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HIDROGELOVI NA BAZI POLI(METAKRILNE KISELINE) DOBIJENI EKOLOŠKI PRIHVATLJIVOM METODOM: BUBRENJE I KONTROLISANO OTPUŠTANJE LIDOKAIN HIDROHLORIDA

POLY(METHACRYLIC ACID) HYDROGELS PREPARED BY ECO-FRIENLDY METHOD: SWELLING AND CONTORLLED RELEASE OF LIDOCAINE HYDROCHLORIDE

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Razvoj efikasnog sistema za dostavu lekova koji može da zaštiti lek, sačuva njegovu aktivnost, poboljša njegovu biodostupnost i kontrolisano ga otpušta predstavlja još uvek pravi izazov. Inkapsulacija leka tokom sinteze sistema za otpuštanje leka je posebno zahtevan deo. U našem prethodnom radu razvili smo jednostavnu i ekološki prihvatljivu sintezu hidrogelova na bazi poli(metakrilne kiseline) kod koje se kao inicijator koristi sistem vodonik peroksid i vitamin C (H_2O_2/VC). U sadašnjem istraživanju se ispituje da li se može postići inkapsulacija lidokain hidrohlorida tokom sinteze hidrogela i kasnije njegovo kontrolisano oslobađanje. Rezultati su pokazali da su blagi uslovi sinteze omogućili efikasnu inkapsulaciju lidokain hidrohlorida i sintezu hidrogelova na bazi poli(metakrilne kiseline) (PMAAL). Lidokain hidrohlorid je lokalni anestetik koji se koristi kod anestezije i kod terapije aritmije, a najčešće se pacijentima daje injekcijom. Njegovo inkapsuliranje i kontrolisano oslobađanje iz hidrogelova predstavljaju dobro rešenje kako bi se sprečile neprijatnosti do kojih dolazi tokom njegove administracije i kako bi se smanjio broj doza potrebnih za terapiju. Karakterizacija dobijenih PMAAL hidrogelova je zatim izvedena primenom FTIR i SEM analize, kao i ispitivanjem otpornosti ovih materijala na kompresiju. Bubrenje PMAAL hidrogelova i kontrolisano oslobađanje leka analizirani su u dve sredine sa pH 1 i pH 6,8, koje su simulirale pH sredine u ljudskom želucu i crevima. Rezultati pokazuju da se oko osam puta veća količina lidokain hidrohlorida oslobađa u sredini sa pH 6,8 zbog pH osetljivog bubrenja PMAAL hidrogelova. Takođe je ispitan uticaj promene količine umreživača na bubrenje PMAAL hidrogelova i otpuštanje leka. Povećanje količine umreživača dovodi do smanjenja otpuštene količine. Ovo istraživanje pokazuje da metoda kod koje se koristi H_2O_2/VC kao inicijator može da se koristi za efikasnu inkapsulaciju lidokain hidrohlorida. Takođe, ovaj lek se može kontrolisano otpuštati iz PMAAL hidrogelova tokom 24 časa u sredini sa pH 6,8, kao što su ljudska creva gde je apsorpcija leka najveća.

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Design of efficient drug delivery system which can protect drug, preserve its activity, improve its bioavailability, and release it in control manner still presents quite challenge. Encapsulation of drug during the synthesis of drug delivery system is especially complex part. In our previous research we have developed simple and eco-friendly synthesis of hydrogels based on poly(methacrylic acid) that employing hydrogen peroxide and vitamin C (H_2O_2/VC) as initiator. Present study investigates if the encapsulation of lidocaine hydrochloride during the synthesis of hydrogel and later its controlled release, can be achieved by using this method. Results show that mild synthesis conditions enable efficient encapsulation of lidocaine hydrochloride and synthesis of hydrogels based on poly(methacrylic acid) (PMAAL). Lidocaine hydrochloride is local anesthetic which is used in anesthesia and in antiarrhythmic therapy, and it is usually applied by injection. Its encapsulation and controlled release from the hydrogels present good solution to overcome unpleasantness during its application and to reduce required number of dosages. Obtained PMAAL hydrogels are further characterized by employing FTIR and SEM analysis, as well as single compression tests. PMAAL swelling and controlled release of the drug are analyzed in two environments with pH 1 and pH 6.8 simulating pH environments in human stomach and intestines. The results show that around eight times higher amount of lidocaine hydrochloride is released in environment with pH 6.8 due to the pH dependent swelling of the PMAAL hydrogels. The change in crosslinker amount on the PMAAL swelling and drug release are also investigated. The increase in the crosslinker amount lead to the decrease of amount of drug released from the PMAAL hydrogels. This study shows that the method which employing H_2O_2/VC as initiator can be used for efficient encapsulation of lidocaine hydrochloride. Also, this drug can be released in controlled manner from the PMAAL hydrogels for 24h in environment with pH 6.8, such as human intestines where drug absorption is the highest.

Key words: *poly(methacrylic acid) hydrogels; eco-friendly synthesis; local anesthetic; controlled release*

1. Introduction

Polymer materials such as hydrogels have many desired properties for controlled release of drugs and they are widely employed in many medical fields [1-3]. They are biocompatible because they have highly hydrophilic network due to which they can absorb huge amount of water and biological fluid, which represents suitable environment for cells.

There are many groups of hydrogels, but hydrogels sensitive on external stimuli are extensively investigated for targeted drug delivery [4-6]. pH sensitive hydrogels, such as poly(methacrylic acid) (PMAA), can swell as a result of pH change in external environment. These hydrogels swell if pH of the external medium is higher than pKa of methacrylic acid (4.6) [7, 8], so they can release encapsulated drug in that type of environment. Due to the pH dependent swelling these non-toxic and biocompatible materials can protect encapsulated drug in environments such as human stomach and release it in controlled manner in environments such as human intestines, where drug can be the fastest absorbed. In that manner bioavailability of drug can be increased, side effects reduced, and therapy enhanced.

Conditions during the preparation of drug delivery system directly affects the encapsulation, activity, and bioavailability of the selected drug. Hence, synthesis conditions should be mild and should not include toxic volatile organic solvents. In line with that, eco-friendly method for preparation of hydrogels, developed in our previous research, that employs hydrogen peroxide and vitamin

C as initiator can be used for synthesis *in situ* of hydrogel with encapsulated drug [9]. This method provides that synthesis can be carried out in aqueous solution, under mild, ambient conditions, without the usage of toxic solvent and in very simple manner.

The present study investigates if the encapsulation of lidocaine hydrochloride during the synthesis of hydrogels based on poly(methacrylic acid) and its controlled release can be achieved. Lidocaine hydrochloride is used as local anesthetic for anesthesia and in antiarrhythmic therapy [10]. This drug is usually injected which can be painful and treatment often required several dosages. So, encapsulation of lidocaine hydrochloride into the hydrogels can be good solution because drug can be released in controlled manner and therefore, its application would be less unpleasant and more effective. Hydrogels based on poly(methacrylic acid) with lidocaine hydrochloride (PMAAL) are prepared via free radical polymerization. The PMAAL hydrogels are further characterized, and their swelling behavior and drug release are analyzed at two pH values (pH 1 and pH 6.8) which simulate pH environments in human stomach and intestines. In addition, the effect of change of crosslinker amount on the PMAAL swelling and drug release are analyzed.

2. Materials and methods

2.1. Materials

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

2.2. Preparation of PMAAL hydrogels

Synthesis of PMAAL hydrogels was performed by free radical polymerization in aqueous solution initiated by the hydrogen peroxide/vitamin C (H_2O_2/VC) system. The synthesis was carried out at ambient conditions in following manner. 4 mL of MAA was dissolved in certain amount of distilled water (Table 1.). Parallel to this, aqueous solution of lidocaine hydrochloride was prepared for each sample: 0.2 g of the drug was dissolved in 5 mL of distilled water (the total amount of distilled water used for preparation of each sample is shown in Table 1.). Then a certain amount of crosslinker - MBA was added to the reaction mixture of each sample during the constant stirring of the reaction mixture (Table 1). 100 μL of hydrogen peroxide and 10 mg of vitamin C were used for initiation of polymerization reaction. After their addition to the reaction mixture of each of the samples, further stirring was continued for 15 min. Then, the pre-dissolved model drug was added to the reaction mixture, after which the reaction mixtures are poured into the molds and left at ambient conditions for 24 h. After the reactions of polymerization and cross-linking were completed, the hydrogels were removed from the molds and cut into the discs with a diameter of 7 mm. The prepared discs were left to dry at room temperature, after which they were used to perform further experiments. The samples were labeled as PMAAL-yMBA, where yMBA represented the mol% of used crosslinker. The referent sample without encapsulated drug had 0.4 mol% MBA and was designated as PMAA-0,4 MBA.

2.3. Characterization of PMAAL hydrogels

Fourier Transform Infrared Spectroscopy (FTIR) spectroscopy was applied to investigate the interactions between the components of PMAAL hydrogels. Before the FTIR analysis, the samples were

crashed into the powder. The FTIR spectra of thus prepared PMAAL hydrogels were recorded by using Nicolet™ iS10 FTIR spectrometer in the wavelength range 4000-400 cm^{-1} with a resolution of 4 cm^{-1}.

Table 1. Feed composition

Sample	*Distilled water, mL*	*MBA, mol% with respect to MAA*
PMAA-0,4MBA	13.02	0.4
PMAAL-0,2MBA	14.26	0.2
PMAAL-0,4MBA	12.82	0.4
PMAAL-1,6MBA	9.95	1.6
PMAAL-3,2MBA	15.58	3.2

The morphology of PMAAL hydrogels was investigated by using scanning electron microscopy on a Tescan MIRA 3 XMU Field-Emission Gun Scanning Electron Microscope (SEM). The samples were left to swell to equilibrium in distilled water before SEM analysis, then they were lyophilized and cut in a half. Obtained cross-sections of the samples are coated with a layer of Au-Pd in a POLARON SC502 vacuum vaporizer. The cross-sections of the samples prepared in the described manner were then analyzed by scanning electron microscopy.

The samples were immersed in 0.1M HCl and PB 6.8 and left to swell until equilibrium state was achieved. The samples were then removed, and excess of the media was removed with a paper towel. The samples prepared in that manner were subjected to compression tests at room temperature by using Shimadzu Autograph AGS-X (1kN) apparatus, at a deformation rate of 2 mm/min. Compression strength of the samples was tested up to the limit of the elasticity of the material.

2.4. Monitoring of PMAAL hydrogels swelling

The swelling of PMAAL hydrogels was monitored in two environments: 0.1M HCl and 0.02M phosphate buffer (PB 6.8) which simulated the pH environment in human stomach and intestines, respectively [11]. First, the mass of each xerogel was determined (m_0), and then each sample was immersed in selected environments. At certain time intervals the sample was taken out, the excess of the medium was removed with a towel, its mass was determined (m_t) and immediately the sample was returned into the environment where the swelling was monitored. The swelling of the hydrogels was monitored to the moment when equilibrium state was reached, i.e. until the mass of the sample was not changed. Determined values of the masses were introduced into the Eq. (1) and based on the obtained values of swelling degrees (SD) in each time point, the swelling curves of the hydrogels were constructed for each one.

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

The equilibrium swelling degree (SDeq) of each PMAAL hydrogel was calculated by using the same equation (Eq. (1)), but m_t was replaced with the mass of hydrogel in equilibrium state (m_{eq}).

2.5. Controlled release of lidocaine hydrochloride from PMAAL hydrogels

In order to investigate the release process of encapsulated model drug, PMAAL hydrogels were immersed in two environments: 100 mL of 0.02M PB 6.8 and 100 mL of 0.1M HCl at 37 °C. At previously determined time intervals 3 mL of each medium was removed, analyzed by Shimadzu

UV-Vis spectrophotometer and returned into the certain medium. The wavelength at which the value of absorbance was determined was 265 nm. The data obtained by these measurements were used for construction of curves of cumulative drug release.

3. Results and discussion

3.1. Characterization of PMAAL hydrogels

The FTIR spectra of PMAAL hydrogels are shown in Fig. 1. The FTIR spectra of PMAA-0,4 MBA hydrogel (PMAA hydrogel without encapsulated drug) and lidocaine hydrochloride are also shown in Fig. 1. for comparison. Analysis of the FTIR spectra showed that the characteristic peaks of poly(methacrylic acid) at: 2995 cm^{-1} and 2933 cm^{-1} (vibrations of the C-H bond of the methyl group), 1691 cm^{-1} (stretching vibrations C=O bonds in carboxyl group) and 1396 cm^{-1} (stretching and bending vibrations of bonds in the -CH3 group), were present in the FTIR spectrum of all samples (Fig. 1.) [12]. The characteristic peaks of lidocaine hydrochloride were not present in the FTIR spectra of the PMAAL samples, probably because the peaks of lidocaine hydrochloride were overlapped with the peaks of the poly(methacrylic acid). The peaks of the poly(methacrylic acid) in the FTIR spectra of the PMAAL samples at: 1250 cm^{-1} (vibrations in the C-O bond plane coupled with vibrations in the O-H bond plane) and 1170 cm^{-1} (asymmetric C-O stretching vibration bonds) were longer than the same peaks in the FTIR spectrum of the PMAA-0,4MBA (Fig. 1.). This could be the consequence of hydrogen bonds established between the carboxyl group of poly(methacrylic acid) with one of the chemical groups of lidocaine hydrochloride, such as -NH- or =O. An increase in the peak size due to the formation of hydrogen bonds between the encapsulated drug and the polymer carrier was also observed by F. Kazemianrad et al. in the analysis of FTIR spectra of their samples [13].

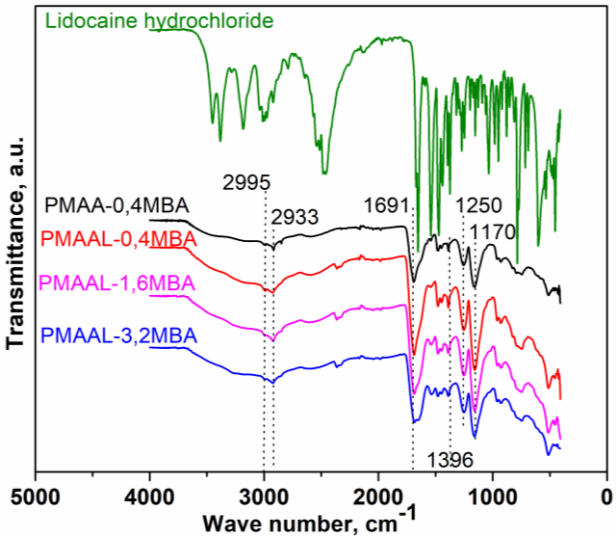

Figure 1. The FTIR spectra of the PMAAL hydrogels

The SEM micrographs of the cross-sections of the PMAAL hydrogels are shown in Fig. 2. Based on the presented SEM microgrpahs can be concluded that all PMAAL hydrogels have regular porous structure, which is characteristic for the hydrogel structure [9]. The increase in the degree of cross-linking led to the decrease in the pore diameter of the polymer network of PMAAL hydrogels (Fig. 2. a), b), c) and d)). The sample with the highest amount of crosslinker - PMAAL-3,2MBA had the highest porosity. The influence of the obtained carrier structure and established interactions between the components of the PMAAL hydrogel on the compressive strength of the PMAAL

hydrogels, their swelling and release of encapsulated drug in two environments: 0.1M HCl and PB 6.8 was further tested.

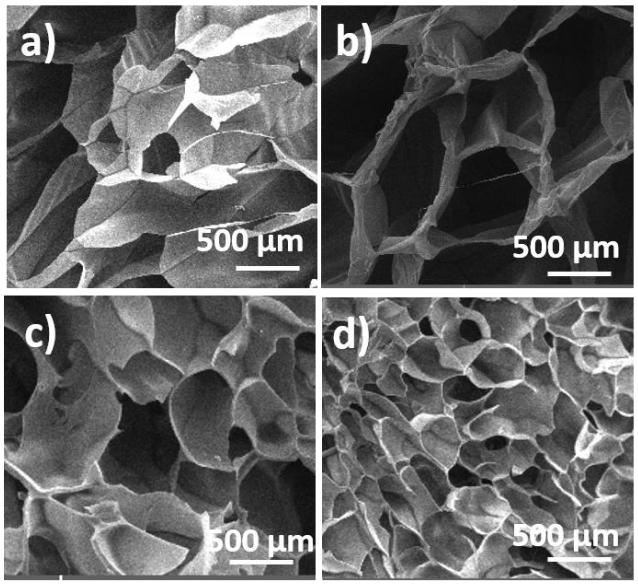

Figure 2. The SEM micrographs of: a) PMAA-0,4MBA; b) PMAAL-0,2MBA; c) PMAAL-0,4MBA and d) PMAAL-3,2MBA

In order to examine the effect of change of crosslinking degree on the mechanical properties of PMAAL hydrogels, their compressive strength (σ) and the deformation that occurs during the compression were analyzed. Obtained results for PMAAL hydrogels swollen in 0.1M HCl and in PB 6.8 are shown in Table 2.

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

Sample	*0.1M HCl*		*PB 6.8*	
	Maximal compressive stress, N/mm²	*Maximal stoke strain, %*	*Maximal compressive stress, N/mm²*	*Maximal stoke strain, %*
PMAA-0,4MBA	421.0	65.27	47.1	55.27
PMAAL-0,2MBA	-	-	-	-
PMAAL-0,4MBA	1017.5	60.13	136.4	53.67
PMAAL-1,6MBA	1055.8	59.08	173.9	51.60
PMAAL-3,2MBA	1417.8	55.34	306.3	49.18

It could be concluded that the values of compressive strength of PMAA of hydrogels swollen in PB 6.8 was lower than these values of the same samples swollen in 0.1M HCl. Obtained result could be explained by the fact that PMAAL hydrogels swelled more in PB 6.8, so their polymer network was weaker compared to polymer network of the same samples swollen in 0.1M HCl [9]. Polymer network of the PMAAL hydrogels swollen in PB 6.8 absorbed larger amount of external medium, which led to the weakening of the interaction between hydrogel components. This led to the

deterioration of the mechanical properties of PMAAL hydrogel, and the deformations were irreversible almost immediately after the application of compression force [14]. Better mechanical properties and elastic response of the PMAAL hydrogels swollen in 0.1 M HCl could be similarly explained: the samples swelled less in 0.1 M HCl, so the interactions between components of the sample were stronger than the interactions between the components of the same sample swollen in PB 6.8. The analysis of mechanical properties of the PMAAL hydrogels showed that with an increase in the amount of the crosslinker, the values of compressive strength increased. This result was expected because the stiffness of the polymer network of the PMAAL hydrogels increased with increase in the crosslinking degree. Mechanical properties of the PMAAL-0,2MBA sample swollen to equilibrium in PB 6.8 could not be analyzed, because the network of this sample was on the cross-linking limit and the sample had a very high swelling degree, due to which it did not have a defined shape. The PMAAL-3.2MBA sample had the best mechanical properties and elastic response.

3.2. Swelling of PMAAL hydrogels and drug release

The swelling curves of the PMAAL hydrogels in 0.1M HCl and PB 6.8 are shown in Fig. 3. a) and b), respectively, and the pictures of corresponding samples swollen to equilibrium are presented below the graphs. Swelling curves of the referent sample - PMAA-0,4MBA are published by M. Marković et al. [9], and its SDeq value is shown in Table 3. for comparison with the SDeq values of the PMAAL hydrogels.

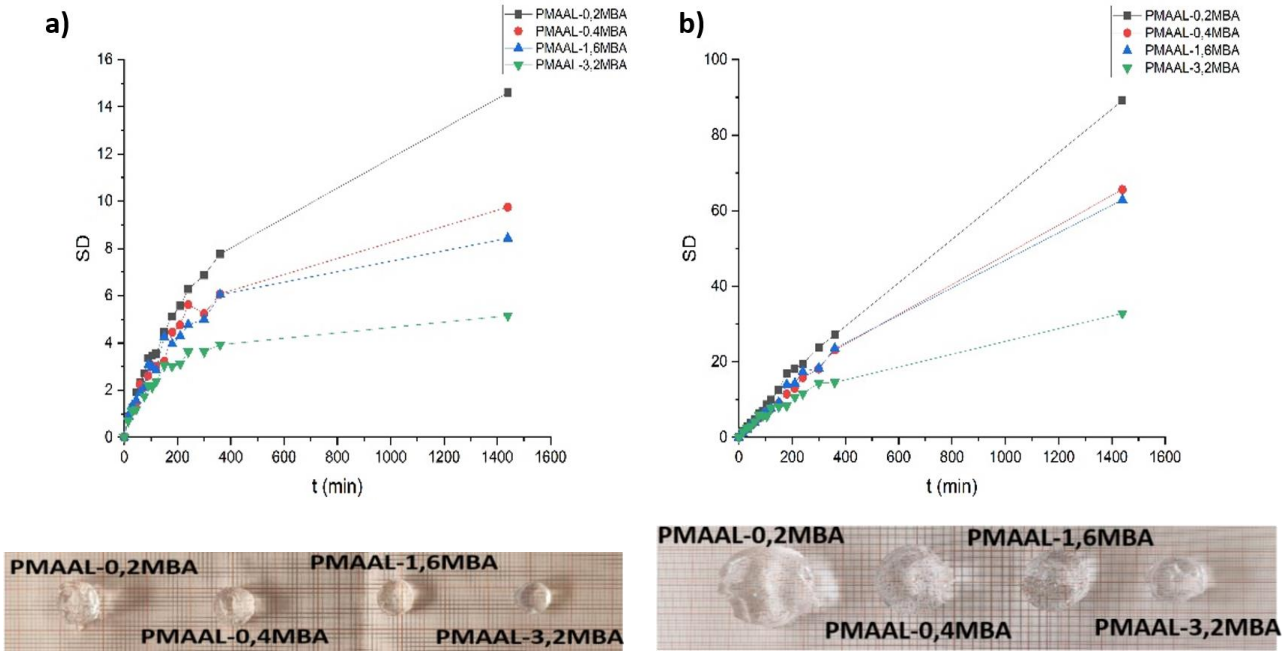

Figure 3. The curves of PMAAL hydrogels swelling in: a) 0.1M HCl and b) PB 6.8 and (the pictures below the graphs present corresponding PMAAL hydrogels swollen to equilibrium in investigated medium)

Based on the obtained results could be concluded that the values of the equilibrium swelling degree of the samples swollen in PB 6.8 were about 8 times higher than those swollen in 0.1M HCl. This result confirmed the pH-sensitive swelling behavior of the PMAAL hydrogels. The swelling of the PMAAL hydrogels occured when the pH value of the external environment was higher than the pKa of MAA (such as PB 6.8) [15]. In this type of environment, ionization of carboxyl groups on the polymer chains of PMAAL hydrogel, generation of negative charge and repulsion of polymer chains occured, which led to the swelling of the PMAAL hydrogels. Also, by comparing the SDeq value of PMAA-

0,4MBA with the SDeq value of the PMAAL-0,4MBA, could be concluded that the encapsulation of the drug in PMAA hydrogel led to a slight decrease in the SDeq values. This could be a consequence of the established interactions between the hydrogel and the drug (lidocaine hydrochloride), which hindered the diffusion of the external medium into the hydrogel network [16]. Also, the equilibrium swelling degree decreased with an increase in the degree of cross-linking. This behavior was expected because hydrogel with higher crosslinking degree had less mobility of polymer chains and smaller network pores, so the diffusion of the external medium into the network was hindered [16].

The curves of cumulative release of lidocaine hydrochloride from the PMAAL with encapsulated lidocaine hydrochloride in 0.1M HCl and PB 6.8 are presented in Fig. 4. a) and b), respectively. Lidocaine hydrochloride was released in controlled manner for 24 h. Based on the curves of cumulative drug release could be concluded that the amount of released lidocaine hydrochloride decreased with an increase in the amount of crosslinker. Higher degree of crosslinking led to the formation of polymer network with pores that have smaller diameters, so release of the drug was hindered.

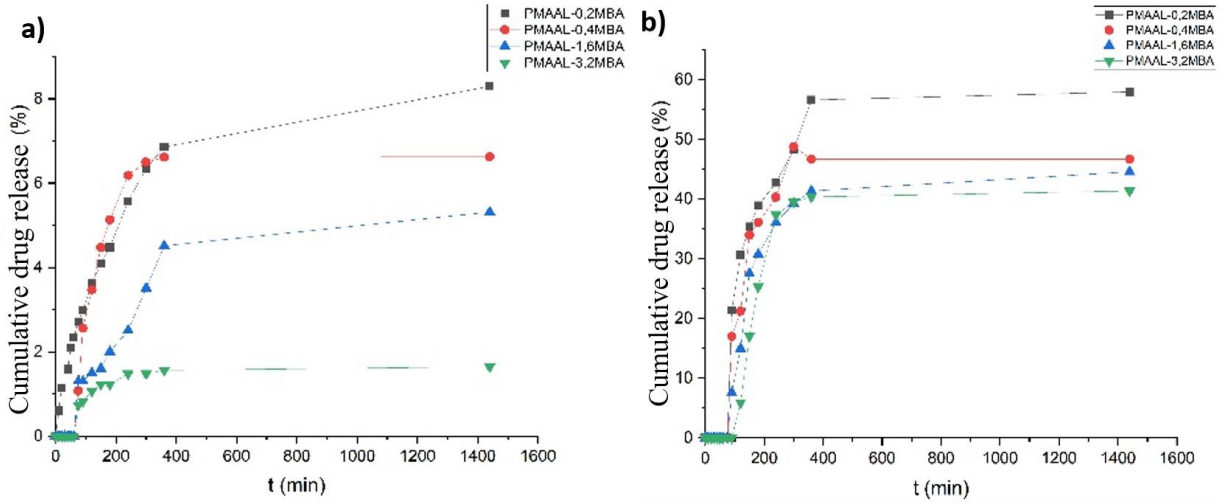

Figure 4. The profiles of lidocaine hydrochloride release from PMAAL hydrogels in: a) 0.1M HCl and b) PB 6.8

Also, the amount of released lidocaine hydrochloride was about ten times higher in PB 6.8 than in 0.1M HCl (Fig. 4. And Table 2.), which was a consequence of pH dependent swelling of the PMAAL hydrogels. Namely, the PMAAL hydrogels swell more in PB 6.8, therefore higher amount of drug was released in this environment.

Table 2. The SDeq values of the PMAAL hydrogels and amount of released drug in 0.1M HCl and PB 6.8

Sample	SD_{eq}		Cumulative drug release, %	
	0.1M HCl	*PB 6.8*	*0.1M HCl*	*PB 6.8*
PMAA-0,4MBA	12.04	76.78	-	-
PMAAL-0,2MBA	14.60	89.14	8.29	57.96
PMAAL-0,4MBA	9.75	65.60	6.63	46.66
PMAAL-1,6MBA	8.43	62.90	5.31	44.54
PMAC-3,2MBA	5.15	32.84	1.65	41.34

4. Conclusions

In this study, hydrogels based on poly(methacrylic) with encapsulated local anesthetic - lidocaine hydrochloride (PMAAL) were synthesized and characterized. The FTIR analysis confirmed the composition of the synthesized hydrogels and revealed that hydrogen bons were established between carboxyl groups of poly(methacrylic acid) with one of the chemical groups of lidocaine hydrochloride, such as are -NH- or =O. The SEM analysis showed that the synthesized PMAA hydrogels have a porous structure and that increase in the crosslinking degree led to the decrease in the pore diameter of the polymer network of the PMAAL hydrogels. The analysis of the mechanical properties of the PMAAL hydrogels showed that increase in the amount of crosslinker led to the increase in the values of the compressive strength of the PMAAL samples. The analysis also showed that the values of compressive strength of the PMAAL samples swollen in PB 6.8, were lower than the values of those of the same samples swollen in 0.1M HCl. This could be explained by the fact that PMAAL hydrogels swell more in PB 6.8, so large volume of this medium was presented in the hydrogel network, due to which polymer network of the samples swollen in PB 6.8 was weaker compared to polymer network of the same samples swollen in 0.1M HCl. This result was expected because the stiffness of the network of PMAA hydrogels increased with the increase in the degree of crosslinking. The SDeq values of the PMAAL hydrogels were around eight times higher in PB 6.8 than in 0.1M HCl, confirming pH sensitive swelling of synthesized samples. The results showed that the encapsulation of the drug led to the slight decrease in the SDeq value, which could be a consequence of interactions established between the encapsulated drug and the hydrogel. Also based on the obtained swelling curves, could be concluded that the equilibrium swelling degree of the PMAAL hydrogels decreased with increase in the crosslinking degree. This was consequence of the lower mobility of polymer chains and smaller network pores, so the absorption of the external medium into the network was hindered. Lidocaine hydrochloride was released in controlled manner for 24 h. Around three times higher amount of drug was released into PB 6.8 than in 0.1M HCl due to the pH dependent swelling of the PMAAL hydrogels. Also, increase in the crosslinker amount led to the decrease of the release amount of drug.

Based on the obtained result can be concluded that PMAAL hydrogels prepared by eco-friendly method have potential for controlled release of local anesthetic – lidocaine hydrochloride.

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