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Dual responsive hybrid hydrogels for controlled release of local anesthetic

Inteligent hydrogels, such as pH sensitive hydrogels based on poly(methacrylic acid) (PMAA) are widely used for targeted drug delivery. Still, PMAA lack of good mechanical properties often limits its application. In order to overcome this limitation nanocellulose (NC) was extracted from wood waste material and then added to PMAA because NC is biocompatible, non-toxic and has excellent mechanical properties. Further, carboxymethyl cellulose (CMC) (cellulose derivate widely used for controlled release of drugs) was added. CMC can stabilize magnetite nanoparticles (MN) which is then also added. MN can significantly improve mechanical properties of hydrogels and also possess magnetic properties due to which MN can be used for targeted drug delivery. The as-prepared material can protect drug, deliver it to the site of action, control its release rate and enable in that way its efficient application with reduced side effects. Local anesthetic - lidocaine hydrochloride (LH) is often administrated by injection which can induce severe side effects. This problem is solved in present study by encapsulating LH into hydrogels based on PMAA, NC, CMC and MN (PMNC/MN-L). PMNC/MN-L hydrogels were characterized by FTIR and SEM spectroscopies and single compressive tests and then their swelling behavior and LH release were analyzed. Present study offers unique approach for green synthesis of dual responsive hydrogels with improves properties and their application for controlled release of local anesthetic with reduced side effects.

1 Introduction

Materials based on hydrogels sensitive to external stimuli are found great application in drug delivery systems [1]. These materials respond to the changes in external environment (such as pH value, the strength of the magnetic field etc.) by changing one of the structural properties such as swelling due to which encapsulated drug can be released at the site of action. Poly(methacrylic acid) (PMAA) hydrogels are one of the pH sensitive hydrogels which are biocompatible and non-toxic because of which they are widely used as targeted drug delivery system. Still, PMAA lack of good mechanical characteristics often can limit PMAA application. To overcome this limitation nanocellulose was added to PMAA in this study. Nanocellulose (NC) can be extracted from natural materials rich in this polysaccharide, such as wood waste material. NC is non-toxic, biocompatible and possesses excellent mechanical properties [2]. Cellulose derivate carboxymethyl cellulose (CMC) was used for further improvement of the samples based on PMAA and NC. CMC is non-toxic and biocompatible and is often used as stabilizer [3-5]. CMC was use for stabilization of magnetite nanoparticles which were added to the samples as well. Magnetite nanoparticles (MN) are often used for improvement of mechanical properties of hydrogels [6]. MN possess magnetic properties due to which they are used for targeted drug delivery [7, 8]. By applying external magnetic field it would be possible to control the path of the carriers through the human body to the site of action. The as prepared pH- and magnetic- sensitive hybrid hydrogels can be used for targeted drug delivery and controlled release of drug such as local anesthetic - lidocaine hydrochloride. Lidocaine hydrochloride (LH) is used for anesthesia [9], in antiarrhythmic therapy [10], dental treatments [11] and usually is applied by injections [12]. This kind of LH application can cause several side effects such as breathing problems, nausea and heart attack [11, 13] and often several doses are necessary for therapy. Therefore, samples based on PMAA, NC, CMC, MN with encapsulated LH (PMNC/MN-L) were prepared in this study. Synthetized samples were then characterized by FTIR, SEM and by using single compressive tests. In addition, swelling behavior and LH release from PMNC/MN-L samples were investigated depending on variable MN wt%.

Present study provides useful directions towards green synthesis of drug carriers based on hydrogels and their application for controlled release of local anesthetic which further lead to its efficient application with reduced side effects.

2 Materials and methods

2.1 Materials

Methacrylic acid (MAA) (99.5%) was supplied from Merck, Germany. Nanocellulose (NC) was extracted from the Eucalyptus wood chips (Eucaliptus globulus) which were purchased from Agronelli Agroindustria (Brasil). Propylene glycol (≥98%), methane sulfonic acid (≥98%) and lidocaine hydrochloride (LH) was supplied from Sigma-Aldrich (USA). Carboxymethyl cellulose - 9M31F (CMC) (99.5%) was purchased from Ashland (USA). Iron (II) chloride (99%) and iron (III) chloride hexahydrate (97%) were purchased from CARLO ERBA Reagents (France). 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 supplied

from 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). All chemicals were used as received.

2.2 Synthesis of PMNC/MN-L samples

Nanoparticles of magnetite (MN) were prepared by co-precipitation reaction in the following way. 2.7 g of iron (III) chloride hexahydrate and 2.55 g of iron (II) chloride were dissolved in 200 ml of distilled water. Then, 10 ml of ammonium hydroxide was added rapidly at room temperature. Stirring (250 rpm) was continued for 15 min at 75°C. Obtained MN was appeared as black residue which was separated from the mixture with permanent magnet and washed three times with distilled water. Synthetized MN was used for further preparation of PMNC/MN-L samples.

Nanocellulose was extracted from the Eucalyptus wood chips using approach which is described in details by M. Kunaver et al. [14]. Briefly, propylene glycol and low concentration of acid catalyst (methane sulfonic acid) were used for liquefaction of ligninocellulose biomass. Nanocellulose was appeared as precipitated, so it was separated from cellulose with highly disordered domains, lignine and hemicellulose. Isolated nanocellulose (Table 1.) was then added to the 3% of aqueous solution of carboxymethyl cellulose. Obtained mixture was stirred for 30 min at room temperature in the ultrasonic bath. Then, MN was added (Table 1.) and the stirring was continued at the magnetic stirrer for 15 min. Prepared mixture of NC, CMC and MN was used for further synthesis of PMNC/MN-L samples.

PMNC/MN-L samples were synthetized in the following way [15-17]. 2 ml of methacrylic acid was added to the adequate amount of distilled water (See Table 1. for Feed composition). Lidocaine hydrochloride (2 wt% in respect to total mass of final reaction mixture [18]) was then added and dissolved. In order to achieve complete neutralization of methacrylic acid, adequate amount of sodium hydroxide was added to the reaction mixture. After complete neutralization of methacrylic acid, 3 ml of previously prepared mixture of NC, CMC and MN were added and stirring was continued until reaction mixture became homogenous. N, N'-methylenebisacrylamide (MBA) - cross-linker (0.4 mol% with respect to the methacrylic acid) was then added and dissolved followed by the addition of initiator - 2, 2'-azobis-[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-044) (0.9 ml of 1 wt% aqueous solution). Obtained reaction mixture was stirred for 4 min and then poured into the glass moulds (plates, 12 x 12 cm, separated by a 2 mm thick PVC hose) and left in the air oven at 60°C for 5h. At the end of 5th hour, the disc-shape samples (7 mm in diameter) were cut and used for further experiments.

Synthetized samples are denoted as PMNC/xMN-L, where xMN represents wt% of magnetite nanoparticles (1 wt%, 2 wt% and 3 wt%). In order to facilitate FTIR analysis, several samples were also synthetized: neat poly(methacrylic acid) (PMAA), sample based on poly(methacrylic acid) and nanocellulose (PMNC), sample based on poly(methacrylic acid), nanocellulose and lidocaine hydrochloride (PMNC-L) and sample based on poly(methacrylic acid), nanocellulose, carboxymethyl cellulose and lidocaine hydrochloride (PMNC/0MN-L) and their composition are presented in Table 1.

Table 1. Feed composition

Sample	NC, wt%*	CMC, ml	H_2O, ml	LH, wt%	MN, wt%*
PMAA	-	-	4.74	-	-
PMNC	1	-	4.69	-	-
PMNC-L	1	-	4.49	2	-
PMNC/0MN-L	1	3	1.49	2	-
PMNC/1MN-L	1	3	1.44	2	1
PMNC/2MN-L	1	3	1.39	2	2
PMNC/3MN-L	1	3	1.34	2	3

*with respect to total mass of final reaction mixture

2.3 Methods

The Fourier Transform Infrared (FTIR) spectra of dry disks of the PMAA, PMNC, PMNC-L and PMNC/MN-L samples were recorded in transmittance mode for the wavelength range of 400÷4000 cm-1 with a resolution of 4 cm-1, using Nicolet™ iS10 FTIR Spectrometer.

The Scanning Electron Microscopy (SEM) analyses of the PMNC/MN-L samples were performed using a Tescan MIRA 3 XMU field-emission gun scanning electron microscope with an acceleration voltage of 20 kV. Prior to SEM analysis, the PMNC/MN-L samples were swollen to equilibrium and were freeze-dried. The samples were then fractured in half and obtained cross-sections of the samples were Au-Pd coated using a POLARON SC502 sputter coater. Then, the so-prepared cross-sections of the samples were used for the SEM analysis.

PMNC/MN-L samples were swollen to equilibrium in phosphate buffer with pH=6.8 (PB 6.8) and used for single compression test. The 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 PMNC/MN-L samples was performed to the moment of the collapse of the samples network. Each experiment was conducted in triplicate and the mean values are presented in the Results and discussion section.

The strength of magnetic field of the dry PMNC/MN-L samples swollen in PB 6.8 to equilibrium is measured by Gauss/Teslameter FH 51. Each experiment was conducted in triplicate and the mean values are presented in the Results and discussion section.

The analysis of swelling behavior of PMNC/MN-L samples was performed in PB 6.8 at 37°C (as a simulation of buccal environment [18] or pH environment of human intestines [19]) until equilibrium state was reached. Dry discs of PMNC/MN-L samples were first weight (m_0, g) and then immersed into 100 ml of PB 6.8 and left to swell. At predetermined time intervals samples were removed from PB 6.8 and their mass was measured (m_t, g) until equilibrium state was reached (me, g). Each experiment was conducted in triplicate and the mean values are used for further calculations. The swelling degree (SD) of the PMNC/MN-L samples was determined according to Eq. (1), whereas equilibrium swelling degree (SD_e) of the PMNC/MN-L samples was calculated according to the Eq. (2):

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

$$SD_e = (m_e - m_0)/m_0 \quad (2)$$

Each experiment was conducted in triplicate and the mean values are presented in the Results and discussion section.

The controlled release of lidocaine hydrochloride from the PMNC/MN-L samples was carried out at same experimental conditions as was the swelling of the PMNC/MN-L samples. At predetermined time intervals 3 ml of solution was withdrawn, its absorbance was measured at 265 nm using the UV-Vis Shimadzu UV-1800 spectrophotometer and then returned back into the medium. The measurements were performed until equilibrium state was reached. Each experiment was conducted in triplicate and the mean values are used for construction of the curves of LH release from the samples which are presented in the Results and discussion section.

3 Results and discussion

3.1 Characterization of PMNC/MN-L samples

FTIR spectra of neat PMAA, NC, LH, PMNC sample (PMAA with NC) and PMNC-L sample (PMAA with NC and LH) are presented in Fig. 1. a). FTIR spectra of neat CMC, MN and FTIR spectra of PMNC/MN-L samples with different wt% of MN are presented in Fig. 1. b). In order to facilitated FTIR analysis of synthetized PMNC/MN-L samples, FTIR spectrum of PMNC-L sample is also presented in Fig. 1. b). Characteristic peaks of PMAA are presented in FTIR spectra of all PMNC/MN-L samples (Fig. 1. a) and b)): peaks at 2930 cm^{-1} and at 3000 cm^{-1} (methylene groups), 1404 cm^{-1} and 1541 cm^{-1} (symmetric and asymmetric stretching vibrations of C(=O)-O−, respectively) [15].

By comparing the FTIR spectra of neat PMAA and PMNC sample (Fig. 1. a)) it can be notices the presence of a new peak at 1116 cm−1 in FTIR spectrum of PMNC sample. This peak is attributed to the glycosidic C-O-C deformation of the β-glycosidic link in cellulose and is present in FTIR spectra of all PMNC/MN-L samples [14]. This peak confirmed the presence of NC in PMNC/MN-L samples. The addition of NC did not affected the position and intensity of the peaks presented in FTIR spectra of PMNC/MN-L samples (Fig. 1. a) and b)), therefore NC is physically entrapped within the PMAA network.

When FTIR spectra of neat lidocaine hydrochloride, PMNC and PMNC-L are compared, the presence of three new peaks at 1246 cm^{-1}, at 1458 cm^{-1} and at 3021 cm^{-1} in FTIR spectrum of PMNC-L are noticed (Fig. 1. a)). These three peaks are attributed to C-C stretching vibration, C=C bond and benzene ring of lidocaine hydrochloride [20], respectively. Their presence in FTIR spectra of all PMNC/MN-L samples (Fig. 1. b)) confirmed the presence of lidocaine hydrochloride in PMNC/MN-L samples. The shift of characteristic peak of LH from 1240 cm^{-1} to 1246 cm^{-1} can be attributed to the hydrophobic interactions which were established between LH and polysaccharides such as NC [21].

By comparing FTIR spectra of CMC, PMNC-L and PMNC/0MN-L the presence of a new peak at 1055.9 cm^{-1} in FTIR spectrum of PMNC/0MN-L sample can be noticed (Fig. 1. b)). This is CMC characteristic peak and is attributed to the -CO stretching vibration [22]. Due to the fact that this peak is presented in all PMNC/MN-L samples and any change in peak position can be noticed, it can be concluded that CMC is bonded through the physical entanglement within the network of samples.

The presence of magnetite characteristic peak at 850 cm^{-1} (Fe-O lattice vibrations [23]) in FTIR spectrum of PMNC/1MN-L sample (which did not exist in FTIR spectrum of PMNC/0MN-L sample) was the conformation of the MN presence (Fig. 1. b)). This peak was presented in FTIR spectra of PMNC/2MN-L and PMNC/3MN-L samples (Fig. 1. b)), as well. The intensity of this peak slightly increased with increase of wt% of MN.

The SEM micrographs of synthetized PMNC/MN-L samples with different wt% of MN are presented in Fig. 2. All samples have sponge like structure which is characteristic for hydrogels. It can be noticed that domains of NC are coated by PMAA and they cover the walls of the pores of hydrogels network (Fig. 2.). Also, the nanosized round shape particles of magnetite are noticeable in the network of all PMNC/MN-L samples (Fig. 2.). The increase in wt% of MN did not affect the size of the pores, i.e. all samples had similar diameter of the pores.

The magnetic properties of PMNC/MN-L samples are confirmed by measuring the strength of magnetic field of the PMNC/MN-L samples. The strength of magnetic field of PMNC/MN-L samples increased with increase in MN wt%, in following order: PMNC/1MN-L < PMNC/2MN-L < PMNC/3MN-L. The strength of magnetic field of these samples was 0.02 mT, 0.05 mT and 0.2 mT, respectively. Magnetic properties of synthetized PMNC/MN-L samples can be used for targeted drug delivery to the specific site in human body. Namely, external magnetic field could control the path of PMNC/MN-L samples through the human body right up to the site of action.

The mechanical properties of PMNC/MN-L samples are investigated by using single compressive test according to the procedure described in 2.3. Methods Section. Obtained values of maximal compressive strength (σ) and maximal stroke strain (MSS) of the samples swollen in PB 6.8 to equilibrium are presented in Table 2. By comparing σ and MSS values of PMAA i PMNC it can be concluded that the addition of nanocellulose induced increase of σ values and decrease of MSS values. This could be due to the increased rigidity of the samples network caused by the presence of nanocellulose compared to the network of the neat PMAA. Encapsulation of LH (PMNC and PMNC-L samples) and addition of CMC (PMNC-L and PMNC/0MN-L samples) did not affect the σ and MSS values. PMNC and PMNC-L samples had similar σ and MSS values which indicated that encapsulation of LH did not have any effect on mechanical properties of the samples. When σ and MSS values of PMNC-L and PMNC/0MN-L samples are compared it can be noticed that they are similar. Hence, the addition of CMC did not affected mechanical properties of the samples. The increase in MN wt% led to the increase of σ values (PMNC/0MN-L < PMNC/1MN-L < PMNC/2MN-L < PMNC/3MN-L) and to the decrease of MSS values (PMNC/0MN-L > PMNC/1MN-L > PMNC/2MN-L > PMNC/3MN-L) of the samples. This could be a consequence of increased rigidity of the samples network caused by the presence of MN in pores of PMNC/MN-L samples.

Table 2. Maximal compressive strength and maximal stroke strain of the samples swollen in PB 6.8 to equilibrium

Sample	Maximal compressive strength σ (N/mm^2)	Maximal stroke strain (MSS) of the samples calculated at entire areas (%)
PMAA	0.0529	72.0
PMNC	0.110	58.9
PMNC-L	0.112	58.7
PMNC/0MN-L	0.112	58.8
PMNC/1MN-L	0.114	53.2
PMNC/2MN-L	0.121	49.3
PMNC/3MN-L	0.200	45.9

Results showed that synthetized samples can protect drug and deliver it to the site of action in human body. Beside mechanical properties of drug carriers based on hydrogels, swelling is also important property. Swelling of the hydrogel controls the rate of drug release at the site of action and therefore enables drug safe and efficient application. Hence, swelling behavior of synthetized samples in PB 6.8 are further investigated.

3.2 The analysis of the swelling behavior of PMNC/MN-L samples in PB 6.8

Swelling of synthetized samples is investigated according to the procedure described in 2.3. Methods Section. Constructed curves of PMNC/MN-L samples swelling in PB 6.8 are presented in Fig. 3, whereas values of equilibrium swelling degree of PMNC/MN-L samples are presented in Table 3. It can be noticed that all synthetized samples swell in this medium and that equilibrium state was reached after 24 h. PB 6.8 have pH 6.8 which is higher than pKa(PMAA) (4.6 [16]), so in this medium carboxylic groups of PMAA have been deprotonated and permanent negative charge has been generated on them. This further leads to the repulsion of polymers chains and swelling of PMNC/MN-L samples.

SDe of PMAA is higher than SDe of PMNC, so samples with NC swell less than neat PMAA. Addition of NC to the PMAA network as already mentioned increased rigidity of the network, so less amount of the medium can be absorbed by the network. The same is true for the addition of MN (SDe(PMNC/0MN-L) > SDe(PMNC/1MN-L)). Increase in wt% of MN induced decrease of the SDe values in following order: SDe(PMNC/1MN-L) > SDe(PMNC/2MN-L) > SDe(PMNC/3MN-L). The addition of CMC did not affected SDe value of the samples (SDe(PMNC-L) and SDe(PMNC/0MN-L) were similar).

pH depended swelling behavior of synthetized samples can be used for targeted delivery and controlled release of lidocaine hydrochloride in the environments with pH=6.8 (such as buccal environment and human intestines). Drug release kinetics is crucial for safe and efficient drug application, so LH controlled release in PB 6.8 is further investigated.

3.3 The analysis of lidocaine hydrochloride release from PMNC/MN-L samples

Constructed curves of cumulative LH release from PMNC/MN-L samples in PB 6.8 are presented in Fig. 4. Controlled release of LH from all PMNC/MN-L samples was achieved and lasted for 24h. The values of percent of LH cumulative release from all samples are presented in Table 3.

Table 3. Equilibrium swelling degree of the samples and cumulative LH release from the samples in equilibrium state

Sample	SDeq	Cumulative LH release (%)
PMAA	59.6	-
PMNC	54.2	-
PMNC-L	52.7	60.2
PMNC/0MN-L	49.6	57.9
PMNC/1MN-L	44.9	49.7
PMNC/2MN-L	37.2	40.1
PMNC/3MN-L	29.3	32.4

Cumulative LH release from PMNC/0MN-L was higher than from PMNC/1MN-L, hence addition of MN decreased the release rate of LH. Also, increase in wt% of MN induced decrease of cumulative LH release in following order: PMNC/1MN-L > PMNC/2MN-L > PMNC/3MN-L (Table 3.). Physical presence of MN in the pores of samples network increased rigidity of the network, causing further decrease of SD of the samples (3.2. Section). This could be a reason of the reduced LH release rate from PMNC/MN-L samples.

Obtained results showed that synthetized samples could be used for targeted delivery of LH to the site of action in the human body due to pH and magnetic sensitivity of PMNC/MN-L samples. Also, LH controlled release in the environments with pH=6.8 (such as buccal environment and human intestines) can be achieved for 24 h. In that way more efficient and safer application of LH can be achieved.

4 Conclusions

This study gives innovative approach to synthesis and application of dual responsive hybrid hydrogels. Samples based on poly(methacrylic acid), nanocellulose, carboxymethyl cellulose and lidocaine hydrochloride (PMNC/MN-L) are synthetized via free-radical polymerization. Nanocellulose (NC) was first extracted from waste wood material and added to poly(methacrylic acid) (PMAA) in order to improve PMAA mechanical characteristics. Magnetite nanoparticles (MN) were synthetized via co-precipitation reaction and added in order to further improve mechanical characteristics of the samples and due to MN magnetic properties. Namely, external magnetic field can be used for control of the path of PMNC/MN-L samples through the human body right up to the site of action of lidocaine hydrochloride (LH). Through pH depended swelling of PMAA, release of LH can be controlled and in that way more efficient and safe application of LH can be achieved. LH is usually applied by injection, which have many side effects, such as: breathing problems, nausea and heart attack. By delivering LH to the specific organ of human body and by

controlling LH release rate these side effects can be overcome. FTIR analysis showed that NC, CMC and MN are physically entrapped within the PMAA network and LH was encapsulated thorough physical bonds established between LH and NC. Single compressive tests showed that increase in wt% of MN improved mechanical properties of the samples. Increase in wt% of MN induced decrease in swelling degree of the samples and as a consequence cumulative LH release decreased, as well.

Presented results show that PMNC/MN-L samples can protect encapsulated drug such as lidocaine hydrochloride, due to their good mechanical characteristics. pH- and magnetic- sensitivity of PMNC/MN-L samples can be used for lidocaine hydrochloride targeted delivery to the site of action and its controlled release. Therefore, samples prepared in this study have great potential as LH delivery system which can provide efficient and safe LH application with reduced side effects.

5 Figures

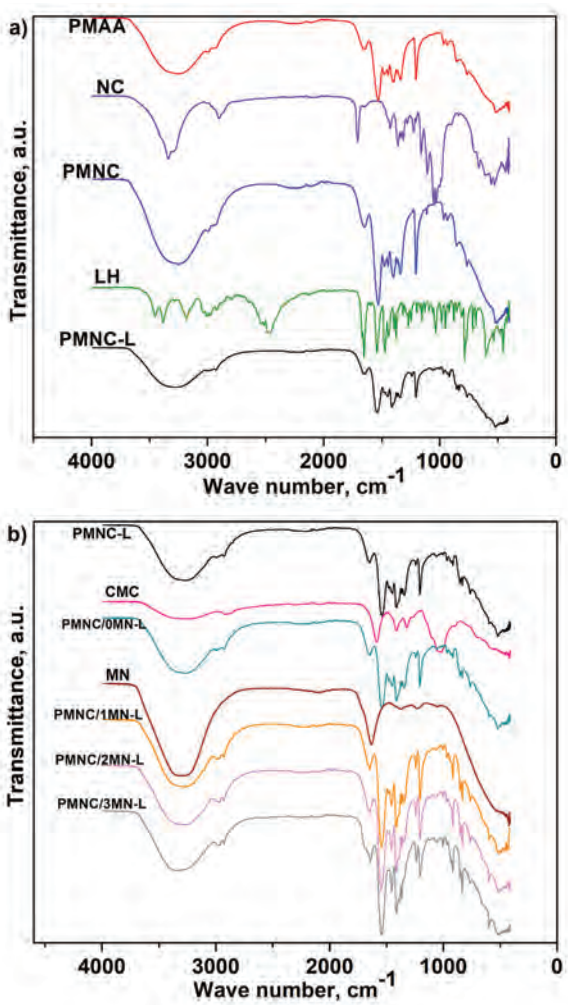

Figure 1: The FTIR spectra of: a) neat PMAA, NC, PMNC, LH and PMNC-L samples; and b) PMNC-L, CMC, MN and PMNC/MN-L samples with different wt% of MN

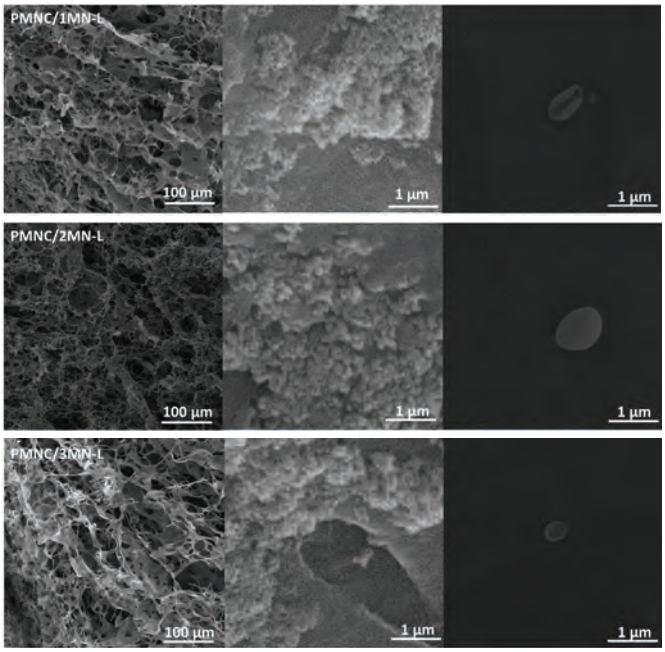

Figure 2: SEM micrographs of: a) PMNC/1MN-L, b) PMNC/2MN-L and c) PMNC/3MN-L samples (For each sample from the left to the right, respectively: sponge like structure of the sample; domains of nanocellulose and magnetite round shape nanoparticles)

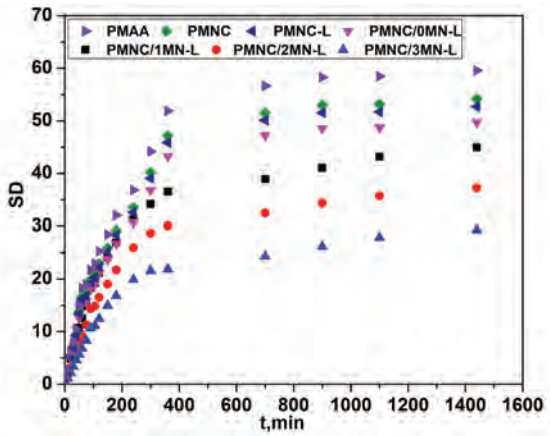

Figure 3: Curves of PMNC/MN-L samples swelling in PB 6.8

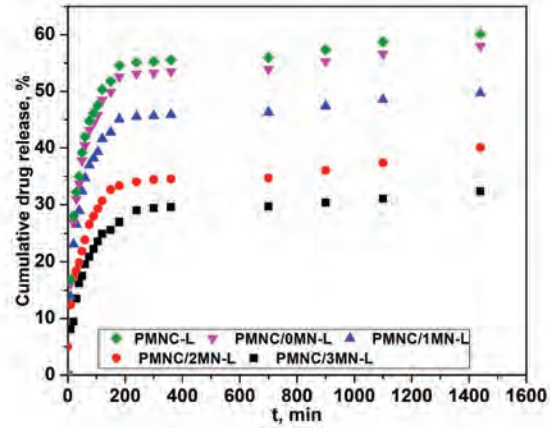

Figure 4: Curves of lidocaine hydrochloride release from PMNC/MN-L samples in PB 6.8

6 Abbreviations

CMC - carboxymethyl cellulose
FTIR - Fourier Transform Infrared spectroscopy
LH - lidocaine hydrochloride
m_{eq} - weight of sample swollen to equilibrium (g)
m_t - weight of swollen sample at time t (g)
MAA - methacrylic acid
MBA - N,N′-methylenebisacrylamide (crosslinker)
MN - magnetite nanoparticles
MSS - maximal stroke strain of the samples (%)
NC - nanocellulose
PB 6.8 - phosphate buffer with pH=6.8
PMAA - poly(methacrylic acid)
PMNC - sample based on poly(methacrylic acid) and nanocellulose
PMNC-L - sample based on poly(methacrylic acid), nanocellulose and lidocaine hydrochloride
PMNC/MN-L - samples based on poly(methacrylic acid), nanocellulose, carboxymethyl cellulose, magnetite nanoparticles and lidocaine hydrochloride
PMNC/0MN-L - sample based on poly(methacrylic acid), nanocellulose, carboxymethyl cellulose and lidocaine hydrochloride (without the magnetite nanoparticles)
SD - swelling degree of the samples
SD_e - equilibrium swelling degree of the samples
SEM - Scanning Electron Microscopy
t - time of the swelling of the PMNC/MN-L samples and time of lidocaine hydrochloride release process (min) from the PMNC/MN-L samples
VA-044 - 2,2′-Azobis-[2-(2-imidazolin-2-yl)propane]dihydrochloride (initiator)

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