

Swelling and Diffusion Studies of Poly(*N*-isopropylacrylamide/itaconic acid) Copolymeric Hydrogels in Water and Aqueous Solutions of Drugs

Betül Taşdelen,¹ Nilhan Kayaman-Apohan,² Olgun Güven,³ Bahattin M. Baysal^{4,5}

¹Chemistry Department, Çekmece Nuclear Research and Training Center, 34831, P.O. Box 1, Istanbul, Turkey

²Department of Chemistry, Marmara University, 81040 Göztepe/ Istanbul, Turkey

³Department of Chemistry, Hacettepe University, 06532 Beytepe/Ankara, Turkey

⁴TUBITAK Marmara Research Center, P.O. Box 21, 41470 Gebze, Kocaeli, Turkey

⁵Department of Chemical Engineering, Boğaziçi University, 80815 Istanbul, Turkey

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ABSTRACT: *N*-Isopropylacrylamide/itaconic acid hydrogels (NIPAAm/IA) containing different amounts of itaconic acid prepared by irradiating with γ -radiation were used in experiments on swelling and diffusion of the model drugs methylene blue, lidocaine, and sildenafil citrate (VIAGRA). The NIPAAm/IA hydrogels containing 0–3 mol % itaconic acid irradiated at 48 kGy has been used for swelling and diffusion studies in water and aqueous solutions containing

the above-mentioned model drugs. For these hydrogels, swelling studies indicated that swelling increased with the following order: water > lidocaine > methylene blue > VIAGRA. Diffusions of water and the drugs within hydrogels were found to be non-Fickian in character. © 2003 Wiley Periodicals, Inc. *J Appl Polym Sci* 91: 911–915, 2004

Key words: hydrogels; radiation; diffusion

INTRODUCTION

Stimuli-sensitive, also called intelligent polymers, change their structure and physical properties in response to physical or chemical stimuli. These smart polymers have a vast potential for applications in pharmaceutical technology, the biotechnology industry, and in solving environmental problems.¹ Among them, temperature- and pH-responsive polymers are the most frequently studied.

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 LCST, and they collapse when heated above the LCST. 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, the gels can be

expected to act as intelligent materials in drug release,^{2–4} immobilization of enzymes and cells,^{5,6} and in separation of aqueous proteins.⁷

There is renewed interest in radiation-induced polymerization and crosslinking in polymeric hydrogels. The advantages of radiation methods are that they are relatively simple and do not require addition of any extra materials for polymerization and crosslinking. Moreover, the degree of crosslinking, which strongly determines the extent of swelling in hydrogels, can be controlled easily by varying the dose rates. Therefore, these methods are found to be very useful in preparing hydrogels for medical applications, where even a small contamination is undesirable. Recently, Nagaoka et al.⁸ have reported for the first time the synthesis of PNIPAAm hydrogel by the γ -radiation technique.

Diffusion in polymers is an important mechanism in pharmacy for the controlled release of drugs. Diffusion in polymeric systems is passive, if the driving force is purely a brownian molecular motion, but diffusion can also be activated by external effects, either by the influence of the release medium by swelling or by the effects of physical forces as electrical, osmotic, or convective forces.⁹ The fundamental of diffusion is based on Fick's law, which describe the macroscopic transport of molecules by a concentration gradient. The Fick's first law is a pertinent modelization for a steady-state diffusional release and the second Fick's law must be used for description of transient phenom-

Correspondence to: B. M. Baysal.

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ena where the concentration profile of the drug in the polymer is not constant during diffusion. Fick's modelization is adapted to passive diffusional systems where the diffusion coefficient (D) may be supposed to be constant. Such systems are so-called Fickian systems.⁹ In this study, the swelling and diffusion studies in water and aqueous solutions of the model drugs such as methylene blue, lidocaine, and VIAGRA for the novel P(NIPAAm/IA) hydrogels were investigated.

EXPERIMENTAL

Materials

N-Isopropylacrylamide (NIPAAm) was obtained from Aldrich Chemical Company. Itaconic acid (IA) was purchased from Fluka Chemical Company. Methylene blue was purchased from Merck AG. VIAGRA and Lidocaine were provided from Istanbul and Marmara University, Faculty of Pharmacology, respectively, as a gift.

Preparation of hydrogels

The hydrophilic NIPAAm monomer was used as a base monomer in the synthesis of hydrogels. The comonomer was IA carrying diprotic acid groups. Aqueous solutions of NIPAAm (10% w/w) were prepared in distilled water. Different amounts of IA were added to 1 mL of NIPAAm solution (NIPAAm/IA mol ratios, 100 : 0, 99 : 1, 98 : 2, 97 : 3). Monomer solutions thus prepared were placed in a glass tube with 5-mm inner diameter. All irradiations were carried out under air at 25°C with a Gammacell 220 type gamma irradiator in Ankara Nuclear Research and Training Centre. The dose range is 48 kGy at a dose rate of 3 kGy/h. Water was chosen as the extraction solvent for the crude hydrogels and employed at room temperature. After polymerization, crosslinked copolymers were removed from tubes and the hydrogels obtained in long cylindrical shapes were cut into pieces of approximately 1-cm length. Each sample was placed in an excess of water, and the solvent was replaced every other day over a period of at least 1 week until no further extractable polymer could be detected. Uncrosslinked polymer and/or residual monomer were removed with this extraction from the gel structure. Extracted gels were dried in vacuum oven at 30°C to constant weight and the gel fraction was calculated. The amount of uncrosslinked IA was determined by titration of extract against NaOH to phenolphthalein end point.¹⁰ The percentage gelation, W_g , was calculated as,

$$W_g = (m_{ae}/m_{be}) \times 100 \quad (1)$$

TABLE I
Characterization of P(NIPAAm/IA) Hydrogels

Sample no.	Mol % of IA		W_g %	Equilibrium % mass swelling
	In feed	In gel		
PNIPAAm(1)	0	0	98	1260
P(NIPAAm/IA)-1	1	0.98	97	3390
P(NIPAAm/IA)-2	2	1.97	96	5890
P(NIPAAm/IA)-3	3	2.98	95	11,200

where, m_{ae} and m_{be} are the weights of dry gels after and before extraction. The composition of hydrogels is given in Table 1.

SWELLING CHARACTERIZATION

Dynamic swelling studies were undertaken to elucidate the mechanism of water and drug diffusion into the polymer samples as determined by the dynamic portion of the gravimetric curve. The water or drug uptake, M_t , was followed as a function of time until equilibrium was attained, M_∞ , to provide the data for dynamic and equilibrium time frames.

Dried polymer cylinders were placed in vials filled with 25 ML of distilled deionized water or aqueous solutions of the drugs [methylene blue (1000 ppm), lidocaine (5000 ppm) and VIAGRA (500 ppm)]. The vials were set in a temperature-controlled bath at $25 \pm 0.1^\circ\text{C}$. The polymer samples were periodically removed from the water, dried superficially with filter paper, weighed, and placed in the same bath. The mass swelling percentage of the hydrogels was calculated from the following relation:

$$\% S = [(m_t - m_o)/m_o] \times 100 \quad (2)$$

where m_o is the mass of the dry gel and m_t is the mass of swollen gel at time t .

The swelling rate constants of the hydrogels were calculated from the following relation.¹¹

$$\text{Percentage mass swelling} = k_s t^{0.5} \quad (3)$$

where k_s is the swelling rate.

To obtain a more quantitative understanding of the nature of the sorption kinetic in NIPAAm/IA copolymeric gels, the initial swelling data were fitted to the exponential heuristic eq. (4),^{12,13}

$$F = M_t/M_\infty = kt^n \quad (4)$$

Here, F is the fractional uptake, M_t/M_∞ , where M_t is the amount of diffusant sorbed at time t , M_∞ is the maximum amount absorbed, k is a constant incorporating characteristics of macromolecular network sys-

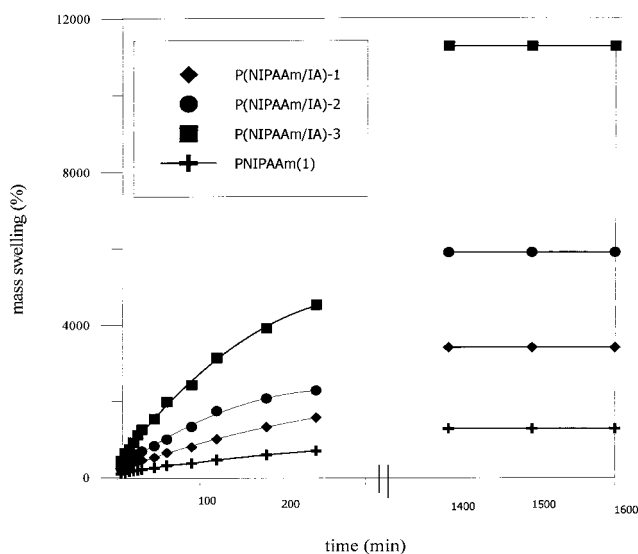


Figure 1 Percentage mass swelling as a function of time for the series of NIPAAm/IA copolymeric hydrogels at 25°C in distilled water.

tem and the penetrant, n is the diffusional exponent, which is indicative of the transport mechanism. Equation (4) is valid for the first 60% of the normalized solvent uptake. For Fickian kinetics in which the rate of penetrate diffusion is rate limiting, $n = 0.5$, whereas values of n between 0.5 and 1 indicate the contribution of non-Fickian processes such as polymer relaxation.

Diffusion coefficients are important penetration parameters of some chemical species to polymeric systems. Using n and k , the the diffusion coefficient (D) of solvent in the matrix could be calculated using the following equation:^{14,15}

$$k = 4[D / \pi r^2]^n$$

$$4 D^n = k(\pi r^2)^n$$

$$D^n = (k/4) (\pi r^2)^n \dots \quad (5)$$

where D is the diffusion coefficient, and r is the radius of gel disc.

RESULTS AND DISCUSSION

Swelling and diffusion

In this work, hydrogels of poly(*N*-isopropyl acrylamide) (PNIPAAm) and poly(*N*-isopropyl acrylamide-*co*-itaconic acid) (P(NIPAAm/IA)) were synthesized by a radiation-induced polymerization technique. The purpose is to emphasize the effect of the ionization degree of the polymeric networks on their swelling kinetics and solute absorption mechanisms. Plots of dynamic water swelling of pure PNIPAAm and P(NIPAAm/IA) copolymeric gels are presented

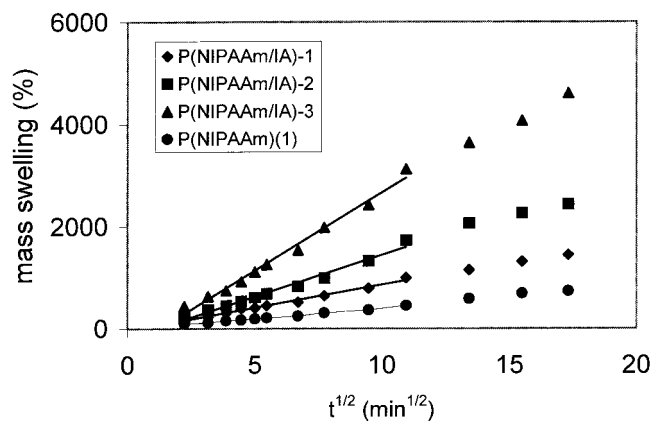


Figure 2 The plot of percentage mass swelling vs square root of time for NIPAAm/IA copolymeric hydrogels at 25°C in distilled water.

in Figure 1. All studies were performed at 25°C and the water uptake was monitored gravimetrically. All data reported are the average of duplicate experiments. The equilibrium percentage mass swelling for each sample is presented in Table I. The same table presents also the hydrogel composition and percentage gelation. The results showed that the mass swelling percentage of an ionic network strongly depends on the concentration of ionizable groups in the network. Increase in the itaconic acid content from 0 to 3 mol % causes immense increase in water uptake in distilled water. The equilibrium percentage mass swelling of NIPAAm/IA copolymeric hydrogel increased from 1260 to 11,280 as the mol % of itaconic acid content increased from 0 to 3.

Swelling rate curves of the NIPAAm/IA copolymeric hydrogels are shown in Figure 2. The swelling rate constants of the hydrogels were calculated from eq. (3) and the initial slopes (k_s) were presented in Table II. The results show that the initial slopes of the curves increase sharply with the increase of the comonomer concentration: this is a result of the electrostatic repulsion of the neighboring carboxylate groups of IA in the ionic network.

To better understand the water absorption behavior of these hydrogels, eq. (4) was used. The plots of $\ln F$ vs $\ln t$ for the series of pure PNIPAAm and P(NIPAAm/IA) copolymeric hydrogel at different IA content are shown in Figure 3. The exponents n and k values were calculated

TABLE II
Initial Slope (k_s) Values of NIPAAm/IA Copolymeric Hydrogels at 25°C in Distilled Water

Gel name	Initial slope (k_s)
PNIPAAm(1)	40
P(NIPAAm/IA)-1	84
P(NIPAAm/IA)-2	136
P(NIPAAm/IA)-3	251

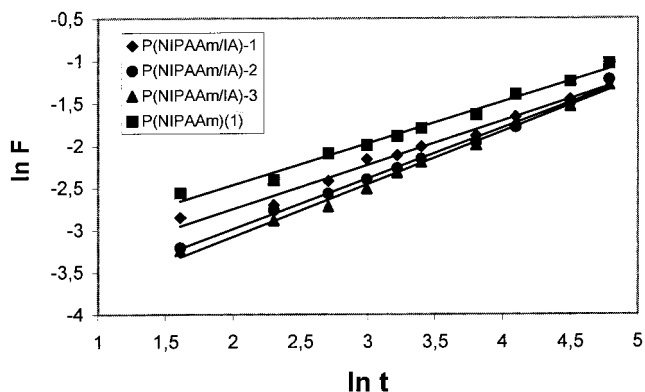


Figure 3 The plot of $\ln F$ vs $\ln t$ for the series of P(NIPAAm/IA) copolymeric hydrogels at different itaconic acid concentration at 25°C in distilled water.

from the slope and intercept of the lines, respectively, and are presented in Table III. As the IA content of the samples increases the water fractional uptake at the same absorption time increases. It is clear from the analysis that as the itaconic acid content in the gel structure increases the diffusional release kinetic exponent n increases from 0.49 to 0.63 for P(NIPAAm/IA) hydrogels. This evidence shows that the swelling transport mechanism was transferred from Fickian to non-Fickian transport with the increasing itaconic acid content in the gel structure.

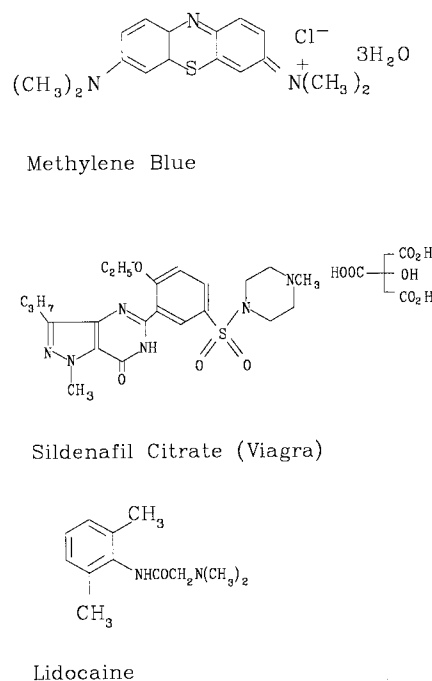
The D values are presented in Table III. The diffusion coefficients D increase with an increase in itaconic acid content in the present hydrogels. This is due to the hydrophilicity for these copolymeric hydrogels in the order of P(NIPAAm)(1) < P(NIPAAm/IA)-1 < P(NIPAAm/IA)-2 < P(NIPAAm/IA)-3, and the more hydrophilic groups in the gel, the easier the diffusion for water molecules. So, P(NIPAAm/IA)-3 has a higher D value.

Diffusion of drugs into P(NIPAAm/IA) hydrogels

To observe the diffusion of drugs into P(NIPAAm/IA) network dry hydrogels were placed in aqueous solutions of VIAGRA, Lidocaine and Methylene Blue, and allowed to equilibrate for 24 h. The molecular formula of the drugs can be seen in Scheme 1. The dynamic swelling curves of P(NIPAAm/IA)-3 copolymeric hy-

TABLE III
Parameters of Diffusion of Water into the P(NIPAAm/IA) Hydrogels

Gel name	$k \times 100$	n	$D \times 10^8 / \text{cm}^2 \text{sec}^{-1}$
PNIPAAm(1)	3.2	0.49	3.2
P(NIPAAm/IA)-1	2.3	0.52	3.4
P(NIPAAm/IA)-2	1.5	0.60	9.6
P(NIPAAm/IA)-3	1.3	0.62	12.2



Scheme 1

drogels in water and the solutions of the drugs are shown in Figure 4. The results illustrate that the equilibrium mass swelling of P(NIPAAm/IA)-3 hydrogel in water is greater (11,280%) than the equilibrium mass swelling of P(NIPAAm/IA) in the aqueous solution of all drugs (2830–2470%). The molecular size of the drugs are larger than the size of water, hence, molecules of water can diffuse into gel pores more easily than molecules of all drugs. Because the molecular weight of the drugs in the following order: water < lidocaine < methylene blue < VIAGRA, the swell-

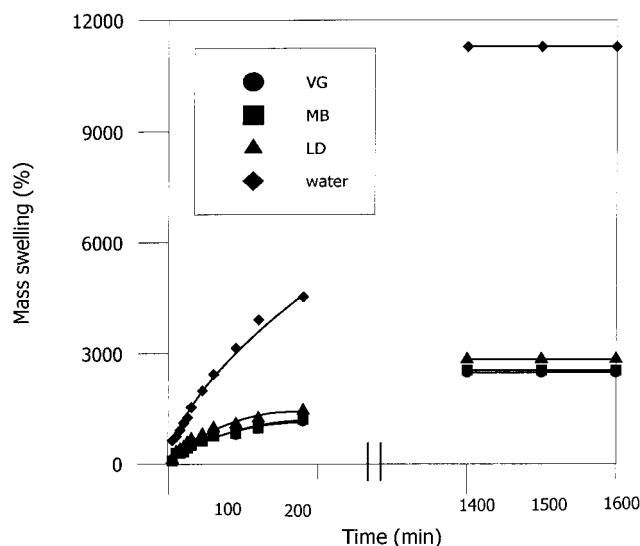


Figure 4 The mass swelling curves as a function of time for P(NIPAAm/IA)-3 hydrogel in the different drug solutions.

TABLE IV
Parameters of Diffusion of Different Drug Solutions into P(NIPAAm/IA) Hydrogels at Different Itaconic Acid Concentration

Gel name	Equilibrium mass swelling %		
	VIAGRA	Methylene Blue	Lidocaine
PNIPAAm(1)	270	280	310
P(NIPAAm/IA)-1	730	760	850
P(NIPAAm/IA)-2	1280	1310	1470
P(NIPAAm/IA)-3	2470	2530	2830

ing of P(NIPAAm/IA)-3 hydrogel in the aqueous solution of drugs follows the reverse order.

The effect of IA content on the swelling behavior of the NIPAAm/IA copolymeric hydrogels in the drug solutions is shown in Table IV. The incorporation of IA into the polymer network with higher IA content will lead to an increase in electrostatic repulsive force between charge sites on carboxylate ions and enhance a more extended configuration. The extended structure with high IA content might cause a higher swelling ratio of the hydrogel in the drug solutions.

The plots of $\ln F$ vs $\ln t$ for P(NIPAAm/IA)-3 copolymeric hydrogels in water and different drug solutions illustrated in Figure 5. The swelling exponent n and constant k calculated using eq. (4) are presented in Table V. The n values were found to be over 0.50. Hence, the diffusion of the drugs into P(NIPAAm/IA) hydrogel was taken to be of non-Fickian character. This is generally explained as being a consequence of the slow relaxation rate of polymer chain in the hydrogel. Diffusion coefficient of water and the aqueous solutions of drugs are also listed in Table V. As expected, the diffusion coefficients increase with an increase equilibrium mass swelling of the present hydrogel in the solutions.

CONCLUSION

N-Isopropylacrylamide/itaconic acid copolymeric hydrogels were prepared by irradiating the ternary mix-

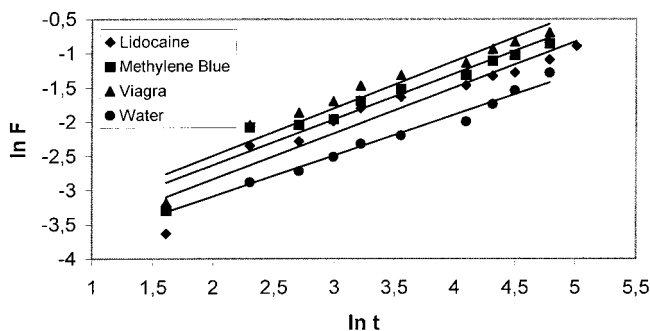


Figure 5 The plot of $\ln F$ vs $\ln t$ for P(NIPAAm/IA)-3 hydrogel in the different drug solutions.

TABLE V
Parameters of Diffusion of Water and the Aqueous Solution of Drugs into P(NIPAAm/IA)-3 Hydrogels

Solution	$k \times 100$	n	$D \times 10^8 / \text{cm}^2 \text{s}^{-1}$
Water	1.3	0.62	12.2
Lidocaine	2.3	0.57	11.4
Methylene Blue	3.1	0.54	9.8
VIAGRA	3.9	0.52	9.4

tures of *N*-isopropylacrylamide/itaconic acid/water by γ -rays at ambient temperature. The swelling ratios of NIPAAm/IA copolymeric gels increase with an increase of itaconic acid content. This has been explained due to the incorporation of more specific acid groups into the network and consequent higher swelling capacity of gels. In the diffusion transport mechanism study, the results indicate that the swelling exponents n for all NIPAAm/IA copolymeric gels at 25°C are in the range from 0.49 to 0.62. This implies that the swelling transport mechanism is a non-Fickian transport. The diffusion coefficients (D) for the copolymeric gels increase with an increase of itaconic acid content, so the water molecule easily infiltrates into hydrogels for gels containing higher IA content. In addition, diffusions of the model drugs within the hydrogels were investigated. In the experiments, the number to determine the type of diffusion (n) was found to be over 0.5. Hence, the diffusion of the drugs into P(NIPAAm/IA) was taken to be of non-Fickian character.

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