



Originalni naučni rad

<https://doi.org/10.24094/ptk.025.1.075>

Ključne reči:
ekološki prihvatljiv inicijator;
vitamin C; pH-osetljivi
hidrogelovi; kontrolisano
oslobađanje; slabo
vodorastvorni lekovi

Key words:
eco-friendly initiator;
vitamin C; pH sensitive
hydrogels; controlled release;
poorly water-soluble drugs

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EKOLOŠKI PRIHVATLJIVI SISTEMI NA BAZI HIDROGELOVA ZA pH-OSETLJIVO OTPUŠTANJE KOFEINA

ECO-FRIENDLY HYDROGEL SYSTEMS FOR pH-RESPONSIVE CAFFEINE DELIVERY

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Kontrolisano oslobađanje lekova ima mnoge prednosti u odnosu na konvencionalne oblike lekova kod raznih terapija, zato što omogućava da se nivo koncentracije leka tokom vremena održava konstantnim. Na ovaj način se smanjuje učestalost doziranja leka i minimizuju neželjeni efekti. pH-osetljivi hidrogelovi, posebno oni na bazi poli(metakrilne kiseline) (PMAA), imaju veliku primenu kao sistemi za dostavu lekova. Metoda sinteze sistema za dostavu lekova predstavlja važan faktor koji utiče na efikasnu inkapsulaciju leka i očuvanje njegove bioaktivnosti. U ovom istraživanju je ispitana mogućnost inkapsulacije slabo rastvornog model leka – kofeina, u PMAA hidrogelove tokom njihove sinteze, a zatim i mogućnost kontrolisanog oslobađanja kofeina iz tako pripremljenih PMAAk hidrogelova. Priprema PMAAk hidrogelova izvedena je primenom inovativne, ekološki prihvatljive metode slobodno-radikalnom polimerizacijom u vodenom rastvoru u ambijentalnim uslovima. Ovakav način sinteze je postignut primenom inicijatorskog sistema na bazi vodonik-peroksida i vitamina C. Pripremljeno je četiri PMAAk hidrogela sa različitim koncentracijama umreživača. Bubrenje PMAAk hidrogelova i kinetika oslobađanja kofeina ispitani su u dve sredine različite pH vrednosti – pH 1 i pH 6,8, koje su simulirale pH sredine u ljudskom želucu i crevima, redom. PMAAk hidrogelovi su imali osam puta veće vrednosti ravnotežnog stepena bubrenja u sredini sa pH 6,8. Kao posledica takvog načina bubrenja, tri puta veća količina kofeina je oslobođena u sredini sa pH 6,8 u odnosu na sredinu sa pH 1. Takođe, povećanje koncentracije umreživača dovodi do smanjenja stepena bubrenja hidrogelova i nižeg stepena oslobađanja model leka. Dobijeni rezultati pokazuju da PMAAk hidrogelovi, dobijeni ekološki prihvatljivom metodom, imaju veliki potencijal za efikasno kontrolisano oslobađanje slabo rastvorljivih lekova.

The controlled release of drugs provides a significant advantage in therapeutic applications by ensuring a stable drug concentration over time. This approach reduces dosage frequency and helps minimize side effects. pH-sensitive hydrogels, particularly those based on poly(methacrylic acid) (PMAA), are widely utilized in drug delivery systems. The synthesis method plays a crucial role in drug encapsulation and preserving its bioactivity. This study explores the incorporation of a poorly

water-soluble model drug - caffeine, into PMAAk hydrogels during synthesis and evaluates its controlled release. A novel, environmentally friendly approach is employed for hydrogel preparation, using a free radical polymerization process in an aqueous solution under ambient conditions. The initiation system, based on hydrogen peroxide and vitamin C, enables the formation of PMAAk hydrogels. Four PMAAk hydrogels with different crosslinker concentrations are prepared. The swelling behavior and caffeine release profiles are analyzed at two pH values, pH 1 and pH 6.8, which simulate the human stomach and intestines, respectively. The PMAAk hydrogels exhibit an eightfold increase in equilibrium swelling degree at the pH 6.8, which lead to a threefold higher caffeine release compared to the environment with pH 1. Additionally, increasing the crosslinker concentration results in reduced swelling degree and lower level of drug release. These findings highlight the potential of PMAAk hydrogels as an effective system for the controlled delivery of poorly water-soluble drugs.

1. Introduction

Hydrogels are polymer materials with tremendous properties due to which they are widely used as systems for controlled release of active substances and have application in cardiology, oncology, immunology, for wound healing and pain treatment [1-4]. These materials have three-dimensional highly hydrophilic polymer network due to which they can absorb and retain a huge quantity of water and/or biological fluids. Due to the presence of such large quantity of fluid in the hydrogel network (usually 70-99% compared to the mass of xerogel), the hydrogel structure is very similar to the human tissues and that is where the biocompatibility of hydrogels comes from.

Amongst other group of hydrogels, hydrogels sensitive to external stimuli attract special attention. These hydrogels can swell/shrink as a response to change of certain stimulus in the external environment due to which they are extensively employed for controlled release of drugs. By employing these materials as systems for drug delivery, efficient therapy can be achieved by applying lower number of drug dosages, whereas side effects can be brought to the minimum. Hydrogels based on poly(methacrylic acid) (PMAA) are one group of pH sensitive hydrogels which are used for targeted drug delivery. These materials are biocompatible, non-toxic and swell in the environments with pH value higher than pKa of methacrylic acid (4.6) [5]. This property of PMAA hydrogels is used for drug delivery to the human intestines (pH~6.8) where absorption of drug is the highest. At the same time, this hydrogel can protect drug from degradation in the human stomach.

The hydrogels synthesis is one of the most important factors that has effect on design of system for controlled release of drug, because it affects the encapsulation of drug and/or its activity. This is the reason why the synthesis of hydrogels is desired to be conducted in the absence of organic solvents and under mild conditions [6,7]. In order to achieve these goals, a "green" method for synthesis of PMAA hydrogels has been developed, which does not involve the use of toxic organic solvents and can be conducted at room temperature by using novel initiator based on hydrogen peroxide and ascorbic acid (vitamin C) [8]. In the present study, we investigate if the encapsulation of poorly water-soluble active substance during the synthesis of PMAA hydrogels and its controlled release from the prepared PMAAk hydrogels can be achieved. Caffeine was chosen as poorly water-soluble model drug, because according to the United States Pharmacopeia (USP) this substance can be considered as poorly soluble [9]. Hydrogels based on PMAA with encapsulated caffeine were synthesized via free radical polymerization. Then, their swelling behavior and caffeine release from the PMAAk were investigated in two media which simulated pH environment in human stomach (pH~1) and human intestines (pH~6.8). The impact of the change in the crosslinker amount on the swelling behavior of the PMAAk hydrogels and caffeine release profiles were further analyzed.

2. Materials and methods

2.1. Materials

Methacrylic acid (99.5%) (MAA) and caffeine were obtained from Merck (Germany). The crosslinker N,N'-methylenebisacrylamide (p.a.) (MBA) was purchased from Aldrich Chemical Co. (USA). Vitamin C was supplied from Alkaloid (N. Macedonia). Hydrogen peroxide (30% v/v) was obtained from Sigma Aldrich (USA). Monobasic sodium phosphate (anhydrous) and dibasic sodium phosphate (anhydrous) were supplied from Merck (Germany). Hydrochloric acid (37%) was obtained from Sigma Aldrich (USA). All chemicals were used as received.

2.2. Preparation and characterization of PMAAk hydrogels

Synthesis of the PMAAk hydrogels was carried out by free radical polymerization in an aqueous solution. The reaction was initiated by the hydrogen peroxide/vitamin C (H₂O₂/VC) system. The synthesis was carried out under ambient conditions as follows.

The total volume of reaction mixture for each sample was 20 mL. 4 mL of methacrylic acid was added to the distilled water (amount for each sample is shown in Table 1). At the same time, 0.2 g of caffeine was dissolved in 5 mL of distilled water (this volume of water is part of the total amount of water used for synthesis of each sample, which is given in Table 1). Then, a certain amount of crosslinker - MBA was added to the reaction mixture with constant stirring (Table 1). For initiation of the reaction of polymerization, 100 µL of hydrogen peroxide and 10 mg of vitamin C were used. After their addition to the reaction mixture of each sample, mixing was continued for another 15 min. Then, prepared aqueous solution of caffeine was added to the reaction mixture, after which the reaction mixture was poured into moulds and left in ambient conditions for 24 hours. After completed polymerization and crosslinking, the hydrogels were removed from the moulds and cut into discs shape samples with a diameter of 7 mm and thickness of 2 mm. Then, the prepared disks were left to dry at room temperature, after which they were used for further analysis.

The samples with encapsulated caffeine in which the amount of crosslinker was varied were designated as PMAAk-yMBA, where yMBA was the amount of MBA in mol% calculated in respect to MAA. The sample in which caffeine was not encapsulated and which had 0.4 mol% MBA was designated as PMAA.

Table 1. Feed composition

| Sample | Distilled water (mL)* | MBA (mol % calculated with respect to MAA) |
|---------------|-----------------------|--|
| PMAA | 13.02 | 0.4 |
| PMAAk-0.2 MBA | 14.26 | 0.2 |
| PMAAk-0.4 MBA | 12.82 | 0.4 |
| PMAAk-1.6 MBA | 9.95 | 1.6 |
| PMAAk-3.2 MBA | 15.58 | 3.2 |

*The total volume of reaction mixture for each sample was 20 mL

The Fourier Transform Infrared (FTIR) spectra of xerogel disks were recorded in transmittance mode for the wavelength range of 600 to 4000 cm⁻¹ with a resolution of 4 cm⁻¹, using Nicolet iS10 FTIR Spectrometer.

The compression tests were conducted as follow. The samples were submerged in 0.1M HCl and 0.2 M phosphate buffer (pH=6.8) - PB 6.8 and allowed to swell until they reached equilibrium. Afterward, they were taken out, and any excess medium was carefully blotted using a paper towel. The prepared samples were then subjected to compression testing at room temperature using a Shimadzu Autograph AGS-X (1kN) apparatus, with a deformation rate of 2 mm/min. The compression strength was measured up to the material's elastic limit.

2.3. Monitoring of PMAAk hydrogels swelling

The swelling of the PMAAk hydrogels was monitored in 0.1 M HCl (pH=1) and PB 6.8. These media simulated the pH environments in human stomach and intestines, respectively [10,11]. Prior the swelling experiments the mass of each hydrogel was first measured (m_0 , g), and then each sample was immersed into the selected media. At certain time intervals, the sample was taken out, excess water was removed with a paper towel, its mass was measured (m_t , g) and it was immediately returned to the medium where the swelling was monitored. The swelling of the hydrogels was monitored until the equilibrium state, i.e. the constant mass of the samples, was reached. The obtained values of hydrogel mass were introduced into the Equation (1), the values of the swelling degree (SD) were determined (Eq. (1)) and then the curves of the hydrogels swelling in each medium were constructed. The equilibrium swelling degree (SDeq) of each sample were calculated according to the Eq. (1) by replacing the m_t value with m_{eq} value which represented the mass of hydrogel in equilibrium state.

$$SD = (m_t - m_0) / m_0 \quad (1)$$

2.4. Controlled release of caffeine from PMAAk hydrogels

The amount of caffeine which was encapsulated into the hydrogels was determined according to so-called extracting method [12].

In order to investigate the process of caffeine release, PMAAk hydrogels were immersed in two media: 100 mL 0.1 M HCl and 100 mL 0.2M PB 6.8 at 37 °C as simulation of pH environments in human stomach and human intestines, respectively [10,11]. 3 mL of each medium was collected at predetermined time intervals, the absorbance was determined by using UV-Vis spectrophotometer (Shimadzu) and analysed sample was returned back. The wavelength at which the absorbance value was determined was 273 nm. The data obtained from these measurements were used to construct cumulative drug release curves. The drug release was monitored until equilibrium state was reached.

3. Results and discussion

3.1. FTIR analysis and compression testing of PMAAk hydrogels

The FTIR spectra of caffeine, the PMAA sample (hydrogel without caffeine) and the PMAAk hydrogels are presented in Fig. 1.

The analysis of the FTIR spectra of the PMAAk hydrogels showed the presence of characteristic peaks of poly(methacrylic acid) at: 2995 cm^{-1} and 2933 cm^{-1} (vibration of C-H methylene group), 1691 cm^{-1} (stretching vibration of C=O bond in carboxylic group) and 1396 cm^{-1} (stretching and bending vibration of bonds in -CH₃ group) [13].

The presence of caffeine in the PMAAk hydrogels was confirmed by the presence of the characteristic peaks of caffeine at: 1023 cm^{-1} (stretching vibration of C-OH bond) and 1629 cm^{-1} (stretching vibration C=O bond) [14, 15]. Most of the characteristic peaks of caffeine were not visible due to

overlapping with the characteristic peaks of poly(methacrylic acid) [16]. The position of characteristic peaks of poly(methacrylic acid) was not changed after encapsulation of caffeine, therefore it can be concluded that caffeine was physically entrapped into the hydrogels' network during the synthesis.

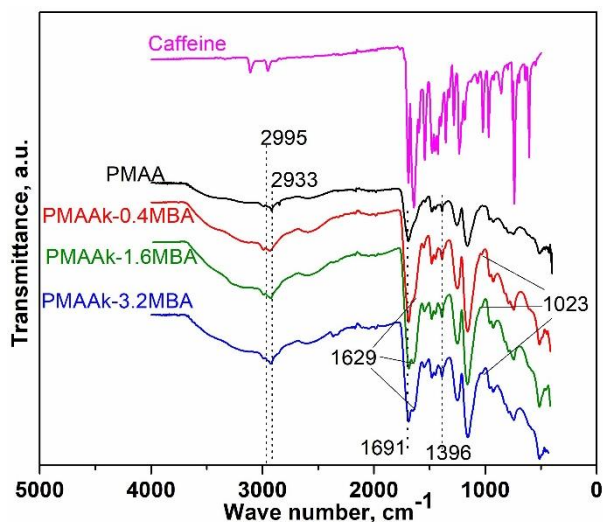


Figure 1. FTIR spectra of the PMAAk hydrogels

Based on the results obtained from the compression testing of the PMAAk hydrogels, it was concluded that the values of compressive stress and the percentage of deformation of the PMAAk hydrogels previously swollen in PB 6.8 were lower than those of the same samples swollen in 0.1M HCl (Table 2). This result was explained by the fact that PMAAk hydrogels swelled more in PB 6.8, leading to a weaker network structure compared to the same samples swollen in 0.1M HCl. In the polymer network of PMAAk hydrogels swollen in PB 6.8, a greater amount of external medium was present, which weakened the interactions between the hydrogel components. As a result, the mechanical properties of PMAAk hydrogels deteriorated, and deformations became irreversible almost immediately after the application of compressive force. Similarly, the better mechanical properties and elastic response of PMAAk hydrogels in 0.1M HCl were explained by the fact that the samples swelled less in 0.1M HCl, resulting in stronger interactions between the sample components compared to those in the same sample swollen in PB 6.8.

Table 2. Compressive stress and maximal stoke strain of the PMAAk hydrogels swollen to equilibrium in 0.1M HCl and PB 6.8

| Sample | 0.1M HCl | | PB 6.8 | |
|--------------|---|-------------------------|---|-------------------------|
| | Maximal compressive stress, N/mm ² | Maximal stoke strain, % | Maximal compressive stress, N/mm ² | Maximal stoke strain, % |
| PMAA-0.4MBA | 421.0 | 65.27 | 47.1 | 55.27 |
| PMAAk-0.2MBA | – | – | – | – |
| PMAAk-0.4MBA | 438.7 | 66.10 | 73.99 | 60.96 |
| PMAAk-1.6MBA | 779.9 | 76.82 | 97.92 | 68.81 |
| PMAAk-3.2MBA | 833.98 | 77.91 | 109.4 | 82.54 |

The compression testing of the PMAAk hydrogels revealed that as the amount of crosslinker increases, both the values of σ and the percentage of deformation during compression rise. This result

was expected since the stiffness of the PMAAk hydrogel network increases with a higher degree of crosslinking. It was not possible to assess the mechanical properties of PMAAk-0.2MBA sample swollen to equilibrium in PB 6.8, as its network structure was at the threshold of crosslinking. Due to its high degree of swelling, this sample lacked a defined shape.

3.2. Swelling behavior of PMAAk hydrogels

Swelling curves of the PMAAk hydrogels in 0.1 M HCl and PB 6.8 are shown in the Fig. 2. a) and b), respectively. The swelling curves of the PMAA were published by M. Markovic et al. [8] and the SDeq values of this sample is presented in Table 3. for comparison with the SDeq values of the PMAAk hydrogels which are also presented in the same table.

The SDeq values of the samples were around eight times higher in PB 6.8 than the corresponding values of the samples swollen to equilibrium in 0.1 M HCl. This result confirms that the PMAA hydrogels swelling depends on the change in the pH value of surrounding medium. The swelling of the PMAA hydrogels is the consequence of the change of pH value of external medium. Namely, when the surrounding medium has pH value higher than the pKa of methacrylic acid (4.6), the ionization of the carboxylic groups occurs and negative charges are generated along the polymer's chains [17, 18]. Polymer chains with identical charges experience electrostatic repulsion, which causes an expansion of the hydrogel network and consequently increases hydrogel swelling capacity. PB 6.8 has pH value which is higher than pKa of MAA, so the PMAAk hydrogels swell in this medium.

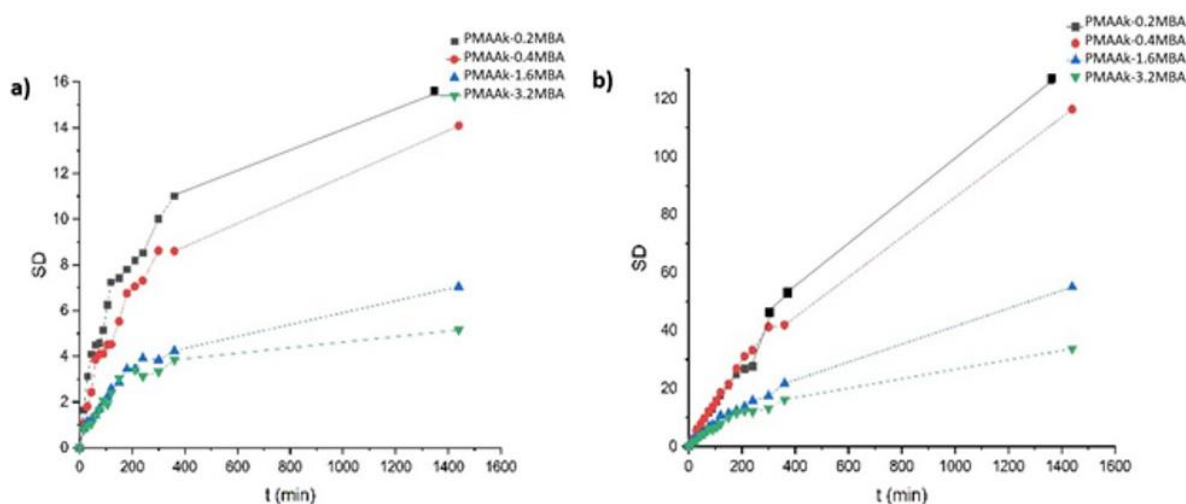


Figure 2. Swelling curves of the PMAAk hydrogels in:
a) 0.1 M HCl and b) PB 6.8

By comparing the SDeq value of PMAA with the SDeq values of the PMAAk hydrogels it was concluded that encapsulation of active substance in the hydrogel network led to the decrease of the SDeq values. This result could be consequence of the presence of caffeine molecules in the pores of hydrogels network which hindered diffusion of the external medium into the hydrogels network [19, 20].

It was also concluded that an increase in the crosslinker amount led to the decrease in the SDeq values (Fig. 2.). Hydrogels with a higher crosslinker content contain a greater number of crosslinking points, resulting in reduced polymer chain mobility and a more rigid network structure. Consequently, the expansion of the hydrogel network is restricted, limiting the diffusion of the external medium into the hydrogel [21].

3.3. Controlled release of caffeine from PMAAk hydrogels

The encapsulated amounts of caffeine in the PMAAk-0.2 MBA, PMAAk-0.4 MBA, PMAAk-1.6 MBA, PMAAk-3.2 MBA hydrogels were 90.18%, 89.12%, 86.41% and 83.39%, respectively.

Based on the data obtained by monitoring the caffeine release from the PMAAk hydrogels at 37 °C, the curves of cumulative drug release in 0.1 M HCl and PB 6.8 are constructed and shown in Fig. 3. a) and b), respectively. The values of cumulative drug release in equilibrium state are presented in Table 3.

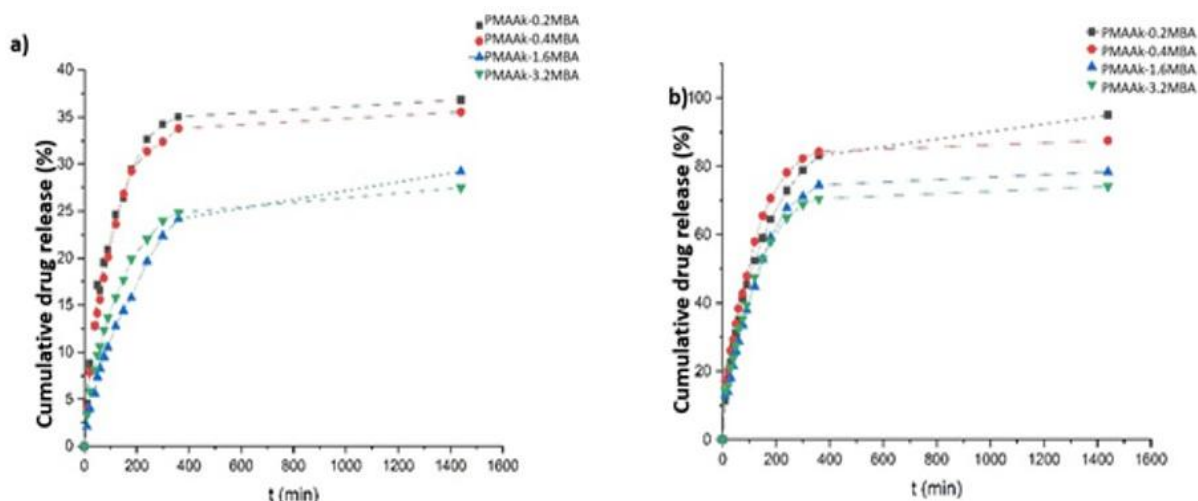


Figure 3. The profiles of caffeine release from the PMAAk hydrogels in:
a) 0.1 M HCl and b) PB 6.8

Amount of caffeine that was released from the PMAAk hydrogels into the PB 6.8 was three times higher than in 0.1 M HCl. This was consequence of the pH dependent swelling of the PMAA hydrogels (Section 3.2).

Table 3. The $SDeq$ values of the PMAAk hydrogels and cumulative caffeine release in two media

| Sample | 0.1M HCl | | PB 6.8 | |
|---------------|----------|----------------------------|--------|----------------------------|
| | $SDeq$ | Cumulative drug release, % | $SDeq$ | Cumulative drug release, % |
| PMAA | 12.04 | - | 76.78 | - |
| PMAAk-0.2 MBA | 16.13 | 36.83 | 80.51 | 94.99 |
| PMAAk-0.4 MBA | 11.08 | 35.54 | 72.28 | 87.59 |
| PMAAk-1.6 MBA | 7.05 | 29.21 | 55.06 | 78.44 |
| PMAAk-3.2 MBA | 5.16 | 27.49 | 33.79 | 74.14 |

Based on the cumulative drug release curves, it was concluded that the amount of released caffeine decreased with an increase in crosslinker content. This result was consistent with the fact that PMAA hydrogels with a higher crosslinker content swelled less and had smaller pore diameters, thereby hindering the diffusion of caffeine from the hydrogels into the external medium [21].

4. Conclusions

Obtained results show that novel method for preparation of the PMAAk hydrogels enables encapsulation of poorly water-soluble substance – caffeine into the hydrogels during the process of synthesis. Also, controlled release of caffeine from the PMAAk hydrogels into the medium which simulated pH environment in human intestines is achieved. In addition, the kinetic of caffeine release can be easily adjusted only by changing the amount of crosslinker. Therefore, the PMAAk hydrogels are good candidate for encapsulation and controlled release of poorly water-soluble substance.

5. Acknowledgement

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Contract No. 451-03-136/2025-03/200287).

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