1st International Conference
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ICCBIKG 2021

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1st International Conference on
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BOOK OF PROCEEDINGS

October 26-27th, 2021,
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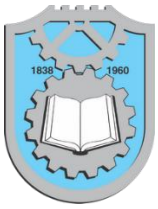

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EFFECT OF CROSSLINKER AMOUNT ON HYBRID HYDROGELS SWELLING AND DRUG RELEASE

Maja D. Markovic[1], Vesna V. Panic[1], Julijana D. Tadic[2,3], Rada V. Pjanovic[3]

[1] Innovation Center of Faculty of Technology and Metallurgy,
University of Belgrade, Karnegijeva 4, 11000 Belgrade, Serbia
e-mail: mmarkovic@tmf.bg.ac.rs
[2] Vinča Institute of Nuclear Sciences – National Institute of the Republic of Serbia, University of Belgrade, Mike Petrovića Alasa 12-14, 11001 Belgrade, Serbia
[3] Faculty of Technology and Metallurgy,
University of Belgrade, Karnegijeva 4, 11000 Belgrade, Serbia
e-mail:vpanic@tmf.bg.ac.rs , jtadic@tmf.bg.ac.rs, rada@tmf.bg.ac.rs

Abstract:

Targeted drug delivery is powerful tool which researchers use to achieve safer and more efficient therapy of many diseases, including various types of cancer. Many chemotherapeutics are poorly water-soluble, so their encapsulation and targeted delivery remain quite challenge. Hydrogels based on poly(methacrylic acid) (PMAA) are widely investigated for targeted drug delivery due to their pH sensitivity, non-toxicity and biocompatibility. Still, due to the PMAA highly hydrophilic nature, PMAA can only be used for encapsulation and targeted delivery of water-soluble drugs. Our previous research was directed towards overcoming this limitation: PMAA was modified with amphiphilic protein – casein and poorly-water soluble model drug – caffeine – was encapsulated (PMAC). Present study is focused on investigation how variation of amount of one of the most important hydrogels network parameter such as crosslinker affect PMAC swelling properties and caffeine release. The group of hybrid hydrogels – PMAC – was synthesized with various amount of crosslinker: 0.4mol%, 0.8mol%, 1.6mol% and 3.2mol% with respect to methacrylic acid. Swelling behavior of hybrid hydrogels and caffeine release was investigated in two environments which simulated human stomach and intestines. Obtained results showed that targeted delivery of poorly water-soluble model drug was achieved and that its release can be prolonged up to 24h. Also, kinetic of poorly water-soluble drug release can be easily modified only by changing crosslinker amount. PMAC hybrid hydrogels have huge potential for targeted delivery of poorly water-soluble active substances.

Key words: poly(methacrylic acid), casein, crosslinking, hydrogels swelling, drug release

1. Introduction

Researchers are faced with a lot of challenges in their attempts to find new or to improve existing drug delivery systems to achieve safer and more efficient therapy of various diseases. This is especially significant in cancer therapy, since many anticancer drugs are poorly water soluble and have severe side effects [1]. Encapsulation and targeted delivery of these drugs can improve their bioavailability, decrease side effects and reduce the number of required therapeutic dosages. Hydrogels based on poly(methacrylic acid) (PMAA) are widely used for targeted drug delivery. These extraordinary materials are pH sensitive, biocompatible, non-toxic and their morphology is similar to human tissues [2]. Their highly hydrophilic nature, however, limits their application only to encapsulation and targeted delivery of water-soluble drugs. In our previous research, we overcome this limitation by modifying PMAA with amphiphilic casein, which enabled encapsulation of poorly water soluble model drug - caffeine (PMAC) [3, 4]. Casein is non-toxic, biocompatible, pH sensitive milk protein, which use is

approved by Food and Drug Administration (FDA)[3]. This study is focused on the investigation how crosslinker amount affects swelling of these hybrid PMAC hydrogels and caffeine release, because degree of crosslinking of the hydrogels network are one of the most important parameters which affect the hydrogels properties and consequently drug release.

2. Materials and methods

2.1 Materials

Methacrylic acid (99.5%) and caffeine were purchased from Merck (Germany). Sodium caseinate was supplied from Lactoprot Deutschland GmbH (Germany). The crosslinker N,N'-methylenebisacrylamide (p.a.) (MBA) and sodium hydroxide (p.a.) were supplied from Aldrich Chemical Co. (USA). The initiator, 2,2'-azobis-[2-(2-imidazolin-2-yl)propane] dihydrochloride (99.8%) was purchased from Wako Pure Chemical Industries (Japan). 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 Samples preparation

The process of the samples preparation and characterization are described in details in our previous research [3, 4]. In this study we varied the amount of crosslinker. Briefly: after 4 ml of MAA and 0.2 g of caffeine dissolution in distilled water (see Table 1. for Feed composition), sodium hydroxide was added in order to completely neutralized MAA. Then, the temperature of reaction mixture was elevated to 60ºC and during vigorously stirring of the reaction mixture 4 g of casein was added. After casein dissolution, a certain amount of crosslinker (Table 1.) was added and dissolved, followed by the addition and dissolution of the initiator (0.9 cm^3 of 1wt% aqueous solution). Then, the reaction mixture was quickly poured in glass molds and left in the air oven at 60°C for 5h after which disc shaped samples were cut and dried at room temperature. Synthetized samples were denoted as PMAC-xM-0.2, where xM represents the amount of crosslinker (2M, 4M and 8M = 0.8mol%, 1.6mol% and 3.2mol% of crosslinker, respectively).

Table 1. Feed composition

Samples	Distilled water (ml)	Crosslinker amount (mol%*)
PMAC-0.2	6.20	0.4
PMAC-2M-0.2	3.30	0.8
PMAC-4M-0.2	8.93	1.6
PMAC-8M-0.2	8.81	3.2

*with respect to the MAA amount

2.3 Samples swelling

The experiments of the samples swelling were conducted at 37ºC in two environments 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). The mass of each sample was first measured (MO, g) and then each sample was immersed in each environment. At previously defined time intervals sample was removed from the environment, its mass was measured (MT, g) and then the sample was immersed again. The experiment was conducted until equilibrium state was reached (i.e. until mass of the sample did not change). The swelling degree (SD) was calculated according to the following equation:

$$SD = \frac{MT-MO}{MO} \quad (1)$$

2.4 Drug release from the samples

The drug release process was investigated in the same environments and at the same experimental conditions as the process of the samples swelling. At predetermined time intervals 3 ml of the solution was colected and UV analyzed at 273 nm, after which the solution was returned back. Each experiment

was conducted three times and mean value of absorbance was used for further determination of concentration of drug released in the environment.

3. Results and discussion

Samples with various amount of crosslinker – MBA– were synthetized in order to investigate how the degree of crosslinking of samples network affect the process of samples swelling and drug release. The curves of the process of the samples swelling in two environments with different pH values – 0.1M HCl and PB 6.8 – are presented in Fig. 1 a) and b). The values of equilibrium swelling degree (SDeq) of the samples are presented in Table 2.

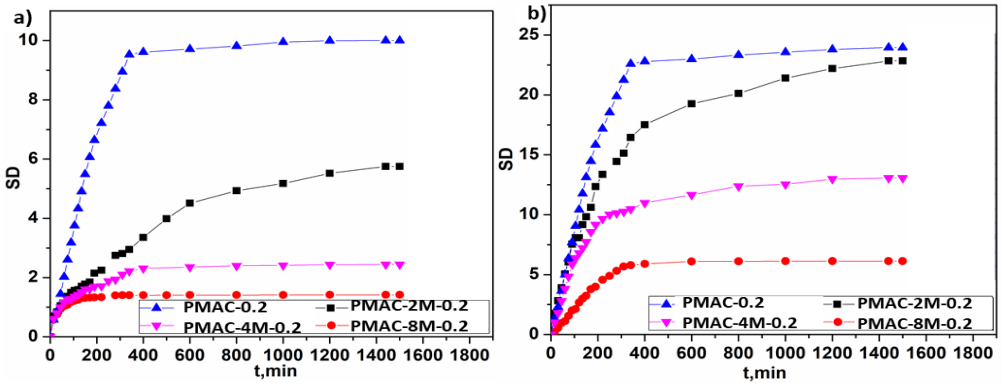

Fig. 1. The curves of samples swelling in: a) 0.1M HCl and b) PB 6.8

As it can be seen in Fig. 1 a) and b), the samples swell more in PB 6.8 than in 0.1M HCl. The values of SDeq are around five times higher in PB 6.8 than in 0.1M HCl. This specific pH- dependent swelling behavior of the samples can be explained by deproteinization of the carboxylic groups in environments with pH value higher than pKa of PMAA and pI of casein (such as PB 6.8) [2, 5, 6]. Consequently, negative charges on polymeric chains are generated, which further leads to the repulsion between polymeric chains and samples swelling.

Table 2. The values of equilibrium swelling degree (SDeq) of the samples

Samples	0.1M HCl	PB 6.8
PMAC-0.2	12.4	23.9
PMAC-2M-0.2	5.75	22.8
PMAC-4M-0.2	2.44	13.1
PMAC-8M-0.2	1.42	6.12

Based on the swelling curves of the samples presented in Fig. 1. a) and b) and the results presented in Table 2. it can be concluded that the values of SDeq decrease with increase of crosslinker amount. These results are in accordance with the fact that hydrogels with higher degree of crosslinking of network have smaller pores and more rigid polymers chains [6].

The profiles of drug release from the samples in 0.1M HCl and PB 6.8 are presented in Fig. 2. a) and b), respectively. All samples release higher amount of drug in PB 6.8 than in 0.1M HCl due to the specific pH dependent swelling behavior. The profiles of drug release showed that increase of crosslinker amount led to decrease of the drug release rate. Increase of crosslinker amount led to the decrease of the diameter of the pores of the hydrogels network, which prolonged drug diffusion from the samples [7]. Drug amount which was released from the sample with 3.2 mol% of crosslinker (PMAC-8M-0.2) in PB 6.8 was around four times less than drug amount released from the referent sample with 0.4 mol% of crosslinker (PMAC-0.2).

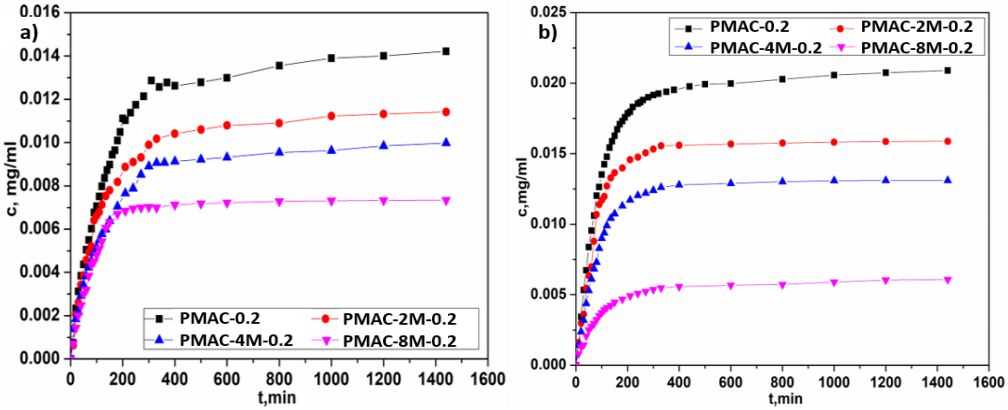

Fig. 2. The profiles of drug release from the samples in: a) 0.1M HCl and b) PB 6.8

4. Conclusions

In this paper, the group of the samples based on poly(methacrulic acid) and casein with encapsulated poorly water soluble model drug – caffeine – were prepared. The amount of crosslinker was varied in order to investigate how the degree of crosslinking of the hydrogels network affect swelling behavior of the samples and drug release. The increase of the crosslinker amount led to the decrease of the samples swelling and consequently to the decrease of the rate of drug release. Presented results showed that drug release kinetics could easily be tuned just by changing crosslinker amount. Present study gives good fundamentals for future investigation of targeted delivery of certain poorly water-soluble drugs (such as chemotherapy agents) which is of great importance in cancer therapy.

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