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Kneza Miloša 7a/II,
11000 Beograd

Predsednik Društva za procesnu tehniku
pri SMEITS-u
prof. dr Aleksandar Jovović, dipl. inž.

Urednici
Prof. dr Marko Obradović, dipl. inž.
Prof. dr Miroslav Stanojević, dipl. inž.
Prof. dr Aleksandar Jovović, dipl. inž.

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Savez mašinskih i elektrotehničkih
inženjera i tehničara Srbije (SMEITS),
Društvo za procesnu tehniku
Kneza Miloša 7a/II, 11000 Beograd
Tel. +381 (0) 11 3230-041, +381 (0) 11 3031-696,
tel./faks +381 (0) 11 3231-372
E-mail: office@smeits.rs
web: www.smeits.rs

BIOHIDROGELOVI POLI(METAKRILNE KISELINE): BUBRENJE I KONTROLISANO OTPUŠTANJE KOFEINA

BIOBASED POLY(METHACRYLIC ACID) HYDROGELS: SWELLING PROPERTIES AND CONTROLLED RELEASE OF CAFFEINE

Maja D. MARKOVIC[1*], Pavle M. SPASOJEVIC[1], Sanja I. SAVIC[2], Olga J. PANTIC[2], Vesna V. PANIC[1]

[1] University of Belgrade, Innovation Center of Faculty of Technology and Metallurgy, Belgrade

[2] University of Belgrade, Institute of Chemistry, Technology and Metallurgy, Belgrade

Savremeno društvo je suočeno sa mnogim izazovima u tretamanu raznih bolesti, naročito ozbiljnih oboljenja kao što je rak. Glavni ciljevi naučnika su da se postigne bezbednija i efikasnija terapija pacijenata koji se leče od raka. Jedan od dobrih načina da se to postigne su sistemi za dostavu lekova. Ipak, mnogi antikancerogeni lekovi su slabovodorastvorni, pa bi veliki izazov mogao da bude inakpsulacija i njihovo kontorlisano otpuštanje iz sistema za dostavu lekova. Cilj ovog rada je da se unapredi sistem za dostavu lekova na bazi hidrofilne poli(metakrilne kiseline) i amfifilnog kazeina sa inkapsuliarnim slabo vodorastvornim kofeinom, koji je razvijen tokom našeg prethodnog istraživanja. U ovom radu sintetisani su hidrogelovi sa 1,6mol% umreživača i 100% neutralisanom metakrilnom kiselinom (PMAC-100N-4M). Procesi bubrenja PMAC-100N-4M hidrogelova i kontrolisanog otpuštanja kofeina su ispitivani u dve sredine koje simuliraju želudac i tanko crevo čoveka. Takođe je ispitano kako promena količine inkapsuliranog kofeina i dodatak lipozomne suspenzije sa inkapsuliranim kofeinom utiče na procese bubrenja PMAC-100N-4M hidorgelova i otpuštanje kofeina. Rezultati pokazuju da je proces kontrolisanog otpuštanje kofeina unapređen, a samim tim je moguće unaprediti i celokupnu terapiju.

Ključne reči: *pH osetljivi hidrogelovi; kazein; lipozomi; kontrolisano otpuštanje; slabovodorastvorni lekovi*

Modern society are faced with lot of challenges in the treatment of many diseases, especially with serious ones such as cancer. Safer and more efficient treatment of the cancer patients are main goals which researchers are aiming. One of the good approaches can be drug delivery systems. Still, a lot of anticancer drugs are poorly water-soluble and their encapsulation and controlled release can be quite challenging. Present study is focused to improve drug delivery system based on hydrophilic poly(methacrylic acid) and amphiphilic casein with encapsulated poorly water-soluble caffeine, which has been developed through our previous research. The hydrogels with 1.6mol% of crosslinker and 100% of neutralization degree of methacrylic acid are synthetized (PMAC-100N-4M). The swelling process of the PMAC-100N-4M hydrogels and caffeine release are analyzed in two environments which simulate human stomach and intestines. It is also investigated how the change in the encapsulated caffeine weight and the addition of liposomes with encapsulated caffeine, affect swelling degree of the PMAC-100N-4M hydrogels and release of caffeine. The results show that controlled release of caffeine is improved, therefore overall therapy can be enhanced.

Key words: *pH sensitive hydrogels; casein; liposomes; controlled release; poorly water-soluble drugs*

1 Introduction

Everyday struggle of humankind with wide range of diseases urge scientists to find new solutions or improve existing ones in order to enhance the therapies. One of the promising solutions which is extensively investigated for over two decades is certainly controlled release of the drugs. Hydrogels are polymeric materials with huge potential as drug delivery systems. One group of these

* Corresponding author, e-mail: mmarkovic@tmf.bg.ac.rs

materials are pH sensitive hydrogels based on poly(methacrylic acid) (PMAA). Nontoxicity, biocompatibility, pH sensitivity, the ability to absorb and retain large amount of fluids make the PMAA hydrogels one of the best choices for controlled release of drugs [1-4]. The PMAA hydrogels swell in the media with pH value higher than pKa of PMAA (4.6 [5-7]). This is due to the deprotonation of carboxylic groups along the polymeric PMAA chains and generation of negative charges which further leads to the repulsion of polymers chains and hydrogels swelling. The specific pH dependent PMAA hydrogels swelling are employed for targeted drug delivery and controlled release in such environments (such as human intestines).

Beside many desirable properties of the PMAA hydrogel, there are some imitating factors which affect PMAA application, such as: poor mechanical properties and highly hydrophilic nature due to which only soluble drugs can be encapsulated into the PMAA hydrogels. Good solution can be find in natural polymeric materials which could be used as interpenetrates to improve mechanical properties and enable encapsulation of drugs with wider range of solubility. We used that kind of approach and employed casein, natural pH sensitive polymer, to enchase the PMAA hydrogel properties and extend the range of its application [8, 9]. Casein is non-toxic, amphiphilic protein approved by Food and Drug Administration (FDA) [5, 10-12]. In our previous research we prepared hydrogels based on PMAA and casein with various amount of crosslinker (PMAC-100N-4M) and demonstrated that poorly water soluble model drug – caffeine can be successfully encapsulated and released in controlled manner in medium which simulated human intestines [13]. Based on these results, we chose sample with 100% neutralized methacrylic acid and 1.6 mol% of crosslinker which had optimal properties for drug delivery and in the present study we investigated how the change of synthesis parameters affect both swelling process of the hydrogels and caffeine release. We wanted to improve the drug carrier so it could be easily adjusted to the specific demands of the therapy. In that manner, bioavailability of the drug can be improved, as well as safety and efficacy of the therapy.

Hydrogels based on poly(methacrylic acid) and casein with 100% neutralized methacrylic acid and 1.6mol% of crosslinker are synthetized in present study. The caffeine was encapsulated either direct into the hydrogel network or liposomes suspension with encapsulated caffeine was embedded into the hydrogel. Swelling behavior of the PMAC-100N-4M hydrogels and caffeine release are analyzed in two media which simulated the environments in the human stomach and intestines. The influence of encapsulated caffeine weight and the addition of liposomes suspension on the swelling process of the PMAC-100N-4M hydrogels and caffeine release profiles are analyzed.

2 Materials and methods

2.1 Materials

Methacrylic acid (99.5%) and caffeine were supplied from Merck (Germany). Sodium caseinate was obtained from Lactoprot Deutschland GmbH (Germany). The crosslinker N,N'-methylenebisacrylamide (p.a.) (MBA) and sodium hydroxide (p.a.) were purchased from Aldrich Chemical Co. (USA). The initiator, 2,2'-azobis-[2-(2-imidazolin-2-yl)propane] dihydrochloride (99.8%) was obtained from Wako Pure Chemical Industries (Japan). NATIPIDE®II containing phospholipids from soybean >20% (with 3-sn-phosphatidylcholine 76+ 3%) was supplied from Lipoid (Germany). Monobasic sodium phosphate (anhydrous) and dibasic sodium phosphate (anhydrous) was supplied from Centrohem (Serbia). Hydrochloric acid (37%) was supplied from Zorka Pharma (Serbia). All chemicals were used as received.

2.2 Preparation of 2.3 PMAC-100N-4M hydrogels

The synthesis path of the PMAC and PMAC/L hydrogels and their characterization are described in details in our previous research [5]. In this study, the encapsulated mass of caffeine was varied. Also, the liposomes with encapsulated caffeine (20 mg/ml) was added into the reaction mixture of one PMAC-100N-4M hydrogel. Briefly, 4 ml of methacrylic acid and various weights of caffeine were dissolved in distilled water (Table 1.), followed by the addition of sodium hydroxide in order to completely neutralized methacrylic acid (100N). In one reaction mixture, the liposomes

suspension with encapsulated caffeine (20 mg/ml) was added instead of caffeine (Table 1.). Subsequently, the temperature of reaction mixture was elevated to 60 ºC and during vigorously stirring 4 g of casein was added and dissolved. Next step was the addition of MBA (1.6 mol% with respect to methacrylic acid) and dissolution, followed by the addition and dissolution of the initiator (0.9 ml of 1 wt% aqueous solution). Final step was pouring of the obtained mixture in glass molds, that were left in the air oven at 60 °C for 5 h after which disc shaped samples were cut and dried at room temperature. Prepared samples are denoted as PMAC-100N-4M-x, where x represents the weight of caffeine which was added during the synthesis of the samples. The sample with embedded liposomes is denoted as PMAC-100N-4M-L where L represents the symbol for the liposomes suspension with encapsulated caffeine (20mg/ml).

Table 1. Feed composition

Sample	*Liposome suspension with caffeine (20mg/ml), % in respect to distilled water*	*Distilled water, ml*	*Caffeine weight, g*
PMAC-100N-0.2	-	6.17	0.2
PMAC-100N-4M-0.2	-	8.93	0.2
PMAC-100N-4M-1	-	8.13	1
PMAC-100N-4M-2	-	7.13	2
PMAC-100N-4M-L	50	4.56	-

2.3 PMAC-100N-4M hydrogels swelling

The swelling experiments of the PMAC-100N-4M hydrogels were conducted at 37 ºC in two media with different pH values: 0.1M HCl with pH of 1 (as simulation of human stomach) and phosphate buffer with pH of 6.8 - PB 6.8 (as simulation of human intestines) [5, 14, 15]. The weight of each PMAC-100N-4M hydrogel was first measured (m_0, g) and then each hydrogel was immersed into the investigated mediums. At previously defined time intervals PMAC-100N-4M hydrogel was removed from the medium, its weight was measured (m_t, g) and then the PMAC-100N-4M hydrogel was immersed into the medium again. The experiment was performed until equilibrium state was reached. The swelling degree (SD) was calculated according to the following equation:

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

The equilibrium swelling degree (SDeq) of each PMAC-100N-4M hydrogel was calculated by using the same equation (Eq. (1)) in which m_t was replaced with m_{eq} (the weight of hydrogel in equilibrium state).

2.4 Controlled release of caffeine from PMAC-100N-4M hydrogels

Release process of caffeine from the PMAC-100N-4M hydrogels was analyzed in the same media and at the same experimental conditions as was the PMAC-100N-4M hydrogels swelling analyzed. At predetermined time intervals 3 ml of the solution was collected and UV analyzed at 273 nm (caffeine maximum peak value), after which the solution was returned back into the medium. Each experiment was conducted three times and mean value of absorbance was used for further determination of caffeine concentration released into the medium.

3 Results and discussion

The swelling curves of the PMAC-100N-4M hydrogels in two media are presented in Fig. 1. a) and b). Obtained SDeq values of the PMAC-100N-4M hydrogels are listed in Table 2. The PMAC-100N-4M hydrogels had significantly higher SDeq values in PB 6.8 than in 0.1M HCl. This swelling behavior of the PMAC-100N-4M hydrogels can be explained by deprotonation of carbox-

ylic groups of PMAA and casein. Deprotonation of -COOH groups is favored in the media with pH values higher than pKa of MAA and pI of casein (4.6 [4][16]), such as PB 6.8. Deprotonation of carboxylic groups leads further to the repulsion of polymer chains due to which medium diffuses more easily into the polymer network leading to the higher SDeq values.

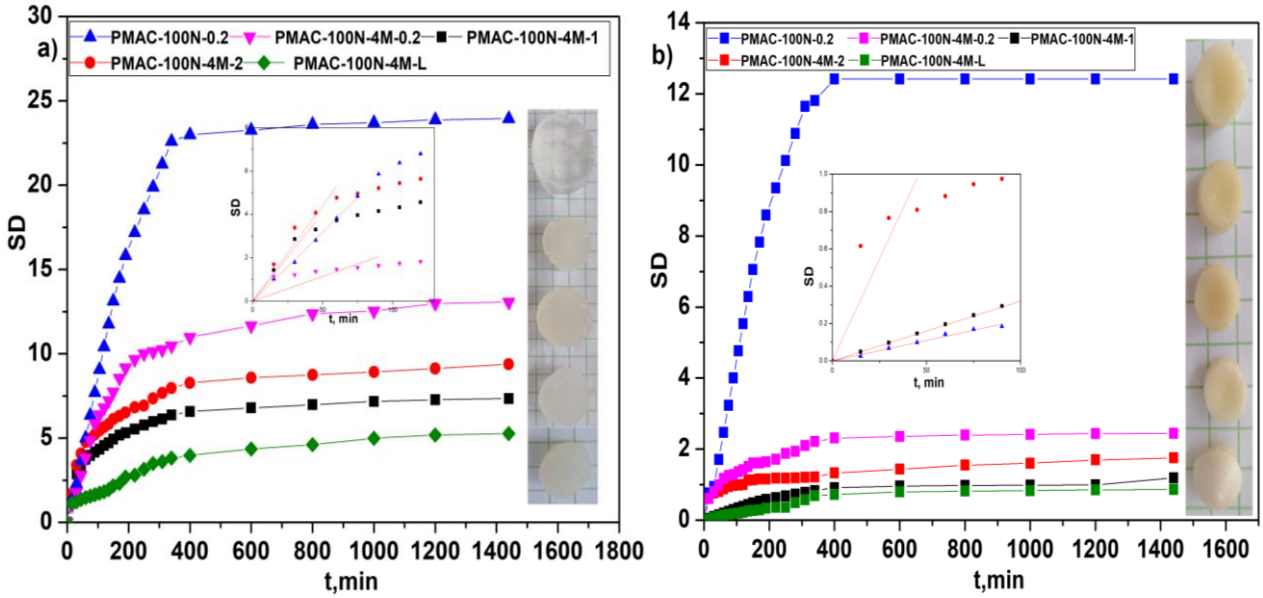

Figure 1. The curves of PMAC-100N-4M hydrogels swelling in: a) PB 6.8 and b) 0.1M HCl (the pictures present PMAC-100N-4M hydrogels swollen to equilibrium in investigated medium)

The increase in the MBA amount led to the decrease in the SDeq values (PMAC-100N-0.2 and PMAC-100N-4M-0.2 samples). Namely, higher amount of crosslinker led to the increase in the crosslinking density and diffusion of the medium into the carrier network was hindered. The increase in the encapsulated weight of caffeine led first to the decrease in the SDeq values (samples PMAC-100N-4M-0.2 and PMAC-100N-4M-1). Then, the SDeq value of the sample with the highest amount of the encapsulated caffeine (PMAC-100N-4M-2) increased. This could be a consequence of the unregular distribution of caffeine within the hydrogels network. Namely, some amount of the encapsulated caffeine was probably located near or at the surface of the PMAC-100N-4M hydrogel [17]. This led to the distribution of the lower amount of the drug within the carrier network, so the path of the medium (PB 6.8) into the polymer network was not interfered. In addition, the repulsion of polymer chains (favored in PB 6.8) led to the easier diffusion of the medium into the carrier network [17, 18]. The lowest SDeq value had the sample with embedded liposomes (PMAC-100N-4M-L) because the liposomes occupied the pores in the hydrogels network interfering in that manner diffusion of the medium into the hydrogel network.

Table 2. SDeq values of PMAC-100N-4M hydrogels in 0.1M HCl and PB 6.8

Sample	SD_{eq}	
	0.1M HCl	*PB 6.8*
PMAC-100N-0.2	12.4	23.9
PMAC-100N-4M-0.2	2.44	13.1
PMAC-100N-4M-1	1.19	7.35
PMAC-100N-4M-2	1.75	9.39
PMAC-100N-4M-L	0.860	5.27

The curves of caffeine release from the PMAC-100N-4M hydrogels are presented in Fig. 2. a*) and b*). The released amounts of the caffeine from the PMAC-100N-4M hydrogels was notice-

ably higher in PB 6.8 than in 0.1M HCl due to the pH dependent swelling behavior of the hydrogels. Namely, the PMAC-100N-4M hydrogels had higher SDeq values in PB 6.8, hydrogels network expanded more in this medium, enabling easier diffusion of caffeine from the samples. It can be noticed that around two times higher amount of caffeine was released in PB 6.8 than in 0.1M HCl. The increase in the crosslinker amount significantly decreased the amount of released caffeine (PMAC-100N-0.2 and PMAC-100N-4M-0.2 samples). This was due to the increase in the crosslinker density which hindered the diffusion of caffeine from the hydrogel into the surrounding medium. Increase in the weight of encapsulated caffeine led to the increase in the release rate and release amount of the drug in both media [17]. Also, the addition of the liposomes drastically decreased the release rate of caffeine. This was due to the presence of the wall of liposomes particle which represented additional barrier for drug release, so drug release was slower.

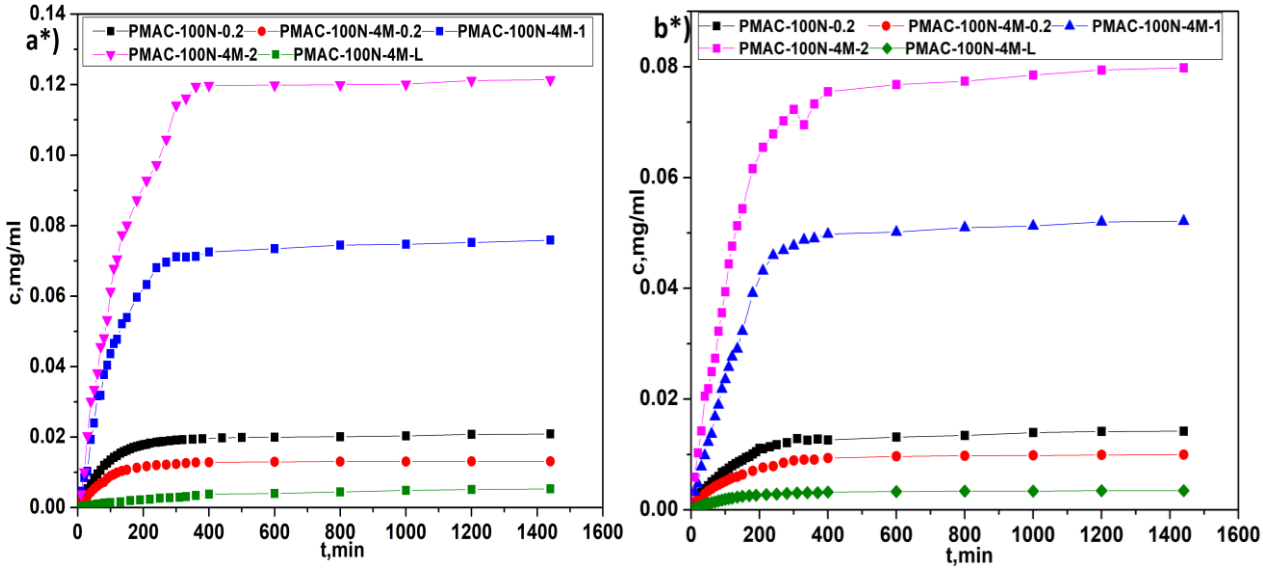

Figure 2. The profiles of caffeine release from PMAC-100N-4M hydrogels in: a) PB 6.8 and b*) 0.1M HCl*

4 Conclusions

In present study, the hydrogels based on methacrylic acid and casein with 1.6mol% of crosslinker, 100% neutralized methacrylic acid (PMAC-100N-4M) were prepared. It was investigated how the change in the encapsulated amount of caffeine and addition of the liposomes suspension affect the swelling behavior of the PMAC-100N-4M hydrogels and caffeine release. The swelling behavior of the PMAC-100N-4M hydrogels and the process of the caffeine release were investigated in two media which simulated environment in human stomach and intestines (0.1M HCl and PB 6.8).

The analysis of the PMAC-100N-4M swelling process showed that these hydrogels had significantly higher SDeq values in PB 6.8 than in 0.1M HCl. Namely, pH value of PB 6.8 is higher than pKa of PMAA and pI of casein, which leads to the formation of negative charges along the polymer chains. This further caused the repulsion of polymer chains and swelling of the PMAC-100N-4M hydrogels. The increase in the encapsulated weight of caffeine induced decrease in the SDeq values of the PMAC-100N-4M hydrogels. This could be a consequence of the increase in the number of interactions established between caffeine and casein. Such high number of casein/caffeine interactions led to the more compact polymer network and diffusion of surrounding medium was interfered. Further increase in the encapsulated weight of caffeine led to the increase in the SDeq value because some amount of caffeine was located near or at the surface of the hydrogels which enabled easier diffusion of the medium into the PMAC-100N-4M network and swelling of the PMAC-100N-4M hydrogels. The addition of the liposomes into the PMAC-100N-4M hydrogels led to the decrease in the SDeq values of the PMAC-100N-4M hydrogels. The liposomes particles physically occupied the hydrogels pores hindering in that manner swelling of the PMAC-100N-4M

hydrogels. The same trend was observed for the process of caffeine release from the PMAC-100N-4M hydrogels. The increase in the encapsulated amount of caffeine led to the increase in the released amount of caffeine in both media. The increase in the crosslinker amount and the addition of the liposomes led to the decrease in the amount of released caffeine.

Results obtained in this study showed that the PMAC-100N-4M hydrogels have huge potential for controlled release of poorly water-soluble active substance such as caffeine. Also, the kinetic of release of poorly water-soluble active substance can be easily adjust according to the demands of specific application of the PMAC-100N-4M hydrogels. So, the potential of these hydrogels for encapsulation of higher amount of poorly water-soluble drug and its release will be investigated in our future research.

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