

PVA hydrogel deformation in response to change in temperature or pH

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Abstract. Biocompatibility, biodegradability and non-toxicity are the main attributes of any material to be used in biomedical applications. Among all the potential stimuli, pH, salt and temperature exist naturally in the internal environment of the human body. Hence internal stimuli responsive hydrogels can be exploited for specific drug delivery and tissue replacement. Poly(vinyl alcohol) (PVA) is the world's largest volume synthetic polymer, produced for its excellent chemical resistance, physical properties and complete biodegradability, which has resulted in broad practical applications. PVA could be considered a suitable host material due to its good thermo-stability, chemical resistance and film-forming ability. It is also an important material because of its large-scale applications. Novel data analysis techniques were developed to analyze the response of PVA to external stimuli, including temperature and/or pH. The presented non-contact method shows that the PVA polymer gel, physically cross-linked by freezing and thawing, shrinks and swells under the influence of temperature, which is a reversible phenomenon. Under the given conditions, such as temperature, pH and mechanical load, the dominant factor affecting the swelling or contraction of the hydrogel is the change in the temperature of the liquid in which the PVA hydrogel sample is immersed.

Key words: PVA; hydrogel; non-contact method; thermal deformation; pH-sensitivity.

1. Introduction

A hydrogel is a three-dimensional network of polymers made from natural or synthetic materials, and possessing a high degree of flexibility due to high water content. Under physiological conditions, these materials are capable of swelling or shrinking reversibly in water and retaining a large volume of liquid in the swollen state. Hydrogels can be designed to have controllable swelling or shrinking responses related to changes in the external environment. They may feature a dramatic volume transition in response to a variety of physical and chemical stimuli, where the physical stimuli include temperature, electric or magnetic fields, light, pressure and sound, while the chemical stimuli include pH, solvent composition, ionic strength and molecular species [1–3].

Temperature-sensitive hydrogels are one of the most commonly studied classes of environmentally sensitive polymer systems. The common characteristic of temperature-sensitive polymers is the presence of hydrophobic groups, such as the methyl, ethyl and propyl groups. Temperature-responsive polymers, or thermo-responsive polymers, exhibit drastic and discontinuous changes in their physical properties with changes in temperature. The most studied synthetic responsive polymer is poly(N-isopropylacrylamide) (PNIPAAm). Poly(N-vinyl caprolactam) (PVCL), poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO) and propylene oxide (PPO) are among the important polymers in this class. These materials are used in the pharmaceutical industry as surfactants, and their ability to change from a low viscosity solution state to a semi-solid gelled struc-

ture when raised to body temperature makes them very suitable for injectable drug-dosing applications [4, 5]. Thermo-sensitive hydrogel PEG-PLGA-PEG is biocompatible and can be used as a wound dressing and scaffold [6, 7]. pH-sensitive hydrogels contain pendant acidic (e.g. carboxylic and sulfonic acids) or basic (i.e. ammonium salt) groups that either accept or release protons in response to changes in environmental pH. Polymers with a large number of ionizable groups are known as polyelectrolytes. Hydrogels made of crosslinked polyelectrolytes display a significant difference in swelling properties, depending on the pH in their environment. Hydrogels made of poly(methacrylic acid) (PMA) grafted with poly(ethylene glycol) (PEG) manifest unique pH-sensitive properties. pH-sensitive hydrogels have been used most frequently to develop controlled release formulations for oral administration. pH-sensitive hydrogels have also been used to make biosensors and permeation switches [7].

Poly(vinyl alcohol) (PVA) is the world's largest volume synthetic polymer, produced for its excellent chemical resistance, physical properties and complete biodegradability, which has resulted in broad practical applications. PVA could be considered a suitable host material due to its good thermo-stability, chemical resistance and film-forming ability. PVA is used in surgical devices, sutures, hybrid islet transplantation, implantations, blend membranes and synthetic cartilages in reconstructive joint surgery [3]. PVA hydrogels are classified as polymers sensitive to salt [8–11]. However, in the literature, it is difficult to find studies on the influence of pH and temperature on PVA reactivity. In several papers the thermal studies of PVA hydrogels, using the differential scanning calorimetry (DSC) technique, concern only the determination of the glass transition, melting and crystallization temperatures [12–15]. In turn, determinations of PVA reactivity to pH change only relate to the complex hydrogel network of poly(acrylic acid) PAA and PVA [12, 14, 16–18], poly(aspartic acid)/poly(vinyl alcohol) IPN Hydrogel

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[19], poly(vinyl alcohol/poly 6-acrylamidohexanoic acid hydrogel [20] and also collagen-PVA complex material [21].

The main goals of this paper are discussions related to the complex study of the pH-thermo-mechanical properties of PVA hydrogels. As PVA has found applications as a biomaterial, it is very important to understand not only the responses to individual salts, as occurring in body fluids, but also the responses to temperature and pH. Moreover, a major problem associated with oral-controlled drug release is the sensitivity of the dosage form properties to variations in pH. Although PVA hydrogels are not classified as thermo-/pH-sensitive hydrogels, the influence of these factors can have a significant effect on the resultant value of deformation. With this knowledge, it will then become possible to predict the potential effect of applications of the hydrogel in the human body and also to overcome a major problem associated with oral-controlled drug release. Due to the selected ultrasonic non-contact method used to measure the deformation of the sample, it remains in the same environment during the tests. As a result, the proposed method does not disturb the thermal and chemical environment of the samples and should be more precise as compared to the contact methods applied in the quoted papers [10–11, 15–17, 22].

2. Materials and method

25 wt% samples of poly(vinyl alcohol) hydrogels were prepared by the freezing-thawing procedure described in [3, 23]. The sample size of the PVA hydrogels was: sample height: 12.47 ± 0.07 mm, sample diameter: 37.75 ± 0.18 mm.

The measurements system is shown in Fig. 1. The system includes the measurement chamber with a loading system and ultrasonic transducer, ultrasonic testing apparatus (OPTEL OPBOX 01/100) and a computer. The measurement chamber was linked with a thermostat (HAAKE DC 30/DL30) to stabilize the temperature during the tests. The PMMA sample chamber shown in Fig. 1b consists of two rings, placed between stainless steel panels. For the thermal deformation measurements, the hydrogel sample was placed in a chamber filled with distilled water. For the measurements of response to changes in pH, the sample was immersed in a buffer solution of pH: 4, 7 and 9.22. All measurements were conducted between 15 and 37°C.

The diameter of the samples was smaller than that of the chamber, thanks to which the samples could freely deform in the radial direction. For each study, a preload force of 6 N was

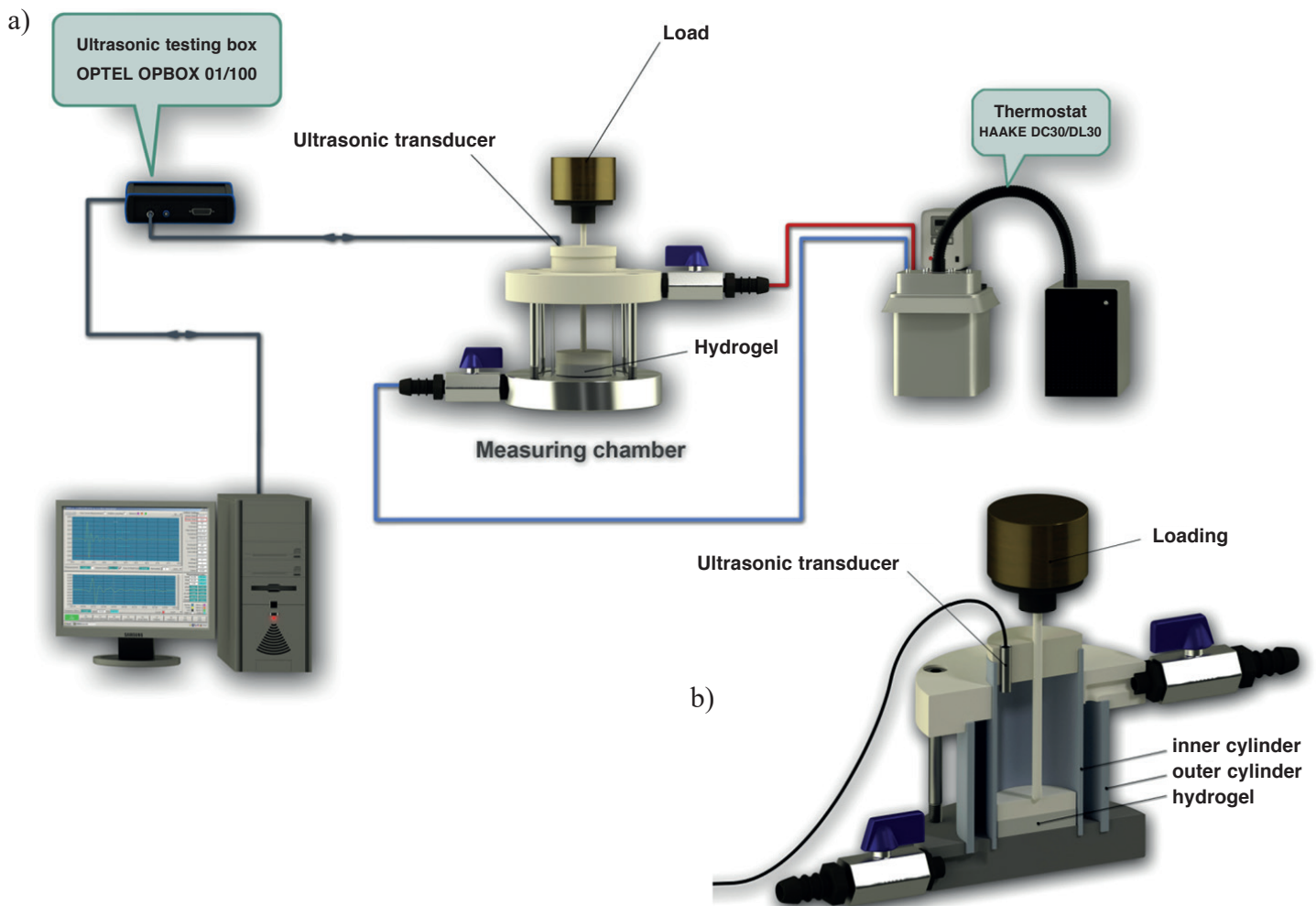


Fig. 1. Layout of the system (a) and cross-section of the measurement chamber (b)

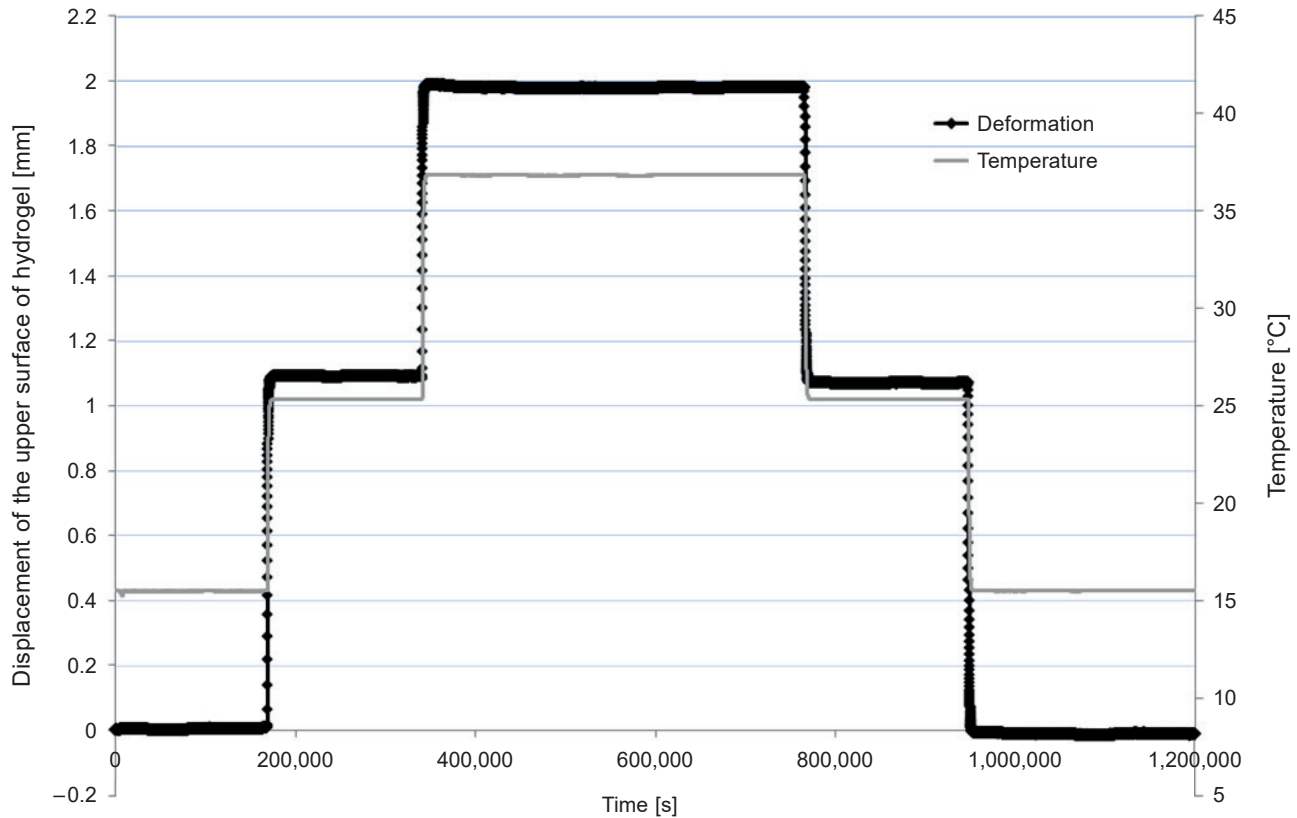
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Fig. 2. Change in the displacement of the upper base of the PVA hydrogel samples at various temperatures

applied to fix the positions and the shape of the samples. The displacement (settlement/swelling) of the upper surface of samples under mechanical, thermal or chemical (pH) loads was continuously recorded by means of the time of flight method, using the ultrasonic system with a transducer of primary frequency of 5 MHz. The ultrasonic signals were registered every 60 s and transferred to the computer. The settlement of the sample was calculated using the correlation method. In the correlation method of calculation of time difference between two signals, the resolution of the time step ΔT is approximately equal to the reciprocal of the sampling frequency, i.e. $\Delta T = 1/f$ (where f – the sampling frequency used, which is 10^8 s), and in this case it is equal to 10^{-8} s. The sensitivity of the displacement measurement was assessed using the longitudinal wave in water in which velocity is approximately $v_p = 1.5 \cdot 10^3$ m/s. Then the sensitivity can be approximated as the product of the longitudinal wave velocity and the time step resolution, and for the adopted values it is: $C_z \approx v_p \cdot \Delta T \approx 1.5 \cdot 10^3 \cdot 10^{-8} = 1.5 \cdot 10^{-5}$ m = 0.015 mm.

This means that the sensitivity of the method is 15 micrometers. The temperature was measured with an accuracy of $\pm 0.2^\circ\text{C}$ in the temperature range of $-200 \div 200^\circ\text{C}$.

3. Results and discussion

3.1. Thermal deformation. Temperature is an important environmental factor used to appraise hydrogels. Figure 2 presents the temperature-dependent swelling/shrinking of PVA hydrogel

with distilled water at the temperatures of 15, 25 and 37°C . To ensure the equilibrium state of the hydrogel immersed in the distilled water, each temperature stage lasted at least 2 days. All changes in the chamber water temperature and the change in hydrogel height were recorded every 60 s. The tests for each temperature were repeated at least three times.

The test results, presented in Fig. 2, show that an increase in temperature causes a relatively fast swelling reaction of the hydrogel, while a decrease in temperature causes its contraction. Moreover, they prove that the temperature sensitivity phenomenon is reversible, i.e. the differences in the deformation when returning to the same temperatures are negligible. Table 1 presents the mean deformation results for the three tests and the averaged values for individual temperatures.

Table 1
Mean deformation results for the three tests
and averaged values for individual temperatures

Temperature [°C]	ΔD [mm]	ΔD [mm]	ΔD [mm]	ΔD [mm]
	Sample 1	Sample 2	Sample 3	Average
15				
25	1.22	1.12	1.09	1.14 ± 0.07
37	0.95	0.84	0.89	0.89 ± 0.06
25	0.95	0.95	0.90	0.93 ± 0.03
15	1.11	1.12	1.08	1.10 ± 0.02

The results presented in Table 1 indicate that increasing/decreasing the temperature by 10 degrees causes a change of about 1 mm, i.e. 10% of the deformation sample. This means that the temperature has a great influence on the behavior of hydrogels, even those not classified as a thermally sensitive material, such as PVA. Similar temperature tests for PVA hydrogels (but chemically cross-linked) confirm that PVA hydrogels swell with increasing temperature [13]. In the cited work, the PVA samples were also tested at higher temperatures, up to 80°C. After exceeding a temperature of 40°C, the PVA hydrogels begin to shrink [13]. The same effect is also observed for poly(N-isopropyl acrylamide)/polyaspartic acid IPN thermo-sensitive hydrogels. For a temperature change from 25 to 40°C these hydrogels swelled, and then after exceeding a temperature of 40°C there was a rapid contraction [23].

The thermo-sensitivity of the hydrogel can be described by the interaction of the molecular bonds with the network structure. If the hydrogel is at a low temperature, the H-bonds compress the network structure to a shrinking and bonding status, which results in a minor swelling ratio. As the temperature increases, the hydrogen bond effects are weakened and the twisted polymer molecular chain extends gradually. As a consequence, the probability of polymer molecular chains connected with water molecules grows larger, thus the swelling ratio increases slowly. When the temperature is too high, the network structure can collapse due to the hydrogen bond breaking between the water molecules and PVA in the networks [19].

To compare thermal deformation and mechanical deformation during the temperature test, the hydrogel samples were subjected to a constant load of 11.09 N. Figure 3 presents the mechanical and temperature-dependent swelling/shrinking of PVA hydrogel at distilled water temperatures of 15, 25 and 37°C.

The deformation process indicates a clear contraction of the hydrogel under the influence of mechanical load and a clear influence of temperature on the size of the generated swelling with temperature increase and shrinking with temperature decrease. The displacement values of the upper hydrogel layer are presented in Table 2.

Table 2
 Mean deformation results for the three tests and averaged values for individual temperatures and mechanical load

Temperature [°C]	ΔD [mm]	ΔD [mm]	ΔD [mm]	ΔD [mm]
	Sample 1	Sample 2	Sample 3	Average
15				
LOAD	0.10		0.18	0.14 ± 0.06
25	1.08	1.09	0.83	1.00 ± 0.15
37	0.91	0.91	0.73	0.85 ± 0.10
25	0.92	0.91	0.81	0.88 ± 0.06
15	1.09	1.08	0.85	1.01 ± 0.13

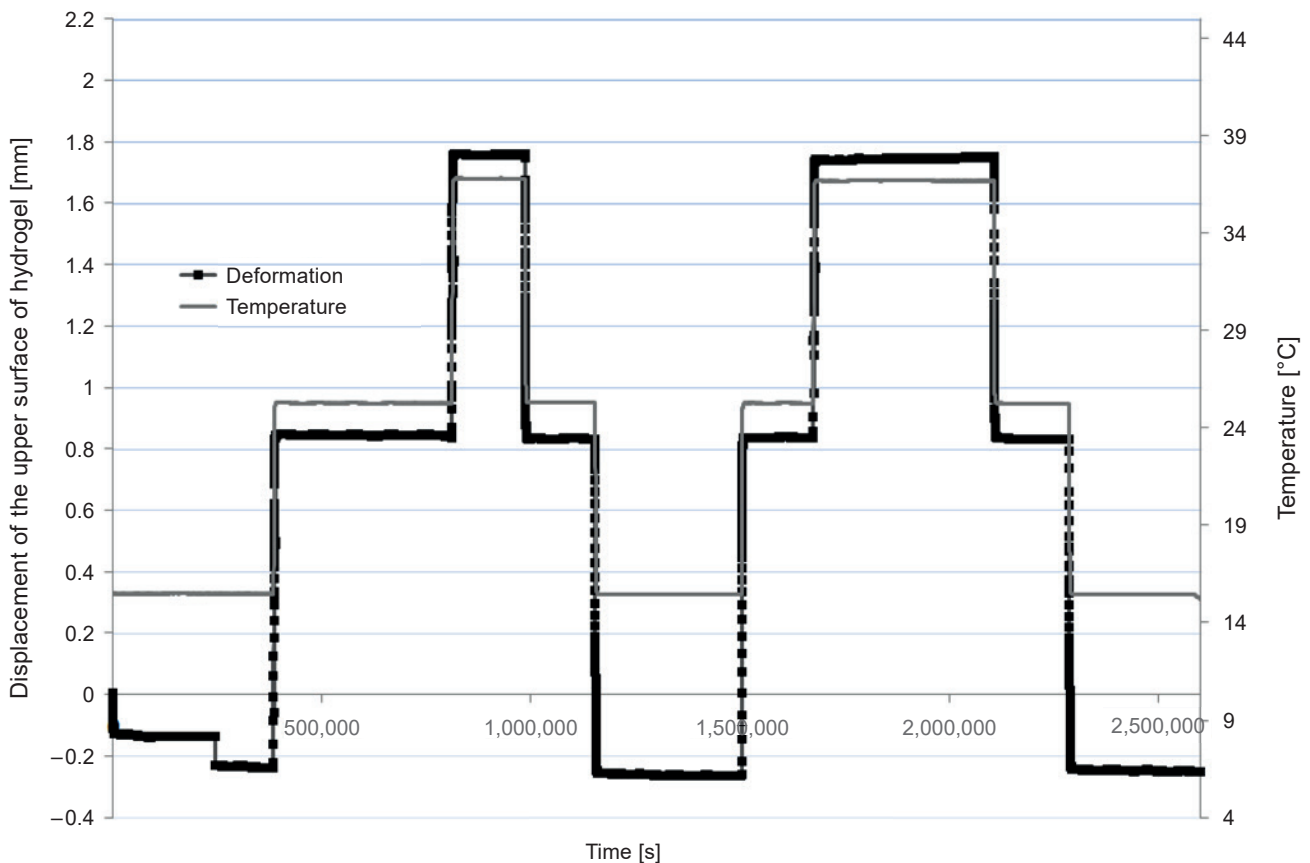


Fig. 3. Change in the displacement of the upper base of the PVA hydrogel samples at various temperatures and under mechanical load

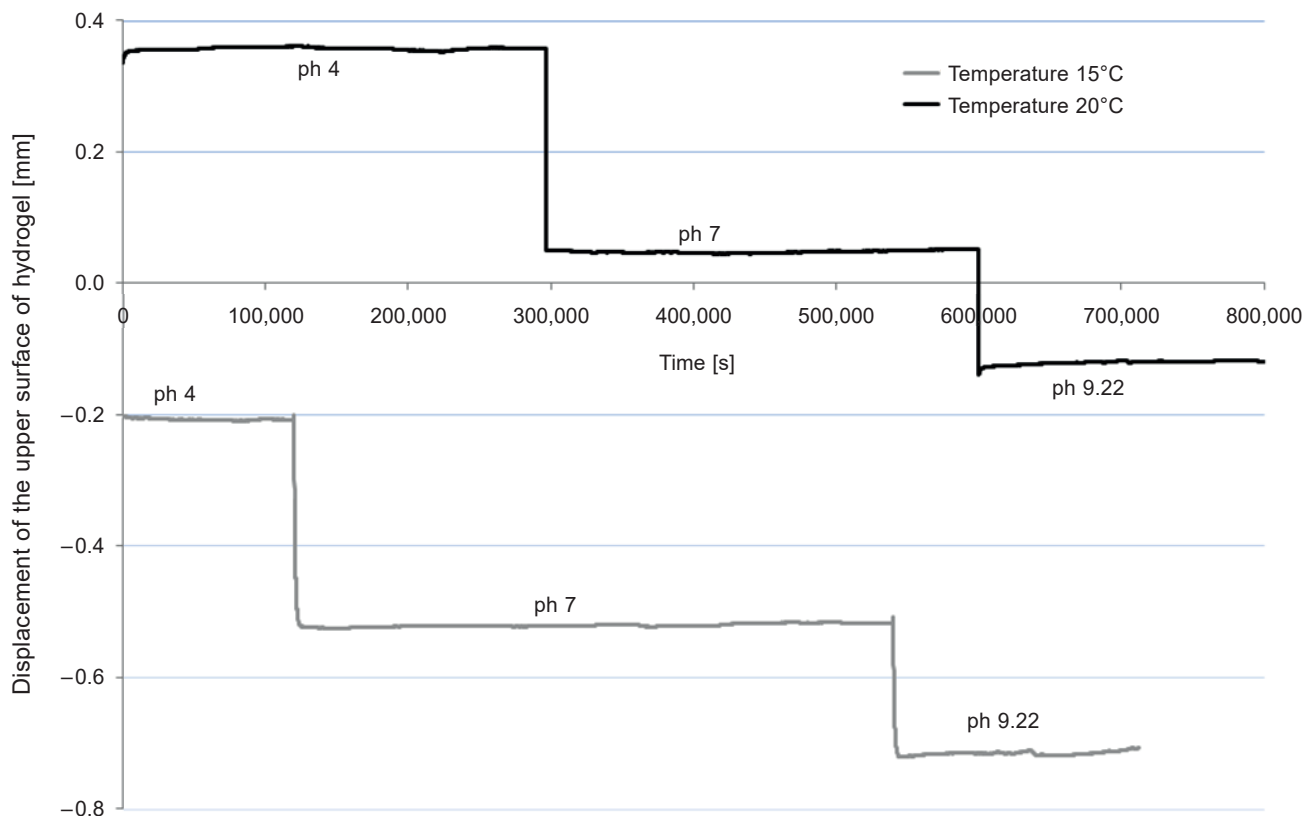
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Fig. 4. Swelling of PVA hydrogel in different buffer solutions at 15 and 20°C

The deformation related to the mechanical load is less than that for the thermal deformation, at about 1%, while thermal deformation is around 6–8% for a temperature change of 10 to 12 degrees. The data in Tables 1 and 2 show that the thermal deformation for samples additionally loaded mechanically is, as expected, slightly less than the thermal deformation of samples that are not mechanically loaded. Moreover, for the two tests of thermo-sensitivity, the increase in hydrogel swelling is higher for lower temperatures, i.e. greater swelling occurs as the temperature increases from 15 to 25°C than from 25 to 37°C for the test with increasing distilled water temperature, and, similarly, shrinking for the test with decreasing temperature.

PVA hydrogels physically cross-linked by freezing and thawing shrink and swell under the influence of temperature, and this phenomenon is reversible. Under the given experimental conditions, the dominant factor affecting the swelling or contraction of the hydrogel was the change in the temperature of the liquid in which the PVA hydrogel sample was immersed.

3.2. Deformation in response to change in pH. The pH-sensitive characteristics of PVA hydrogels in terms of swelling were tested using the pH values of 4, 7 and 9.22. The swelling kinetics of PVA hydrogel in different buffer solutions were studied at buffer solution temperatures of 15 and 20°C. The hydrogel sample, initially swollen in distilled water, was installed in the measuring chamber and immersed in successive buffer solutions, from pH 4 to 9. This system ensured continuous testing without removing the sample. After taking the measurements

using the first buffer solution, the solution was removed from the chamber and replaced with another, with a higher pH. The changes in hydrogel height were recorded every 60 s. The pH sensitivity tests for each temperature were repeated at least two times. To ensure the equilibrium state for the hydrogel immersed in a particular buffer solution, each measurement was taken over approximately two days. Figure 4 shows the swelling kinetics of PVA hydrogel in different buffer solutions for the solution temperatures of 15 and 20°C.

As shown in Fig. 4, the swelling of the PVA hydrogel decreased as the pH value increased. The equilibrium state of hydrogels occurred very quickly for both 15 and 20°C.

As mentioned in the introduction, there is little research on the sensitivity of pure PVA hydrogel to pH change. One of the works [22] investigated the swelling of originally dry PVA in buffers of pH 4 and 6.8. These studies showed minimum difference in the time profiles of PVA swelling in pH 4 and 6.8 [22]. Similar results are presented in [17], where a PVA/PAA blend was tested. For samples prepared in this way, the greatest changes in the volume of hydrogels occurred only at low pH values of 1.2 and high values above 10. In the research on the swelling of polymers composed of poly(aspartic acid)/triazole modified poly(vinyl alcohol) in the presence of buffers [16], the authors observed a slight decrease in the swelling of hydrogels for the pH range from 4 to 7, with a slight increase for pH 7 to 9 at room temperature. For the complex of PVA-collagen material, the authors of the study [21] confirm that such material clearly shrinks in the pH range from 2 to 8 and stabilizes in the

pH range of 8 to 10. According to the authors, the PVA cannot be ionized in the solution, the pH-dependent swelling properties of the collagen-PVA complex being mainly due to collagen, and its sensitivity is less than that of collagen.

There are several interpretations in the literature about the swelling of chemically and physically modified PVA-based hydrogels in the presence of different pH conditions [25–27]. It can be seen that the equilibrium swelling ratio of hydrogels is strongly affected by the type of cross-linking, admixtures and pH of the swelling media, and it is also influenced by the hydrogen bonds and attractive/repulsive electrostatic interaction among a functional group under different pH conditions. On the other hand, according to the Donnan equilibrium theory, the swelling of the hydrogel is mainly determined by the balance of osmotic pressure between the internal and external medium of the hydrogel network [19].

Regardless of the temperature at which the measurements were carried out (i.e. 15 or 20°C), the hydrogel shrinkage kinetics, as shown in the results presented in Table 3, are almost identical. The difference in the equilibrium levels for the two different temperatures (where the temperature increase is 5°C) for pH 4, 7 and 9.22 is respectively 0.56 mm, 0.57 mm and 0.60 mm. For samples tested in distilled water for a temperature increase of 10°C, the deformation increment was 1.2 mm. Thus the temperature influences the initial deformation value but does not influence the amount of deformation when the pH changes. Moreover, deformations under the influence of pH are much smaller than under the influence of temperature. A change in pH from 4 to 7 causes a deformation of 2.5% and a change in pH from 8 to 9.22 causes a deformation of 1.6%.

Table 3
Mean deformation results for the three buffers at 15 and 20°C

pH [–]	Deformation [mm]	ΔD [mm]	Deformation [mm]	ΔD [mm]
	Temperature of 15°C		Temperature of 20°C	
4	–0.207 ± 0.001		0.357 ± 0.006	
7	–0.520 ± 0.009	0.31	0.048 ± 0.002	0.31
9.22	–0.715 ± 0.009	0.20	–0.120 ± 0.002	0.17

4. Conclusions

Biocompatibility, biodegradability and non-toxicity are the main attributes of any material to be used in biomedical applications. Among all the possible stimuli, pH, salt and temperature exist naturally in the internal environment of the human body. Hence internal stimuli responsive hydrogels can be exploited for specific drug delivery and tissue replacement.

Novel data analysis techniques were developed to analyze the response of PVA to external stimuli, including salt concentration, temperature and/or pH. The presented ultrasonic non-contact method of measuring the height of the sample does not require removal of the sample from the environment in which it is located. Only the liquid is replaced, which results

in a quick reaction to the change of environment. The presented measurements show that the PVA polymer gel, physically cross-linked by freezing and thawing, shrinks and swells under the influence of temperature, which is a reversible phenomenon. Under the given conditions, such as temperature, pH and mechanical load, the dominant factor affecting the swelling or contraction of the hydrogel is the change in the temperature of the liquid in which the PVA hydrogel sample is immersed.

Thus PVA hydrogels are expected to find widespread application in biomedical and biotechnology fields. The controlled release behavior of PVA also has great perspectives in controlled release drugs for clinical applications.

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