Swelling Kinetics of a Hydrogel of Poly(ethylene glycol) and Poly(acrylamide-*co*-styrene)

A. K. BAJPAI, MUDITA SHRIVASTAVA

Bose Memorial Research Laboratory, Department of Chemistry, Government Autonomous Science College, Jabalpur 482 001, India

Received 5 June 2001; accepted 3 October 2001

ABSTRACT: A hydrogel incorporating the hydrophilic polymer poly(ethylene glycol) and a copolymer of acrylamide and styrene was synthesized, and the dynamics of the water-sorption process were studied. The effects of the composition of the hydrogel and the temperature of the swelling medium were investigated with respect to the water-sorption characteristics of the hydrogel, and the kinetic parameters, including the swelling exponent and diffusion constant, were evaluated. The hydrogel was also judged for the antithrombogenic property of its surface. The experimental findings were explained on the basis of the core–shell polymeric structure of the hydrogel. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 85: 1419–1428, 2002

Key words: hydrogels; core-shell polymers; swelling; biocompatibility

INTRODUCTION

Polymeric materials possessing high water-absorption capacity (>20%) have great potential for applications in medical science, engineering, technology, and agriculture.[1] The high water contents of these materials make possible hydrogels, which are promising candidates for many biomedical applications, such as artificial implants,[2] dialysis membranes,[3] burn dressings,[4] contact lenses,[5–7] cardiovascular devices,[8] drug-delivery systems,[9] and protein enrichment technology.[10]

All these applications and many others are fundamentally related to the water-sorption behavior of the hydrogels, which has recently become an area of active and intensive research.[11,12] The study of the swelling status of a hydrogel is important because this not only describes the amount of water contained within the hydrogel at equilibrium but also gives insight into the network structure of the gel and the transport mechanisms of the water-uptake process.

Among the various synthetic polymers used for designing hydrogels with desired properties, poly(ethylene glycol) (PEG) has been the object of great interest in the biotechnical and biomedical communities,[13–15] primarily because PEG is unusually effective at excluding other polymers from its presence in an aqueous environment. This property translates into protein rejection, the formation of two-phase systems with other polymers, nonimmunogenicity, and nonantigenicity. In addition, the polymer is nontoxic and does not harm active proteins or cells, although it interacts with cell membranes.[16–18] Moreover, the capacity of PEG to form hydrogen-bonded polymer complexes with acrylic polymers has been exploited to develop responsive hydrogels.

In this article, we report results for the water-sorption dynamics of a hydrogel composed of PEG and poly(acrylamide-*co*-styrene) (PAMS). The use of a copolymer in the preparation of a hydrogel is

Correspondence to: A. K. Bajpai (akbmrl@yahoo.co.in).
Contract grant sponsor: University Grants Commission of India; contract grant number: F.12-43/98.

Journal of Applied Polymer Science, Vol. 85, 1419–1428 (2002)

advantageous, in that a proper balance between the hydrophilic and hydrophobic monomers in the copolymer regulates the swelling characteristics of the hydrogel. The maximum hydration degree and diffusion of the swelling agent into the gel, as well as the organization of water molecules in the gel, will change with the chemical composition and the distribution of the hydrophobic monomeric units along the macromolecular chains.[19,20] This has also led to new trends in the preparation of contact-lense systems with hydrophobic microdomains smaller than the wavelength of light.

EXPERIMENTAL

Materials

PEG (molecular weight = 600) was obtained from Loba Chemie (Bombay, India) and was used as received. Acrylamide (Ottkemi, Bombay, India) was crystallized twice from methanol (guaranteed reagent-grade) and dried over anhydrous silica *in vacuo*. Styrene (Research Lab, Poona, India) was freed from its inhibitor through successive washing with 0.1*N* sodium hydroxide, 0.1*N* sulfuric acid, and twice distilled water and distillation *in vacuo*. *N,N′*-Methylene bisacrylamide (MBA) (Loba Chemie) was employed as a crosslinking agent, and potassium persulfate (Loba Chemie) was used as a polymerization initiator. All other chemicals were analytical-grade, and twice distilled water was used throughout the experiments.

Preparation of the Hydrogel

The hydrogel was prepared by a free-radical polymerization method described in another article.[21] In brief, to a petri dish (2 in., Corning) were added PEG (0.56 g), acrylamide (7.04 m*M*), styrene (17.3 m*M*), MBA (0.064 m*M*), potassium persulphate (KPS) (0.037 m*M*), and twice distilled water (0.55*M*). The mixture was homogenized by proper mixing of all the chemicals, and the petri dish was kept at 80°C for 30 min so that the whole fluid polymerized into a gel-like mass. This was then dried at 60°C for 18 h, at which point it changed into a thin and semitransparent circular film. The film was equilibrated with twice distilled water for 1 week so that the unreacted chemicals and monomers could be washed out. Thereafter, the film was dried and stored in an air-tight container. Because the humidity of the room was low (36%), the hydrogel films were always dry during storage.

Swelling Measurements

A gravimetric procedure was adopted for following the progress of the swelling process.[22] In brief, a preweighed piece of the dry gel (0.04 g) was immersed into twice distilled water at 27°C and taken out at desired time intervals. The swollen piece of the hydrogel was gently pressed between two pieces of filter paper for the removal of excess water and was finally weighed. The swelling ratio was calculated with the following equation:

$$\text{Swelling Ratio} = \frac{\text{Weight of the Swollen Gel}}{\text{Weight of the Dry Gel}} \quad (1)$$

Blood-Compatible Studies

To evaluate the blood-compatible nature of the hydrogel surface, we performed a clot-formation test according to a procedure developed elsewhere.[23] The method may be outlined as follows. Before the compatibility tests were performed, the hydrogel samples were hydrated in saline water (a 0.9% NaCl solution) at 27°C for 24 h. To these swollen and equilibrated hydrogel samples were added 0.5 mL of acid citrate dextrose blood, which was followed by the addition of 0.03 mL of a $CaCl_2$ solution (4*M*) to initiate thrombus formation. The reaction was stopped by the addition of 4.0 mL of deionized water, and the thrombus formed was separated by being soaked in water for 10 min at room temperature, and then it was fixed in a 36% HCHO solution (2.0 mL) for another 10 min. The fixed clot was placed in water for 10 min, and after it dried, its weight was recorded. The same procedure was repeated for the glass surface and other hydrogels, and the respective weights of the thrombi formed were noted.

Kinetics of Swelling

The progress of the water-intake process was monitored by the determination of the swelling ratio of the hydrogel at desired time intervals as previously described. For the kinetic analysis of the results, Fick's law[24] was applied:

$$W_t/W_\infty = kt^n$$

where k is the swelling rate front factor; n is the swelling exponent; and W_t and W_∞ are the water

intakes at time t and the equilibrium time, respectively. The equation is a phenomenological rate law in which n provides insight into the type of water-sorption mechanism that is operative. For instance, $n = 0.5$ shows Fickian kinetics in which the sorption is diffusion-controlled, whereas a value of n between 0.5 and 1.0 indicates a non-Fickian process in which chain relaxation also contributes to the water-sorption process.

The diffusion constant of water (D) through the hydrogel was calculated according to the following equation:[25]

$$\frac{W_t}{W_\infty} = 4\left(\frac{Dt}{\pi l^2}\right)^{1/2}$$

where l is the thickness of the hydrogel.

RESULTS AND DISCUSSION

Mechanism of Dynamic Sorption

Because PEG is a hydrophilic polymer and the copolymer PAMS is partially hydrophobic in nature, the hydrogel may contain hydrophilic and hydrophobic domains in its network, and within these domains may be found patches of free volumes that are further occupied by the solvent molecules when the hydrogel is put into contact with a compatible solvent.[26]

Now, to visualize the dynamics of the water-sorption process, let us consider a situation in which the hydrogel contacts a swelling solvent. As the penetrant solvent invades the hydrogel surface, a moving front is observed that clearly separates the unsolvated glassy polymer region ahead of the front from the swollen and rubbery gel phase behind it.[27] Just ahead of the front, the solvent plasticizes the polymer and causes it to undergo a glass–rubber transition.[28] Now, the two following possibilities arise.

First, if the glass-transition temperature of the polymer is well below the experimental temperature, the polymer will be in the rubbery state and the polymer chains will have a higher mobility, which will allow easier penetration of the solvent.[29] This clearly results in Fickian diffusion (case I), which is characterized by a solvent diffusion rate (R_{diff}) slower than the polymer relaxation rate (R_{relax}): $R_{diff} \ll R_{relax}$. The whole mechanism is modeled in Figure 1(a), which clearly indicates that the swollen part of the gel has well-relaxed chains because of the greater polymer relaxation rate, whereas the smaller number of water molecules within the hydrogel pockets implies a low diffusion rate.

Second, if the experimental temperature is below the glass-transition temperature, the polymer chains may not be sufficiently mobile to permit immediate penetration of the solvent into the polymer core. This gives rise to a non-Fickian diffusion process that includes case II and anomalous diffusion, depending on the relative rates of diffusion and chain relaxation (for case II, $R_{diff} \gg R_{relax}$; for anomalous, $R_{diff} \sim R_{relax}$). The anomalous diffusion is modeled in Figure 1(b), which reveals that the swollen gel has fewer relaxed chains because of the lower polymer relaxation rate, whereas the greater number of water molecules within the network suggests a higher diffusion rate.

Effect of PEG Variation

The effect of increasing the concentration of PEG in the feed mixture on the swelling ratio of the hydrogel was investigated with variations in the amount of PEG (0.28–1.68 g). The results depicted in Figure 2 reveal that, from 0.28 to 0.56 g, the swelling ratio increases, whereas beyond 0.56 g, there is a fall in the degree of swelling of the hydrogel. The observed results can be explained by the fact that initially the increased hydrophilic content in the hydrogel results in a greater binding of water molecules to the gel network, and this obviously increases the swelling ratio. However, beyond an optimum concentration of PEG (0.56 g in this case), the network density becomes so high that the extent of diffusion of penetrant water molecules and the extent of relaxation of macromolecular chains of the hydrogel network become smaller, and so the swelling ratio decreases. Similar results have also been reported by other workers for other hydrophilic hydrogels.[30]

Morphology of Swelling Curves

A remarkable feature that is clearly visible in the curves of the swelling ratio versus time is that initially the swelling ratio increases with increasing time, whereas after a definite time interval (between 60 and 120 min), the swelling remains almost constant for a definite time period (a horizontal portion appears in the curve), and then the swelling ratio increases again. The plateau

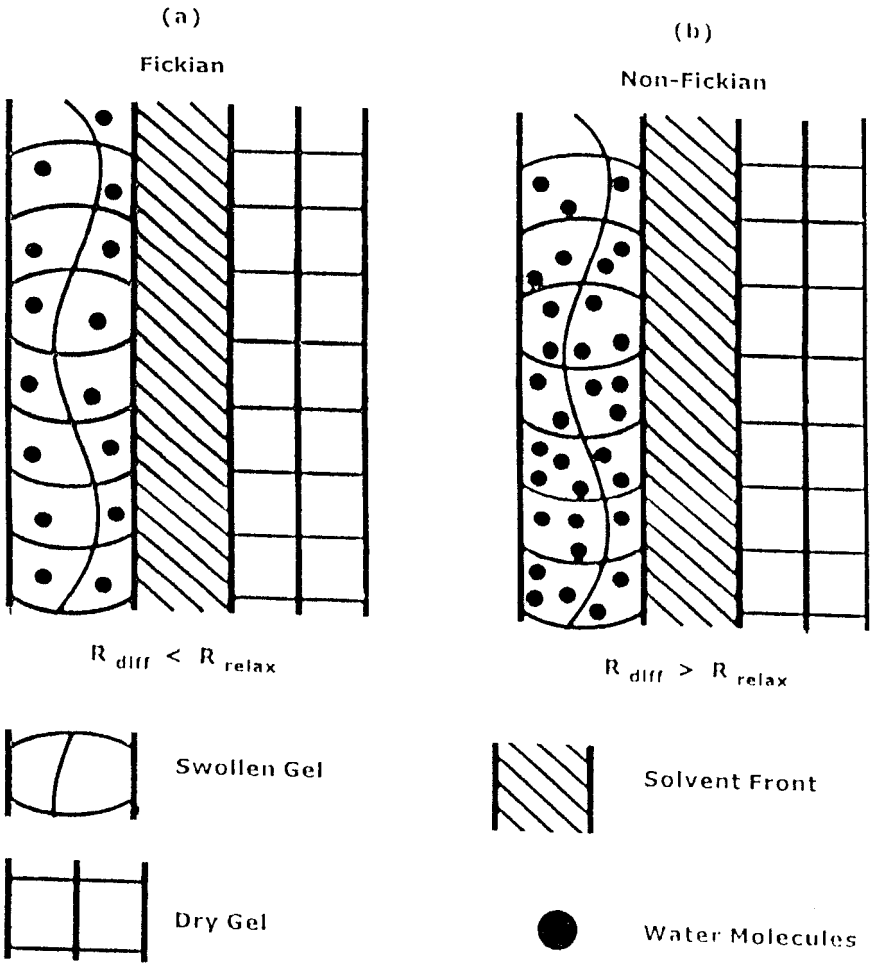

Figure 1 Dynamic sorption model of the hydrogel undergoing (a) Fickian ($R_{\text{diff}} < R_{\text{relax}}$) and (b) non-Fickian ($R_{\text{diff}} > R_{\text{relax}}$) water-transport mechanisms.

portion in the middle part of the swelling curves has not been reported by other workers. However, in a kinetic study of water sorption in hydrophobic, ionizable copolymer gels, Firestone and Siegel[31] observed biphasic or sigmoidal swelling curves characterized by an initial phase of relatively slow water uptake followed by an accelerated phase observed just before the establishment of swelling equilibrium. A plausible explanation for the observed plateau portion (constant swelling) in the swelling curves may be given on the basis of the core–shell macromolecular structure of the hydrogel (which is discussed next).

It is well known that PEG in an aqueous solution acts as a highly mobile molecule with a large extrusion volume. Relaxation time studies show rapid motion of the polymer chain,[32] and gel chromatography shows that PEGs are much larger in solution than many other molecules of comparable molecular weights.[33] Interesting consequence of this property are that PEG excludes other polymers and, if the concentration of PEG is high enough, will form two-phase systems with other polymers. Because the hydrophilic content in the hydrogel (PEG and acrylamide) is greater than the hydrophobic content (styrene), we can assume that the hydrogel network may have a shell-type structure, as shown in Figure 3. In the postulated shell-type model, the outermost shell is hydrophilic PEG, the middle shell is hydrophobic polystyrene segments, and the innermost shell is hydrophilic polyacrylamide segments. It is notable that, when explaining the biphasic swelling curves, Firestone and Siegel[31] also proposed a disc model of their hydrophilic/hydrophobic gel that consisted of a relatively unpenetrated glassy core surrounded by a swollen, rubbery gel periphery. Now, in light of the proposed model, we can

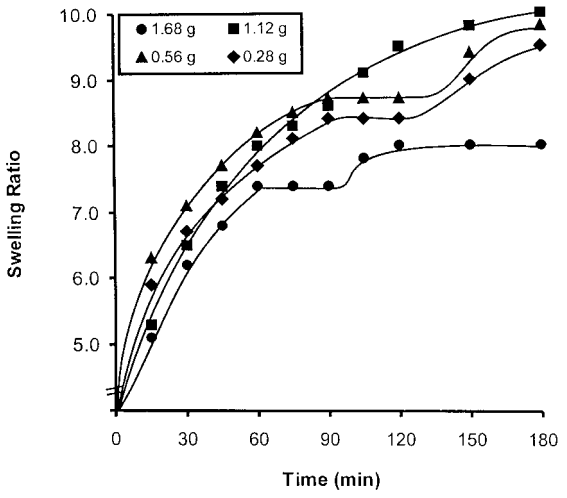

Figure 2 Effect of PEG variation on the degree of swelling of the hydrogel.

plausibly explain the observed plateau portions of the swelling curves as follows:

1. In the initial stage of contact between the gel and aqueous medium (solvent front), the outer hydrophilic shell first swells, accommodating water molecules between the macromolecular chains. This obviously gives the initial rising portion of the swelling curve.
2. After the outermost hydrophilic shell is fully swollen, the solvent front comes into contact with the hydrophobic shell. Because the approaching shell is hydrophobic in nature, the swelling of the network chains is restrained, and for a definite time period, the swelling ratio remains nearly constant. This explains the plateau portion of the swelling curve.
3. After the penetrant water molecules have crossed the hydrophobic shell, they again come across the hydrophilic domain of the gel and, therefore, cause reswelling of the hydrogel, giving the uppermost ascending portion of the swelling curve. The whole swelling mechanism is depicted in Figure 4.

Effect of Monomer Variation

One of the components of the hydrogel in this case is a copolymer of a hydrophilic monomer (acrylamide) and a hydrophobic monomer (styrene). The effect of increasing amounts of acrylamide in the feed mixture on the swelling ratio of the hydrogel was investigated in the concentration range 7.04–18.3 m*M*. The results (not shown) reveal that an increasing content of acrylamide lowers the swelling ratio of the hydrogel. This is a common finding and has been frequently reported in many other investigations.[34] The reason for the observed fall in the degree of swelling is that increasing acrylamide in the feed mixture results in greater number of polyacrylamide (crosslinked) chains that directly enhance the crosslinking density in the hydrogel; therefore, the swelling ratio decreases.

The inclusion of a hydrophobic monomer in the gel matrix often results in a fall in the swelling ratio[35] because of the decreased hydration degree of the gel. The effect of increasing the styrene content in the feed mixture on the swelling ratio of the hydrogel was observed with variations in the styrene content in the range 4.34–25.9 m*M*. The results are presented in Figure 5 and imply that between 4.34 and 17.3 m*M* styrene, the swelling ratio constantly increases, whereas beyond 17.3 m*M*, there appears to be a fall in the swelling ratio. The increase observed in the swelling ratio could be attributed to the fact that, in the initial range of increasing styrene concentration in the feed mixture, the polystyrene segments, because of the presence of voluminous phenyl rings as pendent groups, cause repulsions among themselves and, consequently, cause expansion of the hydrogel. Therefore, because of increased segmental mobility, the penetration of water molecules becomes relatively easier, and the swelling increases. However, beyond an optimum styrene concentration (17.3 m*M*), the hydrophobicity of the gel dominates the expansion ef-

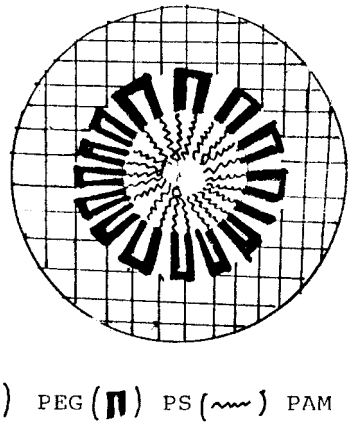

Figure 3 Proposed model depicting the shell-type structure of the hydrogel.

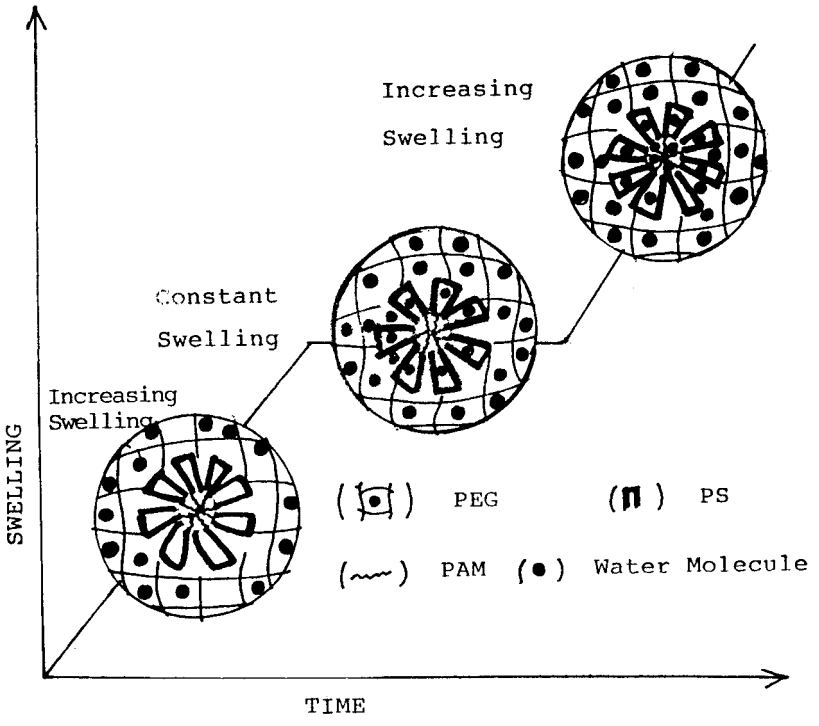

Figure 4 Swelling of the hydrogel with various PEG contents.

fect of the network, which obviously decreases the swelling ratio.

Effect of Crosslinker Variation

Varying the crosslinking density in a hydrogel is also one of the ways of modifying the swelling behavior pattern of the hydrogels.[36] In this work, the concentration of the crosslinker (MBA) was varied between 0.064 and 0.256 m*M*, and the curves of the swelling ratio versus time of respective hydrogels are displayed in Figure 6. The results clearly reveal that with increasing crosslinker content in the hydrogel, the swelling ratio significantly decreases. The observed results are quite common and may be explained by the

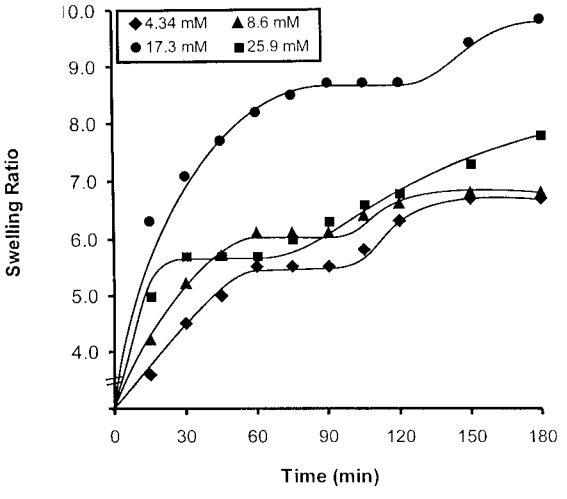

Figure 5 Effect of variation in the hydrophobic monomer styrene on the swelling ratio of the hydrogel.

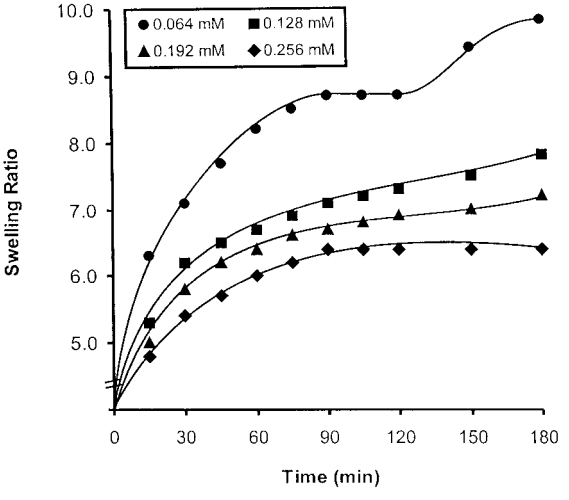

Figure 6 Effect of crosslinker variation on the swelling ratio of the hydrogel.

fact that the greater number of crosslinks in the hydrogel results in a restrained mobility of the macromolecular chains that does not permit water penetration and brings about a depression in the swelling ratio.

Another explanation for the observed findings may be that the increasing number of crosslinks in the hydrogel lowers the molecular weights between the crosslinks[37] and thereby reduces the free volumes between the macromolecular chains, which then become accessible to penetrant water molecules. This clearly lowers the degree of swelling of the hydrogel.

Several authors[38] have reported that the introduction of larger amounts of a crosslinking agent to the hydrogel also enhances the glass-transition temperature of the polymer, which restricts the segmental mobility of the macromolecular chains, thereby suppressing the degree of swelling of the hydrogel.

The curves of the swelling ratio versus time, as depicted in Figure 6, also indicate that the plateau portion completely disappears at higher concentrations of the crosslinker. The observed results can be attributed to the fact that with higher amounts of the crosslinker in the feed mixture, the polyacrylamide chains will be greatly crosslinked, and so the innermost hydrophilic shell will be in a highly crosslinked state. Now, after the swelling of the outermost hydrophilic shell, the central shell; that is, hydrophilic polystyrene segments and the innermost highly crosslinked polyacrylamide shell, will exhibit a similar type of sorption behavior, that is, reluctance toward water sorption. Obviously, this will result in lower and almost constant swelling at a higher crosslinking density.

Effect of Temperature

Temperature has a direct effect on the swelling behavior of a hydrogel because it affects both the segmental mobility of hydrogel chains and the diffusion of penetrant molecules through the hydrogel. In this study, the effect of temperature on the swelling ratio of the hydrogel was investigated with variations in the temperature of the swelling medium from 10 to 40°C. The results are depicted in Figure 7 and reveal that the swelling ratio increases with increasing temperature in the range 10–27°C, but beyond 27°C, a fall in the degree of swelling is observed. The increase can be explained by the fact that, with the increasing

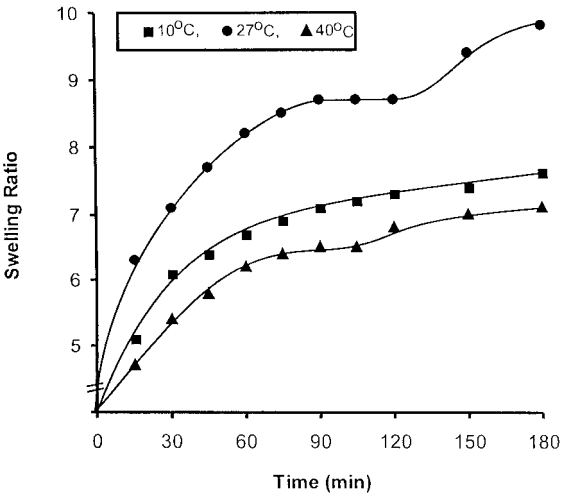

Figure 7 Effect of temperature on the swelling ratio of the hydrogel.

temperature of the swelling medium, the network chains also undergo faster relaxation due to increased kinetic energy and so facilitate the water-sorption process. At higher temperatures, the diffusion of outer molecules is also enhanced, and this speeds up the water-sorption process. A similar increase has been reported elsewhere.[22] However, when the temperature increases beyond 27°C, the observed decrease in the swelling ratio may be attributed to the breaking of the hydrogen bonds between PEG and water molecules.

Analysis of Kinetic Data

Dynamic sorption data not only reflect the progress of the swelling process but also provide information about the water-transport mechanisms, as revealed by eqs. (2) and (3). The values of n and D calculated on the basis of eqs. (2) and (3) for various swelling curves of different hydrogels of various compositions are summarized in Table I. The values presented in the table were analyzed for the prediction of water-transport mechanisms.

When the hydrophilic polymer (PEG) varies in the concentration range 0.56–1.68 g, n decreases from 0.60 to 0.52, thereby indicating a shift in the water-transport mechanism from the anomalous type to the Fickian type. The results can be attributed to the fact that increasing the PEG content in the hydrogel results in a network with a greater number of macromolecular chains, and this will lead to a restricted diffusion of water

Table I *D* Values for Different Compositions of the Hydrogel

Sample	PEG (g)	Acrylamide (m*M*)	Styrene (m*M*)	MBA (m*M*)	*n*	$D \times 10^{12}$ (cm^2 s)	Mechanism
1	0.56	7.04	17.3	0.064	0.60	7.1	Anomalous
2	1.12	7.04	17.3	0.064	0.55	4.4	Anomalous
3	1.68	7.04	17.3	0.064	0.52	4.2	Fickian
4	0.56	10.5	17.3	0.064	0.62	5.8	Anomalous
5	0.56	14.08	17.3	0.064	0.86	3.3	Anomalous
6	0.56	18.3	17.3	0.064	0.90	5.9	Case II
7	0.56	7.04	4.3	0.064	0.53	2.5	Fickian
8	0.56	7.04	8.6	0.064	0.57	6.9	Anomalous
9	0.56	7.04	17.3	0.097	0.66	0.10	Anomalous
10	0.56	7.04	17.3	0.128	0.72	0.80	Anomalous
11	0.56	7.04	17.3	0.256	0.76	0.09	Anomalous

molecules. This obviously makes the swelling process diffusion-controlled, that is, Fickian in nature. A slowed diffusion process indicates a lower degree of swelling, and in the aforementioned range of PEG concentrations, the swelling ratio decreased, as mentioned previously.

When the concentration of the hydrophilic monomer acrylamide is increased in the feed mixture of the hydrogel in the range 7.04–18.3 m*M*, there is observed an increase in *n* from the Fickian range to non-Fickian range (case II), as indicated in Table I. This clearly implies that the water-sorption process tends to become relaxation-controlled in the whole range of acrylamide variations. This may be because with an increasing content of the crosslinked polyacrylamide chains, the network density of the hydrogel increases, thereby resulting in a slower relaxation of the invading molecules. This clearly makes the swelling process relaxation-controlled, that is, non-Fickian in nature.

A variation in the hydrophobic monomer (styrene) results in just the opposite behavior. It is clear from the table that increasing the styrene content in the feed mixture of the hydrogel in the range 4.3–17.3 m*M* results in an increase in *n* from the Fickian type to the anomalous type. The reason for the observed shift in the water-transport mechanism is quite obvious because increasing the polystyrene content in the hydrogel results in a slow relaxation of the network chains due to steric hindrance and dispersion forces operative between the polystyrene chains in the hydrogel that give rise to a compact network. This clearly explains the relaxation-controlled nature of the swelling process.

The crosslinker MBA also influences the water-transport mechanism. It is clear from the table that with increasing MBA concentration, *n* shifts from an anomalous value of 0.66 to a more anomalous value of 0.76. The observed results may be attributed to the fact that with an increasing number of crosslinks in the hydrogel, the relaxation of network chains become rather slower, and so the water sorption tends to become relaxation-controlled.

Table I also contains *D* values for various compositions of the hydrogel. It is clear from the data that the *D* values vary with the mechanism of water transport.

Blood Compatibility

A hydrogel can be recognized as a biomaterial only when, apart from showing a water-uptake property, it exhibits antithrombogenic behavior, that is, a lesser tendency to initiate the formation of blood clots[40] on the surface. For judging the biocompatible nature of the hydrogels, we performed clot-formation tests on the surfaces of hydrogels of various compositions, and the weights of the blood clots from respective hydrogels were compared with those produced on a neat and clean glass surface. The data summarized in Table II clearly present variations in the weights of the blood clots with various compositions of the hydrogels. It is clear from the summarized data that a hydrogel with greater PEG and styrene content and lower acrylamide content results in a more antithrombogenic surface, that is, smaller blood clots. However, the glass surface is the most thrombogenic.

Table II Blood Clots Formed on Various Hydrogel Surfaces

Sample	PEG (g)	Acrylamide (m*M*)	Styrene (m*M*)	Weight of Blood Clot (mg)
1	0.56	7.04	17.3	10.0
2	1.68	7.04	17.3	8.4
3	0.56	7.04	17.3	10.0
4	0.56	14.08	17.3	12.8
5	0.56	7.04	8.6	14.2
6	0.56	7.04	17.3	10.0
7		Glass surface		19.4

CONCLUSIONS

The hydrogel of PEG and PAMS displays typical swelling behavior that suggests a hydrogel with a hydrophilic and hydrophobic core–shell structure. The water uptake of the hydrogel varies sensitively with various contents of the hydrophilic polymer, copolymer, and crosslinking agent and the temperature of the swelling medium. An increased proportion of PEG in the hydrogel results in a shift of the water-transport mechanism from the anomalous type to the Fickian type. The hydrophilic monomer (acrylamide), when varied in the hydrogel, tends to move the swelling mechanism toward a non-Fickian (anomalous) nature, whereas an increasing content of the hydrophobic monomer (styrene) shifts the water-sorption mechanism from the Fickian type to the anomalous type. The crosslinking agent also enhances the non-Fickian nature of the swelling process.

The hydrogel also exhibits temperature-dependent swelling, and its surface shows a much lesser tendency to initiate a clot-formation reaction when coming into contact with acid citrate dextrose blood. The results suggest that a hydrogel with more PEG and styrene and less acrylamide results in good antithrombogenicity.

REFERENCES

1. Standt-Bickel, C.; Lichtenthaler, R. N. J Polym Sci 1994, 36, 1628.
2. Williams, D. F. Concise Encyclopedia of Medical and Dental Materials; Pergamon: Oxford, 1990.
3. Paul, W.; Sharma, C. P. Bull Mater Sci 1994, 17, 1065.
4. Rosiak, J. M.; Ulanski, P.; Pajewski, L. A.; Yoshii, F.; Makuuchi, K. Radiat Phys Chem 1995, 46, 161.
5. Franklin, V. J.; Bright, A. M.; Tighe, B. J. Trends Polym Sci 1993, 1, 9.
6. Chirila, T. V.; Constable, I. J.; Crawford, G. J.; Vijayasekaran, S.; Thompson, D. E.; Chen, Y. C.; Fletcher, W. A.; Griffin, B. J. Biomaterials 1993, 14, 26.
7. Carenza, M. Radiat Phys Chem 1992, 39, 485.
8. Kim, S. W.; Bae, Y. H.; Okano, T. Pharm Res 1992, 9, 283.
9. Kim, Y. H.; Bae, Y. H.; Kim, S. W. J Controlled Release 1994, 28, 143.
10. Gehrke, S. H.; Vaid, N. R.; McBride, J. F. Biotechnol Bioeng 1998, 58, 416.
11. Kabra, B. G.; Gehrke, S. H.; Hwang, S. T.; Ritschel, W. A. J Appl Polym Sci 1991, 42, 2409.
12. Mathur, A. M.; Hammonds, K. F.; Klier, J.; Scranton, A. B. J Controlled Release 1998, 54, 177.
13. Harris, J. M. In Poly(ethylene glycol) Chemistry; Harris, J. M., Ed.; Plenum: New York, 1992.
14. Zalipsky, S. Adv Drug Delivery Rev 1995, 16, 157.
15. Sawhney, A. S.; Pathak, C. P.; Hubbel, J. A. Macromolecules 1993, 26, 581.
16. Yamazaki, M.; Ito, T. Biochemistry 1990, 29, 1309.
17. Krause, T. L.; Bittner, G. D. Proc Natl Acad Sci USA 1990, 3A, 87.
18. Geron, N.; Meiri, H. Biochim Biophys Acta 1985, 819, 258.
19. Chirila, T. V.; Chen, Y. C.; Griffin, B. J.; Constable, I. J. Polym Int 1993, 32, 221.
20. Peniche, C.; Zaldivar, D.; Gallardo, A.; San Roman, J. J Appl Polym Sci 1994, 54, 959.
21. Bajpai, A. K.; Shrivastava, M. J Macromol Sci Pure Appl Chem 2000, 37, 1069.
22. Vazquez, B.; Roman, J. S. Macromolecules 1997, 30, 8440.
23. Imai, Y.; Nose, Y. J Biomed Mater Res 1972, 6, 165.
24. Berens, A. R.; Hopfenberg, H. B. Polymer 1978, 19, 489.
25. Crank, J. The Mathematics of Diffusion; Clarendon: Oxford, 1978.
26. Colombo, P. Adv Drug Delivery Rev 1993, 11, 37.
27. Alfrey, T.; Gurnee, E. F.; Lloyd, W. G. J Polym Sci Part C: Polym Symp 1966, 12, 249.

28. Davison, G. W. R., III; Peppas, N. A. J Controlled Release 1986, 3, 243.
29. Grinsted, R. A.; Clark, L.; Koenig, J. L. Macromolecules 1992, 25, 1235.
30. Graiver, D.; Hyon, S. H.; Ikada, Y. J Appl Polym Sci 1995, 57, 1299.
31. Firestone, B. A.; Siegel, R. A. J Appl Polym Sci 1991, 43, 901.
32. Nagoka, S.; Mori, Y.; Takiuchi, H.; Yokota, K.; Tanzawa, H.; Nishiumi, S. In Polymers as Biomaterials; Shalaby, S. W.; Hoffman, A. S.; Ratner, B. D.; Horbett, T. A., Eds.; Plenum: New York, 1985; p 361.
33. Ryle, A. P. Nature 1965, 206, 1256.
34. Firestone, B. A.; Siegel, R. A. J Appl Polym Sci 1991, 43, 901.
35. Periche, C.; Zaldivar, D.; Gallardo, A.; Roman, S. J. J Appl Polym Sci 1994, 54, 959.
36. Robert, C. R.; Buri, P. A.; Peppas, N. A. J Appl Polym Sci 1985, 30, 301.
37. Flory, P. J. Principles of Polymer Chemistry; Cornell University Press: Ithaca, NY, 1953.
38. Ramaraj, B.; Radhakrishnan, G. Polymer 1994, 35, 2167.
39. Iza, M.; Stoianovici, G.; Viora, L.; Grossiord, J. L.; Couarrze, G. J Controlled Release 1998, 52, 41.
40. Hukins, D. W. L.; Leahy, J. C.; Mathias, K. J. J Mater Chem 1999, 9, 629.