissue, and some of them also possess excellent biocompatibility [3]. Ongoing investigations on natural and synthetic hydrogels have established their potential for use in several biomedical applications [3–5] such as controlled drug delivery sys-

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tems, soft contact lenses, and implants. Other practical applications include the immobilization of enzymes, food processing technology, electrophoresis, and phase transfer catalysis [6–8]. Currently hydrogels are referred to as "intelligent materials" because they can respond to external stimuli by either shrinking or swelling. The stimulus could be a change in the bath composition, its pH, ionic strength, or temperature [9–14].

The hydrogel-forming ability of several natural polymers such as proteins and polysaccharides has been well documented [15–22]. In an attempt to mimic the biological tissues, we have been working with protein–polysaccharide systems; specifically gelatin and sodium carboxymethyl cellulose. Gelatin, a well-characterized protein fragment obtained by the partial degradation of the water-insoluble collagen fibers, forms a gel when hot (100°C), concentrated (>5%) aqueous solutions are cooled [23]. Inter- and intrachain hydrogen bonds are formed during gelation. Hence these are thermoreversible gels, the sol ⇔ gel transition taking place at 37–40°C depending upon the molecular weight of gelatin and its weight percentage in solution. Sodium carboxymethyl cellulose, often abbreviated NaCMC, is highly water-soluble anionic polysaccharide. A hot, homogeneous aqueous solution consisting of both gelatin and NaCMC in the required weight ratio solidifies to a gel when cooled. Unsubstituted hydrogel groups in NaCMC interact with the carboxyl groups in gelatin to form hydrogen bonds [24]. Treating the Gel-NaCMC gel with glutaraldehyde (Gelx) introduces both inter- and intrachain covalent crosslinks between the ε-amino groups of the lysine residues of gelatin [25]. Thus, in principle, this system is a semi-interpenetrating network.

When immersed in a compatible solvent, a glassy polymer network swells. If the gel is clear, then a distinct boundary between the swollen and dry regions can be observed during the penetration of the solvent into the polymer. The solvent invades into the dry network until the transition from the glassy to the rubbery state is complete [26, 27]. The driving force for swelling, the swelling pressure π, develops from the difference in the chemical potential of the solvent within the gel (μ_g) and in the bath (μ_b). Mathematically, this is written as

$$\pi = \frac{\mu_g - \mu_b}{V_i} \tag{1}$$

where V_i is the molar volume of the solvent. At equilibrium, $\pi = 0$ because $\mu_g = \mu_b$.

Several models have been developed to explain the swelling of networks [28–30]. It has been accepted that the volume change or the swelling of a crosslinked network is brought about by three interrelated processes: 1) the mixing of the solvent with the polymer network, 2) structural changes within the gel due to chain stretching and 3) the complicated interactions of the network ions and counterions with each other and the solvent. That is, the swelling pressure is a composite term with three components:

$$\pi_{\text{swelling}} = \pi_{\text{swelling}} + \pi_{\text{elastic}} + \pi_{\text{ionic}} \tag{2}$$

The ionic interactions of the Gelx–NaCMC matrix is due to the presence of ionizable groups in gelatin and the carboxylic group in NaCMC. When the matrix is crosslinked with 4% glutaraldehyde solution, the ε-amino groups of lysine in the gelatin chain form an aldimine linkage [25]. Other than lysine, the reactive groups

in gelatin are the hydroxyl and the carboxyl groups from hydroxyproline, aspartic acid, and glutamic acid [31]. In 1 g of NaCMC, 4.5 mmol carboxyl groups are present, hence the free carboxyl groups of gelatin and NaCMC along with hydroxyl groups could interact with the ions in the swelling medium. In this paper we report the swelling characteristics of this weakly ionic hydrogel.

EXPERIMENTAL

Gelatin and NaCMC were supplied by Loba Chemicals Bombay. Glutaraldehyde was supplied by Ubi Chem/Loba as a 25% aqueous solution. The other reagents used were the highest grade of purity. Double distilled water was used for all the experiments.

Gelx–NaCMC hydrogels were prepared as reported earlier [32, 33]. A hot aqueous solution (at 100°C) consisting of gelatin and NaCMC, in the desired ratio, was poured between two rectangular glass plates separated by a Teflon gasket (0.5 cm thick). It was then allowed to gel overnight, the gelled slab was dislodged carefully and then cut into circular disks with a cork borer (1.6 cm diameter). The disks were treated with 4% glutaraldehyde solution for 6 hours in order to facilitate crosslinking, and then allowed to dry at room temperature until they attained constant weight.

The compositional details of the hydrogels are given in Table 1. To facilitate gelation, the NaCMC content had to be maintained low, at about 1/4th of the protein content. With higher contents of the NaCMC, the system remained a viscous fluid.

Swellings were monitored as a function of composition (gelatin to NaCMC ratio), temperature (from 30 to 60°C with intervals of 5°C), and pH (ranging from 3 to 10). For pH-dependent studies the following buffers were employed: acetate buffers for pH 3.2, 4.6, and 5; phosphate buffers for pH 5.7, 6.7, and 7.8; and borate buffers for pH 8.8 and 10.0. In addition, swelling was recorded in aqueous KCl and $MgCl_2$ solutions (10^{-4} to 1.0 M). In a typical case the dried gel disk was weighed (w_i) and transferred into the required medium. At regular intervals the disk was removed from the solvent, its surface was pressed gently with tissue paper to remove the excess solvent on the surface, weighed (w_t), and then returned to the medium. This process of swelling and weighing was continued until the disk attained a constant final weight (w_f). The calculations were done as follows.

TABLE 1. Composition of Gelx–NaCMC Hydrogels Ratio

Sample	Gelx–NaCMC (w/w)
A	1.0:0.05
B	1.0:0.10
C	1.0:0.15
D	1.0:0.20
E	1.0:0.25

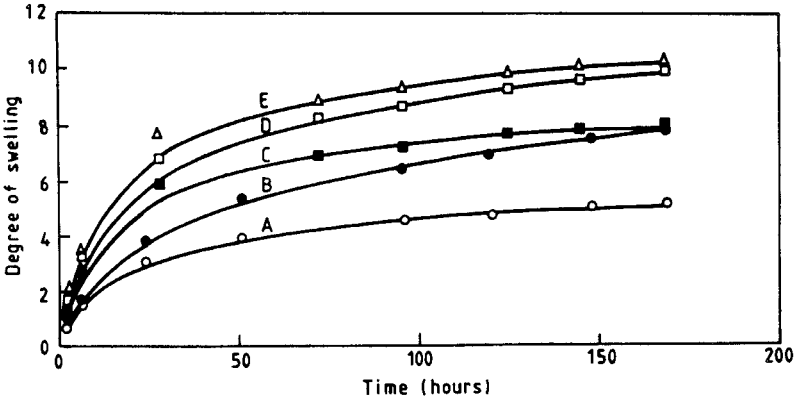

FIG. 1. Dynamic swelling profiles of Gelx-NaCMC gels at 25°C. A, B, C, D and E have the same values as in Table 1.

$$\text{Degree of swelling at time } t,\ D_t = \frac{W_t - W_i}{W_i} \tag{3}$$

$$\text{Percentage swelling, } Q_t = D_t \times 100 \tag{4}$$

For equilibrium swelling, $t = \infty$.

RESULTS AND DISCUSSION

The initial rate of swelling and equilibrium swelling depend on the NaCMC content (Fig. 1). This is because NaCMC is extremely hydrophilic and hence enhances water uptake. An increase in the ambient temperature speeds up the swelling (Fig. 2). For example, at 30–35°C the gels took about 168 hours to reach equilib-

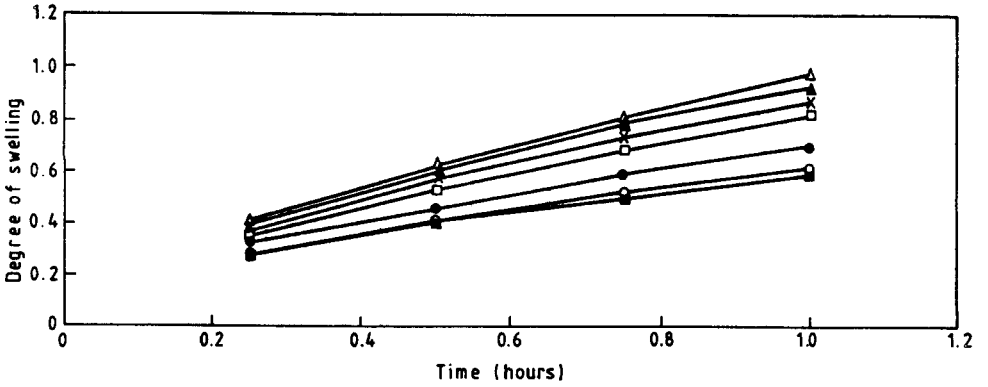

FIG. 2. Swelling of Gelx-NaCMC gels of composition 1.0:0.05 for the initial 1 hour at different temperatures: (○) 30°C, (●) 35°C, (■) 40°C, (□) 45°C, (×) 50°C, (▲) 55°C, (△) 60°C.

rium, whereas at 40–45°C this was reduced to 100 hours. At 50°C and above, the gels reached equilibrium in less than 50 hours. Equilibrium swelling increased with temperature up to 50°C. Above this temperature the swelling declined, presumably because degradative processes in the protein chain could set in (Fig. 3).

A critical analysis of the swelling process reveals two underlying molecular processes: penetration of the solvent molecules into the void spaces in the network and subsequent stretching of the network segments. The fundamental equation [34]

$$(Q_t/Q_\infty) = kt^n \tag{5}$$

where Q_t and Q_∞ are the percentages of swelling at time t and at equilibrium, respectively, and k and n are constants, defines three situations:

1. For a perfectly Fickian process where the rate of solvent penetration is the slowest and hence is the rate-limiting step, the value of $n = 0.5$.
2. When the penetrant velocity is far greater than the chain stretching rate, then the solvent uptake is proportional to the time, i.e., $n = 1$.
3. When the two rates are comparable, then the value of n falls between 0.5 and 1.

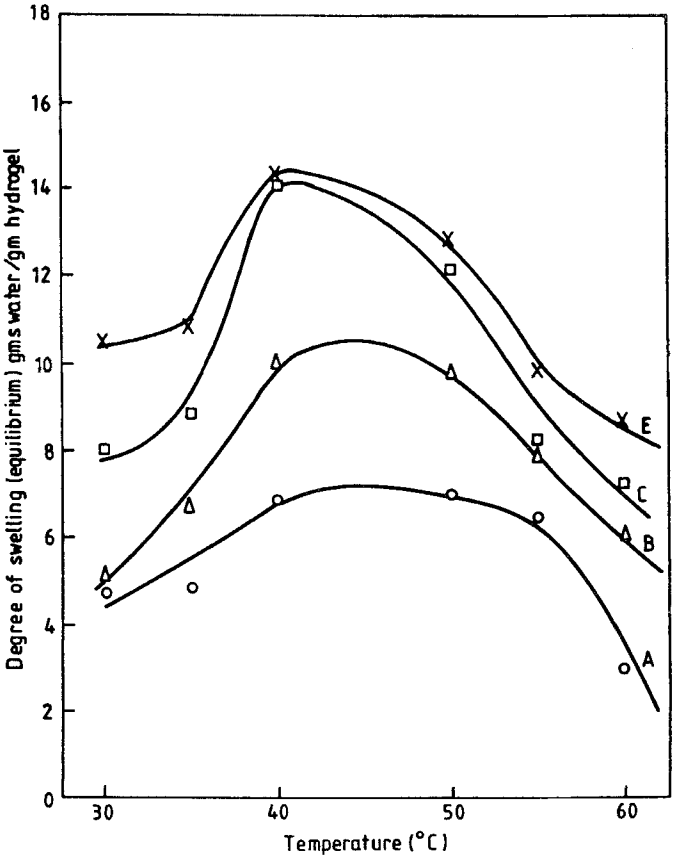

FIG. 3. Degree of swelling at equilibrium for Gelx-NaCMC hydrogels as a function of temperature. A, B, C, and E have the same values as in Table 1.

The value of n was estimated from the slope of a double logarithmic plot of Eq.(5). This comes out to be 0.7 ± 0.05, suggesting a type 3 situation. The activation energy for this initial phase of swelling was also calculated. The values are in the range of 50 to 70 kcal/mol water/g hydrogel. In comparison with the values reported earlier [35, 36], the values obtained in the present study are definitely on the higher side because, while the earlier studies were merely for the passive diffusion of the penetrant into the polymer matrix, the present values are for the entire process of solvent entry, stretching of the network segments, and consequent large-scale dimensional changes in the network.

Ionic interactions are best explained by the Donnan equilibrium theory [28–30]. The swelling of ionic networks depends on the stationery ions in the network, their mobile counterions, and also the ions in the bathing medium. For example Gelx-NaCMC has carboxyl groups which can dissociate in alkaline medium and which are protonated in acidic medium. The presence of an electrolyte generally suppresses the swelling of an ionic network which, in essence, behaves like a Donnan membrane because the charges on the network cannot move. This leads to a difference in the chemical potential of the ions within and outside the gel. Movement of ions and solvent molecules takes place to ensure equivalent chemical potentials of all the species concerned within the gel and in the medium outside.

The Donnan effect is exactly balanced at swelling equilibrium by the retractive elastic force of the network. The degree of neutralization, ionic strength of the bathing solution, valence of the ions involved, and the crosslink dimensions of the network influence the swelling of an ionic network [28].

Gelatin with a molecular weight of 1.24×10^5 is mostly composed of nonionic glycine residues (335 for every 1000 residues). NaCMC, on the other hand, is definitely ionic with a degree of substitution of 0.8 and a molecular weight 2.5×10^5. However, it should be borne in mind that the NaCMC content of the hydrogel is very low. The ratio of gelatin to NaCMC is never more than 1.0:0.25. Under these conditions the Gelx-NaCMC hydrogels exhibit only a weak ionic character, and our results show precisely this.

The equilibrium swelling of the hydrogels as a function of pH is shown in Fig. 4. As the pH increases, equilibrium swelling increases, presumably because ioniza-

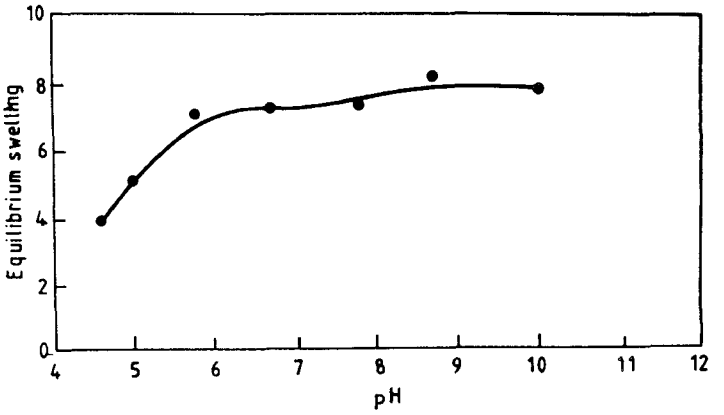

FIG. 4. Equilibrium swelling vs pH for the Gelx-NaCMC system of composition 1.0:0.10.

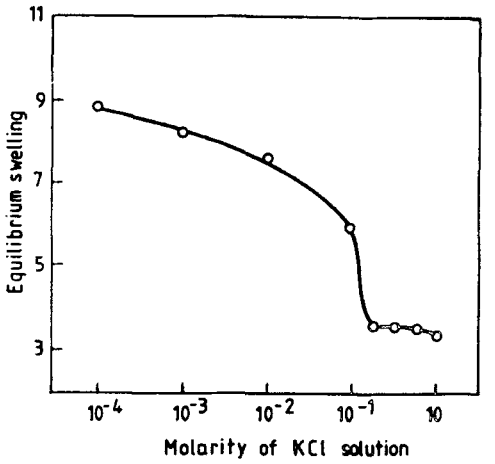

FIG. 5. Influence of KCl concentration on the equilibrium swelling of Gelx–NaCMC gels of composition 1.0:0.1.

tion of the carboxylic groups in the NaCMC occurs and reaches a limiting value. As might be expected for weak ionic systems, there is not much difference in swelling at and above neutral pH.

Figures 5 and 6 show the behavior of these hydrogels when they are immersed in aqueous salt solutions of various concentrations. The swelling decreases rapidly with an increase in salt concentration in the medium. Depending on the NaCMC content, 1 g of the gel picks up about 3–6 g of water from concentrated salt solutions (≥ 0.25 M) as against 6–10 g from pure water. The equilibrium swelling values in divalent salt solutions are less than those in monovalent salt solutions. The network contains fixed anionic charges, and fewer multivalent cations are required to neu-

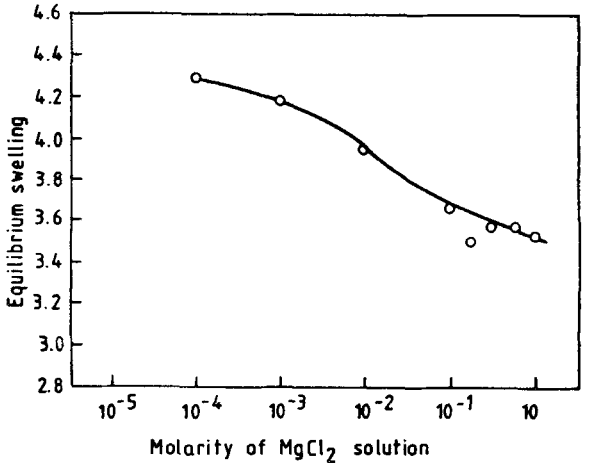

FIG. 6. Influence of $MgCl_2$ concentration on the equilibrium swelling of Gelx–NaCMC hydrogels of composition 1.0:0.1.

tralize an equivalent number of fixed charges on the network. As the concentration of the multivalent cation increases in the solution, the concentration of counterinons inside the hydrogel declines, reducing the counterion osmotic swelling pressure and consequently the swelling.

CONCLUSIONS

The swelling of Gelx-NaCMC hydrogels is very sensitive to ambient temperature, pH, and low electrolyte concentrations. However, consistent with expectation, the response is subdued at high electrolyte concentrations.

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