Effect of Hydrophobicity of a Drug on Its Release from Hydrogels with Different Topological Structures

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ABSTRACT: The effect of the topological structure; that is, the network heterogeneity, of hydrophobically modified, slightly acidic hydrogels on the binding and release of low molar mass drugs has been studied using ibuprofen and ephedrine as model compounds with varying water solubility. The difference in the heterogeneity of the gels has been produced by the choice of the hydrophobe copolymerized into the polymer network. The effect of the drug loading on the release kinetics has been investigated as well. The release of hydrophobic ibuprofen was slower from a strongly aggregated heterogeneous gel than from a more homogeneous one, because of the strong hydrophobic interaction between ibuprofen and the heterogeneous hydrogel. The release of hydrophilic ephedrine from the homogeneous gel with an initial drug content of 30 wt % of dry polymer showed negative time dependence, indicating that during and after the swelling of the gel, ephedrine started to bind to the polymer. However, the release of ephedrine from a heterogeneous hydrogel increased with time. This shows that the heterogeneous, aggregated polymer binds the hydrophobic substance more strongly than the homogeneous one does, and that the homogeneous network has higher affinity for the basic hydrophilic substance than the heterogeneous one does. The loading contents of ibuprofen and ephedrine affect the release rates in different ways because of the different binding and release mechanisms. The number of binding sites accessible for ephedrine inside the polymer network is assumed to change upon the swelling of the gel. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 73: 1031–1039, 1999

Key words: *N*-isopropylacrylamide; network heterogeneity; drug release; hydrophobic interaction

INTRODUCTION

Poly(*N*-isopropylacrylamide) (PNIPAAM) hydrogels are attracting more and more interest in biomedical applications, because they exhibit a well-defined lower critical solution temperature (LCST) in water, around 31–34°C, which is close to the body temperature. PNIPAAM hydrogels swell when cooled below the LCST, and they collapse when heated above the LCST. By finding out the right balance of hydrophobic and hydrophilic comonomers and by adjusting the number of electric charges in the chain as well as the degree of crosslinking, the structure and physical properties of PNIPAAM hydrogels can be changed.[1–9] Mechanical properties as well as the swelling and shrinking behavior of the gels change in response to physical or chemical stimuli, such as temperature, pH, ionic strength, solvent composition, and electric fields. Hence, these gels can be expected to act as intelligent materials in controlled or targeted drug release,[2,10–14] immobilization of enzymes and cells,[15,16] and in separation of aqueous proteins.[16,17]

In their studies on the drug release mechanism of thermoresponsive PNIPAAM gel, Okano and

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coworkers[2] observed that the drug permeability through poly(NIPAAM-*co*-alkyl methacrylate) gel membranes depends upon temporal structural changes of the gels and that the swelling and the shrinking behaviors of the gel change at several temperatures, yielding different patterns of drug release profiles. According to these authors, the release profiles for indomethacin from a poly-(NIPAAM-*co*-butyl methacrylate) gel exhibited sigmoidal patterns with accelerating release rates, following the swelling patterns below the LCST. It was also shown that during the temperature-regulated transition from "on" state (below the LCST) to "off" state (above the LCST), a heterogeneous skin layer formed during the gel collapse. Initially the skin prevented the drug release from poly(NIPAAM-*co*-alkyl methacrylate) hydrogels. After a certain period, the drug was again rapidly released through the skin bubbles with the convective outflow of water caused by accumulated internal pressure.[13,18]

Drug release from the homopolymeric and copolymeric PNIPAAM gels is affected not only by temperature but also by the dimensions of the gel, the hydrophobicity of the polymer, the topological structure of the network, as well as by pH. With increasing the thickness of the gel membrane, the drug release rate decreases. Lim et al.[14] have studied the release of indomethacine from PNIPAAM/polyurethane IPNs. It was shown that with increasing the hydrophobicity of the gel, the equilibrium drug release and the time to reach the equilibrium decreased because of the decrease of the drug loading and the equilibrium swelling ratio. The release rate of indomethacin[18] as well as that of sodium dodecyl sulfate (SDS)[19] from hydrophobically modified PNIPAAM gels has been shown to decrease because of the hydrophobic interactions between drugs and the network chains. When acrylic acid was introduced to PNIPAAM network,[20] the release of indomethacin was observed to occur at a much higher rate at pH 7.4 than at pH 1.4. The release rate decreased at pH 7.4, but increased at pH 5.0 with increasing poly(acrylic acid) (PAA) content in PNIPAAM/PAA interpenetrating polymer networks[14] because of the repulsion between the ionized groups.

When PNIPAAM hydrogels are synthesized in water at temperatures above the LCST, heterogeneous gels with macroporous structures are obtained. These types of hydrogels usually have higher swelling ratios below the LCST, and they exhibit faster deswelling and reswelling rates than the corresponding homogeneous gels prepared either in organic solvents or in water below the LCST. The heterogeneous gels allow the absorption of macromolecules plus rapid delivery in response to temperature change through the LCST because of a bicontinuous, interconnected porous structure.[12,21,22]

Until now, macroporous PNIPAAM hydrogels have mostly been obtained by polymerization in water above the LCST. However, in our recent study, it has been observed that the topological structures of copolymeric PNIPAAM hydrogels can also be affected by the choice of the hydrophobic comonomers, even though the hydrogels are synthesized below the LCST.[9] PNIPAAM gels containing hexafluoroisopropyl methacrylate (HFIPMA) are homogeneous, transparent ones. The corresponding gel modified with methacrylic acid swells more than the neutral one does and has a higher storage modulus in pure water below the LCST, showing the behavior typical of a polyelectrolyte gel. However, PNIPAAM gels containing hexafluorobutyl methacrylate (HFBMA) are heterogeneous, and the corresponding acidic gel swells less than the neutral one does and has a lower storage modulus in pure water below the LCST, not showing the polyelectrolyte effect.[9] The homogeneous gels have considerably higher storage moduli G' than the heterogeneous ones. The differences in the gel structures may be attributable to the larger size and flexibility of the partially fluorinated *n*-butyl side chains when compared to the protonated or fluorinated isopropyl groups, monomer solubility, aggregation, and different polymerization behavior in aqueous media. By using nitroxide radicals with varying polarity, it has been shown[23] that the release of low molar mass substances from the gels depends upon the chemical structure of the network. We have recently also observed[23] that the interactions of ephedrine and iburofen with the PNIPAAM hydrogels containing fluorinated comonomers strongly depend upon the hydrophobicity/hydrophilicity of the drugs and the polymers.

This article describes the release kinetics of hydrophobic ibuprofen and hydrophilic ephedrine from terpolymer PNIPAAM hydrogels below the critical temperature. The comonomers are those mentioned above, that is, a hydrophobe (HFIPMA or HFBMA), and methacrylic acid. Fluorinated comonomers are known to cause much stronger hydrophobic aggregation than the corresponding hydrocarbon comonomers. It turns out to be nec-

essary to compare the properties of the gels with different topological structures, and, thus, the purpose of this article is to show the important effect of the network heterogeneity on the release of the drugs.

EXPERIMENTAL

Materials

N-Isopropylacrylamide (NIPAAM) purchased from Polysciences Inc. was purified by recrystallization in hexane. The comonomers, hexafluoroisopropylmethacrylate (HFIPMA, Polysciences), hexafluorobutylmethacrylate (HFBMA, Polysciences Inc.), and methacrylic acid (MAA, Polysciences) were used without further purification, as were the initiator, potassium persulfate (Merck), crosslinker, N,N′-methylene bisacrylamide (Serva), accelerator N,N,N′,N′-tetramethylethylene diamine (TEMED, Aldrich) and surfactant, sodium dodecyl sulfate (SDS, Fluka). Low molar mass drugs ephedrine and ibuprofen were from Sigma. Water used for polymerizations and UV measurements was deionized in an Elgastat UHQ-PS purification system.

Syntheses of Polymer Gels

The polymer gels were prepared by radical crosslinking polymerization in water below the LCST. The syntheses have been described in detail elsewhere.[11] The product crosslinked polymers are abbreviated as HGNIM and HGNBM, containing either HFIPMA or HFBMA as a hydrophobic monomer and MAA as a hydrophilic monomer. The mole ratios of the monomers were: NIPAAM : HFIPMA : MAA = NIPAAM : HFBMA : MAA = 80 : 15 : 5.

Drug Loading and Release

Dried polymers were cut into disks with approximate dimensions of 1 mm (diameter) × 1 mm (thickness). The mass of the disks was 0.6–0.8 mg. The cylindrical gels were equilibrated at 20°C for 2 days in excess ethanol solutions containing a proper amount of ibuprofen or ephedrine. The amount of ibuprofen or ephedrine dissolved in ethanol was 10, 30, and 60 wt %, respectively, of the mass of the dry gels in the case of HGNIM, and 30 wt % for the gel HGNBM. Then, ethanol was evaporated at room temperature for 1 week.

Gel particles loaded with drugs were placed in quartz cuvettes containing 3 mL aqueous SDS solutions (100 mg/mL). The released amount of drugs was measured from the aqueous phase with a UV spectrophotometer (UV-1201, Shimadzu Co., Japan), at 222.7 nm and 208.0 nm wavelengths for ibuprofen and ephedrine, respectively. The majority of the UV measurements were carried out at 20°C. Some tests were also conducted at 50°C. The measurements were conducted as functions of time, and the results are given in relative units M_t/M_p and M_t/M_∞, where M_t is the instantaneous mass of the drug released at time t, M_p is the mass of the dry polymer, and M_∞ is the total mass of the drug released at equilibrium.

RESULTS AND DISCUSSION

Swollen polymer gels are always more or less heterogeneous.[24] The gels used in this work, chemically differing from each other only by the structure of the hydrophobic comonomers, are for simplicity called homogeneous (HGNIM) and heterogeneous (HGNBM) gels. The purpose is to emphasize the difference in the heterogeneity of the polymer networks, observed not only as their different visual appearance but also as differences in their swelling behavior, as well as in their mechanical properties.[9] The LCST and the degree of swelling of NIPAAM-based copolymer gels may be altered within a wide range by the choice of the comonomers. For example, the LCST of the gels HGNIM and HGNBM are around 38 and 42°C, respectively.

Hydrophobic drug ibuprofen is a weak acid slightly soluble in water, and it binds into the gels through the hydrophobic interactions. Ephedrine is a water soluble, slightly basic substance, and it has specific interactions with polyacid gels through electrostatic interactions.[23] In this article, the focus is on the varying network topologies of the gels, thus, we discuss the release of the two drugs from the polymers swollen in equilibrium.

Release of Ibuprofen from the Gels

Figure 1 shows the time dependence of the release of ibuprofen from a unit mass of gels HGNIM and HGNBM, both having the same initial drug loading of 30 wt %. The time needed for both samples to reach equilibrium is similar around 6 h, but the equilibrium release from the gel HGNIM is significantly higher than that from HGNBM. The

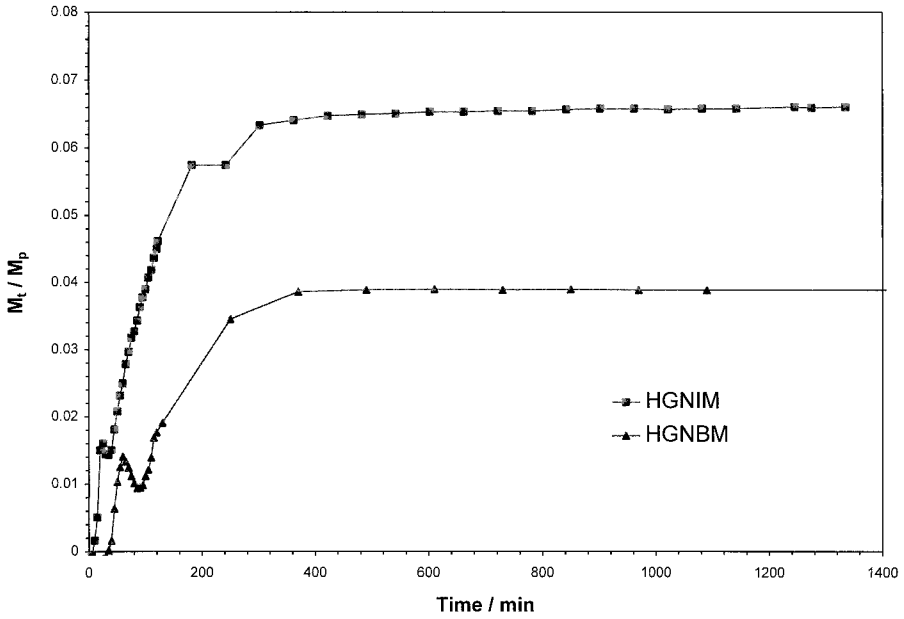

Figure 1 The release of ibuprofen per unit mass of the homogeneous gel HGNIM and the heterogeneous gel HGNBM as a function of time. The initial drug loading content of both gels was 30 wt %.

fractional ibuprofen release from the gels HGNIM and HGNBM is shown against time in Figure 2. Before the equilibrium, the release rate of ibuprofen is faster from HGNIM than from HGNBM.

HGNIM gel, containing hexafluoroisopropyl methacrylate as a hydrophobe, has a relatively homogeneous network structure; whereas, the HGNBM gel with hexafluorobutyl methacrylate as a hydrophobe is heterogeneous. In pure water, the swelling ratio of HGNIM is higher than that of HGNBM below the LCST.[9] The differences between the gels seen in Figures 1 and 2 are impor-

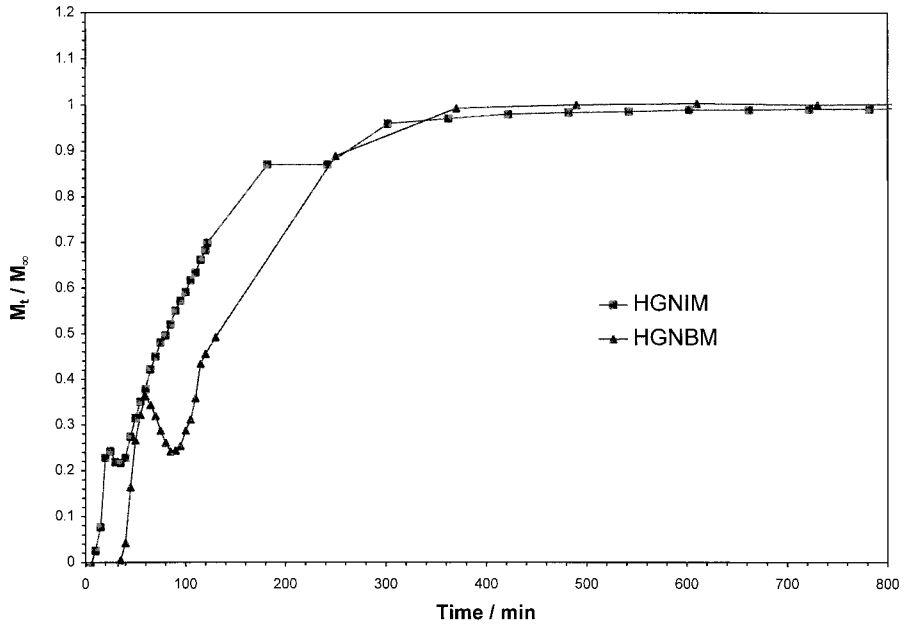

Figure 2 Time dependence of the fractional ibuporfen release from the gels HGNIM and HGNBM.

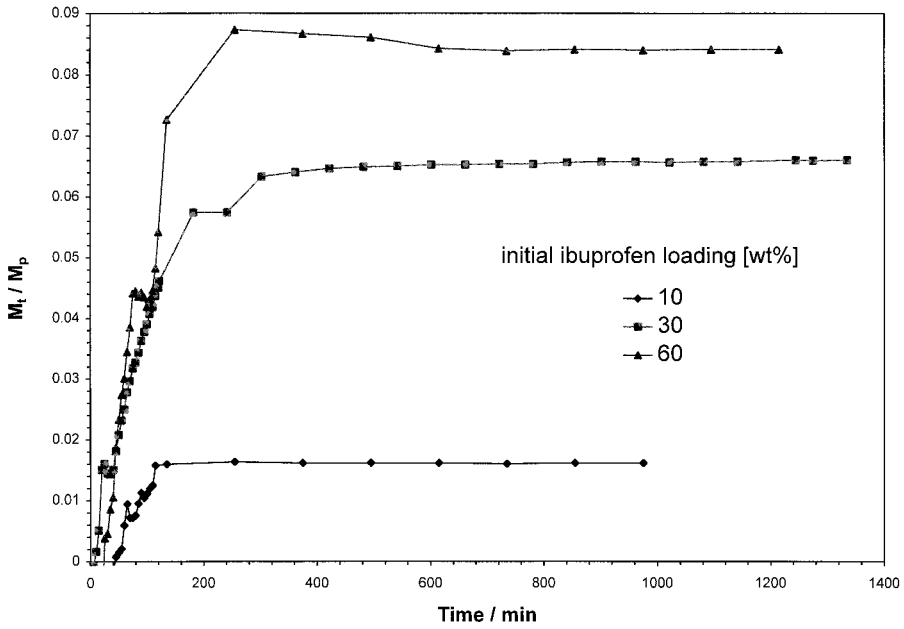

Figure 3 Effect of the initial drug content on the release of ibuprofen per unit mass of polymer.

tant. The heterogeneities (aggregates) in the HGNBM structure enhance the hydrophobic interaction between HGNBM and ibuprofen, and, therefore, retard the release of the drug. Consequently, the equilibrium release content and the release rate are affected by the topological structure of the gels.

As seen from Figure 2, during the initial stages of the swelling of the gels, ibuprofen release from both gels has a maximum. This indicates that when the gels are immersed in aqueous SDS, a certain amount of ibuprofen from the surface layer of the particles is quickly solubilized; however, upon further swelling of the gel and thereafter, part of the solubilized ibuprofen diffuses back to the polymer. The drug reuptake is probably because of the competition between the binding of the drug into SDS micelles and into the polymers. A clear difference is seen in the swelling rates of the gels containing ibuprofen. The heterogeneous gel HGNBM swells more slowly than the homogeneous one. An opposite behavior has been observed when pure polymers were swollen in deionized water,[9] which, again, shows that the aggregated polymer network binds hydrophobic molecules more strongly than the homogeneous network does. A possibility remains that ibuprofen is not in equilibrium inside the gel. The effect of the drug loading conditions on its release is subject to further studies. Polymerization of the gels in the presence of dissolved drug and its subsequent release would perhaps serve as a useful comparison for these loading questions.

The effect of the loading level on the release of ibuprofen from unit mass of the gel HGNIM is shown in Figure 3. As expected, the equilibrium drug release content increases with drug loading. However, the release is not directly proportional to the initial loading at higher drug contents. This implies that with increasing the amount of ibuprofen in the hydrophobically modified polymers, the mechanism of the binding of the drug changes. Most probably, at high loading, the drug forms insoluble clusters in the polymer. The fractional drug release rates for samples with varying ibuprofen loading are shown in Figure 4. Although the amount of the drug released is dependent upon its initial concentration, the kinetics of the release is only slightly affected.

Release of Ephedrine from the Gels

The release of ephedrine differs considerably from that of ibuprofen. Figure 5 shows the time dependence of the release of ephedrine from a unit mass of the homogeneous HGNIM and the heterogeneous HGNBM, both having the same initial drug loading of 30 wt %. Both curves in Figure 5 show an initial maximum; in this case, the rates of

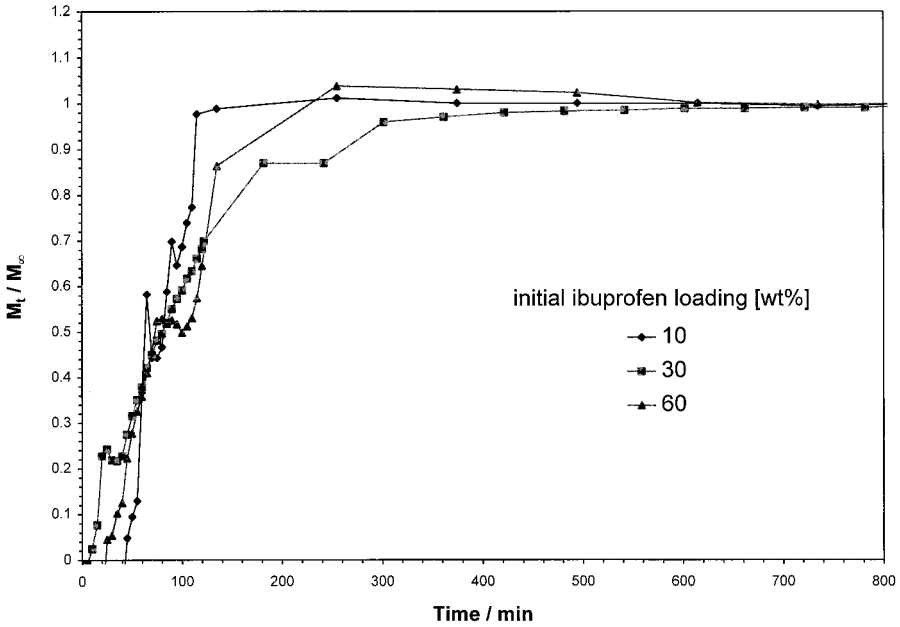

Figure 4 Effect of drug loading on the fractional ibuporfen release from HGNIM.

swelling of the gels seem to be closely identical. Although the initial maximum value of the release is higher in the case of the homogeneous gel HGNIM, the equilibrium release from the homogeneous gel is much lower than that from the heterogeneous gel HGNBM. An even more striking difference between the samples is that the amount of ephedrine released from the homogeneous HGNIM decreases with time; whereas, the amount of the drug released from the heterogeneous gel increases. This difference is seen more clearly in Figure 6, showing the time dependence

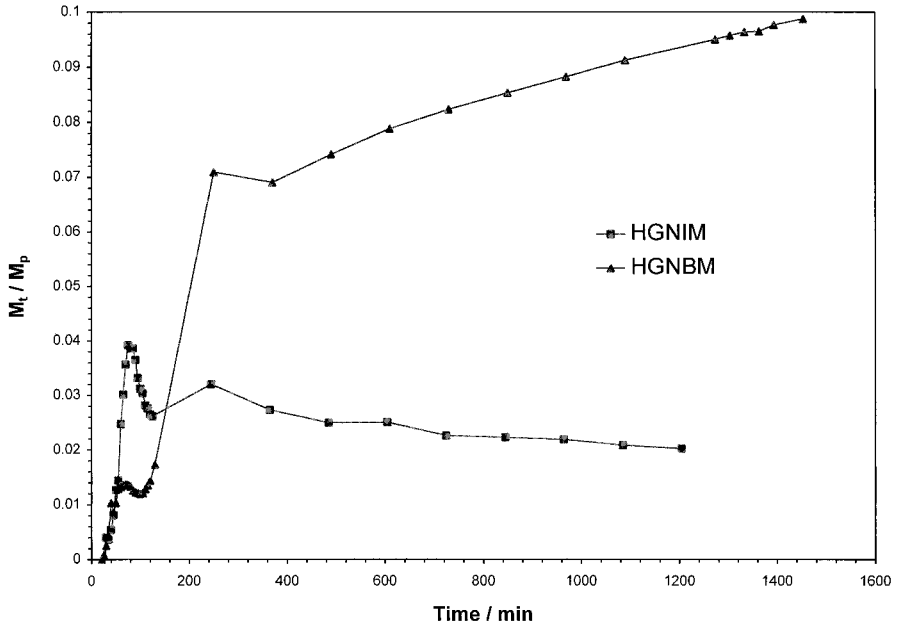

Figure 5 Release of ephedrine per unit mass of the homogeneous gel HGNIM and the heterogeneous gel HGNBM as a function of time. The initial drug loading content of both gels was 30 wt %.

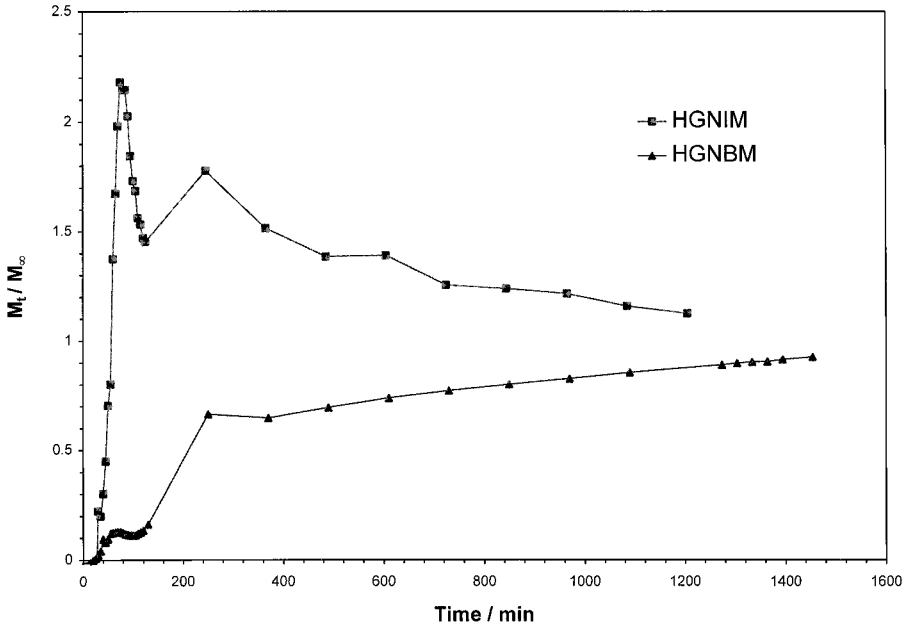

Figure 6 Time dependence of the fractional ephedrine release from the gels HGNIM and HGNBM.

of the fractional ephedrine release from the gels HGNIM and HGNBM. The release of ephedrine from homogeneous HGNIM first rapidly reaches a maximum during the initial swelling of the gel but then starts to decrease. The swelling of the gel continues after the observation of the first maximum. SDS micelles and the polymer compete for binding ephedrine molecules, but the drug is drawn into the gel because of two factors. First, the diffusion of water into the polymer matrix favors convection of ephedrine to the polymer. Second, the polymer containing strongly hydrophobic as well as acidic substituents offers more favorable binding sites for the drug than SDS micelles do. However, the release of ephedrine from heterogeneous HGNBM shows different kinetics. There are four stages of drug release. At first, ephedrine release increases linearly (initial swelling of the gel), then after a slight decrease, it increases rapidly again, after which the release is slow but nearly linear. These kinetics probably result from the large pore size of HGNBM gel structure, which totally changes the mechanism of the gel swelling. The most important conclusion from Figure 6 is that in a homogeneous gel, the hydrophobic, slightly acidic binding sites are evenly distributed through the polymer and are, thus, acceptible for the water-soluble basic ephedrine. However, in a heterogeneous network, this is not the case, because part of the binding sites are trapped in the aggregates. The effect of the network heterogeneities on the binding of drugs is totally different, depending upon the bacicity and water solubility of the drug. In Figure 6, the first maximum of the ephedrine release from the homogeneous HGNIM has a surprisingly high value of the fractional release M_t/M_∞. This is because the value used as the equilibrium release value is that measured after 20 h, and checked after further 24 h.

The effect of the loading level of the drug on the release of ephedrine from a unit mass of the gel HGNIM is shown in Figure 7. Logically, the release is highest from the sample with the highest ephedrine content. However, the release from both of the samples with the loading either 10 or 30 wt % is of the same order of magnitude. Furthermore, the release shows negative time dependence only in the case of 30 wt % loading. As is the case with ibuprofen, we suppose that the mechanism of binding of ephedrine changes with changing drug loading. Clearly, the binding sites in the polymer containing 60 wt % ephedrine are all saturated, and ephedrine may freely diffuse into the aqueous SDS. The difference between the samples having the ephedrine contents of 10 and 30 wt % is interesting and may be understood by assuming that the polymer with higher drug content is on the limit of saturation and that the swelling of the gel reveals more accessible binding

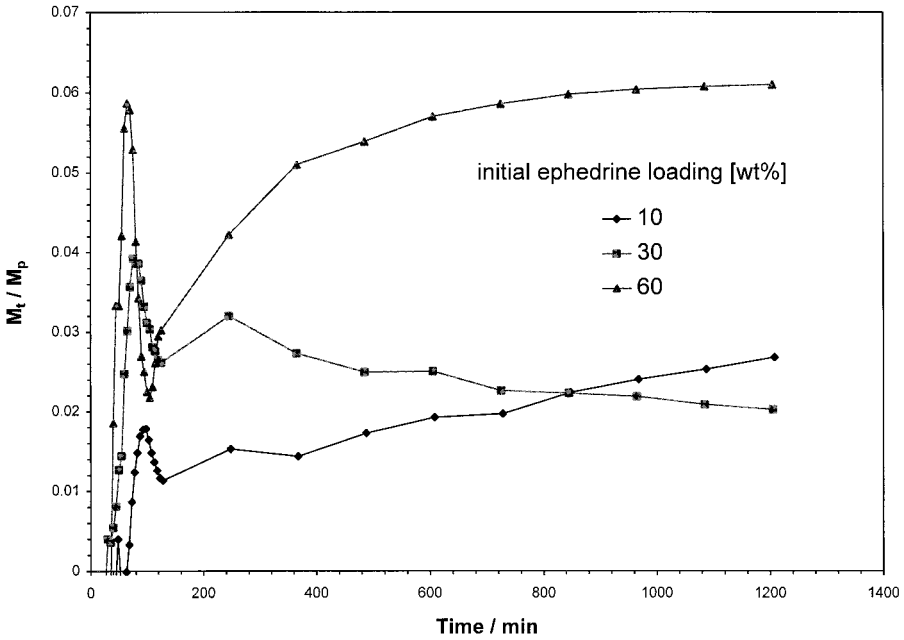

Figure 7 Release of ephedrine per unit mass of the homogeneous gels HGNIM with varying drug contents.

sites than there are in the dry state or during the initial swelling. This hypothesis is simple enough to be accepted at this stage but needs verification in further experiments. That the sample with 30 wt % loading behaves totally differently from the other two, is clearly seen in Figure 8, which shows the fractional release of ephedrine from the samples with varying loading. The result is in accordance with the hypothesis suggested above. Finally, it is necessary to point out that after the release measurements conducted at 20°C, no more release was

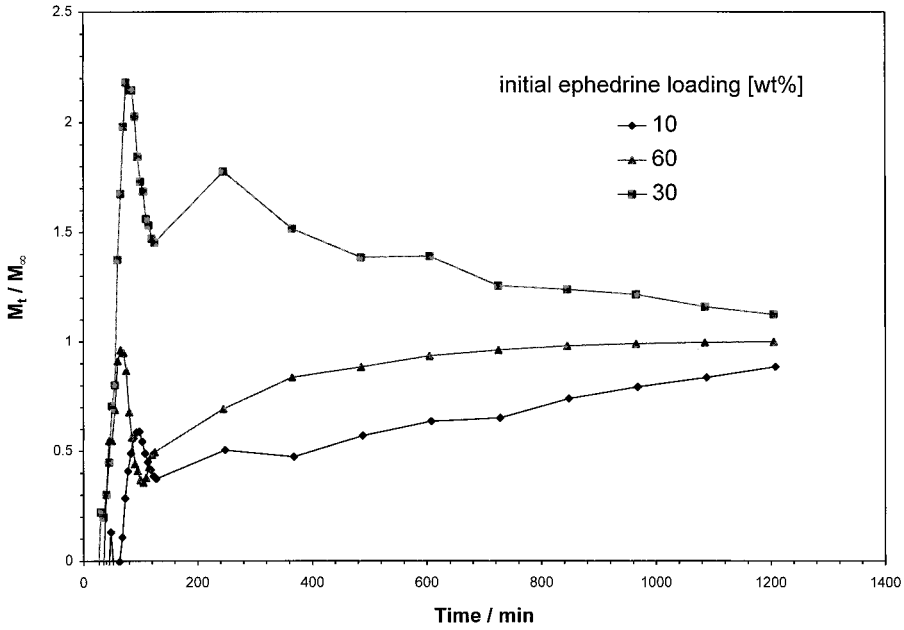

Figure 8 Effect of drug loading on the fractional ephedrine release from HGNIM.

observed when the temperature was increased above the LCST at 50°C.

CONCLUSIONS

The above described tests have revealed several important factors that affect the release of drugs from hydrophilic, hydrophobically modified crosslinked polyelectrolytes. The water solubility of the drug, as well as the specific interactions of the drug with the polymer are the key factors affecting the release. However, the heterogeneity of the network has been shown to have a noticeable effect on the interactions. The hydrophobic interactions between the polymer and the drug increase with increasing heterogeneity of the gel; that is, the aggregated polymer network binds hydrophobic molecules more effectively than the network with more homogeneous structure does. The opposite is seen to be true with the hydrophilic drug ephedrine, which binds to the polymer not only by hydrophobic interactions but also by acid-base interactions. In this case, the drug shows higher affinity toward a homogeneous than a heterogeneous gel, thus indicating that in the former one, the acidic groups are more easily acceptible for the drug.

The amount of the released drug is not linearly dependent upon the initial drug loading of the polymer. We assume that the mechanism of binding of the low molar mass substances to the polymers changes with increasing drug loading, and that the number of accessible binding sites in the polymer network changes upon the swelling of the gel.

REFERENCES

1. Shibayama, M.; Tanaka, T.; Han, C. C. J Chem Phys 1992, 97, 6842.
2. Yoshida, R.; Okuyama, Y.; Sakai, K.; Okano, T.; Sakurai, Y. J Membrane Sci 1994, 89, 267.
3. Yoshioka, H.; Mikami, M.; Mori, Y. J Macromol Sci—Pure Appl Chem 1994, A31, 121.
4. Brazel, C. S.; Peppas, N. A. Macromolecules 1995, 28, 8016.
5. Shibayama, M.; Mizutani, S. Y.; Nomura, S. Macromolecules 1996, 29, 2019.
6. Kawasaki, H.; Sasaki, S.; Maeda, H. J Phys Chem B 1997, 101, 4184.
7. Zhang, X. M.; Hu, Z. B.; Li, Y. J Appl Polym Sci 1997, 63, 1851.
8. Huglin, M. B.; Liu, Y.; Velada, J. L. Polymer 1997, 38, 5785.
9. Lowe, L. T.; Benhaddou, M.; Tenhu, H. Macromol Chem Phys 1999, 200, 51.
10. Ratner, B. D.; Hoffman, A. S. Hydrogels for Medical and Related Applications, Andrade, J. D.; Ed.; American Chemical Society: Washington, DC, 1976; pp 1–36.
11. Hoffman, A. S. Polymer Gels—Fundamentals and Biomedical Application, DeRossi, D.; Kajiwara, K.; Osada, Y.; Yamauchi, A.; Eds.; Plenum Press: New York, 1991; pp 289–297.
12. Wu, X. S.; Hoffman, A. S.; Yager, P. J Polym Sci Part A: Polym Chem 1992, 30, 2121.
13. Kaneko, Y.; Yoshida, R.; Sakai, K.; Sakurai, Y.; Okano, T. J Membrane Sci 1995, 101, 13.
14. Lim, Y. H.; Kim, D.; Lee, D. S. J Appl Polym Sci 1997, 64, 2647.
15. Koopmann, J.; Hocke, J.; Gabius, H.-J. Biol Chem Hoppe-Seyler 1993, 374, 1029.
16. Galaev, I. Y.; Mattiasson, B. Enzyme Microb Technol 1993, 15, 354.
17. Wu, J. Z.; Sassi, A. P.; Blanch, H. W.; Prausnitz, J. M. Polymer 1996, 37, 4803.
18. Okano, T.; Yoshida, R.; Sakai, K.; Sakurai, Y. Polymer Gels—Fundamentals and Biomedical Applications, DeRossi, D.; Kajiwara, K.; Osada, Y.; Yamauchi, A.; Eds.; Plenum Press: New York, 1991; pp 299–308.
19. Yu, H.; Grainger, D. W. Macromolecules 1994, 27, 4554.
20. Dong, L. C.; Hoffman, A. S. J Controlled Release 1991, 15, 141.
21. Kabra, B. G.; Gehrke, S. H. Polym Commun 1991, 32, 322.
22. Yan, Q.; Hoffman, A. S.; Polymer 1995, 36, 887.
23. Lowe, L. T.; Virtanen, J.; Tenhu, H. Polymer 1999, 40, 2595.
24. Shibayama, M. Macromol Chem Phys 1998, 199, 1.