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ENGINEERING, ENVIRONMENT AND MATERIALS IN PROCESS INDUSTRY EEM2021

BOOK OF ABSTRACTS

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Karakaj 34a, 75 400 Zvornik
Republic of Srpska, B&H
Phone: +387 56 260 190
e-mail: sekretar@tfzv.ues.rs.ba
web:https://eem.tfzv.ues.rs.ba/

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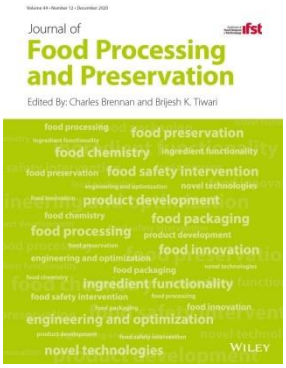

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HYDROGELS BASED ON POLY(METHACRYLIC ACID) AND NANOCELLULOSE WITH POTENTIAL APPLICATION IN DENTAL TREATMENTS

Maja D. Markovic[1]*, Sanja I. Seslija[2], Julijana D. Tadic[1], Pavle M. Spasojevic[1]

*[1] Innovation Center of Faculty of Technology and Metallurgy, University of Belgrade, 4 Karnegijeva Street, 11000 Belgrade, Serbia, * mmarkovic@tmf.bg.ac.rs*
[2] Institute of Chemistry, Technology and Metallurgy, University of Belgrade, 12 Njegoseva Street, 11000 Belgrade, Serbia

Abstract

pH sensitive hydrogels, such as hydrogels based on poly(methacrylic acid) (PMAA), are tremendous materials with great properties due to which they have application in many fields, such as: targeted drug delivery, tissue engineering, as contact lenses etc. Hydrogels based on PMAA are non-toxic, biocompatible and able to absorb and retain huge amount of water. These hydrogels are widely used for targeted drug delivery due to their specific pH swelling behavior which enable drug release in environments with pH values higher than pKa(PMAA). However, poor mechanical properties of hydrogels based on PMAA often limit their application. In order to overcome this limitation, green approach is used in present study. Namely, nanocellulose (NC) extracted from wood waste material is added to PMAA due to NC non-toxicity, biocompatibility, biodegradability and great mechanical properties (which is used for improvement of hydrogels mechanical characteristics). Further improvement of hydrogels based on PMAA and NC is achieved by adding carboxymethyl cellulose (CMC). CMC is non-toxic, biocompatible, biodegradable, pH-sensitive derivate of cellulose widely used in drug delivery systems. Drug delivery system prepared in that way can enable controlled release of drug (such as lidocaine hydrochloride (Lid)) for prolonged period of time and therefore, reduce the number of acquired drug dosages which further lead to safe and efficient drug application. Therefore, Lid is encapsulated in hydrogels based on PMAA, NC and CMC (PM/NC-Lid). Lid is local anesthetic often used in dental treatment and it is usually administrated by injection, which is painful, unpleasant and treatment is often required several dosages. These limitations can be overcome by applying PM/NC-Lid hydrogels as buccal patches for controlled release of lidocaine hydrochloride. Present study describes green synthesis and characterization of PM/NC-Lid hydrogels (using the Fourier Transform Infrared spectroscopy (FT-IR), the Scanning Electron Microscopy (SEM) and the single compression tests). Also, PM/NC-Lid swelling behavior and Lid controlled release from PM/NC-Lid hydrogels is investigated depending on the variable synthesis parameter (NC wt%) in simulated buccal environment. Results presented in this study show that PM/NC-Lid hydrogels are promising materials for controlled release of anesthetic drugs and for potential application as buccal patches in dental treatments.

Key words: *poly(methacrylic acid), nanocellulose, lidocaine hydrochloride, pH sensitive hydrogels, controlled release, dental treatments.*

Introduction

Hydrogels sensitive to external stimuli, especially pH sensitive hydrogels, are widely used in large number of areas such as tissue engineering (Yu et al., 2020), drug delivery systems (Demirdirek and Uhrich, 2017), lenses (Yang et al., 2013), cosmetics (Wang et al., 2020) etc. These materials can respond to the changes in pH values of external environment by swelling/contracting and consequently, releasing encapsulated active substance. Hydrogels based on poly(methacrylic acid) (PMAA) are recognized as materials with huge potential as drug delivery systems due to their non-toxicity, biocompatibility, high swelling capacity (derived from theirs sponge like structure) and pH sensitivity (Marković et al., 2020; Zhang et al., 2017). PMAA based hydrogels swell in environments with pH value higher than pKa of PMAA (4.6 (Marković et al., 2020)). In such type of environments, carboxylic groups of PMAA have been deprotonated, negative charges have been generated and consequently, repulsion of polymers chains occurs, leading further to the hydrogel swelling. However, poor mechanical properties of PMAA hydrogels often limit their application. The solution can be found in green chemistry and natural materials, such as wood waste materials. These materials are rich in nanocellulose (NC), natural polysaharide which is non-toxic, biocompatible, biodegradable, pH sensitive and possesses huge swelling capacity (Dimic-Misic et al., 2021). Also, NC has tremendous mechanical properties (Mendoza et al., 2020) because of which it is used for improvement of mechanical characteristics of hydrogels (Al-Sabah et al., 2019). Therefore, NC is extracted from wood waste material and it is added to PMAA in present study. In order to further improve hydrogels based on PMAA and NC, carboxymethyl cellulose (CMC) was added as well. CMC is cellulose derivate which is non-toxic, biocompatible, biodegradable, pH-sensitive and it is widely used in drug delivery systems (Hanna et al., 2020). The so prepared drug delivery system would be able to provide targeted delivery and controlled release of drug, enabling in that way safe and efficient drug application. Therefore, lidocaine hydrochloride was encapsulated in hydrogels based on PMAA, NC, CMC in order to facilitate its protection and controlled release. Lidocaine hydrochloride (Lid) is a type of local anesthetic and it is used for anesthesia and in antiarrhythmic therapy (Merey et al., 2020). Lid is usually administrated by injection (for example in dental treatment), but this kind of application is painful and unpleasant and often several dosages are required for a treatment. So, Lid encapsulation into the hydrogels can provide Lid controlled release into human mouth and therefore, its less painful and more effective application.

Synthesis of hydrogels based on PMAA, NC, CMC and Lid (PM/NC-Lid samples), their characterization and investigation of their potential application as buccal patches in dental treatments are presented present study. Swelling behavior of PM/NC-Lid hydrogels and controlled release of Lid from the samples are analyzed depending on the variable synthesis parameter (NC wt%) in simulated buccal environment. Present study offers interesting approach to green synthesis of drug delivery system and its application in buccal treatments.

Materials and Methods

Materials

Methacrylic acid (MAA) (99.5%) was purchased from Merck, Germany. Nanocellulose (NC) was isolated from the Eucalyptus wood chips (Eucaliptus globulus) which were supplied from

Agronelli Agroindustria, Uberaba (Brasil). Propylene glycol (≥98%), methane sulfonic acid (≥98%) and lidocaine hydrochloride (Lid) was purchased from Sigma-Aldrich (USA). Carboxymethyl cellulose - 9M31F (CMC) (99.5%) was supplied from Ashland (USA). N, N'-methylenebisacrylamide (MBA) (p.a.) and sodium hydroxide (p.a.) (NaOH) were supplied from Aldrich Chemical Co. (USA). The initiator, 2, 2'-azobis-[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-044) (99.8%) was purchased by Wako Pure Chemical Industries (Japan). Monobasic sodium phosphate (anhydrous) (NaH_2PO_4) (98%) and dibasic sodium phosphate (anhydrous) (Na_2HPO_4) (99%) were purchased from Centrohem (Serbia).

Preparation of PM/NC-Lid samples

NC was extracted from the Eucalyptus wood chips according to the procedure which is described in details by M. Kunaver et al. (Kunaver et al., 2016). Briefly, lignocellulosic biomass was liquefied by the propilen glycol and with low concentration of acid catalyst - methane sulfonic acid. In that manner, nanocrystalline cellulose (appeared as solid residue) was separated from lignine, cellulose with highly disordered domains and hemicellulose. Extracted NC was then added to the 2% aqueous solution of carboxymethyl cellulose and the mixture was stirred for 15 min at room temperature in the ultrasonic bath. Prepared mixture was further used for PM/NC-Lid samples.

PM/NC-Lid samples were prepared according to the following procedure (feed composition is presented in Table 1.) (Markovic et al., 2020a; Marković et al., 2020; Markovic et al., 2020b; Markovic et al., 2019). Four milliliters of methacrylic acid are dissolved in adequate amount of distilled water (Table 1.) followed by the addition of lidocaine hydrochloride (2 wt% in respect to total amount of reaction mixture (Favatela et al., 2021)). After complete dissolution of lidocaine hydrochloride, sodium hydroxide was added and stirred until complete neutralization of MAA was achieved. Then, 5 ml of the previously prepared mixture of CMC and NC was added to the reaction mixture and stirring was continued for 15 min. Crosslinker - MBA (0.4 mol% with respect to MAA) was then added and dissolved followed by the addition of initiator - VA-044 (0.9 ml of 1 wt% aqueous solution). The reaction mixture was stirred for 5 min and then poured into the glass moulds (plates, 15 x 15 cm, separated by a 2 mm thick PVC hose) and left in the air oven at 60°C for 5h. After the reaction was completed, the disc-shape samples (7 mm in diameter) were cut and used for further experiments.

Prepared samples are denoted as PM/xNC-Lid, where xNC represents wt% of nanocellulose (1 wt%, 2 wt% and 3 wt%). Also, neat poly(methacrylic acid) (PMAA), sample based on poly(methacrylic acid) and 1 wt% of nanocellulose (PM/1NC) and sample based on poly(methacrylic acid), 1 wt% of nanocellulose and lidocaine hydrochloride (PM/1NC-L) are synthetized and their composition are presented in Table 1.

Table 1. Feed composition

Sample	**NC, wt%**	**CMC, ml**	**H_2O, ml**	**Lid, wt%**
PMAA	-	-	10.4	-
PM/1NC	1.00	-	10.3	-
PM/1NC-L	1.00	-	9.90	2.00
PM/1NC-Lid	1.00	5.00	4.90	2.00
PM/2NC-Lid	2.00	5.00	4.80	2.00
PM/3NC-Lid	3.00	5.00	4.70	2.00

Methods

The Fourier Transform Infrared (FT-IR) spectra of xerogel PM/NC-Lid disks were recorded in transmittance mode for the wavelength range of 600–4000 cm^{-1} with a resolution of 4 cm^{-1}, using Nicolet™ iS10 FTIR Spectrometer.

The Scanning Electron Microscopy (SEM) analyses were performed using a Tescan MIRA 3 XMU Field-Emission Gun Scanning Electron Microscope with an acceleration voltage of 20 kV. Before the SEM analysis of the samples, PM/NC-Lid samples left to swell to equilibrium and then were freeze-dried. Further, the samples were fractured in half in frozen state and cross-sections of the samples were Au-Pd coated using a POLARON SC502 sputter coater. Then, the SEM analysis of the samples was performed.

PM/NC-Lid samples were swollen to equilibrium in phosphate buffer with pH 6.8 (PB 6.8). The samples were then withdrawn and used for compression tests. The single compression tests were performed at room temperature using a Shimadzu Autograph AGS-X (1kN) testing machine at a constant strain rate of 2 mm per minute. Compression of the PM/NC-Lid samples was performed to the moment of the collapse of the samples network. Each measurement was repeated three times and the presented results were given as the average value.

Swelling of PM/NC-Lid samples

Synthetized samples were first weight (m_0, g) and then immersed in phosphate buffer with pH 6.8 (PB 6.8) at 37°C. These experimental conditions are chosen because they are the most common for investigation of buccal drug delivery systems, according to the literature (Favatela et al., 2021). After predetermined time period the samples were withdrawn, weighted (m_t, g) and immersed again into the medium. The samples were left to swell until equilibrium state was achieved. The measurements were conducted in triplicate and the averages mass values were then used for determination of the swelling degree (SD) and equilibrium swelling degree (SDeq) of the samples according to the Eq. (1) and Eq. (2), respectively:

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

$$SD_{eq} = (m_{eq} - m_0)/m_0 \quad (2)$$

where m_{eq} is the mass of the samples in equilibrium state.

Controlled release of lidocaine hydrochloride from the PM/NC-Lid samples

The experiments of lidocain hydrochloride release from the samples were conducted in the same medium and at the same experimental conditions as were experiments of the swelling of the samples. Each of the PM/NC-Lid sample was immersed into the 100 ml of PB 6.8 medium at 37°C. Then, 3 ml of the solution was withdrawn at the predefined time intervals and the absorbance of lidocain hydrochloride in the solution was monitored by UV-Vis Shimadzu UV-1800 spectrophotometer at 265 nm (Rasool et al., 2020). The solution was immediately returned into the medium after the UV-Vis analysis. The absorbances were monitored until the equilibrium state was reached. The experiments were conducted in triplicate and average values of the absorbance were used for the construction of the curves of cumulative Lid release from

each sample.

Results and Discussion

Characterization of PM/NC-Lid samples

FTIR spectra of neat PMAA, NC, Lid, PM/1NC sample (PMAA with NC) and PM/1NC-L sample (PMAA with NC and Lid) are presented in Fig. 1. a). FTIR spectra of neat CMC and FTIR spectra of PM/NC-Lid samples with different wt% of NC are presented in Fig. 1. b). FTIR spectrum of PM/1NC-L sample is also presented in Fig. 1. b) in order to facilitated FTIR analysis of synthetized PM/NC-Lid samples. Characteristic peaks of PMAA are presented in FTIR spectra of all PM/NC-Lid samples (Fig. 1. a) and b)): peaks at 3000 cm^{-1} and at 2930 cm^{-1} (methylene groups), 1540 cm^{-1} and 1405.4 cm^{-1} (symmetric and asymmetric stretching vibrations of C(=O)-O−, respectively) (Markovic et al., 2019).
When FTIR spectra of neat PMAA and PM/1NC (Fig. 1. a)) are compared a new peak at 1115 cm^{-1} in FTIR spectrum of PM/1NC sample is noticed. This peak is present in FTIR spectra of all PM/NC-Lid samples and is attributed to the glycosidic C-O-C deformation of the β-glycosidic link in cellulose (Kunaver et al., 2016). This is the evidence of the presence of NC in PM/NC-Lid samples. The position and intensity of the peaks presented in FTIR spectra of PM/NC-Lid samples are not changed by the addition of NC (Fig. 1. a) and b)), hence NC is physically entrapped throughout the PMAA network. In addition, the intensity of characteristic peak of NC at 1115 cm^{-1} slightly increases with increase in NC wt% in PM/NC-Lid samples (Fig. 1. b)).

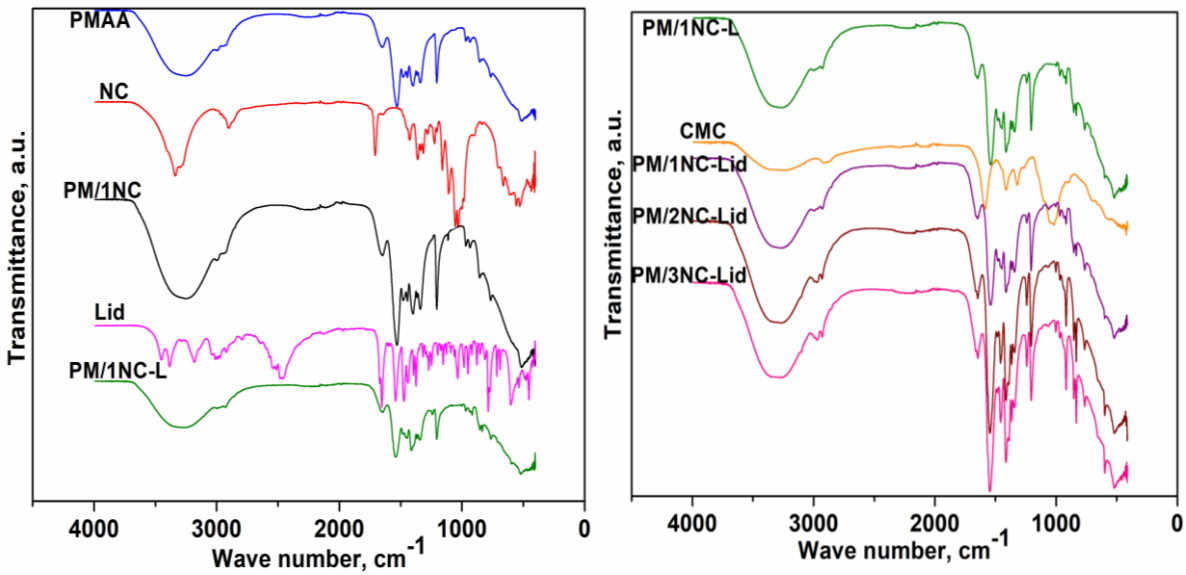

Figure 1. FTIR spectra of: a) the components of PM/NC-Lid samples and b) PM/NC-Lid samples with different wt% of NC

By comparing FTIR spectra of neat lidocaine hydrochloride, PM/1NC and PM/1NC-L the presence of three new peaks at 3022 cm^{-1}, at 1457 cm^{-1} and at 1247 cm^{-1} in FTIR spectrum of PM/1NC-L can be noticed (Fig. 1. a)) and they are attributed to Lid benzene ring, C=C bond and C-C stretching vibration (Chou et al., 2016), respectively. These three peaks are also presented in FTIR spectra of all PM/NC-Lid samples (Fig. 1. b)) and confirmed the presence of lidocaine hydrochloride in PM/NC-Lid samples. The shift of characteristic peak of Lid from 1240 cm^{-1} to

1247 cm^{-1} can be attributed to the hydrophobic interactions which were established between Lid and polysaccharides such as NC (Kola-Mustapha et al., 2016).

When FTIR spectra of neat CMC, PM/1NC-L and PM/1NC-Lid are compared a new peak at 1056.8 cm^{-1} in FTIR spectrum of PM/1NC-Lid sample is noticed (Fig. 1. b)). This is characteristic peak of CMC and is attributed to the -CO stretching vibration (Mallick et al., 2015). This peak is presented in all PM/NC-Lid samples without any noticeable change in peak position, indicating that CMC is physically entangled within the samples network.

SEM micrographs of PM/NC-Lid samples with different wt% of NC are presented in Fig. 2. SEM analysis of the samples revealed sponge like structure which is characteristic for hydrogel based materials. The diameter of the pores of the samples network slightly decreases with increase in NC wt% (Fig. 2.). Stability and rigidity of the hydrogels network increase with increase in NC wt% (Al-Sabah et al., 2019), so the cavities i.e. pores inside the network become smaller. NC is uniformly distributed through the network and coated with PMAA. Increase in NC wt% resulted in larger surfaces of the pores walls covered by NC (Fig. 2.).

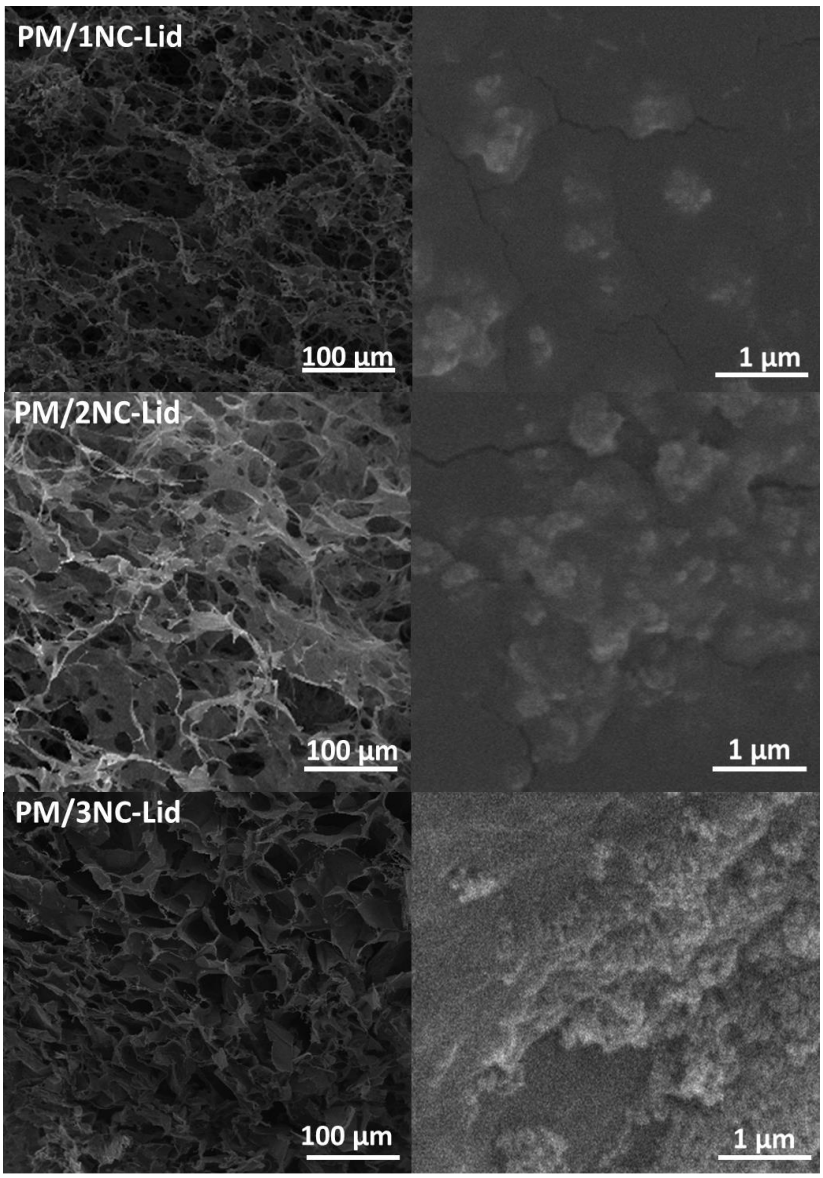

Figure 2. SEM micrographs of PM/NC-Lid samples with different wt% of NC

Mechanical properties of hydrogels are very important characteristic which can limit their

application as drug carriers. In order to investigate the effect of NC on the mechanical properties of synthetized PM/NC-Lid samples single compressive test are employed according to the procedure described in 2.3. Section. Obtained values of maximal compressive strength (σ) and maximal stroke strain (MSS) of neat PMAA, PM/1NC-L (PMAA with NC and Lid) and PM/NC-Lid samples are presented in Table 2. It can be concluded that the addition of NC to PMAA increased σ value (σ(PMAA) < σ(PM/1NC-L)), whereas the value of maximal stroke strain decreased (MSS(PMAA) > MSS(PM/1NC-L)). Also, the values of maximal compressive strength and maximal stroke strain of PM/1NC-L and PM/1NC-Lid samples are similar; hence the addition of CMC did not affect mechanical properties of PM/NC-Lid samples. Increase in NC wt% leads to increase of σ value of PM/NC-Lid samples and to decrease of the value of maximal stroke strain of PM/NC-Lid samples. This could be a consequence of increasing stability and rigidity of the hydrogels network caused by the presence of NC (Al-Sabah et al., 2019) in the samples network (SEM micrographs).

Table 2. Maximal compressive strength, maximal stroke strain and equilibrium swelling degree of the samples and cumulative Lid release from the samples in equilibrium state

Sample	**Maximal compressive strength σ (N/mm^2)**	**Maximal stroke strain of the samples calculated at entire areas (%)**	**SDeq**	**Cumulative Lid release (%)**
PMAA	0.0531	74.0	58.4	-
PM/1NC-L	0.112	59.3	53.6	-
PM/1NC-Lid	0.112	57.2	51.6	59.7
PM/2NC-Lid	0.113	53.2	44.7	48.1
PM/3NC-Lid	0.114	49.3	34.9	38.8

The analysis of the swelling behavior of PM/NC-Lid samples in PB 6.8

The curves of PM/NC-Lid samples swelling in PB 6.8 are presented in Fig. 3, whereas the values of equilibrium swelling degree are presented in Table 2. The PMAA based materials swell in the environments with pH value that is higher than pKa of PMAA (4.6 (Marković et al., 2020)). In that kind of environments carboxylic groups of PMAA have been deprotonated, negative charges have been generated leading to the repulsion of the polymers chains of hydrogels network and further to the swelling of PMAA based hydrogels. This is the reason of the PM/NC-Lid samples swelling in PB 6.8 Based on the analysis of the swelling curves presented in Fig. 3. it can be concluded that addition of NC to the PMAA induced decrease in the SDeq value (SDeq (PMAA) > SDeq (PM/1NC-L)). Also, addition of CMC did not have any significant impact on the SDeq values (SDeq values of PM/1NC-L and PM/1NC-Lid were similar). Increase in NC wt% led to decrease of the SDeq values in following order: PM/1NC-Lid > PM/2NC-Lid > PM/3NC-Lid. The increase in NC wt% can cause increase in rigidity of hydrogels network and decrease of pores size, which further induce less swelling of the sample.

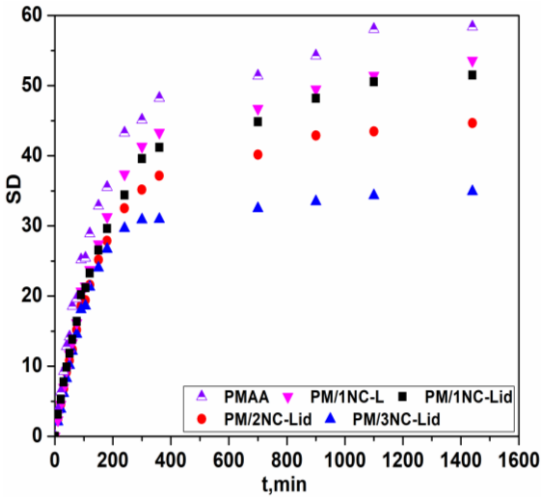

Figure 3. The curves of PM/NC-Lid samples swelling in PB 6.8

pH dependent swelling of the samples can be used for targeted delivery of encapsulated active substance. Therefore, the potential of prepared PM/NC-Lid samples for controlled release of lidocain hydrochloride in the medium which simulated buccal environment is investigated.

The analysis of lidocain hydrochloride release from PM/NC-Lid samples in PB 6.8

Curves of cumulative Lid release from PM/NC-Lid samples in PB 6.8 are presented in Fig. 4, whereas percent of cumulative Lid release from the samples in equilibrium state are presented in Table 2. Lidocain hydrochloride was released from all PM/NC-Lid samples in PB 6.8 as a consequence of specific pH dependent swelling behavior of the samples (Section 3.2.). Controlled release of Lid from synthetized samples can be achieved for 24 h. It can be also concluded that increase in NC wt% lead to decrease of the percent of cumulative Lid release in following order: PM/1NC-Lid > PM/2NC-Lid > PM/3NC-Lid. The percent of cumulative Lid release from PM/1NC-Lid, PM/2NC-Lid and PM/3NC-Lid was 59.7%, 48.1% and 38.8%, respectively.

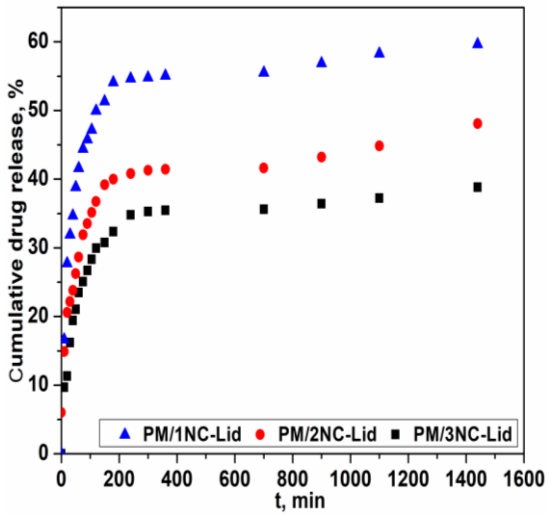

Figure 4. Cumulative lidocain hydrochloride release from PM/NC-Lid samples

Based on all obtained results it can be concluded that prepared PM/NC-Lid samples possessed desirable characteristics and can be used for controlled and prolonged release (up to 24h) of

lidocain hydrochloride in environments such as buccal. Therefore, PM/NC-Lid samples have huge potential to be used as patches for controlled release of lidocain hydrochloride in dental treatments.

Conclusions

Novel hydrogels based on poly(methacrylic acid), nanocellulose, carboxymethyl cellulose with encapsulated lidocain hydrochloride (PM/NC-Lid) are synthetized, characterized and their potential application as buccal patches are investigated in the present study. Hydrogels are prepared by green approach using nanocellulose extracted from the wood waste material. FTIR analysis of the synthetized samples showed that NC is physically entrapped throughout the PMAA network. Encapsulation of lidoacin hydrochloride (Lid) was achived through the hydrophobic interactions established between this active substance and the NC. All synthetized samples have regular porous structure and the size of the pores decreased with increase in NC wt%, as SEM analysis showed. The addition of NC improved PMAA mechanical properties and therefore enhanced PMAA application as drug carrier. The analysis of the swelling behavior of PM/NC-Lid samples and controlled release of lidocain hydrochloried are performed in phosphate buffer with pH=6.8 at 37℃ (PB 6.8), conditions at which buccal drug delivery systems are investigated. Obtained results showed that all samples swell in PB 6.8 and that controlled release of lidocain hydrochloried from all samples is achived. Increase in NC wt% led to decrease of equlibrium swelling degree of the samples and to decrease of precents of cumulative Lid release. Based on all results it can be concluded that prepared PM/NC-Lid samples are promising materials with huge potential for preparation of buccal patches used in dental treatments.

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