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ORIGINAL PAPER

# Swelling behaviour and paracetamol release from poly(*N*-isopropylacrylamide-itaconic acid) hydrogels

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**Abstract** Copolymer hydrogels of *N*-isopropylacrylamide and itaconic acid (IA), crosslinked with *N*,*N*′-methylenebisacrylamide, were prepared by radical copolymerization. These hydrogels were investigated with regard to their composition to find materials with satisfactory swelling and drug release properties. A paracetamol is used as a model drug to investigate drug release profile of the hydrogels. It was found that the investigated hydrogels exhibited pH- and temperature-dependent swelling behaviour with restricted swelling and lower equilibrium degree of swelling at lower pH values and temperatures above the LCST value of PNIPAM (around 34 °C). The diffusion exponent for paracetamol release indicate that the mechanism of paracetamol release are governed by Fickian diffusion, while in all release media initial diffusion coefficient was lower than late time diffusion coefficient. Furthermore, the paracetamol release rate depends on the hydrogel degree of swelling and it increased in the first stage of diffusion process, whereas was no significant difference thereafter. The presence of the IA moieties incorporated into the network weakened the shear resistance of the hydrogels. In order to calculate the pore size the characteristic ratio for PNIPAM, $C_n = 11.7$, was calculated. Based on the pore size, the investigated hydrogels can be regarded as microporous. According to the obtained results swelling behaviour, mechanical properties, drug-loading capacity and the drug release rate could be controlled by hydrogel composition and crosslinking density, which is important for application of the investigated hydrogels as drug delivery systems.

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## Introduction

The aim of controlled release systems is to make a dosage form that could deliver a drug at a specified rate, keeping the drug concentration in the body at the therapeutically effective level. Furthermore, the efficiency of a drug would be increased if it could be delivered to a specified target in the body. Among controlled release drug delivery systems, hydrogels have been of interest due to their unique tuneable time-dependent swelling behaviour.

Hydrogels are three-dimensional polymer networks which can absorb a large amount of water or biological fluids and swell to several thousands times the dry gel volume. Depending on their method of preparation, ionic charge and physical structure features, they are classified in a number of ways. A special class of hydrogels, which are called 'intelligent' or stimuli-responsive hydrogels, go through reversible volume transitions in response to small changes in temperature, pH, electric field, etc. Among the most studied 'intelligent' gels for pharmaceutical applications are pH or temperature-sensitive hydrogels, as well as those which respond to both stimuli. These types of hydrogels have extensively been used in the development of drug delivery systems [1, 2].

A series of papers have been published about pH-sensitive copolymer hydrogels obtained by $\gamma$-irradiation, based on polyacrylamide (PAAm) or poly(*N*-isopropylacrylamide) (PNIPAM) and acrylic and maleic acid [3–14]. In some studies, hydrogels based on PAAm or PNIPAM and itaconic acid (IA) or its esters were investigated [15–18]. However, the hydrogels of PAAm or PNIPAM and IA synthesized by free radical copolymerization with different concentrations of crosslinking agent and monomer ratio have not been extensively studied. IA has two ionisable groups with different $pK_a$ values. The main advantage of IA application compared to the others carboxylic acids is the fact that it can be obtained from renewable resources, i.e. from carbohydrate materials such as molasses and hydrolysed starch, by fermentation. Owing to these properties it may serve as a substitute for petrochemical based acrylic and methacrylic acid which are used for hydrogel preparation. Further, acrylic and methacrylic acids have one ionisable group, while IA has two, indicating a more pronounced pH sensitivity in the system. Hence, these properties make it very interesting for pharmaceutical and medical applications [19, 20].

In our previous study, the swelling behaviour, as well as paracetamol release from copolymer hydrogels of acrylamide and IA were investigated. The influence of hydrogel composition and pH value of the dissolution media on drug release were evaluated. However, there were no significant changes in drug release rate with changing a pH of the external media. Furthermore, the drug release was rapid, while the amount of released paracetamol was high (more than 60% after 2 h) [21]. In order to improve the obtained hydrogel properties and make them suitable for controlled release in the colon, we prepared a series of hydrogels where the acrylamide was changed by *N*-isopropylacrylamide (NIPAM).

Poly(*N*-isopropylacrylamide) is one of the most commonly studied thermoreversible polymer, owing to the lower critical solution temperature (LCST) in water at around 34 °C, which is close to the temperature of the human body [22]. Hydrogels based on NIPAM swell below and collapse above the LCST being very interesting for controlled release drug delivery systems. On the other hand, the presence of ionic components may provide pH-sensitivity to non-ionic PNIPAM gels, which could be very useful for the delivery of drugs to a site with specific pH value [9, 23]. For example, the change of pH through the gastrointestinal tract (GIT) varies from the acidic pH of the stomach [24], increasing progressively in the small intestine to neutral or slightly basic pH in large intestine. These changes play an important role in the selective release of drugs. pH-sensitivity of PNIPAM hydrogels can be obtained by incorporating the ionisable groups of acrylic, methacrylic acid, maleic acid or IA [9, 23].

In the present study, swelling behaviour of poly(*N*-isopropylacrylamide-co-itaconic acid) (PNIPAM/IA) copolymer hydrogels with different crosslinking agent concentration and IA content, as a response to pH and temperatures of the external media was investigated. Mechanical properties and diffusion characteristics of the prepared hydrogels were investigated too. In order to evaluate the feasibility of using a particular hydrogel as a drug delivery system, the hydrogels were loaded with paracetamol, as a model drug. Paracetamol is a highly permeable and highly soluble drug and it is in a non-ionized form through the GIT ($pK_a = 9.5$) which means that observed changes in hydrogels behaviour are due to their respond to pH and temperature [25]. The release of model drug from (PNIPAM/IA) hydrogels have been discussed for the evaluation on the release rate and mechanism, as well as diffusion coefficient.

The swelling analysis showed that the hydrogels are pH- and temperature-sensitive, depending on their composition. The introduction of charged groups into the PNIPAM gel shifted the LCST to a higher values, which is in accordance to literature [26]. The dual sensitivity allows control of the swelling and mechanical properties by adjusting the structure and the degree of crosslinking of the copolymers, which could be very useful for the delivery of active substances to a specific site in the GIT.

## Experimental part

### Materials

Itaconic acid and NIPAM were obtained from Fluka (Switzerland) and Acros (Belgium), respectively. The crosslinking agent *N*,*N*′-methylenebisacrylamide (MBA) was obtained from Serva (Germany). Potassium persulphate (PPS) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED), the initiator and accelerator, respectively, were purchased from Merck (Germany) and Acros, respectively. NIPAM, 99% purity, was recrystalized from benzene/*n*-hexane mixture (35/75) before use. Other materials were used as received, without purification. Paracetamol (Merck, Germany) was used as the model drug.

### Preparation of copolymer hydrogels

The hydrogels were obtained by radical copolymerization at 25 °C under a $N_2$ atmosphere for 48 h. The weight ratios of NIPAM/IA monomer in the initial mixture were: 99:1, 95:5 and 90:10. The monomers were dissolved in water with the redox couple PPS and TEMED (both 1.0 wt %), while the concentration of the MBA was 2.0 and 3.0 wt %, with respect to the other monomers was used. The reaction mixture was placed between two glass plates sealed with a rubber spacer. At the end of the reaction, the gels were cut into discs and immersed in water for a week to remove unreacted monomers, PPS and TEMED. The water was changed daily. The discs were dried at room temperature to xerogels ($1.0 \pm 0.2$ mm thickness and $5.0 \pm 0.3$ mm diameter).

The PNIPAM hydrogel was synthesized under the same conditions as were used for the copolymer hydrogels. The first and second number in the sample name correspond to the weight ratios of NIPAM and IA, and the third one corresponds to the concentration of the MBA.

## Characterization

### Equilibrium swelling studies

The swelling behaviour of the obtained hydrogels was studied as a function of pH at different temperatures: 18, 25, 31, 35, 37, 40, 47 and 55 °C. Three aqueous media with different pH values were used, namely: USP hydrochloric acid buffer (pH 2.2), 0.05 M $KH_2PO_4$ (pH 4.5) and USP phosphate buffer (pH 6.8). The solution of pH 4.5, which is above the $pK_{a1}$ value of IA ($pK_{a1} = 3.85$ and $pK_{a2} = 5.44$ [27]), was chosen in order to investigate how the ionization of the first COOH group of the IA residues affects the degree of swelling. The progress of the swelling process was monitored gravimetrically and the equilibrium degree of swelling was calculated as follows:

$$q_e = W_e/W_o \quad (1)$$

where $W_e$ is the weight of swollen hydrogel at equilibrium state [28]. Every data point was determined as the average value of three independent measurements.

### Dynamic mechanical analysis

Strain–frequency sweeps were performed on hydrogel discs swollen to equilibrium, using a Rheometrics 605 mechanical spectrometer, with parallel plates geometry (25 mm in diameter). The complex shear moduli were measured as a function of frequency ($\omega$), from 0.1 to 100 rad/s, at 37 °C. The strain applied was 10%.

### Loading of drug

Hydrogels were loaded with paracetamol by immersing the dry discs in an aqueous drug solution (10 mg/ml) at room temperature for 2 days. Preliminary tests revealed

that 2 days was the minimum time to ensure maximal drug loading. After that time, the hydrogels were removed from the drug solution and left to dry to constant weight. The paracetamol content was determined spectrophotometrically.

## Results and discussion

### Swelling behaviour of hydrogels

According to the results presented in Fig. 1, there is a pronounced difference in the swelling behaviour of the copolymer hydrogels compared to that of the PNIPAM gel. All the samples exhibited a temperature dependent behaviour together with a pH dependent swelling of the copolymers. When the non-ionic PNIPAM gel was below its LCST, it swelled, but there was not a significant pH dependence of the $q_e$ of swelling. In contrast, the swelling of the copolymeric hydrogels was strongly dependent on the pH value of the external medium. At low pH values, the degree of swelling was low because the carboxylic groups in the side chains were not ionized and intermolecular complexation via H-bonds occurred. This complexation results in increased hydrophobicity of the network and lower $q_e$ values [29]. As the degree of ionization increased above the nominal $pK_a$ values of IA, the greater degrees of swelling was observed due to the three reasons: most of H-bonds are broken, $COO^-$ ions are more hydrophilic than COOH groups and the electrostatic repulsion between the $COO^-$ ions pushes the network chains apart. The most pronounced pH-sensitivity was observed for the samples with highest acid content (10 wt%).

On the other hand, the pH induced swelling of the copolymers was controlled by temperature. Below the LCST value, which is around 34 °C for PNIPAM gels, a hydration shell is formed around the hydrophobic groups by hydrogen bonding between the hydrophilic groups in the side chains and water, causing water uptake and swelling of the PNIPAM hydrogel.

The increase of the external temperature leads to scission of the H-bonds and hydrophobic interactions prevail. The LCST represents the temperature at which the hydrophobic forces (due to interaction of the $–NCH(CH_3)_2$ groups), which lead to insolubility in an aqueous environment, are balanced by H-bonding with water,

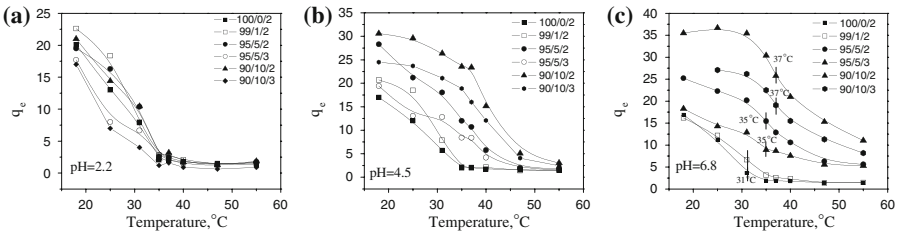


**Fig. 1** The equilibrium degrees of swelling versus temperature and the LCST values of the PNIPAM and copolymer PNIPAM/IA hydrogels: **a** pH = 2.2, **b** pH = 4.5, **c** pH = 6.8

which maintains a polymer in solution. All the investigated hydrogels undergo a rapid volume change in response to small changes in the external temperature. In accordance with the IA content in the copolymers the $q_e$ values were higher and the LCST value shifted to higher temperatures with increasing acid content (Fig. 1).

The change of $q_e$ with pH for the copolymers was more pronounced than the change of $q_e$ with temperature. This behaviour is favourable for the potential application of the investigated copolymers as drug delivery systems in lower part of the GIT, because the hydrogel almost does not swell at gastric pH values (pH about 2.2), but swells at intestinal pH (pH about 6.8). At body temperature, the swelling was restricted owing to the contraction of the NIPAM component.

## Network parameters

The most important parameters characterizing a hydrogel network structure are the molar mass between two neighbouring crosslinking points ($M_c$), the pore size ($\xi$) and polymer–solvent interaction parameter ($\chi$). Peppas and Merill [30] described the molar mass between two neighbouring crosslinks for neutral polymer networks:

$$\bar{M}_c = -\frac{(1-2/\phi)V_1 \upsilon_{2r}^{2/3}\upsilon_{2s}^{1/3}}{\overline{v}\left[\ln(1-\upsilon_{2s})+\upsilon_{2s}+\chi\upsilon_{2s}^2\right]} \tag{2}$$

where $\upsilon_{2s}$ is the volume fraction of polymer in the swollen gel, $\upsilon_{2r}$ is the polymer volume fraction in the relaxed state (after crosslinking, but before swelling), $V_1$ is the molar volume of water, $\phi$ is the crosslinking agent functionality, $\overline{v}$ is the specific volume of the polymer and $\chi$ is the Flory polymer–solvent interaction parameter [31]:

$$\chi = \frac{\ln\left(1-\upsilon_{2,s}\right)+\upsilon_{2,s}}{\upsilon_{2,s}^2} \tag{3}$$

Further, Şen et al. derived a modified equation for hydrogels with two carboxylic groups [22, 32, 33]:

$$\left(\frac{[2K_{a1}K_{a2}+10^{-\mathrm{pH}}K_{a1}]}{2\left[(10^{-\mathrm{pH}})^2+10^{-\mathrm{pH}}K_{a1}+K_{a1}K_{a2}\right]}\right)^2\left(\frac{V_1\upsilon_{2m}^2X^2}{4I^2\overline{v}^2}\right) = \ln(1-\upsilon_{2m})+\upsilon_{2m}+\chi\upsilon_{2m}^2+\frac{(1-2/\phi)V_1\upsilon_{2r}^{2/3}}{\overline{v}\,\overline{M_c}} \tag{4}$$

$K_{a1}$ and $K_{a2}$ are the first and second dissociation constants of a diprotic acid, $X$ is the weight fraction of ionisable polymer in the system, $I$ is ionic strength of the swelling medium.

In the present study Eq. 2 was used for non-ionic PNIPAM hydrogel as well as for the copolymer hydrogel PNIPAM/IA 99/1/2, because the IA content was low and this hydrogel was very similar to the pure PNIPAM hydrogel, according to its swelling and mechanical properties. Equation 4 was used for the copolymer hydrogels with higher IA contents.

The pore size, $\xi$, can be calculated from the following equation [28]:

$$\xi = \upsilon_{2,s}^{-1/3} \cdot l \cdot \left( \frac{C_n \cdot 2\overline{M}_c}{M_r} \right)^{1/2} \tag{5}$$

where $C_n$ is Flory characteristic ratio which is a constant for a given polymer–solvent system ($C_n$ 4.63 for PIA) [34], $l$ is the carbon–carbon bond length (for vinyl polymers $l = 1.54$ Å), $M_r$ is the weight of the repeating units from which the polymer chain is composed. The characteristic ratio for PNIPAM ($C_n = 11.7$) was calculated using the following equations [35]:

$$C_n = 2 \cdot \sigma^2 \tag{6}$$

$$\sigma = \frac{\left(\overline{r}_o^2\right)^{1/2}}{\left(\overline{r}_{of}^2\right)^{1/2}} = \frac{\left(\overline{r}_o^2/M\right)^{1/2}}{2.18 \cdot M_r^{1/2}} \tag{7}$$

where $\overline{r}_o^2$ represents the mean-square end-to-end distance at theta conditions, $\overline{r}_{of}^2$ refers to the mean-square end-to-end distance of a freely rotating chain, $M$ is the weight-average molar mass. The value of $\left(\overline{r}_o^2/M\right)^{1/2} = 7.88 \times 10^{-9}$ cm was taken from the literature [36]. The effective crosslinking density ($v_c$) was calculated as $v_c = \rho/M_c$. According to the potential application as drug delivery systems in the colon, the calculations were done for the results obtained at pH = 6.8 and 37 °C (Table 1).

It can be seen that the effective crosslinking density decreased with increasing IA content, while the molar mass between two neighbouring crosslinks and the pore size increased. Increasing the IA content in the hydrogels led to a decrease of the polymer–solvent interaction ($\chi$) parameter for the samples with the same amount of MBA. Further, it was slightly increased for the sample with a higher percent of MBA (3%), which is in accordance with the swelling behaviour. Lower values of $\chi$ show better solubility and a greater possibility for swelling. On the contrary, the $M_c$ values were higher for the samples with a higher degree of swelling because the increase of the content of IA in hydrogels led to better swelling. Based on pore size, the investigated hydrogels can be regarded as microporous [28].

**Table 1** The network parameters $M_c$, $v_c$, $\xi$ and $\chi$ for the PNIPAM and PNIPAM/IA copolymer hydrogels at 37 °C and pH 6.8

| PNIPAM/IA | G′, Pa | $M_c \times 10^{-3}$, kg/mol | $v_c \times 10^3$, mol/l | $\chi$ | $\xi$, μm |
|---|---|---|---|---|---|
| 100/0/2 | 1,050 | 0.02 | 0.505 | 0.797 | 0.012 |
| 99/1/2 | 887.6 | 0.39 | 0.473 | 0.682 | 0.019 |
| 95/5/2 | 343.8 | 0.24 | 0.407 | 0.527 | 0.025 |
| 95/5/3 | 492.0 | 0.18 | 0.440 | 0.537 | 0.020 |
| 90/10/2 | 339.8 | 0.43 | 0.389 | 0.513 | 0.041 |
| 90/10/3 | 481.8 | 0.32 | 0.400 | 0.523 | 0.033 |

## Dynamic mechanical properties

The shear storage moduli of hydrogels at equilibrium swelling decreased with increasing water content in the gels, which is to be expected. The G′ values depended on the hydrogel composition: with increasing IA content, lower shear moduli were recorded. Hence, the PNIPAM/IA 90/10/2, which exhibits the largest swelling, had the lowest G′ value. The lower G′ values of the copolymer hydrogels compared to the pure PNIPAM gel are due to the presence of the IA moieties incorporated into the network, which weakened the shear resistance (Table 1).

## Drug release

In order to evaluate the potential application of the prepared hydrogels as drug delivery systems, paracetamol, as a model drug, was loaded into the PNIPAM/IA hydrogels. According to the swelling results, the hydrogels with 5 and 10 wt % content of IA were selected for this investigation.

For application of drug delivery device in the colon, it is necessary to make hydrogel which almost does not swell at acidic medium and it has good swelling properties at neutral or basic media. From that point of you, the (PNIPAM/IA) hydrogels have the desired release profile: the release of paracetamol is low and not completed at pH 2.2, while it is fast and completed at pH 6.8 (Fig. 2).

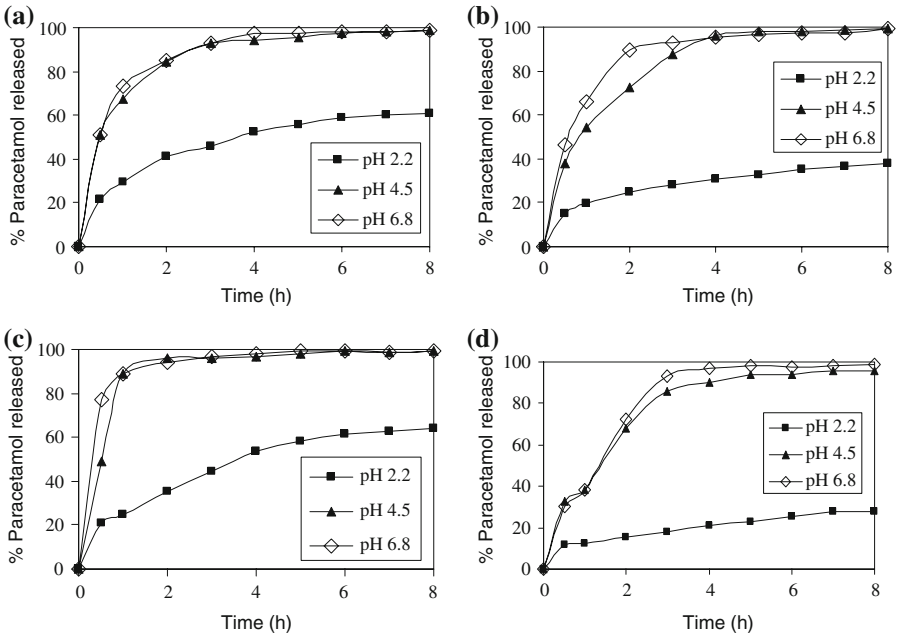


**Fig. 2** Drug release profiles obtained at different pHs for PNIPAM/IA hydrogels: **a** 95/5/2, **b** 95/5/3, **c** 90/10/2 and **d** 90/10/3 (standard deviation error *bars* were omitted because they overlap symbols)

Analyzing the paracetamol release profiles, two phases of the release process could be distinguished: an initial burst which is followed by a phase with a slower release. The burst effect is caused by the release of paracetamol close to the surface of the hydrogel disc, while the lower release occurs by the pore diffusion mechanism. The permeation through hydrogel was fast because the hydrodynamic radius of paracetamol ($r_h = 0.042$ nm) is less than pore size. The $r_h$ of the paracetamol was calculated using the following equation:

$$(r_h)^2 = \left(\frac{3V}{4\pi N_A}\right)^{2/3} \tag{8}$$

where $N_A$ is Avogadro's number, $V$ is the molar volume of the paracetamol [37, 38].

The release profiles showed a reduction in the release rate and amount of paracetamol at all pH values as the MBA concentration was increased owing to the higher network density and small available free volume between the chains. On the other hand, as the IA content increase, more paracetamol was released from the hydrogel, which could be explained on the basis of the swelling behaviour of hydrogels, as a function of IA ionization. Paracetamol was released after approximately 6 h at pH = 2.2 and after approximately 2 h at pH = 6.8. In all experiments, most of the drug was delivered in the first five hours. Similar results were reported by Gutowska et al. [39], who studied the application of NIPAM-co-BMA-co-DEAEMA as a temperature-sensitive mechanical squeezing hydrogel for oral drug delivery. The pronounced effect of pH at 37 °C was due to the synergistic effect of pH and temperature. Upon the effect of the stimuli, the gel began to swell opening the releasing pores and mechanically squeezing some of the drug solution from the gel and the drug release rate was proportional to the rate of squeezing of the drug loaded hydrogel. The synergistic effect has been also observed in copolymer hydrogels of NIPAM and methacrylic acid [40, 41].

As already mentioned, in our previous study, the swelling behaviour and the release of paracetamol from hydrogels of IA and AAm were investigated [21]. But, compared to PNIPAM/IA hydrogels, there were no big differences in the drug release profiles from PAAm/IA hydrogels with changing pH of the external media.

These differences were additionally documented with the calculated values of the similarity factors $f_2$ as proposed by FDA Guidance [42]:

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{n=1}^{t}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \tag{9}$$

where $R_t$ and $T_t$ are percent dissolved at each time point for the reference sample and the test sample, respectively. Using the $f_2$ values dissolution profiles are considered dissimilar if $f_2$ is less than 50 (Table 2).

As can be seen, the values of the similarity factor $f_2$, are lower than 50 in all cases. Compared to the others, the most pronounced differences were observed for samples with 10 wt% of IA for both crosslinking agent concentration. By changing the AAm monomer with temperature-sensitive NIPAM monomer, the aim of the investigation was achieved: slower and non completed paracetamol release in

**Table 2** Values of similarity factors ($f_2$) for investigated dissolution profiles

| Sample | 90/10/2 PAAm/PNIPAM | 90/10/3 PAAm/PNIPAM | 95/5/2 PAAm/PNIPAM | 95/5/3 PAAm/PNIPAM |
|---|---|---|---|---|
| pH 2.2 | 33.03 | 12.83 | 36.07 | 18.88 |
| pH 4.5 | 22.79 | 36.03 | 31.13 | 45.09 |
| pH 6.8 | 20.05 | 28.90 | 27.31 | 32.70 |

acidic, but rapid and completed in neutral medium, which could be used for the potential application of those hydrogels as colon-specific drug delivery systems.

To establish a correlation between drug transport mechanism, the dissolution data were evaluated by applying the Peppas kinetic model: $M_t/M_e=kt^n$, where $M_t$ and $M_e$ are the amounts of drug released at any time t and at equilibrium, respectively; $k$ is the kinetic constant, $n$ is diffusion exponent which characterizes the mechanism of drug release [43].

The values of the diffusion exponent $n$ were lower than 0.5 indicating a Fickian paracetamol release kinetics. Paracetamol release depends on buffer migration into the device and paracetamol diffusion through continuously swelling hydrogels (Table 3). On the contrary, in the case of (PAAm/IA) hydrogels, both diffusion and polymer relaxation control the overall rate of buffer uptake and consequently paracetamol release kinetics [21]. The observed differences indicate the influence of hydrogel composition on the drug release.

The diffusion coefficient were calculated from the early-time and the late-time approximation [44]:

Early-time:

$$\frac{M_t}{M_\infty} = 4\sqrt{\frac{D_E t}{\pi\delta^2}} \tag{10}$$

Late-time approximation:

$$\frac{M_t}{M_\infty} = 1 - \left(\frac{8}{\pi^2}\right)\exp\left[\frac{(-\pi^2 D_L t)}{\delta^2}\right] \tag{11}$$

**Table 3** Diffusion coefficients and diffusion exponents for paracetamol release from PNIPAM/IA hydrogels

| Sample | pH 2.2 | | | pH 4.5 | | | pH 6.8 | | |
|---|---|---|---|---|---|---|---|---|---|
| PNIPAM/IA | $D_E \times 10^4$ (cm$^2$/min) | $D_L \times 10^4$ (cm$^2$/min) | $n$ | $D_E \times 10^4$ (cm$^2$/min) | $D_L \times 10^4$ (cm$^2$/min) | $n$ | $D_E \times 10^4$ (cm$^2$/min) | $D_L \times 10^4$ (cm$^2$/min) | $n$ |
| 95/5/2 | 0.48 | 0.77 | 0.41 | 0.57 | 3.94 | 0.37 | 0.54 | 4.30 | 0.37 |
| 90/10/2 | 0.71 | 1.47 | 0.46 | 0.38 | 4.24 | 0.48 | 0.11 | 3.97 | 0.43 |
| 95/5/3 | 0.16 | 0.40 | 0.33 | 1.24 | 6.34 | 0.48 | 0.63 | 4.14 | 0.47 |
| 90/10/3 | 0.09 | 0.26 | 0.32 | 1.43 | 3.54 | 0.53 | 1.60 | 4.99 | 0.63 |

where $D_E$ is the coefficient of paracetamol diffusion for the early stages of the process, while $D_L$ is the coefficient of paracetamol diffusion for longer diffusion times. From the release studies of paracetamol it has been observed that 50% of the total release occurred in 120 min at higher pH (4.5 and 6.8), while it was slower at pH = 2.2 (240 min). Both, $D_E$ and $D_L$ coefficients increase with increasing IA content and decreasing of degree of crosslinking, which lead to higher hydrophilicity and ionization of the polymer network increasing the electrostatic repulsion between the $COO^-$ ions. However, in each release medium initial diffusion coefficient was lower than late time diffusion coefficient, due to the larger degree of swelling at equilibrium.

Comparing the paracetamol release in acidic and neutral medium, the most pronounced differences was observed for sample 90/10/3. Hence, it is interesting to study the paracetamol release rate for this sample. The dependence of the migration rate on time can be determined using the derivatives of Eqs. 9 and 10. For the first stages of the release process, it can be obtained from the derivative of Fick's second law:

$$\frac{dM_t}{dt} = 2M_\infty \sqrt{\frac{D_E}{\pi \delta^2 t}} \tag{12}$$

And for longer time, the dependence of the migration rate on time can be determined using the derivative of Eq. 12:

$$\frac{dM_t}{dt} = \frac{8D_L M_\infty}{\delta^2} \exp\left[-\frac{\pi^2 D_L t}{\delta^2}\right] \tag{13}$$

The paracetamol migration rate from sample 90/10/3 is shown in Fig. 3.

As usual, the migration rate is higher at the early stage of delivery process because of a higher drug concentration gradient, which lies between inner and outer sides of the hydrogel and it decreases rapidly. The reason is that the drug concentration gradient decreased more as the migration rate became higher in the first stage. The drug migration rate is dependent of the pH of external medium, as

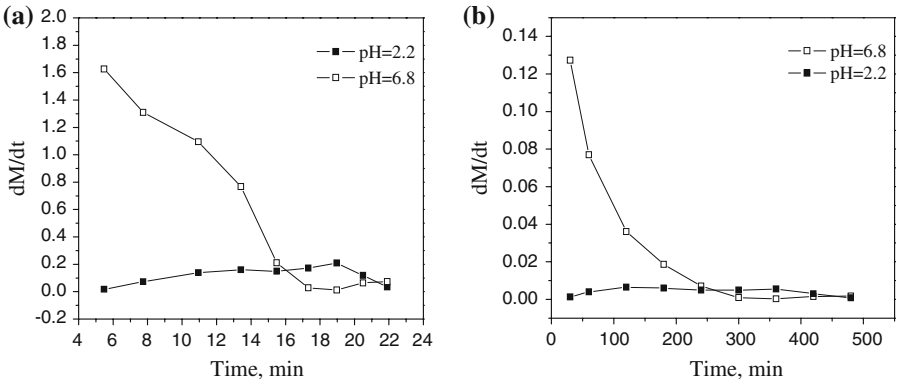


**Fig. 3** The paracetamol migration rate from sample 90/10/3: during early (**a**) and late (**b**) stages of the release process

expected. It can be observed that paracetamol release from sample 90/10/3 is slow at pH = 2.2 in both cases, early and late stage of release process. On the other hand, by increasing the pH, the migration rate increases. As it was shown in Fig. 3, the migration rate at acidic medium is very low, so practically there was no differences during time, while at neutral medium the significant differences in migration rate with time is observed. It was higher at the beginning of the release process and decreased rapidly with time.

According to the presented results the investigated PNIPAM/IA hydrogels could be used for the potential application as colon-specific drug delivery systems. As it known, the design of hydrogel-based forms depend on the route of administration. Different shapes of hydrogels for various routes of administration include spherical beads, cylinders and discs for peroral route, drum-shaped, disc-shaped and cylindrical for implants, cylinders for rectal route, cylindrical and torpedo-shaped for vaginal administration [45]. Therefore, the investigated hydrogels could be used for peroral delivery of drug, e.g. from oral capsules. In our previous paper an attempt was made to simulate the pH changes of the gastric fluids in vitro and according to the residence time in the GI tract. Hence, the swelling was monitored in pH 2.2 (the pH value of the gastric fluid) and pH 6.8 (average pH value of the intestine) [23]. Compared that results and results presented in this work, the drug release from the investigated hydrogels correspond to the real need. Hence, these hydrogels could be used for as a colon-specific delivery systems, e.g. for delivery of metoprolol tartrate, a selective $\beta_1$-adrenoreceptor blocking agent. According to our unpublished results, these hydrogels also can be used as a delivery devices for therapeutic proteins.

Owing to their pH and temperature sensitivity, they can be designed in a monophasic or pulsatile pattern. Peroral controlled delivery requires uniform drug release with an increase in pH gradient in different segments of GI tract. On the other hand, a pulsatile pattern of drug release is required in disease states exhibiting a rhythmic pattern. Brazel et al. [41] investigated hydrogels based on NIPAM and methacrylic acid as a pulsatile systems for localized delivery of heparin and streptokinase in response to pulses in temperature and pH. Due to the fact that itaconic acid can be obtained from renewable sources, it would be very interesting to make a hydrogel for that purpose where the methacrylic acid is replaced by itaconic acid.

However, clinical application of NIPAM based temperature-sensitive hydrogels have limitations since they are not biodegradable. This could be overcome by combination with biodegradable polymers such as a chitosan which is also investigated by our research group and the obtained results are submitted for publishing.

## Conclusions

The present study dealt with the swelling behaviour and paracetamol release from copolymer hydrogels of *N*-isopropylacrylamide and IA synthesized by radical crosslinking copolymerization. Swelling of the polymeric networks was affected by

the hydrogel composition and the environmental factors, such as pH and temperature of the external media. From the observation of buffer uptake in the different swelling media and from the release of paracetamol, it can be concluded that the investigated PNIPAM/IA networks are pH- and temperature-sensitive and are able to respond to the environmental changes. Therefore, they can act as targeted drug delivery devices.

Buffer uptake was favoured by increasing pH, decreasing concentration of crosslinking agent and decreasing of temperature. By applying the equilibrium swelling theory, network parameters were calculated, whereby it was shown that the investigated hydrogels were microporous. The swelling behaviour, mechanical properties, drug loading capacity and release rate can be controlled by the composition and crosslinking density of the hydrogel. PNIPAM/IA hydrogels showed slow drug release under acidic conditions and rapid release at higher pH values. This could be used for the potential application of those hydrogels as colon-specific drug delivery systems.

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