THE EVALUATION OF CROSS-LINKER CONTENT IMPACT ON THE SWELLING CAPACITY OF POLY(1-VINYL-2-PYRROLIDONE) HYDROGELS

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Abstract

Poly(1-vinyl-2-pyrrolidone), p(VP), is a polar, hydrophilic, amphoteric polymer, derived from a monomer of 1-vinyl-2-pyrrolidone. It is used in many branches of industry (in the production of glues, paper and detergent). Due to its solubility in water and low cytotoxicity is one of the most used polymers in medicine. The aim of this study was to examine swelling behavior of synthesized poly(1-vinyl-2-pyrrolidone) hydrogels. By free radical polymerization of 1-vinyl-2-pyrrolidone, samples of poly(1-vinyl-2-pyrrolidone) hydrogels with 1.0, 2.0 and 3.0 mol% of ethylene glycol dimethacrylate (EGDM) as cross-linker were synthesized. The polymerization reaction was initiated by the addition of 2,2'-azobis(2-methylpropionitrile) (AZDN) initiator, and the reactants were dissolved in an adequate amount of methanol. Data obtained by scanning electron microscopy (SEM) were used to determine the structure and pore size of the freeze-dried hydrogels, swelled to equilibrium state. Synthesized p(VP) hydrogels were used to test swelling behavior and their sensitivity to changes in pH values (3.0, 6.0 and 9.0) and temperature (25-80°C). The swelling process was monitored gravimetrically. Swelling of hydrogels p(VP) is most intense at room temperature (25°C). The most intensely swelling is in a alkaline fluid, pH=9.0 (αe=141.98 for the sample with 1 mol% EGDM). In a fluid of pH 6.0 they achieved equilibrium degree of swelling αe=67.46. At 25°C the smallest degree of swelling of p(VP) is in the strong acidic fluid, pH=3.0 (αe=34.13). The thermo-sensitivity testing showed that degree of swelling decreases along with temperature increasing. The phase transition is in the temperature interval from 40°C to 45°C. The lowest degree of swelling of p(VP) was achieved in the highest tested temperature at 80°C (α=12.13). Porous structure of p(VP) hydrogels were confirmed by SEM micrographs. It can be concluded that with a decrease in the amount of cross-linker increases the pore size and degree of swelling of synthesized cross-linked p(VP) hydrogels.

Keywords: *Hydrogels, 1-vinyl-2-pyrrolidone, swelling, scanning electron microscopy*

1. INTRODUCTION

Hydrogels are hydrophilic polymer chains [1]. The main characteristic of temperature-sensitive hydrogels is the ability to swell in the presence of a solvent, due to a change in the temperature of the solvent itself, without dissolving [2,3]. pH sensitive hydrogels contain the ionized functional groups of the side. These functional groups react to changes in the pH of the surrounding medium [4]. Hydrogels, more than any other synthetic biomaterial, resemble to natural living tissue [5]. In order to achieve the desired properties and behavior of hydrogels during swelling, biodegradability, stability, strength and biocompatibility, appropriate monomers should be selected as well as adequate synthesis. Poly(1-vinyl-2-pyrrolidone) is a polar, hydrophilic, amphoteric polymer, derived from a monomer of 1-vinyl-2-pyrrolidone. It is used in many branches of industry (in the production of glues, paper and detergents), especially due to its good solubility in water and in a large number of organic solvents. It is intensively used in the pharmaceutical industry as a filler for many drugs due to its low toxicity [6,7]. Poly(1-vinyl-2-pyrrolidone) shows biocompatibility and is safe for use in biological

experiments, is one of the most widely used polymers in medicine due to its solubility in water and low cytotoxicity [8]. The aim of this study was to examine swelling behavior of synthesized poly(1-vinyl-2-pyrrolidone) hydrogels. Data obtained by scanning electron microscopy (SEM) were used to determine the structure and pore size of the freeze-dried hydrogels, swelled to equilibrium state [9].

2. MATERIALS AND METHODS

2.1. Materials

For the synthesis of homopolymer hydrogels, the monomer 1-vinyl-2-pyrrolidone, VP, degree of purity ≥99% (Merck KGaA, Darmstadt, Germany) was used. Ethylene glycol dimethacrylate, EGDM, degree of purity 97% (Fluka Chemical Corp, CH), was used as a crosslinker of chain polymer units. 2,2'-azobis(2-methylpropionitrile), AZDN, 98% purity (Acros Organics, New Jersey, USA) was used to initiate radical polymerization. Methanol (Merck KGaA), 99.5% purity, was used to dissolve the reactants in the polymerization reaction.

2.2. Methods

By radical polymerization of 1-vinyl-2-pyrrolidone monomer, samples of homopolymeric hydrogels of poly(1-vinyl-2-pyrrolidone), p(VP), with 1, 2 and 3 mol% crosslinkers of ethylene glycol dimethacrylate were synthesized. The polymerization reaction was initiated by the addition of 2,2'-azobis(2-methylpropionitrile) initiator, and the reactants were dissolved in an adequate amount of methanol. The measured amounts of reactants for the synthesis of poly(1-vinyl-2-pyrrolidone) homopolymers are listed in Table 1. After homogenization and dissolution of the reactants, the reaction mixtures were injected into glass ampoules, which were then heated. All samples were subjected to a polymerization reaction that was initiated thermally according to the following regime: 30 min. at 70°C, 120 min. at 80°C and 90 min. at 85°C.

mol% EGDM	VP (mg)	EGDM (mg)	AZDN (mg)	methanol (cm^3)
1	522,5	9,32	30,00	0,9
2	522,5	18,64	30,00	0,9
3	522,5	27,96	30,00	0,9

Table 1. Measured amounts of reactants for the synthesis of poly(1-vinyl-2-pyrrolidone)

The synthesized poly(1-vinyl-2-pyrrolidone) hydrogels were separated from the glass ampoules in the form of long cylinders and cut into smaller cylinders. The crosslinked hydrogels p(VP) were then treated with methanol for 48 h at room temperature with occasional stirring (0.5 g of gel was poured over 30 cm^3 of methanol each) to remove any unreacted compounds. After treatment with methanol, the hydrogels were immersed in a solution of methanol/distilled water in a ratio of 75/25 %, 50/50 %, 25/75 % and 0/100 %, v/v, for 24 h, in order to gradually wash the gels from methanol. The hydrogels p(VP) were dried at 40°C to constant weight and then further characterization was performed.

2.3. Characterization of poly(1-vinyl-2-pyrrolidone) hydrogels

2.3.1. Scanning electron microscopy

Samples of swollen p(VP) hydrogel, were first freeze dried for SEM microscopy and then metalized by gold-palladium alloy (15/85) and then recorded on a JEOL scanning microscope JSM-5300.

2.3.2. Swelling behavior

Synthesized samples of poly(1-vinyl-2-pyrrolidone) xerogels were immersed in solutions of appropriate pH (3.0; 6.0 and 9.0) and swelling was monitored gravimetrically, by measuring the mass of the samples at certain time intervals until equilibrium was reached, i.e. until a constant mass of hydrogels is reached at the appropriate temperature (25 to 80°C). The degree of swelling, α, can be calculated according to the equation (1):

$$\alpha = \frac{m - m_0}{m_0} \quad (1)$$

where m_0 is the mass of the dry gel, m is the mass of the swollen gel at time t [10].

The equilibrium degree of swelling, α_e, can be calculated according to the equation (2):

$$\alpha_e = \frac{m_e - m_0}{m_0} \quad (2)$$

where m_e is the mass of the swollen hydrogel in equilibrium.

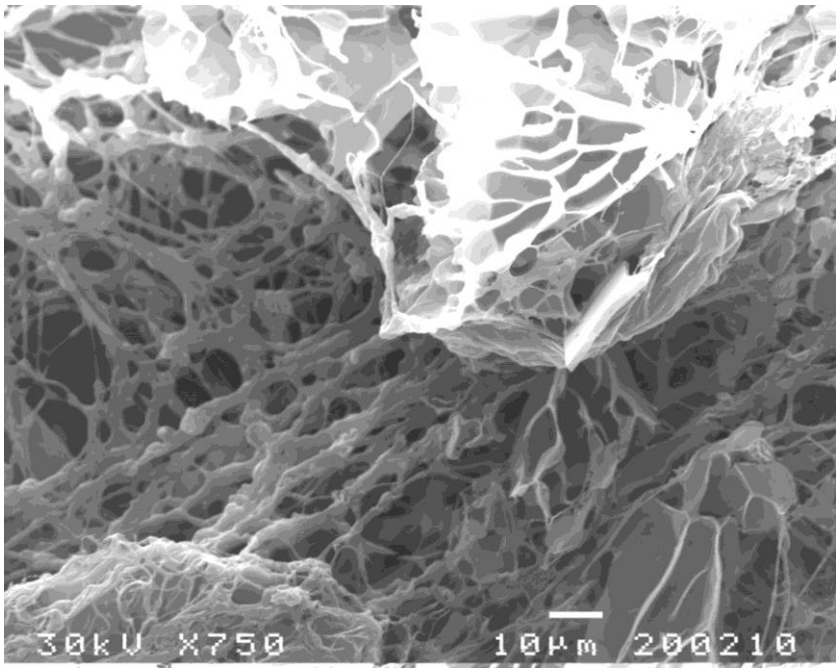
3. RESULTS AND DISCUSSION

3.1. Synthesis of homopolymeric hydrogel poly(1-vinyl-2-pyrrolidone)

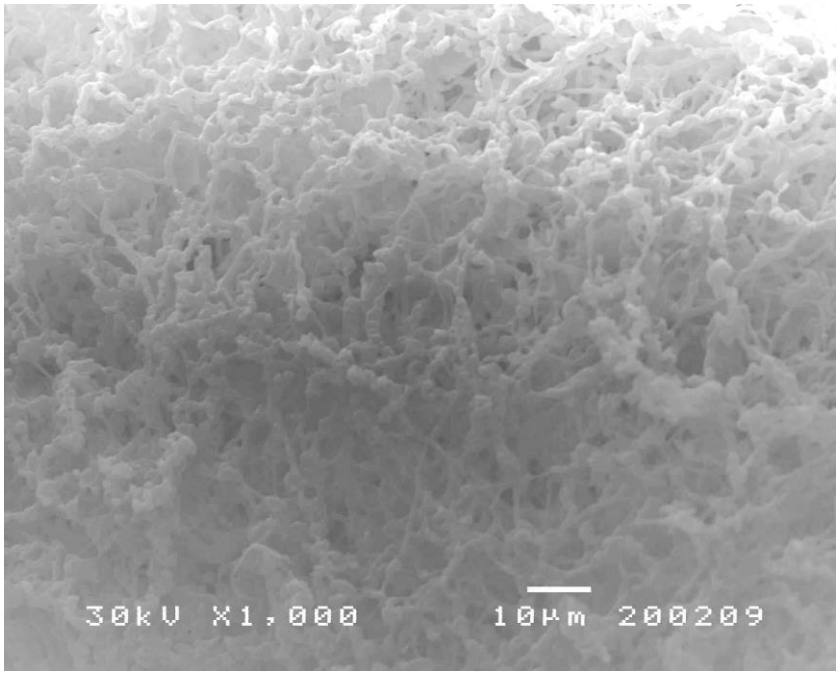
Homopolymeric hydrogels of poly(1-vinyl-2-pyrrolidone) based on 1-vinyl-2-pyrrolidone monomer were synthesized using EGDM crosslinkers and AZDN initiators. After synthesis, further characterization of the hydrogels was performed.

3.2. Morphology characterization of poly(1-vinyl-2-pyrrolidone) hydrogels by SEM method

Data obtained by scanning electron microscopy (SEM) were used to determine the structure and pore size of the freeze-dried hydrogels, swelled to equilibrium state. Figure 1a shows the SEM micrograph of p(VP) with 1 mol% of EGDM cross-linker and 2b with 3mol% of EGDM.



a)



b)

Fig. 1. SEM micrographs of poly(1-vinyl-2-pyrrolidone) with amount of EGDM crosslinker: a) 1 mol% (magnification 750x), and b) 3 mol% (magnification 1000x)

The characteristic porous structure of the hydrogel can be seen in the figure 1. The morphology of the hydrogels has a structure with spherical and ellipsoidal surfaces. All hydrogel sample show a similar surface structure. The micrographs show a decrease in the pore size of the swollen poly(1-vinyl-2-pyrrolidone) hydrogels with an increase in the crosslinking content.

3.3. Thermo- and pH- sensitivity analysis of p(VP) hydrogels

3.3.1. Equilibrium swelling of p(VP) hydrogels at 25°C

3.3.1.1. Equilibrium swelling of p(VP) hydrogels at 25°C and pH=3.0

The degree of swelling, α, of synthesized poly(1-vinyl-2-pyrrolidone) hydrogels with 1, 2 and 3 mol% of EGDM crosslinker in an acidic medium, in a fluid pH value of 3.0 at 25ºC, was calculated as the ratio of absorbed mass of water and xerogel masses as a function of swelling time according to equation (1). The equilibrium degree of swelling, α_e, was calculated for the swollen hydrogel in equilibrium state. The obtained results of the time dependence of the degree of swelling are shown in Figure 2. It is noticed that the amount of crosslinkers of ethylene glycol dimethacrylate affects the degree of swelling of poly(1-vinyl-2-pyrrolidone) hydrogels, i.e. as the amount of crosslinker increases, the degree of swelling of the hydrogels decreases. Hydrogels p(VP) reach the highest degree of swelling after 180 min. The sample of hydrogel p(VP) with 1 mol% of EGDM crosslinker reaches the highest degree of swelling (α=28.07) after 360 min, after which it grows until equilibrium is reached (α=34.13). The hydrogel with 3 mol% EGDM shows a moderate increase in swelling capacity over time and the lowest value of the equilibrium degree of swelling in an acidic environment (α=17.76). The amount of EGDM crosslinker introduced at the beginning of the reaction affects the degree of swelling of poly(1-vinyl-2-pyrrolidone) hydrogels, so that it causes a decrease in the swelling capacity with an increase in the content of EGDM crosslinkers.

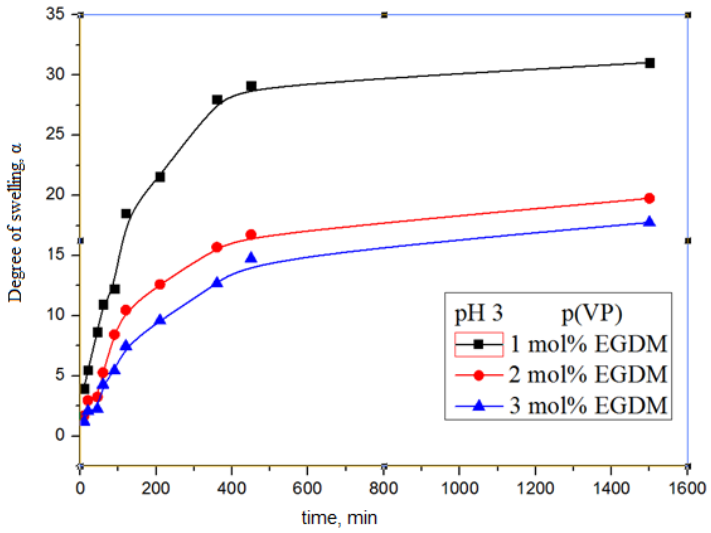


Fig. 2. Degree of swelling, α, for poly(1-vinyl-2-pyrrolidone) hydrogels with 1, 2 and 3 mol% EGDM crosslinker at 25ºC and pH=3 as a function of time

3.3.1.2. Equilibrium swelling of p(VP) hydrogels at 25ºC and pH=6.0

Dependences of change in the degree of swelling, α, for poly(1-vinyl-2-pyrrolidone) hydrogels on the swelling time and on the content of crosslinkers (1, 2 and 3 mol% EGDM) at a temperature of 25ºC in a fluid whose pH value is 6.0 are shown in Figure 3.

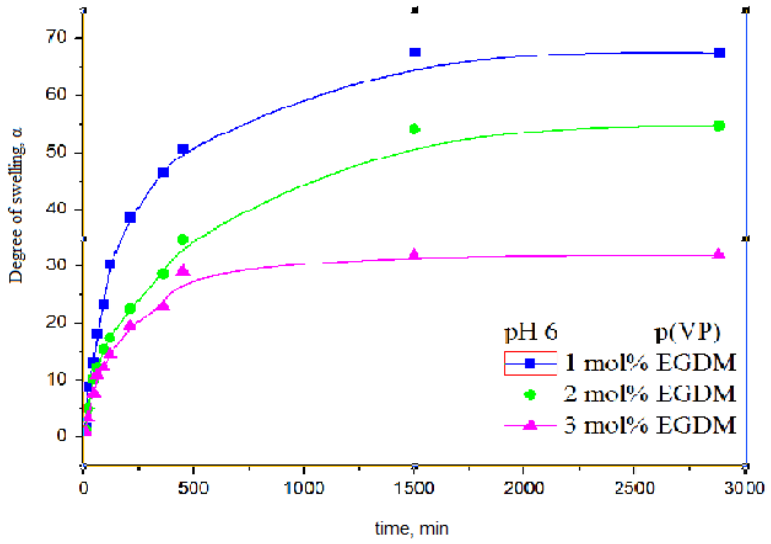


Fig. 3. Degree of swelling, α, for hydrogels p(VP) with 1, 2 and 3 mol% of EGDM cross-linker at 25ºC and pH=6 as a function of time

Even in conditions of weakly acidic environment, in a fluid whose pH value is 6, the amount of crosslinker of ethylene glycol dimethacrylate in poly(1 vinyl-2-pyrrolidone) hydrogels shows an influence on the degree of swelling, so that samples with less crosslinker have a higher degree of swelling. All samples of hydrogels p(VP) with variable content of crosslinkers (1, 2 and 3 mol% EGDM), in fluid with pH=6.0 at 25ºC, reach the highest degree of swelling after 120 min, reaching a

value close to equilibrium. The sample of hydrogel p(VP) with 1 mol% of EGDM crosslinker achieves the highest equilibrium swelling (α=67.58) after 24h. The hydrogel with 3 mol% EGDM shows the lowest value of the equilibrium degree of swelling (α=32.05). The content of EGDM crosslinkers significantly affects the degree of swelling of hydrogels p(VP) at a temperature of 25ºC and a weakly acidic environment (pH=6). Samples with a higher amount of crosslinker (2 and 3 mol%) due to the formation of a denser polymer network show a slightly lower swelling capacity compared to hydrogels with a lower amount of crosslinker (1 mol%) of ethylene glycol dimethacrylate.

3.3.1.3. Equilibrium swelling of p(VP) hydrogels at 25ºC and pH=9

The change in the degree of swelling of homopolymeric hydrogels of poly(1-vinyl-2-pyrrolidone) with 1, 2 and 3 mol% of EGDM crosslinker in the alkaline medium depending on the content of EGDM crosslinker over time at 25ºC (Fig. 4) was monitored. Under alkaline conditions (pH=9), poly(1-vinyl-2-pyrrolidone) hydrogels at room temperature show significantly higher values of the equilibrium degree of swelling compared to the values of swelling achieved in the tested fluids of lower pH values (3 and 6). All samples of hydrogels p(VP) reach the highest degree of swelling after 500 min, reaching a value close to equilibrium. Hydrogel p(VP) with 1 mol% EGDM crosslinker achieves equilibrium degree of swelling (α=141.98) after 2 days, while p(VP) with 3 mol% EGDM shows lower equilibrium degree of swelling (α=109.86). The formed denser polymer network in samples of hydrogels p(VP) with 2 and 3 mol% of EGDM crosslinker significantly reduces the swelling capacity of hydrogels at 25ºC in the alkaline fluid (pH=9) and shows lower values of degree of swelling compared to the sample with 1 mol% of the crosslinker.

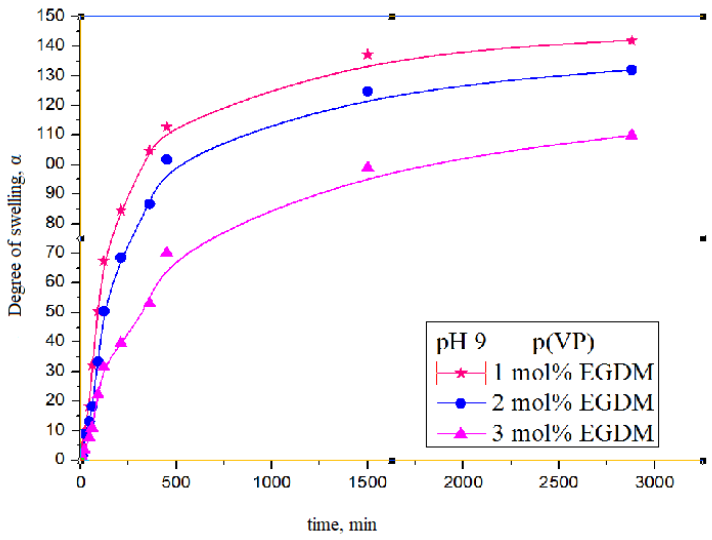


Fig. 4. Degree of swelling, α, for hydrogels p(VP) with 1, 2 and 3 mol% of EGDM cross-linker at 25ºC and pH=9 depending on time

3.3.2. Thermosensitivity analysis of p(VP) hydrogels

Thermosensitivity analysis of synthesized homopolymeric poly(1-vinyl-2-pyrrolidone) hydrogels was performed by monitoring the change in the equilibrium degree of swelling, calculated using equation (2) with increasing temperature from 25 to 80ºC in a solution with a pH value of 6.0 (Figure 5).

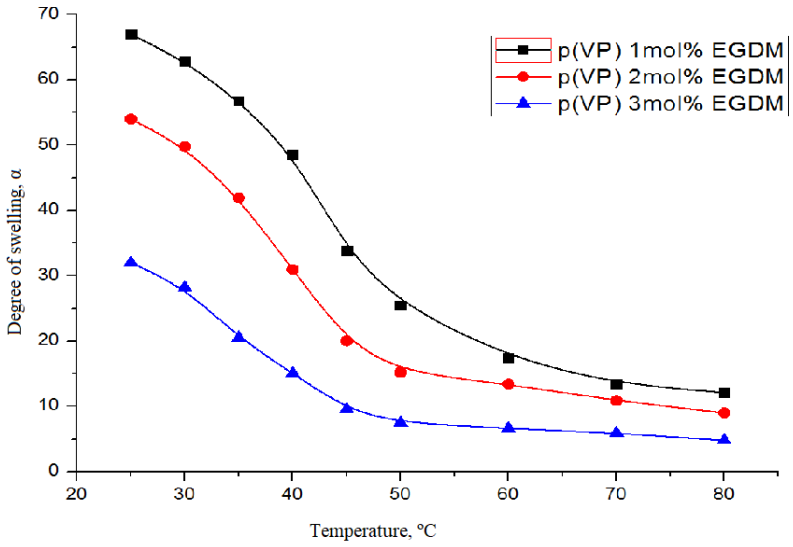


Fig. 5. Change in the equilibrium degree of swelling, α, hydrogel poly(1-vinyl-2-pyrrolidone) with 1, 2 and 3 mol% EGDM crosslinker depending on the temperature in the fluid pH=6.0

The figure 5 shows that the swelling of hydrogels p(VP) is most intense at room temperature (25ºC) and in a solution of pH 6.0 reaches the highest, equilibrium degree of swelling (α=67.46 for the sample with 1 mol% EGDM) , in relation to the values achieved at the highest tested temperature of 80ºC (α=12.13). The equilibrium degree of swelling decreases most intensively with increasing temperature in the interval from 40ºC to 45ºC, where phase transition occurs. With a decrease in the degree of networking, i.e. the amount of crosslinker, there is an increase in the degree of swelling because the polymer matrix has a lower density. Based on examination of the temperature sensitivity of the synthesized homopolymeric hydrogels (1-vinyl-2-pyrrolidone) can be concluded that they show negative thermal sensitivity and have a lower critical solution temperature (LCST).

4. CONCLUSIONS

Cross-linked homopolymeric poly(1-vinyl-2-pyrrolidone) hydrogels with 1, 2 and 3 mol% crosslinkers of ethylene glycol dimethacrylate were synthesized by the method of radical polymerization with thermal initiation. SEM microscopy confirmed the porous structure of hydrogels. At a temperature of 25°C, hydrogels p(VP) swell the lowest in a strongly acidic environment (pH=3), and most intensely in a alkaline fluid (pH=9). The synthesized homopolymeric poly(1-vinyl-2-pyrrolidone) hydrogels show sensitivity to temperature changes and they are negatively thermosensitive, i.e. they swell at lower temperatures and contract at higher temperatures. Based on the performed synthesis and characterization of crosslinked poly(1-vinyl-2-pyrrolidone) hydrogels, it can be concluded that there is a need to find new potential applications of the obtained products.

ACKNOWLEDGMENTS

The financial support of the Republic of Serbia - Ministry of Education, Science and Technological Development, Program for Financing Scientific Research Work, ev. no. 451-03-68/2020-14/200133.

REFERENCES

1. Guiseppi-Elie, A 2010, "Electroconductive hydrogels: synthesis, characterization and biomedical applications", *Biomaterials*, vol. 31, no. 10, pp. 2701-2716.
2. Peppas, NA, Bures, P, Leobandung, W, Ichikawa H, 2000, "Biopharm", *Eur J Pharm*, vol. 50, no. 1, pp. 27–46.
3. Roy, N, & Saha, N 2012, "PVP-based hydrogels: synthesis, properties and applications", *Hydrogels: Synthesis, Characterization and Applications*, pp. 227-252.
4. Kumar, A, Srivastava, A, Galaev, IY, Mattiasson, B 2007 "Smart polymers: physical forms and bioengineering applications", *Progress in polymer science*, vol. 32, no. 10, pp. 1205-1237
5. Murdan, S 2003, "Electro-responsive drug delivery from hydrogels", *Journal of controlled release*, vol. 92, no.1-2, pp. 1-17
6. Antić VV, Antić MP, Kronimus, A, Schwarzbauer, J 2012, "Quantitative determination of poly(vinylpyrrolidone) by 'On-line' pyrolysis coupled with gas chromatography", *Hemijska industrija*, vol.66, no. 3, pp. 357-364
7. Ammar, NEB, Essid, R, Saied, T, Şen, M, Elkahoui, S, Hamzaoui, AH 2020, "Synthesis and characterization of radiation cross-linked PVP hydrogels and investigation of its potential as an antileishmanial drug carrier" *Polymer Bulletin*, vol. 77, no.3, pp. 1343-1357
8. Ahmed EM 2015, "Hydrogel: Preparation, characterization, and applications: A review", *JAR* vol. 6, pp. 105–121
9. Kaewpetch, T, Gilchrist, JF, 2020, "Chemical vs. mechanical microstructure evolution in drying colloid and polymer coatings", *Scientific Reports*, vol.10, no. 1, pp. 1-10
10. Ilić-Stojanović, S, Nikolić, L, Nikolić, V, Petrović, S 2017, "Smart hydrogels for pharmaceutical applications", *Materials Science and Engineering*: *Concepts, Methodologies, Tools, and Applications*, pp. 1133-1164. IGI Global