Transport of paracetamol in swellable and relaxing polyurethane nanocomposite hydrogels

Marta Miotke¹ · Justyna Strankowska¹ · Jerzy Kwela¹ · Michał Strankowski² · Marek Józefowicz¹

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Abstract

Polyurethane hydrogels are potentially attractive materials for biomedical applications. They are able to absorb large amount of water, biological fluids or active substances, and thus, they have potential to be used as absorbents or wound-healing dressings. They are also used for the controlled release of therapeutics because of their capacity to embed biologically active agents in their water-swollen network. The presence of organofillized montmorillonite (Cloisite® 30B) in polyurethane nanocomposite hydrogels remarkably improves the swelling capability, but on the other hand slows down the release process of an active substance from the matrix. The swelling of paracetamol solution by the nanocomposite matrix and the release process of this active substance from the hydrogel were investigated using gravimetric analysis and spectroscopic method. The kinetics of both these processes were accurately analyzed by the use of Korsmeyer–Peppas and modified Hopfenberg and Weibull models. In the present paper, three different nanocomposite systems with various amounts of Cloisite® 30B were studied. The results of these studies confirm beneficial impact of the nanosize effect on the drug diffusion processes in polyurethane nanocomposite hydrogels.

Introduction

Polyurethane hydrogels (PU) are elastic, non-toxic and very often biodegradable and bioresorbable substances [1–4]. Due to their ability to maintain a hydrated environment, great ability to absorb the solution, gas permeability and the ability of the polymer matrix to release active substances [5–9], hydrogels are good

✉ Justyna Strankowska
j.strankowska@ug.edu.pl

¹ Institute of Experimental Physics, Faculty of Mathematics, Physics and Informatics, University of Gdańsk, Wita Stwosza 57, 80-308 Gdańsk, Poland

² Department of Polymer Technology, Chemical Faculty, Gdańsk University of Technology, G. Narutowicza 11/12, 80-233 Gdańsk, Poland

candidates for practical application in medicine and pharmacy. In general, these hydrophilic, but water-insoluble polyurethane hydrogels are obtained by chemical cross-linking of the matrix [10] in the process of incorporation of hydrophilic soft segments, e.g., poly(ethylene glycol) (PEG) [11, 12]. It is well known that hydrogels with cross-linked structures have a higher swelling capacity and ability to slow down the release of an active substance [13] in comparison with the uncross-linked materials. The desired physical and mechanical properties of the polymers can be easily improved by adding a chain extender and a cross-linking agent [14, 15].

In our previous paper [16], we investigated the swelling and release of naproxen sodium from polyurethane nanocomposite hydrogels with two different molecular weight of PEG, doped with various amounts of nanofiller-organically modified montmorillonite with quaternary ammonium salt (Cloisite® 30B). In particular, we examined the influence of this nanofiller on the kinetics of both processes. Earlier, in papers [17, 18], the correlation between mechanical properties and their Cloisite® 30B content was studied using a standard testing machine in static mode and DMA technique (dynamic mode) the response of nanocomposites to deformation as a function of temperature was also performed. Obtained results confirmed that dynamic mechanical properties of polyurethane nanocomposites can be improved by incorporation of Cloisite® 30B and controlled by varying the montmorillonite content in these systems.

In paper [16] the X-ray diffraction technique was used to determine the structure of the PU/PEG nanocomposite materials. For nanocomposite samples PU/PEG 4000 with 0.5% and 1% admixtures of clay mineral any diffraction peaks are not observed, what proves existence of only exfoliated structure of nanocomposites, in which the individual clay layers are separated in a continuous polymer matrix. For higher concentrations of clay, a lower intensity peak is observed at an angle similar to that of Cloisite® 30B. This dependency was also observed in another paper [19].

The thermoporometry measurements by means of DSC technique have also been taken to determine the pores sizes in hydrogel nanocomposites [16]. From the solidification thermograms we obtained that in the case of PU/PEG 4000/Cloisite® 30B materials only one temperature peak was observed, what corresponds to only one size of pores. The average pore radius is 4.27 nm for PU/PEG 4000 and 4.57 nm for PU/PEG 4000 + 0.5% Cloisite® 30B. For PU/PEG 4000 + 1% Cloisite® 30B the solidification thermograms show two peaks, which correspond to two pore sizes: 6.19 nm and about 2.62–3.11 nm, wherein the half-area ratio under the curves shows that smaller pores constitute only 30% of the material. The nanoparticle addition only slightly changes the size of pores. The different porosity of both hydrogel samples leads to different behaviors of these materials in the swelling process observed in our experiments.

In our previous paper [16], we demonstrated the nanosize effect of the nanofiller on the kinetics of the swelling and release of naproxen sodium from polyurethane nanocomposite hydrogels with two different weights of poly(ethylene oxide) doped with various amount of Cloisite® 30B. It was shown that the presence of nanoparticles improves the swelling and also hinders drug diffusion from polymer matrix and consequently slows down the drug release.

As mentioned before, swelling and release are the most important processes to study in the context of possible applications of hydrogels. Depending on many factors, such as molecular weight, molecular structure and porosity, swelling is controlled by both diffusion and relaxation processes [20–22]. When the polymer is in contact with the solvent, the solvent penetrates the polymer until equilibrium is reached. The transport of solutes in swollen gel membranes is subject to two mechanisms. In the first, dissolved substances penetrate the membrane by diffusion through the solvent-filled pores. The second mechanism, relaxation processes, is related to the reaction of the polymer to the stresses imposed by attacking solvent molecules. The speed of the process determines the network's expansion in response to the solvent penetration [23]. An excellent hydrogel material can be designed after studying its behavior in contact with various environments and active substances. Taking into account above, the influence of non-specific and specific solute–solvent interactions on the investigated drug in different environments was presented in our previous studies [24].

In this article, we present a description of hydrogel swelling process and release of the active substance-paracetamol (PAR) from a hydrogel polyurethane matrix doped with Cloisite® 30B. We used the polyurethane hydrogel with the optimal proportion of polyurethane elastic segments (PU/PEG 4000) (see [16]), and we studied the influence of various admixtures of clay nanoparticles (Cloisite® 30B) on swelling and release processes. The kinetics of both these processes were also accurately analyzed. The current study verified whether the release of paracetamol and naproxen sodium by the same polymer matrices is characterized by a similar mechanism.

Materials and methods

Swelling studies in solutions containing the active substance were carried out for the following hydrogel systems:

- PU/PEG 4000/0% Cloisite® 30B (P4),
- PU/PEG 4000/0.5% Cloisite® 30B (P4+0.5%Clo),
- PU/PEG 4000/1% Cloisite® 30B (P4+1%Clo).

In the above notation PU/PEG/Cloisite® 30B (Clo) is the polymer nanocomposite (PU—polyurethane, PEG—poly(ethylene oxide)) with the molecular weight of PEG (4000 g/mol) and the corresponding percentage of the Cloisite® 30B admixture. The process of synthesis of polymer nanocomposites has been described in our previous papers [17, 18]. Paracetamol (*N*-(4-hydroxyphenyl)acetamide) (PAR) was purchased from Sigma-Aldrich Co. (Fig. 1). All of the solvents used for spectroscopic studies were of the highest grade commercially available. The experiments were carried out three times; error bars are a standard deviation of the average taken from three measurements.

Fig. 1 Absorption spectrum in deionized water and the chemical structure of paracetamol (PAR)

Swelling measurements

Swelling measurements of polymer nanocomposites were carried out at room temperature. The material was cut into cylindrical samples about 1 mm thick and 10 mm in diameter. Prior to the measurement, each dry sample of the hydrogel was weighed on a laboratory scale (RADWAG MA 50/1.R) with precision ± 0.0001 g. The sample was then placed in a test tube with 10 ml water/ethanol solvents mixture. After removal from the solution (after 3–6 min), excess solution from the surface of the samples was gently removed by means of filter paper; then, the samples were weighed. The experiment was carried out until the swelling changes in time were unnoticeable.

The swelling (S [%]) as a function of time was studied using the following ratio [25]:

$$S(t) = \frac{M_t - M_0}{M_0} \times 100\%, \quad (1)$$

where M_0 is a mass of dry hydrogel (at the initial moment of time $t = 0$), and M_t is a mass of the swollen hydrogel reached at a given time t .

In addition to swelling studies, the mass of hydrogels was examined during two consecutive processes: swelling and drying in order to obtain hydrogel swelling hysteresis. The tested hydrogels absorbed the solution to equilibrium (after about 300 min) at room temperature (25 °C) and then were dried at 37 °C temperature for the same period of time.

Release measurements

The amount of drug released from hydrogel matrix was investigated by observations of evolution in time of the UV–visible absorption spectra of paracetamol.

Steady-state absorption spectra of PAR during release from hydrogel were carried out using spectrophotometer (UV-2401 PC, Shimadzu, Japan) with the liquid samples placed in quartz cells. The scanning wavelength range was 200–400 nm. As can be seen in Fig. 1, the main absorption band of PAR in water is in the region 220–260 nm with a maximum at around 243 nm. The concentrations of an active substance in the solution were determined on the basis of the recorded absorption spectra. These observations were used to find the kinetic of the release process. Drug release studies were performed for pure PU/PEG 4000 (P4) and for two versions of nanocomposites: PU/PEG 4000 containing 0.5% Cloisite® 30B (P4+0.5%Clo) and PU/PEG 4000 with 1% Cloisite® 30B (P4+1%Clo). Hydrogel sample after 24 h of swelling in 3% PAR was placed in water, after every 3 min, the absorption spectra were recorded, and then, the concentration of the active substance in the water was determined. The measurements were taken until no changes in the absorption spectra were observed (until reaching the equilibrium state).

Absorption and release of paracetamol after 24 h—long-term observations

In these studies we also used the steady-state spectroscopic technique. The procedure began from the preparation of the reference solution: 3% paracetamol in 50% cosolvent ethanol/water (3% PAR) and registration of its absorption reference spectrum. In the next step (see Fig. 2), hydrogel samples were placed into this solution for 24 h (at room temperature). After that time, hydrogel sample was removed and the concentration of paracetamol in the solution was determined on the basis of the absorption spectrum. Comparison between obtained and reference absorption spectra of paracetamol gave us information about the quantity of an active substance which was absorbed by the hydrogel within 24 h of swelling. In the next step, we measured the release of the drug from the hydrogel samples into the water, recording the absorption spectra after 24 h of release. For all absorption measurements, the solutions were diluted to achieve a paracetamol concentration of around 10^{-4} M.

Fig. 2 Schematic presentation of the order of the release measurements: C_0 is a molar concentration of the prepared solution, $C_s^{\max}$ is a molar concentration of paracetamol in solution after 24 h of swelling, and $C(t = 24 \text{ h})$ is a molar concentration of paracetamol in the water after 24 h of the release process

Results and discussion

Swelling studies

The hydrogel swelling kinetics observed by us consist of two stages: diffusion (D) and relaxation (R). The swelling as a function of time can be represented as the sum of two contributions:

$$S(t) = S_D(t \leq t_0) + S_R(t \geq t_0), \quad (2)$$

where S_D is swelling in the first diffusion process and S_R is swelling in the second stage, after the time t_0 (in the relaxation process).

The diffusion mechanism in polymer networks can be determined by the semi-empirical equation [26, 27]:

$$S_D(t) = kt^n, \quad (3)$$

from Korsmeyer–Peppas model, where k is a diffusion rate constant that depends on the structure, shape and dimensions of the material. The diffusional exponent n in Eq. (3) defines which type of mechanism is dominant (diffusional or interfacial) [28]. According to Ritger and Peppas [30] for cylindrical samples depending on the value of the diffusional exponent n three mechanisms may occur. Value of $n = 0.45$ denotes Fickian diffusion mechanism, $n = 0.89$ shows anomalous diffusional mechanism, while $0.45 < n < 0.89$ indicates the existence of both diffusion processes [29].

For the Fickian mechanism, in the case of one-dimensional radial swelling for cylindrical samples of radius r , the swelling S_D is described by the following theoretical equation [30, 31]:

$$S_D(t) = 4 \left[\frac{Dt}{\pi r^2} \right]^{1/2} - \pi \left[\frac{Dt}{\pi r^2} \right] - \frac{\pi}{3} \left[\frac{Dt}{\pi r^2} \right]^{3/2} + \dots, \quad (4)$$

where D is constant diffusion coefficient.

The relaxation is the second mechanism of swelling following diffusion. This process can be described by the expression derived from the Hopfenberg model [32]:

$$S(t > t_0) = S_D^{\max}(t_0) + S_R^{\infty} [1 - \exp(-\kappa(t - t_0))], \quad (5)$$

where $S_D^{\max}(t_0)$ is the final swelling reached by hydrogels in the diffusion process, $t = t_0$ is the initial time for the relaxation process, S_R^{∞} is the maximal swelling which can be reached in relaxation process, and κ is relaxation rate constant. This process is related to the dissipation of stresses in the matrix caused by entry of the penetrant.

The swelling of hydrogels PU/PEG/Cloisite® 30B in 0% and 3% paracetamol solution as a function of time is presented in Fig. 3. As can be seen, hydrogels with 0.5% addition of nanoparticles swell the paracetamol solution much faster and more efficiently. A completely different form of the curve is observed for hydrogels with 1% Cloisite® 30B.

Theoretical analysis of swelling was carried out in order to determine the kinetics of the swelling processes. The experimental data were fitted by Eqs. (3) and (5). However, in the case of PU/PEG 4000 + 1% Cloisite® 30B we were not able to find

Fig. 3 Experimental swelling curves of hydrogels in (a) 0% and (b) 3% paracetamol solution compared with theory. In the case of PU/PEG 4000 + 1% Cloisite® 30B we are not able to find the best fit using the Hopfenberg model

good match between Eq. (5) (describing the second stage of swelling) and experimental points.

As can be seen in Fig. 3, the diffusion process is very rapid. It lasts less than 2500 s. The determination of diffusional parameters from Eq. (3) can be done when weight increase is of the order of 60% [33]. However, for our materials Eq. (3) is right for less than about 40–50% of mass increase; the transition point between diffusion and relaxation occurs when S equals about 120%. This is the consequence of a highly cross-linked network of hydrogel [34]. From the analysis of first sections of curves in Fig. 3, we calculated n and k parameters (see Table 1). For all tested hydrogel systems n values are bigger than 0.45. This trend is valid for materials that can swell and are able to deform and resize [35].

In the very initial phase of swelling (for the first 15–20% of the total swelling process) the swelling as a function of time can be approximated by the first term of power expansion in Eq. (4). Figure 4 presents plots of $S(t)$ versus $\sqrt{t}$ for various investigated nanocomposite materials. The linear parts, relative to $\sqrt{t}$, of the swelling curves were used to find values of diffusion coefficient D , which are contained in slopes of plotted lines (see Table 1).

It follows from Table 1 that the admixture of nanofiller speeds up the process of diffusion. However, in the case of hydrogel with 1% of Cloisite® 30B, the D value is lower than for matrices doped with 0.5% of Cloisite® 30B. Combining obtained values of these parameters with the results of pores size measurements (4.27 nm for PU/PEG 4000, 4.57 nm for PU/PEG 4000/0.5% Cloisite® 30B and 6.19 nm for PU/PEG 4000/1% Cloisite® 30B), we can confirm that the admixture of nanofiller increases the permeability. Cloisite® 30B and paracetamol promote the swelling and facilitate diffusion. However, in the case of PU/PEG 4000 with 1% admixture of nanofiller this trend is slowing down. It can be a consequence of the barrier effect, resulting from too large amount of nanoparticles in hydrogel matrix.

After the end of diffusion, relaxation in the swelling process occurs. This process takes more time than diffusion. In the theory, this process is described by Eq.

Fig. 4 Initial swelling S_D as a function of $\sqrt{t}$

Table 1 Values of parameters describing the diffusion process in hydrogels: n is diffusional exponent, k is diffusional rate constant, r is the radius of the sample, and D is coefficient of diffusion. Statistical errors are given in parentheses

Solution	0% PAR			3% PAR		
	P4	P4+0.5%Clo	P4+1%Clo	P4	P4+0.5%Clo	P4+1%Clo
n	0.57 (0.01)	0.59 (0.01)	0.57 (0.02)	0.54 (0.01)	0.54 (0.01)	0.55 (0.01)
$k [s^{-n} \times 10^{-2}]$	1.48 (0.05)	1.69 (0.16)	1.96 (0.56)	1.97 (0.08)	2.12 (0.12)	1.83 (0.03)
$r [cm]$	0.45 (0.01)	0.46 (0.01)	0.46 (0.01)	0.46 (0.01)	0.46 (0.01)	0.45 (0.01)
$D [cm^2 s^{-1} \times 10^{-5}]$	2.33 (0.02)	3.54 (0.04)	3.21 (0.03)	2.65 (0.01)	3.41 (0.02)	2.75 (0.01)

Table 2 Values of swelling parameters κ and S_∞^R for relaxation process

Solution	0% PAR		3% PAR	
	P4	P4+0.5%Clo	P4	P4+0.5%Clo
$\kappa [s^{-1} \times 10^{-4}]$	1.73 (0.14)	2.73 (0.29)	1.97 (0.05)	2.61 (0.02)
$S_\infty^R [\%]$	408	423	422	424

(5). The values of parameters κ and S_∞^R describing relaxation process obtained by fitting Eq. (5) to the experimental data are presented in Table 2, but in the case of PU/PEG 4000 + 1% Cloisite® 30B we were not able to find the best fit using the Hopfenberg model. The relaxation process is slow and depends on the structure of the hydrogels. In both solutions the κ parameter reaches higher values for nanocomposites than for pure PU/PEG 4000 hydrogel. This effect results from the presence of Cloisite® 30B plates in the polymer matrix, which expand the spaces between the polymer chains, increasing the pores size, which in turn promotes the relaxation.

As it was mentioned earlier, the perfect hydrogel material can be designed after examination of its behavior in contact with active substance of different concentration. Taking into account above we also studied swelling of hydrogels in solutions with different concentrations of paracetamol: 0%, 1%, 3% and 5%. According to Table 3, there is a significant difference in the behavior of swelling of the pure PU/PEG 4000 (P4) hydrogel compared to those with Cloisite® 30B. It can be found that for ethanol/water (0% PAR) solution the difference in swelling between pure PU/PEG 4000 hydrogel and 0.5% Cloisite® 30B nanocomposite reaches 30%. In addition, nanocomposite PU/PEG 4000 with admixture of 0.5% Cloisite® 30B reached higher values of maximum swelling than PU/PEG 4000/1% Cloisite® 30B. It suggests that 0.5% Cloisite® 30B admixture is optimal for the best swelling properties for all studied active substance concentrations.

For all hydrogel systems containing 0.5% Cloisite® 30B amounts of swelled solutions were greater than for pure polyurethane hydrogels (nanosize effect). In contrast, in the case of PU/PEG 4000/1% Cloisite® 30B values of $S_{\max}$ are significantly smaller; the barrier effect occurs. It can be stated that the transport of paracetamol is promoted in nanocomposites containing the optimal amount of the nanocomponent (0.5%). Too much Cloisite® 30B (1%) inhibits the absorption of the paracetamol solution and, on the other hand, hinders the active ingredient from remaining in the matrix. A similar effect was observed also in our previous studies with naproxen sodium [16].

Swelling hysteresis

In order to obtain more insight into the swelling and release of the active substance from polyurethane nanocomposite hydrogels hysteresis measurements were carried out. The masses of hydrogels were registered during two consecutive processes: swelling and drying (see Fig. 5) for three types of hydrogel systems: pure PU/PEG 4000, PU/PEG 4000 containing 0.5% Cloisite® 30B and PU/PEG 4000 containing 1% Cloisite® 30B. Swelling process was examined for 3% paracetamol in 50% cosolvent ethanol/water (3% PAR) solution. As it could be expected, the highest amount of the absorbed solution was observed for hydrogels containing 0.5% of the nanofiller (Table 4). The most interesting result obtained from this measurement is information about the amount of solution retained in hydrogels after drying. It is described by the residual swelling ΔS_0 [%] corresponding to initial mass increase (see Table 4). As it can be seen, amount of investigated solution retained in the matrix is greater for pure hydrogel (P4) than for hydrogels with nanofiller

Table 3 Maximal swelling values $S_{\max} = S_D^{\max} + S_{\infty}^R$ reached by hydrogels during studies of swelling in paracetamol solution

Hydrogel and solution	$S_{\max}$ [%]			
	0% PAR	1% PAR	3% PAR	5% PAR
P4	379	391	395	367
P4+0.5%Clo	409	401	409	398
P4+1%Clo	339	370	348	320

Fig. 5 Swelling hysteresis of PU/PEG 4000, PU/PEG 4000 + 0.5% Cloisite® 30B and PU/PEG 4000 + 1% Cloisite® 30B in solution (3% paracetamol in 50% cosolvent ethanol/water). The residual swellings ΔS_0 [%] after the drying process are listed in Table 4

Table 4 Maximal swelling values reached by hydrogels as well as residual swelling ΔS_0 [%] values in hysteresis measurements

Hydrogel	$S_{\max}$ [%]	ΔS_0 [%]
P4	407	45
P4+0.5%Clo	412	37
P4+1%Clo	347	13

(P4+0.5%Clo and P4+1%Clo). Considering the pores size of the tested hydrogels (4.27 nm for P4, 4.57 nm for P4+0.5%Clo, 6.19 nm for P4+1%Clo), it can be stated that in hydrogels with larger pores the amount of retained substance is lower in comparison with pure hydrogels.

Release studies

The release process can be divided into two parts: diffusion (D) and relaxation (R) [36, 37]. The molar concentration $C(t)$ of drug released into the solution during time t from the polymer matrix can be described as follows:

$$C(t) = C_D(t \leq t_0) + C_R(t \geq t_0), \quad (6)$$

where C_D is the molar concentration in the first process (associated with diffusion release) and C_R is the molar concentration in the second step (relaxation release) after the time t_0 . Molar concentration $C_D(t)$ is described by the semi-empirical equation:

$$C_D(t) = k_r t^n, \quad (7)$$

where k_r is kinetic rate and n parameter characterizing the diffusion mechanism (Korsmeyer–Peppas model) [33, 38]. The second process is described by the following equation:

$$C_R(t) = C_\infty \left[1 - \frac{8}{\pi^2} \exp(-Ft) \right], \quad (8)$$

where F is directly proportional to the diffusion coefficient D [38, 39].

Alternatively, both these processes of release can be described by the empirical Weibull function [40, 41]:

$$C(t) = C_\infty [1 - \exp(-at^b)], \quad (9)$$

which covers the entire drug release process. Weibull function is described by a and b parameters; a is kinetic parameter, and b gives information about the type of diffusion mechanism. The b value in the range of $0.35 \div 0.75$ means the diffusion-dominated drug release process, and b value in the range $0.75 \div 1.0$ indicates a combined diffusion and relaxation mechanism [43, 44].

In order to determine the amount of drug (paracetamol) released from the hydrogel matrix, we studied changes in absorption spectra in the UV range as a function of time. The paracetamol absorption spectra recorded during the release process are shown in Fig. 6. As can be seen, the paracetamol dye dissolved in water possesses intensive absorption band with maximum at around 243 nm. As

Fig. 6 Changes in absorption spectra of paracetamol during release from PU/PEG 4000 hydrogel: **a** in room temperature (23 °C) and **b** in 37 °C

Fig. 7 Changes in molar concentration of drug released from PU/PEG hydrogels: **a** in room temperature (23 °C) and **b** in 37 °C. The experimental data were fitted by Weibull function (Eq. 9)

Table 5 Values of parameters describing the release process for studied hydrogel systems obtained by fitting Eqs. (7) and (8) (Korsmeyer–Peppas model) to two stages of release

Temperature	23 °C			37 °C		
Hydrogel	P4	P4+0.5% Clo	P4+1% Clo	P4	P4+0.5% Clo	P4+1% Clo
$k_r(s^{-n} \times 10^{-6})$	0.26 (0.03)	0.69 (0.09)	0.46 (0.03)	1.47 (0.20)	0.84 (0.15)	0.34 (0.03)
n	0.87 (0.03)	0.68 (0.02)	0.69 (0.03)	0.62 (0.01)	0.63 (0.05)	0.78 (0.01)
$F(s^{-1} \times 10^{-4})$	2.41 (0.06)	2.79 (0.10)	4.37 (0.13)	3.87 (0.09)	5.14 (0.08)	5.77 (0.01)

mentioned earlier, the molar concentrations of paracetamol in solution were calculated from the recorded absorption profiles, comparing the obtained and reference spectra of paracetamol absorption in water (see Fig. 1). In order to clarify the release process of paracetamol from hydrogels, steady-state absorption spectra were measured at two temperatures: 23 °C and in 37 °C (see Figs. 6 and 7). The main conclusion that can be made comparing the figures suggests that the increase in temperature generally speeds up the release process.

The results of spectroscopic measurements were analyzed using models of Korsmeyer–Peppas and Weibull. As it was shown in many papers [27–29], formula (7) is valid for 60% of the drug release. In our case, the fitting procedure shows that we can use Eq. (7) for only 40%. Using the experimental data presented in Fig. 7, the values of n and k_r parameters have been determined and are presented in Table 5. Analyzing the data in the table it is evident that:

- The n values, calculated using Eq. (7), change from 0.68 to 0.87 (at 23 °C) and from 0.62 to 0.78 (at 37 °C), which indicates that in the all studied systems paracetamol is released by anomalous diffusion. (Effects of drug diffusion and relaxation are comparable.)
- The increase of temperature results in the increase the kinetic constant k_r . This behavior clearly confirms that diffusion is faster at higher temperature. Deviation from this regularity was observed for nanocomposite with 1% Cloisite®

Table 6 Parameters derived for the Weibull model of release

Temperature	23 °C			37 °C		
Hydrogel	P4	P4+0.5% Clo	P4+1% Clo	P4	P4+0.5% Clo	P4+1% Clo
$a (s^{-b} \times 10^{-4})$	2.68 (0.08)	3.36 (0.02)	4.75 (0.01)	4.75 (0.02)	6.61 (0.02)	5.19 (0.03)
b	0.82 (0.02)	0.75 (0.01)	0.85 (0.03)	0.80 (0.01)	0.88 (0.01)	0.96 (0.02)

30B. This finding is understandable in terms of barrier effect described in [42].

- Parameter F increases with the increase in temperature. This behavior is expected taking into account fact that parameter F is directly proportional to the diffusion coefficient D .
- The values of the F parameter increase with the larger amount of nanoparticles in the matrix.

In our studies we have also used the semi-empirical description of the whole release process proposed by Weibull. In this model we have two a and b free fitting parameters. The experimental data (presented in Fig. 7) were fitted to Eq. (9). (The fit is perfect, and the average value of parameter r equals $r = 0.98 \pm 0.02$.) The values of the fitted parameters: a and b , are collected in Table 6. The b values fall in the range 0.75–0.96. This indicates a combination of both diffusion and relaxation mechanisms [43, 44].

Long-term observations of swelling and release processes

In order to study the swelling and release processes in the long-term observations we used the steady-state spectroscopic technique. We registered changes in the absorption spectra of an active substance in the studied solution after long-term swelling and release by hydrogels. To analyze quantitatively the both investigated processes, the registered spectra were compared with the reference spectrum (Table 7).

The concentration of the reference solution (paracetamol dissolved in 50% cosolvent ethanol/water) was 1.9×10^{-2} M, what corresponds to 3×10^{21} paracetamol molecules in 25 ml solution. The reference spectrum is presented in Fig. 8a for comparison. In the long-term measurements hydrogel samples were placed into the same volume of solution (25 ml) for 24 h. After this time, the samples were removed and absorption spectra of all solutions were registered. It is important to note that for the steady-state spectroscopic measurements all solutions were diluted to obtain paracetamol concentration about 10^{-4} M. Analyzing the maxima of the absorption bands presented in Fig. 8a, one can state that hydrogels without nanoparticles, as well as those with 0.5% Cloisite® 30B, can absorb about 43% of paracetamol molecules from the solution, whereas hydrogels with 1% Cloisite® 30B absorb much lower number of paracetamol molecules (about 33%). Difference between amount of paracetamol molecules absorbed by pure hydrogel and nanocomposites can be a consequence of possible repulsive interaction between Cloisite® 30B and paracetamol

Fig. 8 **a** Absorption spectra of paracetamol in ethanol/water solution after 24 h of swelling by different nanocomposite hydrogels. **b** Absorption spectra of paracetamol after 24 h of release into the water from various nanocomposite hydrogels. Solid lines present the reference absorption profiles

Table 7 Values of maxima $A^{\max}$ of the main absorption bands and the percentage amount of particles N (%) absorbed by hydrogels from solution

Process	Swelling		
Hydrogel	P4	P4+0.5% Clo	P4+1% Clo
$A^{\max}$ (arb. units)	1.3734	1.3588	1.6043
N (%)	42.7	43.5	33.0

Table 8 Values of maxima of the main absorption bands $A^{\max}$, the amount of paracetamol (PAR) particles absorbed by the hydrogels N_0 , the amount of PAR particles released to the water after 24 h of release N_s and the relative percentage of particles released from different hydrogels N_r (%)

Process	Release		
Hydrogel	P4	P4+0.5% Clo	P4+1% Clo
$N_0 \times 10^{19}$	130	131	100
$A^{\max}$ (arb. units)	0.571	0.441	0.322
$N_s \times 10^{19}$	1.34	1.03	0.75
$N_r(\%)$	1.03	0.79	0.75

(see [45]) considering that nanocomposites have a bigger swelling capacity what has been presented in “Swelling studies” section.

In order to determine the amount of drug (paracetamol) released into the water (after 24 h) from the hydrogel matrix, we also prepared the reference solution (the solid line in Fig. 8b). From recorded absorption profiles the molar concentrations of paracetamol in solution have been computed. In this case, the reference solution of paracetamol was 3.93×10^{-5} M, what corresponds to 1.19×10^{19} paracetamol molecules in 500 ml of water. Taking into account the amount of active substance molecules absorbed by hydrogels in the swelling process N_0 (see Table 8), we can

estimate the amount of molecules released to water N_s . From our calculations, it is clear that $< 1\%$ of absorbed molecules of paracetamol is released into the water from hydrogel matrices after 24 h (N_r). It can be also stated that the amount of paracetamol released from nanocomposites is lower than from pure hydrogels (nano-size effect). Similar behavior was observed for enoxaparin sodium substance [46]. The observed decrease in permeability caused by the polymer–clay nanocomposite structure is caused by the slowed diffusion caused by the clay presence [47]. This effect inhibits the transport of paracetamol from the hydrogel matrix during release.

Conclusions

In the present paper, we examined polyurethane nanocomposite hydrogels doped with various amount of organically modified nanofiller—Cloisite® 30B. In particular, we investigated the influence of Cloisite® 30B on the swelling and release processes.

We found that the presence of nanoparticles speeds up the swelling process. However, excessive amount of nanoparticles may produce the barrier effect—too large amount of nanoparticles can hamper the swelling process. From the studies of the release process, it is obvious that the presence of nanoparticles impedes the diffusion from the polymer matrix and accordingly slows the release of the drug. In long-term observations we noticed that paracetamol (PAR) molecules easier release from nanocomposites than from a pure hydrogel matrix, and that nanocomposites can absorb more PAR molecules from the solution than pure hydrogel.

From the point of view of possible applications of the tested hydrogel material, the influence of the nanofiller on both processes (swelling and release) is beneficial.

We also performed an accurate theoretical analysis of swelling and release processes, and we determined the values of parameters describing them in different theoretical and semi-empirical models.

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