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Nanosize effect of clay mineral nanoparticles on the drug diffusion processes in polyurethane nanocomposite hydrogels

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Abstract. Studies of swelling and release of naproxen sodium (NAP) solution by polyurethane nanocomposite hydrogels containing Cloisite® 30B (organically modified montmorillonite (OMMT)) have been performed. Polyurethane nanocomposite hydrogels are hybrid, nontoxic biomaterials with unique swelling and release properties in comparison with unmodified hydrogels. These features enable to use nanocomposite hydrogels as a modern wound dressing. The presence of nanoparticles significantly improves the swelling. On the other hand, their presence hinders drug diffusion from polymer matrix and consequently causes delay of the drug release. The kinetics of swelling and release were carefully analyzed using the Korsmeyer-Peppas and the modified Hopfenberg models. The models were fitted to precise experimental data allowing accurate quantitative and qualitative analysis. We observed that 0.5% admixture of nanoparticles (Cloisite® 30B) is the best concentration for hydrogel swelling properties. The release process was studied using fluorescence excitation spectra of NAP. Furthermore, we studied swelling hysteresis; polymer chains have not been destroyed after the swelling and part of swelled solution with active substances which remained absorbed in the polymer matrix after the drying process. We have found that the amount of solution with NAP remained in the nanocomposite matrix is greater than in pure hydrogel, as a consequence of NAP-OMMT interactions (nanosize effect).

1 Introduction

In recent years many materials were investigated in order to find the best dressing facilitating wound healing. The main goal is to obtain the optimal moist microenvironment for the wound [1]. A good moisture between the wound and the dressing is possible by an appropriate selection of materials [2], so it is very important to understand their behaviour in the swelling and release processes. Wound dressing should absorb the excess exudate and toxins and should be permeable for oxygen [3]. A drug release ability is also an expected property.

Polyurethane hydrogels are good candidates for wound dressings due to their ability to maintain environment hydrated, to absorb the solution, permeability for gases and ability of the polymer matrix to release active substances [4–6]. They are elastic, non-toxic, and many of them are biodegradable and bioresorbable [7].

The group of hydrogels with crosslinked structures shows higher swelling capacity [8] and a slow-releasing ability of the active substance. Desired physical and mechanical properties of polymers are easy to enhance by adding chain extender [9] and crosslinker. In general, these hydrophilic, but water-insoluble polyurethane hydrogels are obtained by chemical crosslinking of the matrix [10] in the process of incorporation of hydrophilic soft segments, *e.g.* poly(ethylene glycol) (PEG) [11]. Hydrogels based on PU/PEG networks can be used as controlled release materials in many biomedical applications [12].

Nanocomposites consisting of polymer and organically modified montmorillonite (OMMT) nanoparticles are the most common group [13]. Hydrogels containing silicate nanoparticels exhibit considerable barrier properties in the

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diffusion process; small molecules of drug detained in hydrogel network have to move through the crosslinked material with silicate nanoparticles plates. On the other hand, the nanosize effect slows down the drug release from the matrix [14,15]. In addition the size of nanoparticles can be strictly connected with drug release kinetics from the wound dressing material [16]. Interfacial properties are very meaningful in explaining the overall properties of nanocomposite materials especially their mechanical and swelling properties [17].

Swelling and release are the most important properties to study in the contest of hydrogel applications. Depending on many factors, including molecular structure, porosity, and molecular weight, the swelling is controlled by both diffusion and relaxation phenomena. Typical kinetics of swelling in hydrogels consist of three stages: the first phase is the wetting dry solid hydrogels by solution; the second is the very rapid water diffusion into the hydrogel and the third phase is equilibrium swelling after complete relaxation of polymer chains [18]. The main physical process which controls the drug release from polymer dressing is diffusion [19]. A perfect hydrogel material can be designed after examination of its behavior in contact with different environments and active substances.

A series of structural, mechanical and molecular dynamics studies of a new class of hybrid materials, *i.e.* polyurethane nanocomposite hydrogels, containing sodium montmorillonite (Cloisite® 30B) clay mineral modified with a quaternary ammonium salt (OMMT), were presented in our previous papers [20,21]. Polyurethane nanocomposites were synthesized using chainextender (butane-1,4-diol) and crosslinkers (1,2,3-propanetriol and triethanolamine). We investigated the structure of nanocomposite systems by using the X-ray diffraction method [20,21]. The nanofiller possesses a strong maximum with d-spacing equal to 1.96 nm. The absence of diffraction maximum was observed for systems with lower clay content (about 1 wt.%) and indicates successful exfoliation of the clay in these systems. For higher concentrations of clay, a lower intensity peak is observed at an angle similar to that of OMMT. This dependence was also observed in another paper [22].

The correlation between mechanical properties and their Cloisite® 30B content were studied using a standard testing machine, in static mode, and the DMA technique (dynamic mode). The measurement of the response of nanocomposites to deformation as a function of temperature was also performed. The storage modulus (E') analysis indicates that the process of polyurethane segments softening begins at about 60 °C. The obtained results confirmed that the dynamic mechanical properties of polyurethane nanocomposites can be improved by incorporation of Cloisite® 30B and can be controlled by varying the montmorillonite content in these systems [20,21].

Tensile stress of nanocomposite systems was improved in comparison with the unmodified polyurethanes matrix [20, 21]. Molecular dynamics was studied by means of the NMR spectroscopy, DMA and DSC analysis. Polyurethane chains mobility in nanocomposite systems depends on the montmorillonite content in polymeric materials. The nanosize effect of clay mineral nanoparticles were recognized in the studied samples [20]. In paper [21] our preliminary swelling studies of polyurethane nanocomposite hydrogels confirmed improving the influence of montmorillonite platelets content (1.3 wt.%) on swelling parameters.

In the present paper we report the swelling and release properties of these new hybrid materials, *i.e., a* polyurethane hydrogel matrix doped with Cloisite® 30B in contact with active substance, naproxen sodium (NAP). Our goal was to investigate these materials for their potential application as a wound dressing material. We examined the influence of different admixtures of clay nanoparticles (Cloisite® 30B) for swelling and release parameters and the influence of the contribution of polyurethane elastic segments on relaxation time. The kinetics of swelling and release were also carefully analyzed.

2 Materials and methods

The studies of swelling in solutions containing active substances were performed 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 6000/0% Cloisite® 30B (P6);
- PU/PEG 6000/0.5% Cloisite® 30B (P6+0.5%Clo);
- PU/PEG 6000/1% Cloisite® 30B (P6+1%Clo).

In this notation, PU/PEG/Cloisite® 30B is a polymer nanocomposite (PU – polyurethane, PEG – poly(ethylene oxide)) with the molecular weight of PEG (4000 g/mol or 6000 g/mol). The process of synthesis of polymer nanocomposites was described in our previous papers [20, 21]. The organically modified, with a quaternary ammonium salt montmorillonite, Cloisite® 30B (purchased from Southern Clay Products Inc. Texas, USA) was dispersed in the polymer matrix. Cloisite® 30B was dried for 6 h at temperature 90 °C in a thermal vacuum chamber. PEG was dried in a vacuum oven (under lower pressure) at 90 °C for 30 minutes before use. The 4,4′-methylenebis(cyclohexyl isocyanate) (HDMI), triethanolamine (T), acetone were used without purification. All these materials were purchased from Sigma-Aldrich Co.

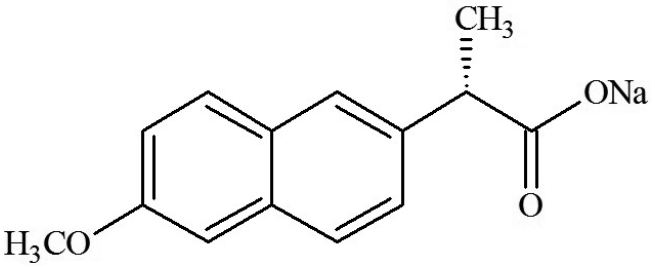

Fig. 1. Chemical structure of naproxen sodium (NAP).

The nanocomponent (Cloisite® 30B) was present in matrices in the following concentrations: 0%, 0.5%, 1%. The Cloisite® 30B was first dispersed in a PEG/acetone solution using a homogenizer (8000 r.p.m., 15 min), then a low molecular weight crosslinker, triethanolamine (T), was added. Finally, the right amount of diisocyanate (HMDI) was dispersed in the mixture and it was stirred at 80 °C for 1 min. The nanocomposites were poured into poly(tetrafluoroethylene) mould and kept at 40–50 °C for 24 h to finish reaction and evaporation of acetone.

The solution consists of ethyl alcohol (99.9%, P.P.H. "STANLAB") and naproxen sodium (Sigma-Aldrich Co.) (fig. 1). The hydrogel system was examined at concentrations of ethanol: 0%, 1%, 5%, 10% and 50% and naproxen sodium: 0%, 1%, 3% and 5%.

The measurements of our hydrogel polymer nanocomposites swelling were carried out at room temperature. After synthesis, the material was cut into samples having a thickness of about 1 mm and diameter of 10 mm. In the first step, 1%, 5%, 10% and 50% ethanol/water solutions were prepared. Next, solutions with naproxen sodium were made.

Before carrying out measurement, each dry hydrogel sample was weighed on a laboratory scale AS 110/C/2 (RADWAG) with precision ±0.0001 g. Using a micrometer screw the sample thickness was measured. Then the sample was placed in a test-tube with 5 ml solution. After each 6 minutes, the sample was removed from the solution, filtered with a paper towel to remove surface water and weighted. The experiment was continued until the plateau in swelling/time dependency has been obtained.

The swelling properties of samples in water and combinations of water/ethanol/naproxen solutions were measured at regular intervals by weighting their water mass gain until reaching equilibrium state. The swelling (S [%]) of hydrogels in our measurements was determined by the ratio [23]

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

where M_0 is the mass of the dry hydrogel at initial time $t = 0$, M_t is the mass of the swollen hydrogel reached in given time t.

The swelling can be also determined in a different form by the ratio M_t/M_∞, where M_∞ is the mass of hydrogel in equilibrium state (see, *e.g.* [24]),

$$S'(t) = \frac{M_t}{M_\infty}, \tag{2}$$

instead of the percentage of mass absorbed in time t. In this equation, M_t/M_∞ represents the fractional uptake of solvent (or release of a solute) normalized with respect to the equilibrium conditions.

Besides the swelling studies, the mass of hydrogels was examined during three consecutive processes: swelling, drying in laboratory oven and subsequent swelling in the same solution. In this way we obtained hydrogel swelling hysteresis. For drying we used a Memmert GH+Co.KG oven, model UNE 200. Examined hydrogels swelled the solution to equilibrium state (after about 300 minutes), and next have been dried at 37 °C for the same period of time and, again, inserted into the solution for the second swelling.

The drug amount released from hydrogel matrix was investigated through changes in the UV-visible absorption and/or fluorescence excitation spectra with time (Shimadzu UV-2401 PC spectrophotometer and Shimadzu RF-3501FC spectrofluorometer). It was shown in our previous paper [25] that the shape and the position of the fluorescence excitation spectrum is quite similar to the absorption spectrum. The observed behavior indicates the existence of the same spatial conformations of NAP in the ground and excited states, which leads to estimate the amount of NAP molecules in the solution.

Drug release studies were conducted for two types of hydrogel systems: pure PU/PEG 4000 (P4) and PU/PEG 4000 containing 0.5% Cloisite® 30B (P4+0.5%Clo). The procedure started from preparation the reference solution: 3% naproxen sodium in 50% cosolvent ethanol+water (3% NAP). Release measurements were carried out in two steps (see fig. 2). In the first step, hydrogels samples were placed in a 25 ml solution for 24 h and fluorescence excitation spectra of NAP in each solution after swelling were registered. In the second step, we measured the release of drug from hydrogel samples to the water registering absorbance changes in the main absorption band ($S_0 \rightarrow S_3$ transition) of NAP in the region 230 nm. For the absorption measurements all these solutions were diluted to obtain NAP concentration on the level of about 10^{-6} M.

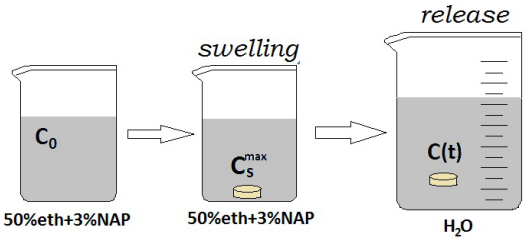

Fig. 2. Schematic presentation of performed by us measurements of release. C_0 is a molar concentration of the prepared solution, whereas $C_s^{\max}$ is a molar concentration of NAP in solution after 24 h of swelling and $C(t)$ is molar concentration of NAP during release process.

We also conducted two complementary measurements of the structure of our materials that explain their behavior in the process of swelling in the solution. The X-ray diffraction technique was used to determine the type of nanoparticle dispersion in the hydrogel matrix, and the thermoporymetry measurements by means of the DSC technique to determine the pores sizes in hydrogel nanocomposites.

The XRD measurements were performed using a Bragg-Brentano X'PERT PHILIPS diffractometer, equipped with a Cu anode X-ray tube and diffracted beam monochromator (40 kV, 30 mA, $\lambda(K_\alpha) = 0.1542$ nm). Hydrogel samples were scanned over the 2θ angle from 2° to 10° at room temperature.

Thermoporometry measurements were carried out on DSC-204 F1 Phoenix Instrument (Netzsch, Germany) under a nitrogen atmosphere. The samples of about 22–23 mg were put in aluminium pans. The heating or cooling took place gradually step by step (the step length was 0.5 °C/min) in order to maintain thermodynamic equilibrium. Care was taken to avoid the undercooling effect by using the following procedure: the sample was first cooled below the freezing temperature of the pure liquid to −60 °C and then heated up and kept isothermally at −0.3 °C below the normal freezing temperature for 10 min. Then, the samples were cooled down to −25 °C.

3 Results and discussion

3.1 Swelling studies

3.1.1 Description of the swelling process

Observed by us kinetics of swelling of hydrogels consists of two stages: diffusion and relaxation. As a function of time, the swelling described by eq. (1) can be represented as a sum of two independent contributions:

$$S(t) = S_D(t \leq t_0) + S_R(t \geq t_0), \tag{3}$$

where S_D is swelling in the first process (diffusion) and S_R is swelling in second stage, after the time t_0 (relaxation) [26].

The mechanism of diffusion in polymeric networks is determined by the following equation [27]:

$$S_D(t) = kt^n, \tag{4}$$

resulting from the Kosmayer-Peppas model [28], where k is the expansion rate constant and depends on structure, shape and dimensions of the material. The diffusional exponent n in eq. (4) determines what kind of mechanism is prevailing (diffusional or interfacial) [29]. The value of $n = 0.50$ means the Fickian water diffusion mechanism, whereas $n = 1.0$ indicates Case II of the diffusional mechanism. For $0.50 < n < 1.0$ the process can be described as anomalous and both diffusion processes control the general amount of solution uptake [30].

Polymer behavior in contact with the solution in the diffusion process can be characterized by the diffusion coefficient D. In the case of one-dimensional radial swelling for cylindrical samples of radius L swelling S_D can be presented in a series of terms containing different powers of the D coefficient [31, 32]:

$$S_D(t) = 4\left[\frac{Dt}{\pi L^2}\right]^{1/2} - \pi\left[\frac{Dt}{\pi L^2}\right] - \frac{\pi}{3}\left[\frac{Dt}{\pi L^2}\right]^{3/2} + \dots . \tag{5}$$

This equation comes from the short-time approximation method.

Equation (4) works only for the initial swelling process, *i.e.* up to 60% of the mass increase of hydrogels [33]. We notice that, in our case, for all hydrogels the diffusion ends faster after about 30–50% its mass increase; the transition point between diffusion and relaxation occurs when S equals about 130%.

The second mechanism of the swelling process is relaxation. This process is related to the dissipation of swelling stresses caused by entry of the active substance from solution. It produces a slow redistribution of free volume through

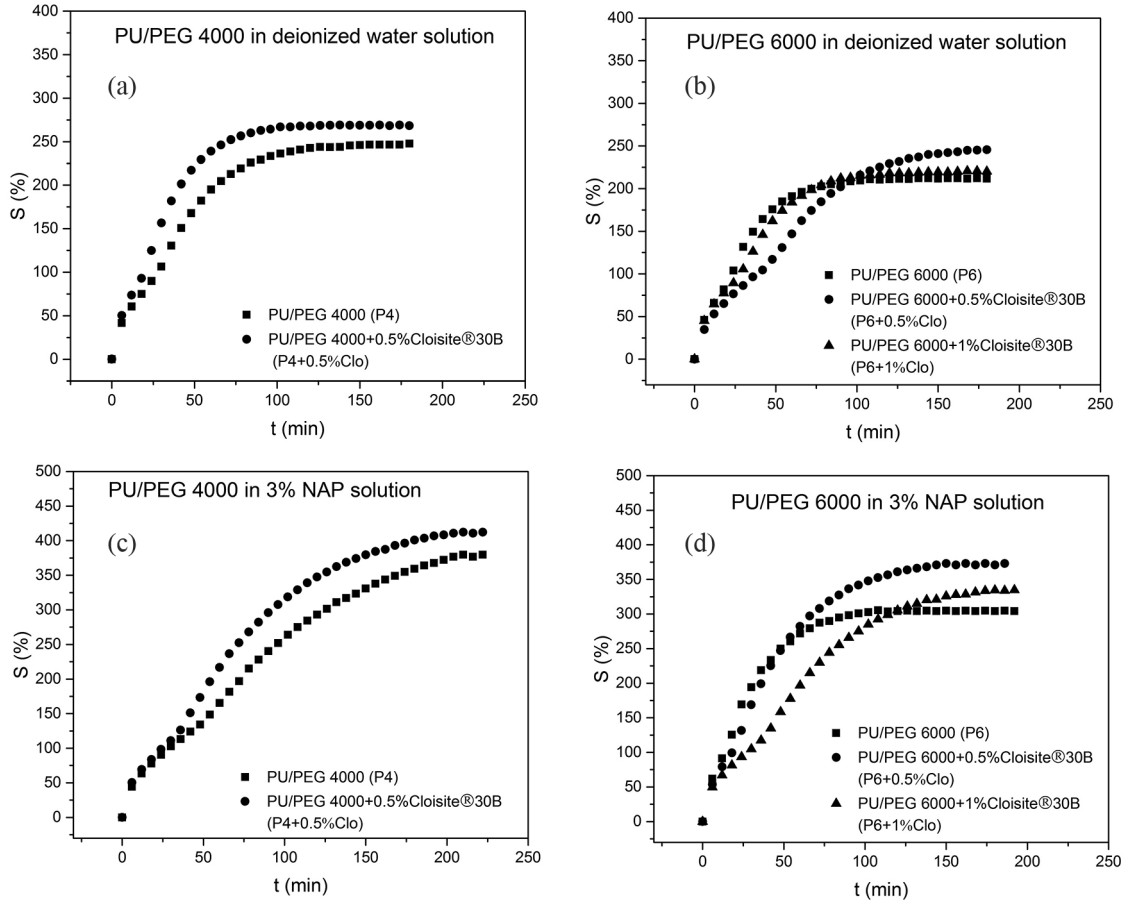

Fig. 3. Comparison between swelling curves of nanocomposite hydrogels in deionized water and 3% naproxen sodium in 50% cosolvent ethanol+water solutions (values of swelling were obtained from eq. (1)).

Table 1. Masses of dry (M_0) and swelled (M_∞) hydrogels and maximum values of swelling $S_{\max}$ in the water solution.

Hydrogel	P4	P4+0.5%Clo	P6	P6+0.5%Clo	P6+1%Clo
M_0 $[g]$	0.090	0.075	0.078	0.115	0.096
M_∞ $[g]$	0.311	0.275	0.244	0.397	0.308
$S_{\max}$ [%]	245	267	213	245	221

relatively large-scale segment motions in the relaxing polymer. In this process the mass changes are described by the following equation:

$$M_{t,R} = M_{\infty,R}\left[1 - \exp(-\kappa t)\right], \tag{6}$$

resulting from the modified Hopfenberg model [26], where $M_{t,R}$ and $M_{\infty,R}$ are masses of the sample at times t and $t = \infty$ (equilibrium state), respectively. The relaxation rate κ depends on the structure of hydrogels.

Swelling of hydrogels S after diffusion process can be described by the following expression:

$$S(t > t_0) = S_D^{\max}(t_0) + S_\infty^R\left[1 - \exp\left(-\kappa(t - t_0)\right)\right], \tag{7}$$

where $S_D^{\max}(t_0)$ is the final swelling achieved by hydrogels in the process of diffusion, $t = t_0$ is the starting point for the relaxation process, S_∞^R is the maximal swelling which can be reached in the relaxation process.

3.1.2 Experimental results

The influence of the nanocomponent. The swelling of PU/PEG/Cloisite® 30B hydrogels in the water solution as a function of time are presented in figs. 3(a) and (b). Masses of investigated samples and maximum values of swelling were collected in table 1.

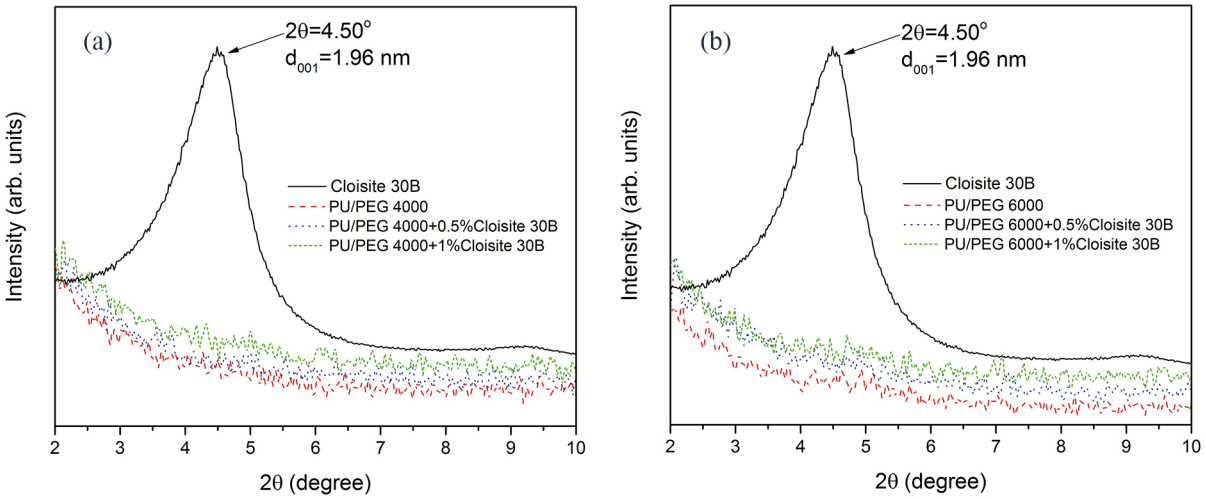

Fig. 4. The XRD-diffraction patterns for Cloisite® 30B and polyurethane nanocomposites.

For all hydrogel systems containing Cloisite® 30B the amounts of swelled solutions were greater than for pure polyurethanes. The exception is for the P6+1%Clo hydrogel. The values of swelling reached by this hydrogel are very similar to those of the hydrogel without nanoparticles (P6). This effect is called the barrier effect, where an overwhelming amount of nanoparticles inhibits the diffusion process. The highest value 267% of water swelling was obtained by PU/PEG 4000 containing 0.5% Cloisite® 30B. The difference in swelling between pure PU/PEG 4000 hydrogel and with admixture of 0.5% nanocomponent is 22%. Similarly, the difference between pure PU/PEG 6000 and with 0.5% Cloisite® 30B is 32%. The nanocomposite of PU/PEG 6000 with admixture of 0.5% Cloisite® 30B reached greater values of maximum swelling than that with admixture of 1% Cloisite® 30B. It suggests that the 0.5% Cloisite® 30B concentration is optimal for the best swelling properties.

We can state that the presence of Cloisite® 30B in the polymer matrix improves hydrogel swelling. All maximum swelling values for hydrogels with nanoparticles are greater than those observed for pure hydrogels. That dependency can be the result of the presence in the polymer matrix of the plates of Cloisite® 30B, which increases free volumes and, in addition, swells the water. However, the excessive amount of Cloisite® 30B aggregates may entail barrier effect in swelling. This occurrence takes place for PU/PEG 6000 with 1% Cloisite® 30B.

Measurement of the relative amount of intercalated and exfoliated form of Cloisite® 30B in the matrix. The X-ray diffraction technique was used to determine the structure of the PU/PEG nanocomposite materials. Figure 4 shows the XRD diffractograms recorded for hydrogel nanocomposite samples with clay mineral and pure Cloisite® 30B in dry states. The nanofiller Cloisite® 30B has a strong diffraction maximum with d-spacing equal to 1.96 nm. For nanocomposite samples PU/PEG 4000, PU/PEG 6000 with 0.5% and 1% admixtures of clay mineral (figs. 4(a) and (b), respectively) any diffraction peaks are observed, what proves the existence of only exfoliated structure of nanocomposites, in which the individual clay layers are separated in a continuous polymer matrix [34].

Determination of the pores size in polyurethane nanocomposite hydrogels by means of DSC measurements: thermoporometry. The thermoporymetry measurements by means of the DSC technique to determine the pores sizes in hydrogel nanocomposites have been conducted. Thermoporometry is a technique to study the porous materials filled with fluid [35]. This method is based on the thermodynamic relationship between the pore size and the solidification temperature of freezable fluid in pores. Figure 5 shows a typical thermograms recorded for hydrogel saturated with water. Temperature peaks corresponding to solidification of water inside the mesopores are detected between −11 °C and −25 °C. The mesopore size calculations were made from these latter exothermal peaks T_s using the formula

$$R_p = -\frac{64.67}{\Delta T} + 0.57, \tag{8}$$

where $\Delta T = T_s - T_0$ and T_0 is the water triple point temperature [35, 36].

From the solidification thermograms we see that in the case of PU/PEG 4000 materials we observed only one temperature peak, which corresponds to only one size of the pores. The average pore radii obtained from eq. (8) varies slightly from 4.27 nm for PU/PEG 4000 to 4.57 nm for PU/PEG 4000+0.5% Cloisite® 30B (see table 2). The nanoparticle addition only slightly changes the size of pores.

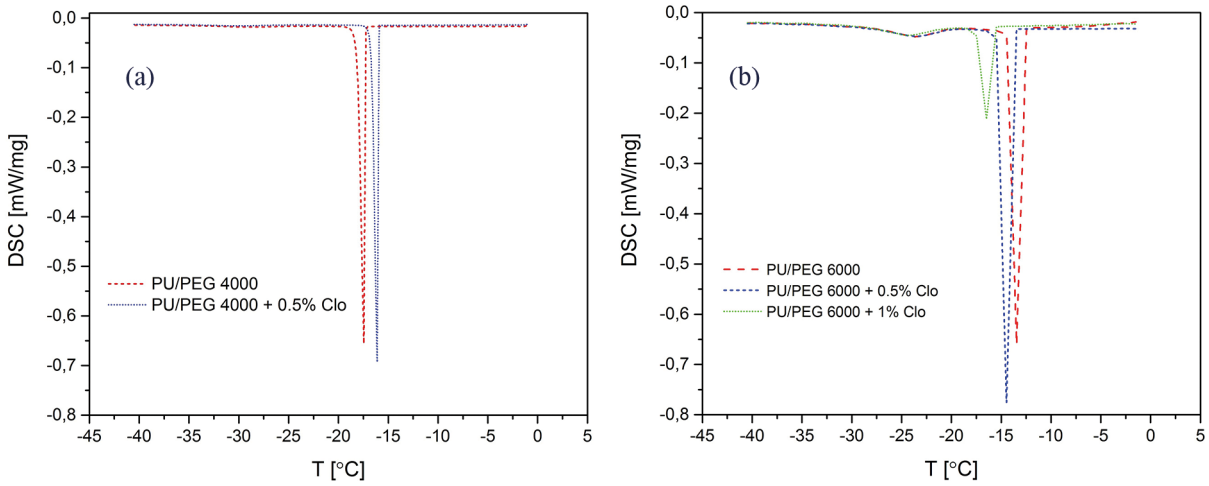

Fig. 5. Solidification thermograms of the water contained in PU/PEG hydrogels.

Table 2. Pore radii R_p obtained from solidification temperature peaks T_s for PU/PEG nanocomposite hydrogels.

Hydrogel	T_s [K]		R_p [nm]	
P4	255.70		4.27	
P4+0.5% Clo	265.98		4.57	
Hydrogel	T_{s1} [K]	T_{s2} [K]	R_{p1} [nm]	R_{p2} [nm]
P6	259.74	249.75	5.39	3.33
P6+0.5% Clo	258.70	249.75	5.04	3.33
P6+1% Clo	256.62	248.70	4.48	3.21

Table 3. Masses of dry (M_0) and swelled (M_∞) hydrogels and maximum swelling values, $S_{\max}$, in the 3% NAP solution.

Hydrogel	P4	P4+0.5%Clo	P6	P6+0.5%Clo	P6+1%Clo
M_0 [g]	0.087	0.080	0.052	0.058	0.085
M_∞ [g]	0.416	0.409	0.209	0.274	0.374
$S_{\max}$ [%]	378	411	302	372	340

For PU/PEG 6000 samples two peaks were obtained from the solidification thermograms. This corresponds to two pore sizes: 5.39 nm and 3.33 nm in the case of pure PU/PEG 6000. In addition, we notice that as the amount of nanocomponents increases, the pore size decreases. Thus, the samples PU/PEG 6000 show a completely different pore structure relative to the PU/PEG 4000 samples.

The different porosity of both hydrogel samples leads to different behaviors of these materials in the swelling process observed in our experiments and described in sect. 3.1.3.

Hydrogels in the naproxen solution. We also studied swelling of our hydrogel systems in the naproxen solution. We found that the best combination of active substances in solution in respect of swelling is 3% naproxen sodium in 50% cosolvent ethanol+water (3% NAP). Results of this experiment are presented in this section.

Figures 3(c) and (d) present the swelling curves for all examined hydrogel systems and table 3 shows masses of dry and swollen hydrogels and maximum swelling values of hydrogels in 50% ethanol and 3% naproxen sodium solution.

We can see that the presence of nanocomponent improves the swelling, however it should be noticed that in all solutions the excessive amount of nanocomponent does not increase the swelling. It occurs for PU/PEG 6000 with 1% Cloisite® 30B; the $S_{\max}$ swelling of PU/PEG 6000 with 0.5% Cloisite® 30B reaches higher values.

Active substances improve swelling of hydrogels. It can be state that in ethanol solution solubility of naproxen sodium and its penetration in the polymer network is better. The best swelling properties have PU/PEG 4000 matrix with 0.5% Cloisite® 30B in 3% NAP solution and this system has been selected for further studies of swelling parameters and swelling hysteresis.

Table 4. Maximal swelling reached by hydrogels in diffusion process $S_D^{\max}$ and the percentage increase of hydrogel masses after diffusion process ($M_t^{\max}/M_0$).

Hydrogel	P4	P4+0.5%Clo	P6	P6+0.5%Clo	P6+1%Clo
$S_D^{\max}$ [%]	149	127	126	99	117
$M_t^{\max}/M_0$ [%]	35	31	41	27	35

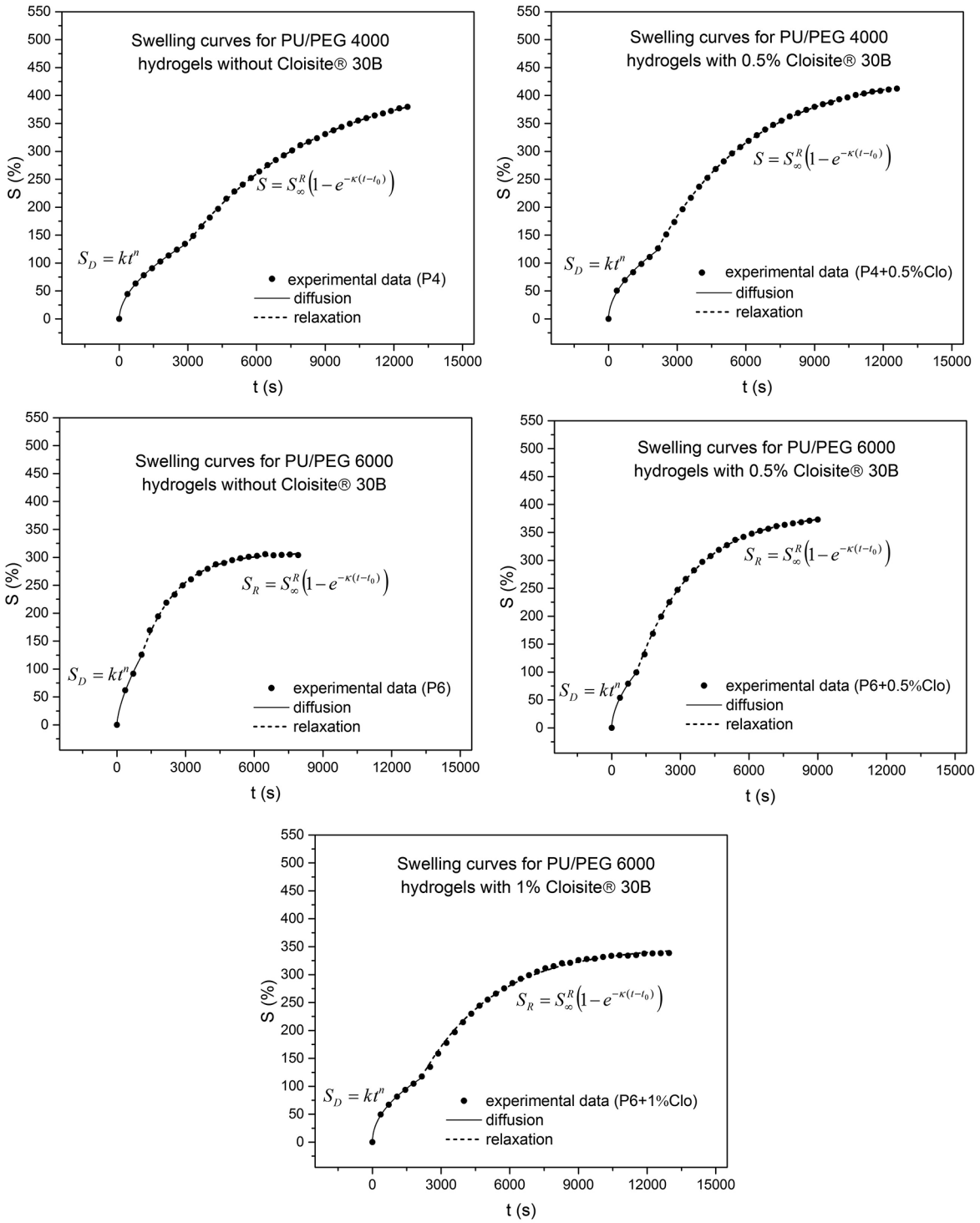

Fig. 6. Experimental swelling curves of hydrogels in the 3% NAP solution compared with theory.

Table 5. Parameters describing the diffusion process in hydrogels: n is diffusional exponent and k is diffusional rate constant.

Hydrogel	n	k [$s^{-n} \cdot 10^{-2}$]
P4	0.54 ± 0.01	1.81 ± 0.09
P4+0.5% Clo	0.53 ± 0.02	2.16 ± 0.31
P6	0.66 ± 0.05	1.23 ± 0.40
P6+0.5% Clo	0.56 ± 0.01	1.99 ± 0.01
P6+1% Clo	0.49 ± 0.01	2.69 ± 0.28

Table 6. Values of diffusion coefficients.

Hydrogel	L [mm]	D [$cm^2 \cdot s^{-1} \cdot 10^{-4}$]
P4	0.98	1.18 ± 0.01
P4+0.5% Clo	1.20	2.07 ± 0.04
P6	0.89	2.53 ± 0.28
P6+0.5% Clo	0.58	0.62 ± 0.02
P6+1% Clo	1.14	1.69 ± 0.03

3.1.3 Theoretical analysis of the swelling process

We performed the theoretical analysis of the swelling process for five hydrogel systems: PU/PEG 4000, PU/PEG 4000/0.5% Cloisite® 30B, PU/PEG 6000, PU/PEG 6000/0.5% Cloisite® 30B and PU/PEG 6000/1% Cloisite® 30B in the 3% NAP solution.

The diffusion is very rapid process (it lasts less than 3000 s). Fitting the diffusional equation (4) is appropriate only for less than about 40% of mass increase (compare with the data in table 4). This is the result of hardly crosslinked network of hydrogel. For other materials it is usually 60% [33].

From the initial sections of curves in fig. 6 we calculated n and k parameters characterizing diffusion. The obtained parameters are shown in table 5.

For all nanocomposite systems with Cloisite® 30B values of k are higher than for pure polyurethanes. The diffusional rate k reaches the biggest value for PU/PEG 6000/1% Cloisite® 30B. For all investigated hydrogel systems n values are greater than 0.5. That tendency is current for materials which can swell and are able to deform and resize. It should be noticed that for hydrogels without nanocomponent values of n are higher than for hydrogels with Cloisite® 30B. In addition, from table 5 it follows that for hydrogels PU/PEG 4000 the admixture of the nanocomponent speeds up the process of diffusion, but in the case of PU/PEG 6000 this tendency is opposite. The process of swelling for these hydrogels is slower as a result of larger number of free volume spaces available for creating the OMMT aggregates. This suggestion was proved by our thermoporymetry measurements.

Process of diffusion can be also characterized by diffusion coefficient D (see eq. (5)). The experimental data were used to calculate D by fitting eq. (5) to the diffusional part of the swelling curves from fig. 6. Values of D determined in such a way are listed in table 6.

For PU/PEG 6000 we can observe that with increasing content of nanocomponent the permeability is lower (lower D). Active substance promotes the swelling and simplifies diffusion. However in the case of PU/PEG 4000 this dependency is opposite. This material is much more crosslinked and diffusion is slower (less free volume spaces available). Furthermore the size of pores is lower in comparison with PU/PEG 6000 (see table 2).

When the diffusion process ends, the relaxation of polymer chains follows. This process takes longer time than diffusion. In theory this process is described by eq. (7). The values describing relaxation process: κ and S_∞^R are presented in table 7. These values have been found by fitting eq. (7) to the experimental data.

The process of relaxation is slow and depends on the structure of hydrogels. For PU/PEG 4000 hydrogels κ is higher for system with Cloisite® 30B, but for PU/PEG 6000 this tendency is opposite. The κ values for PU/PEG 6000 are significantly higher than for PU/PEG 4000 hydrogels; higher molecular weight of poly(ethylene oxide) (PEG) in polymer network increases the relaxation time.

The maximal swelling $S_{\max}$ after both processes of swelling is described by the sum

$$S_{\max} = S_D^{\max} + S_\infty^R, \tag{9}$$

where $S_D^{\max} = S_D(t_0)$ is the maximal value of swelling after diffusion, S_∞^R is maximal swelling after relaxation process. Values of $S_D^{\max}$ were presented in table 4.

Table 7. Swelling parameters κ and S_∞^R for the relaxation process.

Hydrogel	κ [$s^{-1} \cdot 10^{-4}$]	S_∞^R [%]
P4	1.79 ± 0.02	284
P4+0.5% Clo	2.40 ± 0.01	313
P6	6.44 ± 0.01	183
P6+0.5% Clo	4.04 ± 0.04	285
P6+1% Clo	3.12 ± 0.06	233

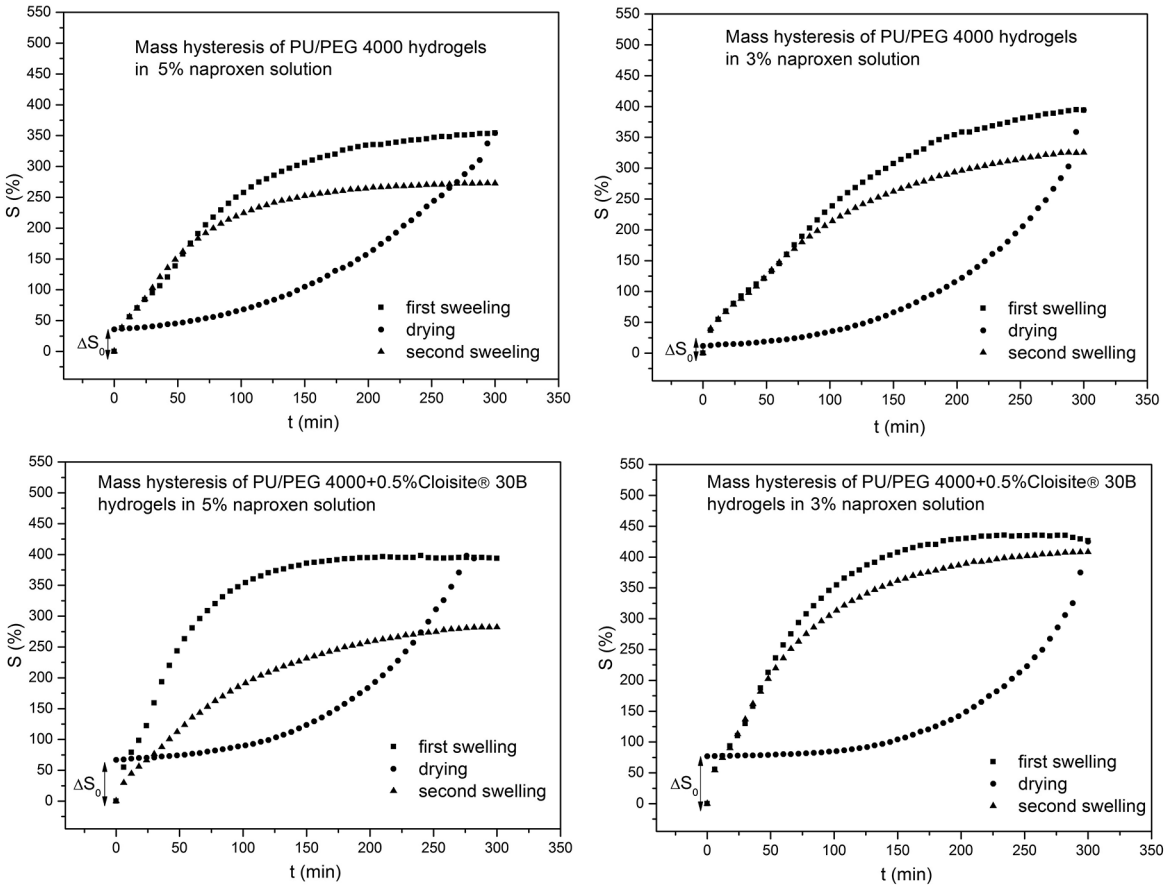

Fig. 7. Swelling hysteresis of PU/PEG 4000 and PU/PEG 4000+0.5% Cloisite® 30B in two solutions: 1) 5% naproxen sodium in 10% cosolvent ethanol+water (5% NAP) and 2) 3% naproxen sodium in 50% cosolvent ethanol+water (3% NAP). The residual swellings ΔS_0 [%] after drying process in hysteresis measurements are listed in table 8.

In the next section we present the swelling hysteresis studies for our systems. These studies show that some amount of active substance can stayed in hydrogel network and can not be released into new environment (for example body fluids).

3.2 Swelling hysteresis

The mass of hydrogels was examined during three consecutive processes: swelling, drying in laboratory oven and subsequent swelling in the same solution (see fig. 7). We studied two types of hydrogel systems: pure PU/PEG 4000 and PU/PEG 4000 containing 0.5% Cloisite® 30B. Swelling was examined for two solutions: 1) 5% naproxen sodium in 10% cosolvent ethanol+water (5% NAP) and 2) 3% naproxen sodium in 50% cosolvent ethanol+water (3% NAP).

Table 8. Maximal swelling values reached by hydrogels during studies of swelling hysteresis in solution 1) (5% NAP) and solution 2) (3% NAP). The residual swelling ΔS_0 [%] after drying process in hysteresis measurements.

Hydrogel and solution	$S_{\max}$ [%]		ΔS_0 [%]
Solution 1)	First swelling	Second swelling	Drying
P4	354	272	12
P4+0.5%Clo	395	282	67
Solution 2)	First swelling	Second swelling	Drying
P4	394	325	63
P4+0.5%Clo	426	408	77

The results (table 8) show clear differences between maximum swelling values ($S_{\max}$) reached by hydrogels in two subsequent swelling processes. From table 8, there follows: 82%, 69%, 113% and 18% differences of the maximal swelling in two subsequent swelling processes. The biggest difference (113%) takes place for PU/PEG/4000+0.5% Cloisite® 30B hydrogel in solution 1) (5% NAP).

The most interesting result received from this measurement is amount of active substances retained in hydrogels after drying. Results in table 8 show that for swelling of solution with higher concentration of naproxen sodium (solution 1)) the values of retained amount of solution are greater.

The phenomenon of different $S_{\max}$ values in two subsequent processes of swelling and the residual swelling ΔS_0 after drying are probably effected by creation free volumes in the polymer matrix as a consequence of polymer chains relaxation in an active substance solution. The second swelling process is much slower and differences between the first and the second swelling are connected mainly with differences in the second stage of swelling (relaxation). From the hysteresis measurements we can state that chains of polymer network has not been destructed and part of active substances stayed linked in the matrix. As can be seen, the amount of solution with NAP remained in matrix with Cloisite® 30B (P4+0.5%Clo) is greater than for pure hydrogel (P4) (table 8). It is a consequence of NAP-OMMT interactions (nanosize effect).

3.3 Release studies

3.3.1 Description of the release process

One of the most versatile empirical model describing release kinetics is Peppas's model (power-law equation) [37]. The release process can be separated into two parts [38, 39]. Therefore, the molar concentration of drug $C(t)$ released in time t from the polymer matrix can be described in the following way:

$$C(t) = C_D\left(t \leq t_0\right) + C_R\left(t \geq t_0\right), \tag{10}$$

where C_D is the molar concentration in the first process (connected with diffusional release) and C_R is the molar concentration in the second stage of release process, after time t_0, relaxational release.

When the hydrogel with an active substance inside is immersed into an external fluid, the first part of the drug release connected with drug dissolution takes place. Molar concentration of drug when diffusion is prevailing $C_D(t)$ is described by a power-law–type equation [40],

$$C_D(t) = kt^n, \tag{11}$$

where k and n are parameters depending on hydrogel system properties. The value of the exponent n determines the prevailing kind of mechanism (Fickan, Case II or anomalous).

The second part of drug release from hydrogel matrix is connected with polymer swelling of external solution and reducing drug delivery outside the matrix. It is strictly connected with relaxation phase in swelling process. The amount of mass molar concentration $C_R(t)$ released in time t is expressed by the following formula [41], where C_∞ is maximal drug molar concentration released in the second stage of release process:

$$C_R(t) = C_\infty\left[1 - \frac{8}{\pi^2}\exp(-Ft)\right], \tag{12}$$

where factor $F = \pi^2 D/L^2$ is connected with the diffusional coefficient D (assumed to be constant) and L is the thickness of the sample [40].

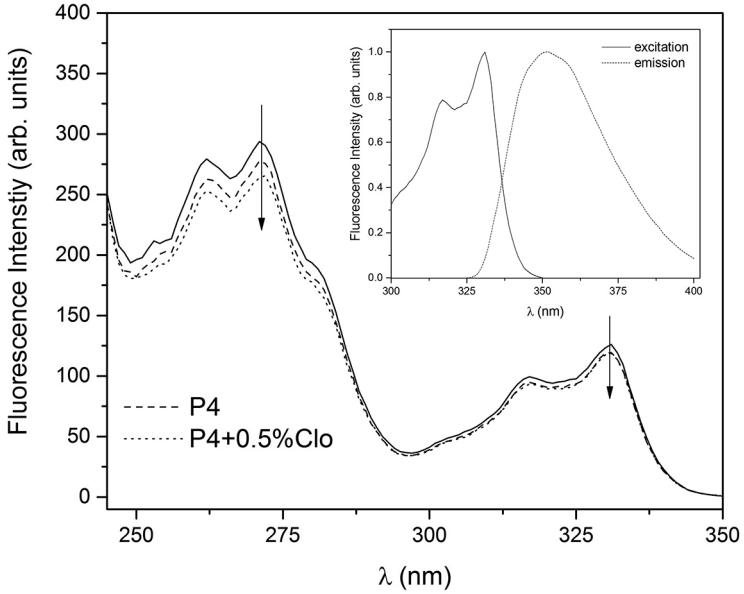

Fig. 8. Fluorescence excitation and fluorescence spectra of NAP in the 3% NAP solution after 24 h of swelling by hydrogels.

3.3.2 Steady-state spectroscopic measurements

As was shown in our previous paper [25], the shape and the position of the fluorescence excitation spectrum of NAP dissolved in different solvents is quite similar to the absorption one. Furthermore, the long-wavelength fluorescence excitation and fluorescence bands of NAP show an approximate mirror symmetry (see insert in fig. 8). Such behavior is possible when the same spatial conformation of NAP exists in the ground and excited states.

Figure 8 presents the fluorescence excitation spectra of NAP in studied solution (3%NAP) after 24 h of swelling by examined hydrogels. The fluorescence excitation spectra were obtained for detection wavelength which corresponds to the maximum of the fluorescence band ($\lambda = 320$ nm). It is important to note that, for the steady-state spectroscopic measurements all solutions were diluted to obtain the same NAP concentration about 10^{-6} M. The solid line presents the fluorescence excitation profile refers to the solution, the dashed line refers to solution after swelling by PU/PEG 4000 hydrogel and the dotted line presents the excitation spectrum after swelling by PU/PEG 4000 with 0.5% Cloisite® 30B. As can be seen, presence of investigated hydrogels in NAP solution causes changes in spectral behavior. For both studied systems, the fluorescence intensity of the short-wavelength (with maximum at about 270 nm) and long-wavelength (with maximum at about 330 nm) bands simultaneously decreases with increasing time of swelling by investigated hydrogels. Analyzing the data presented in fig. 8, it can be clearly seen that hydrogels without nanoparticles can absorb about 10% of NAP molecules, whereas hydrogels with 0.5% admixture of Cloisite® 30B absorb about 6% of NAP from the solution. This effect is understandable in terms of drug interaction with nanoparticles [42]. A similar effect, the time extention of drug diffusion in the release process, was also observed in [43].

In order to determine the amount of drug (NAP) released from the hydrogel matrix we investigated changes in the UV-visible absorption spectrum as a function of time. Absorption spectra of NAP recorded during the release process are presented in fig. 9(a). From recorded profiles the molar concentrations of NAP in solution have been computed. The calculations were based on the Lambert-Beer law ($A = \varepsilon cl$). Calculations were conducted referring to the absorption spectrum of NAP in water. A molar excitation coefficient of NAP for the highest energy (intensive band with maximum located at around 230 nm in water) was used to compute the amount of released NAP dye. As can be seen, the amount of NAP released from hydrogel matrix containing 0.5% Cloisite® 30B is lower than for pure hydrogel (P4) (fig. 9(b)). This effect can be explained by presence of the OMMT platelets dispersed in polymer matrix which inhibit diffusion.

3.3.3 Theoretical analysis of the release process

Obtained data were fitted to the theoretical model of release from cylindrical samples of hydrogels (see fig. 10). It can be seen, that shapes of $C(t)$ show two stages: release, (determined by diffusion process) and relaxation up to equilibrium state.

By fitting the theory (eqs. (11) and (12)) to the experimental data (fig. 10) we found values of free parameters: n, k, F and C_∞ presented in table 9.

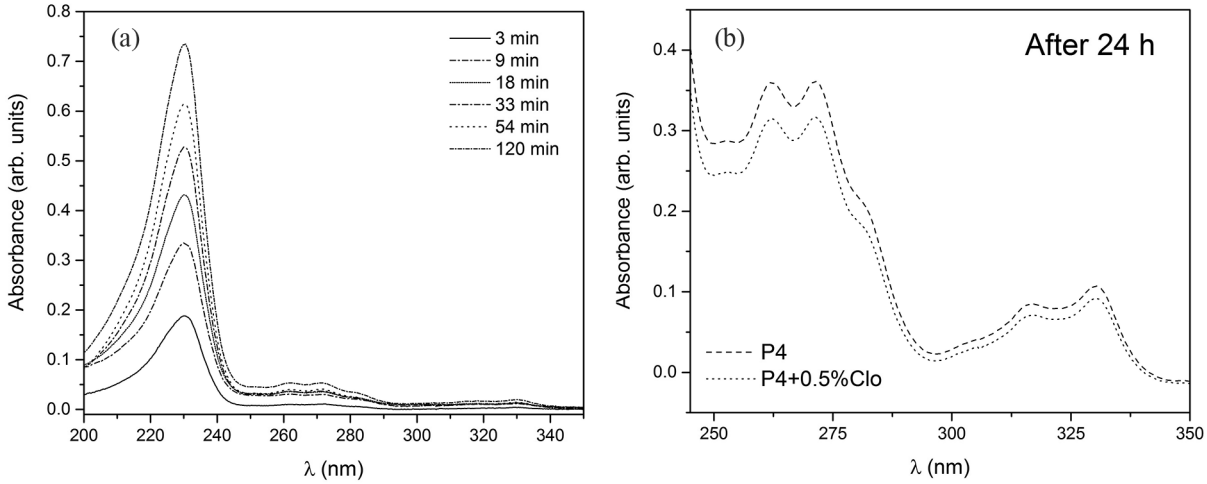

Fig. 9. Absorption spectra of NAP in water. (a) Changes of spectra during release from PU/PEG 4000 hydrogel. (b) Comparison between spectra after 24 h of release from PU/PEG 4000 and PU/PEG 4000 with 0.5% Cloisite® 30B.

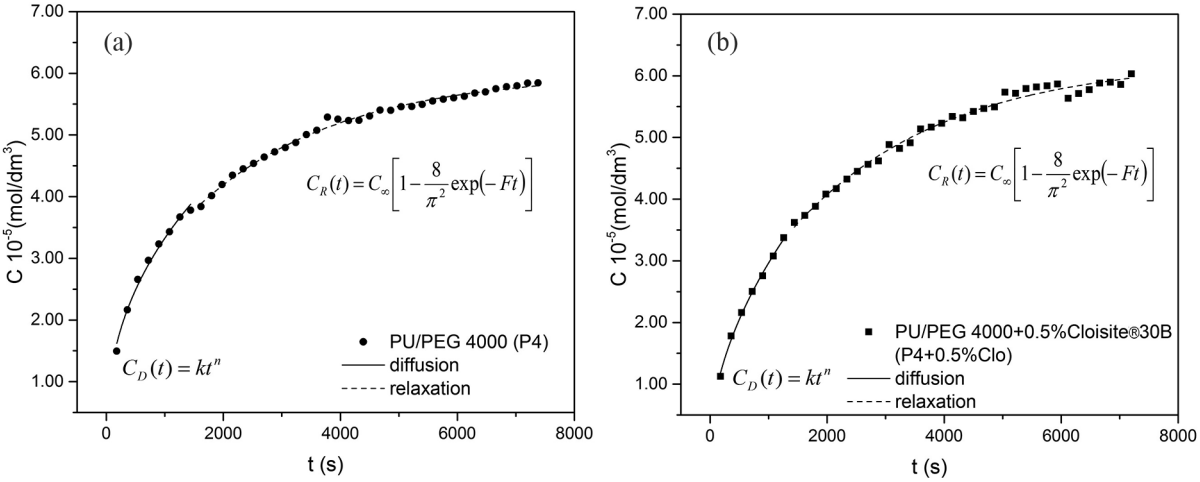

Fig. 10. Molar concentration of drug released from hydrogels: (a) PU/PEG 4000 and (b) PU/PEG 4000 with 0.5% Cloisite® 30B.

Table 9. Values of parameters describing the release process for studied hydrogel systems: n, k ($s^{-n} \cdot 10^{-7}$), F ($s^{-1} \cdot 10^{-4}$) and C_∞ ($mol \cdot dm^{-3} \cdot 10^{-5}$).

Hydrogel	n	k	F	C_∞
P4	0.43(2)	4.45(6)	3.84(8)	1.29(2)
P4+0.5% Clo	0.54(1)	2.04(2)	3.84(5)	1.62(4)

Values of n for all studied systems are close to 0.5 showing that the Fickan diffusion occurs [44]. The parameter k is connected with the hydrogel structure and the speed of the first stage of the release process depends on its value. For P4 hydrogel $k = 4.45 \cdot 10^{-7} \cdot s^{-n}$ and $k = 2.04 \cdot 10^{-7} \cdot s^{-n}$ for P4+0.5% hydrogel. It follows from these data that diffusion process is faster in system with Cloisite® 30B. Five orders of magnitudes lower values of k in release than in swelling process shows that release is a much slower than swelling.

The parameter $F = \pi^2 D/L^2$ describes the transport mechanism in the relaxation stage. In the theoretical model, the second stage process is also connected with diffusion phenomena. Values of diffusion coefficient D obtained from F values are: $D = 3.25 \cdot 10^{-5} \cdot cm^2 \cdot s^{-1}$ and $D = 3.19 \cdot 10^{-5} \cdot cm^2 \cdot s^{-1}$ for P4 and P4+0.5%Clo, respectively. These values have been calculated by taking into account that lengths of samples were $L = 0.134$ cm for P4 and $L = 0.128$ cm for P4+0.5%Clo. It can be noticed, that D values are an order of magnitude lower than those obtained in diffusion analysis in the swelling process (see table 6). This may indicate, that part of the NAP molecules interact with Cloisite® 30B and are hardly removable from hydrogel matrix. We observed the same effect (nanosize effect) by studying swelling hysteresis.

4 Conclusions

We examined polyurethane nanocomposite hydrogels with two different molecular weights of poly(ethylene oxide): PEG doped with various amount of organically modified nanocomponent and Cloisite® 30B. We investigated the influence of Cloisite® 30B on the swelling and release processes.

Maximum swelling values for all hydrogels doped with nanocomponents were greater than for pure hydrogels. Nanocomponent improves swelling by absorbing the solution and widening free volumes in polymer network. However, an excessive amount of nanoparticles may result barrier effect, *i.e., a* too large amount of nanoparticles can hamper the swelling process. We appointed PU/PEG 4000/0.5% Cloisite® 30B as having the best swelling properties.

We also conducted two complementary measurements of the structure of our materials that explain their behavior in the process of swelling in the solution. The X-ray diffraction technique was used to determine the type of nanoparticle dispersion in the hydrogel matrix, and the thermoporymetry measurements by means of the DSC technique to determine the pores sizes in hydrogel nanocomposites.

We found that an active substance in the solution increases absorption. Among the systems studied by us the best swelling properties have PU/PEG 4000 with 0.5% Cloisite® 30B in 3% naproxen sodium in 50% cosolvent ethanol+water solution. This system has been also selected for studies of swelling hysteresis.

It follows from swelling hysteresis that polymer chains have not been destructed after two stages of the swelling. We found also that the value of maximal swelling, in the second swelling process after drying, is lower. It means that some amount of active substances retains in hydrogel matrix after drying as a result of interaction between drug and OMMT nanoparticles.

From the analysis of the release process it can be concluded that the presence of nanoparticles hinders drug diffusion from polymer matrix and consequently slows down the drug release.

We performed also accurate theoretical analysis of both the swelling and release processes and we found values of parameters describing them.

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