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There were 247 submissions. Each submission was reviewed by at least 1, and on the average 2, reviewers. The committee decided to accept papers as follows. Invited papers are included and presented as papers in Sessions.

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- **Special Session dedicated to academician Rajko Tomović**

Moderators:
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- **Special Session: New Materials**

Moderators:
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Prof. Vladimir Srdić: **Ultrafast Spin Dynamics in Multiferroic Oxides;**

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August 27, 2019

Belgrade

Boris Loncar

Soft polymeric networks based on poly(methacrylic acid),itaconic acid, casein and liposomes for targeted delivery and controlled release of poorly water-soluble active substance

Maja Marković, Vesna Panić, Sanja Šešlija, Pavle Spasojević, Vukašin Ugrinović, Nevenka Bošković-Vragolović and Rada Pjanović

***Abstract*—Soft polymeric networks based on poly(methacrylic acid) (PMAA) are attractive candidates for targeted and controlled drug release due to their non-toxicity, biocompatibility and pH-sensitivity. The highly hydrophilic nature of PMAA networks enables transport of hydrophilic drugs only. This limitation has been overcome in present work by a PMAA modification with casein and liposomes. Casein is a natural amphiphilic protein which enabled the encapsulation and targeted and controlled release of the model drug- caffeine. The FTIR spectra showed that the hydrophobic interactions and hydrogen bonds were established between the casein and caffeine. The caffeine *in vitro* release was monitored in two media at 37°C: phosphate buffer pH=6.8, which simulated the pH environment in the human intestines and 0.1M HCl pH=1.2, which simulated the pH environment in the human stomach. The presence of liposomes with the encapsulated caffeine in the carriers caused the decrease in the speed of caffeine release. Introduction of itaconic acid (IA) as a hydrophilic and pH-sensitive substance with two carboxylic groups resulted in a non-regular structure of the carriers with large voids which caused an increase in swelling rate of the carriers and an increase in speed of caffeine release. All obtained results showed that the targeted and controlled release of a poorly water-soluble substance was achieved.**

***Index Terms*—Poly(methacrylic acid); itaconic acid; casein; liposomes; controlled release; poorly water-soluble drug; release kinetic**

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I. Introduction

DRUG delivery carriers for the targeted delivery of the active substances and their controlled release are intensively developed and used in treatment of some serious diseases [1]. pH sensitive soft polymeric networks- hydrogels have a great potential in this field of application because they respond to the pH changes in the external medium by swelling or contracting due to which they release their loadings. pH sensitive hydrogels of much interest for targeted drug delivery are based on poly(methacrylic acid) (PMAA). These hydrogels are biocompatible, non-toxic and contain a large number of ionisable –COOH groups. Ionization of carboxylic groups and generation of the negative charges on them occurs if the pH of the external medium is above the pKa of PMAA (4.6) causing the repulsion of the PMAA polymeric chains and swelling of the PMAA [2]. Although PMAA hydrogels have been shown to be good carriers of a hydrophilic active substance, the limitation for the use of these carriers in controlled release of the poorly water-soluble active substances is imposed by the hydrophilic nature of PMAA and relates to the poor interactions with a poorly water-soluble active substance [3]. In order to overcome this limitation PMAA hydrogels must be modified with amphiphilic substances such as some proteins and phospholipidic nanoparticles. Casein (the major milk protein) is a great candidate for targeted delivery of poorly water-soluble active substances due to its amphiphilic nature, pH sensitivity, non-toxicity and biocompatibility. It is also recognized as a GRAS protein and approved by American Food and Drug Administration. Spherical phospholipidic nanoparticles, such as liposomes which consist of one or more lipidic layers and an aqueous core, could be used for delivery and controlled release of both, hydrophilic and poorly water-soluble substances.

The goal of this research was to develop a hydrophilic polymer carrier for targeted delivery and controlled release of a poorly water-soluble substance. Hence, carriers for poorly water-soluble model drug-caffeine based on poly(methacrylic acid) and casein (PMAC), PMAC with itaconic acid (PMAC/IA) and PMAC with incorporated liposomes(PMAC-L) were synthesized. The successful entrapment of a drug, its

delivery to a specific place in the human body and the controlled release depend on a successful design of a carrier. Therefore, an investigation of the structure of synthesized carriers and of interactions established between the carrier and the drug was conducted. In addition, the influences of the presence of the itaconic acid and the presence of the liposomes on the caffeine release and on the swelling rate of the carriers were also analyzed. In order to control the drug release and to release a desirable concentration of a drug in the specific place in the human body it is important to get an insight into the drug release kinetic, hence two mathematical models were used for the investigation of caffeine release kinetic.

II. Materials and Methods

A. Materials

Methacrylic acid (MAA) (99.5%) was purchased from Merck, Germany. Sodium caseinate (C) powder, containing 88.9 wt. % of protein (the rest was the proteins, lipids, attached moisture and ashes) was supplied from Lactoprot, Deutchland GmbH (Germany). Itaconic acid (IA) (≥99%) was supplied from Aldrich Chemical Co. (USA). NATIPIDE® II containing phospholipids from soybean >20% (with 3-sn-phosphatidylcholine 76+ 3%) was purchased from Lipoid (Germany). Caffeine (Cf) was supplied from Merck (Germany). 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 from Wako Pure Chemical Industries (Japan). Monobasic sodium phosphate (anhydrous) (NaH_2PO4) and dibasic sodium phosphate (anhydrous) (Na_2HPO4) were purchased from Centrohem (Serbia). Hydrochloric acid (37%) was supplied from Zorka Pharma (Serbia). All chemicals were used as received.

B. Preparation of the samples

The PMAC and PMAC/L carriers were obtained via the free-radical polymerization mechanism using the procedure previously described by M. Markovic et al [4]. The PMAC samples were obtained as follow. Firstly, 4 cm^3 of MAA and caffeine were dissolved into an adequate amount of distilled water (Table 1.). For the PMAC samples with itaconic acid had different only the first step of the synthesis was different: 3 cm^3 of MAA, 1 cm^3 of itaconic acid and caffeine were dissolved into an adequate amount of distilled water (Table 1.). Then, after the total neutralization of MAA (or MAA and IA) with NaOH, the mixture was heated to 60°C and 4 g of casein was added and dissolved. Thereafter, crosslinker MBA (Table 1.) was added and after 10 minutes the initiator VA-044 (0.9cm^3 of 1wt% aqueous solution) was added and the polymerization process began immediately. The mixture was poured quickly into the glass moulds (plates 12 cm × 12 cm, separated by a 2 mm tick PVC hose) and left in the air oven at 60°C for 5h. After the polymerization process ended, the disc-shaped samples (7mm in diameter) were cut and dried at room temperature. All obtained samples were stored in an exicator until they were used for further investigation.

The synthesis path of the PMAC/L samples was similar to the synthesis path of the PMAC samples, but the synthesis was carried out at 40°C in order to prevent liposomes degradation. The first step was the addition of the liposomes with the encapsulated caffeine in a drop wise manner to 4 cm^3 of MAA or to 3 cm^3 of MAA and 1 cm^3 of IA in synthesis of the sample with itaconic acid. After total neutralization of MAA (or MAA and IA) with NaOH, the mixture was heated to 40°C and 4 g of casein was added and dissolved. The crosslinker and initiator were added in the same manner as previously. The liposomes with encapsulated caffeine were obtained by pro-liposomic method [5]. The caffeine solution in distilled water (20 mg/ml) was added to NATIPIDE® II (10wt% with respect to the final liposomic dispersion) in a drop wise manner under the constant stirring.

The synthesized samples were denoted as PMAC-xN-y, PMAC-xN-L, PMAC/IA-xN-y and PMAC/IA-xN-L,where N represented the symbol for neutralization, L was the symbol for liposomes, x denoted the neutralization degree of MAA and y denoted the caffeine amount in the carriers (g).

TABLE 1.
FEED COMPOSITION

Samples	H_20 (cm^3)	Caffeine (g)	Liposomes with caffeine (cm^3)
PMAC-100N-0.2	6.20	0.2	-
PMAC/IA-100N-0.2	6.00	0.2	-
PMAC-100N-L	3.10	-	3.10
PMAC/IA-100N-L	3.00	-	3.00

C. Fourier Transform Infrared Spectroscopy (FTIR) and Scanning Electron Microscopy (SEM)

The FT-IR spectra of xerogel 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 SEM analyses were performed using a Tescan MIRA 3 XMU field-emission gun scanning electron microscope (FEG-SEM) with an acceleration voltage of 20 kV.

D. Monitoring of the carriers swelling and caffeine release

Swelling and caffeine release measurements were carried out at 37°C in two media during a 24h period: 0.2 M phosphate buffer (pH=6.8) (PB) (as a simulation of duodenum pH environment) and 0.1 M solution of HCl (as a simulation

of stomach pH environment) [6]. Dry hydrogel disks with known initial weight (m_0) were entirely immersed in the specified solution and left to swell. At predetermined time intervals the disks were removed from solutions and weighed (m_t). This was repeated until the equilibrium was reached (m_{eq}). Swelling degree (SD) at the equilibrium state (SD_{eq}) was calculated as:

$$SD_{eq} = \frac{(m_{eq} - m_0)}{m_0}. \quad (1)$$

The absorbances of the caffeine solutions in release experiments were measured at predefined time intervals at 273 nm using the UV-Vis Shimadzu UV-1800 spectrophotometer. The caffeine release kinetics was investigated by the Kopcha model (2), which involves both diffusion and polymer chains relaxation effects on the drug release [7]:

$$\alpha = \frac{M_t}{M_\infty} = k_D t^{0.5} + k_R t^1, \quad (2)$$

Where α represents the fractional drug release, M_t is the released concentration of drug at time t, M_∞ is the released drug concentration at equilibrium, k_D is the constant of the speed of drug diffusion and k_R is the constant of the speed of drug release by the process of the polymer chains relaxation.

III. Main Results

The FTIR spectra of the synthesized PMAC carriers are presented in Fig. 1. and they have all characteristic peaks of poly(methacrylic acid) and casein.

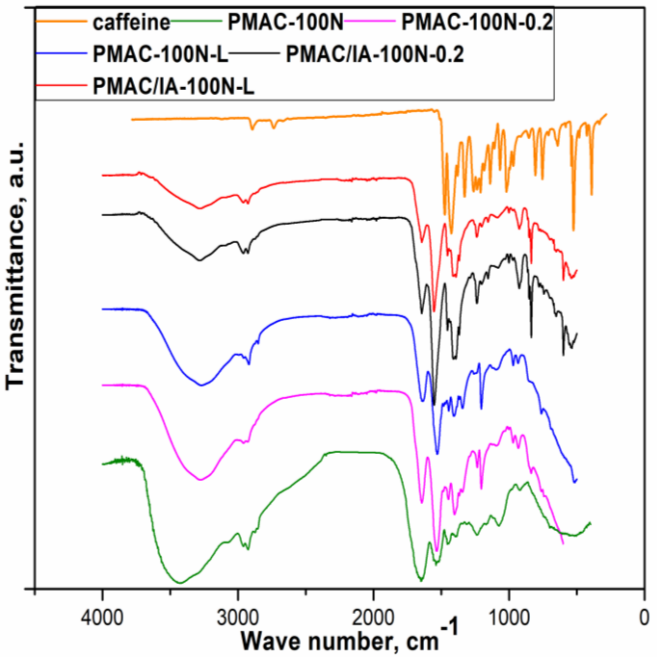

Fig. 1. The FTIR spectra of caffeine and of the PMAC carriers of different formulation

The FTIR spectrum of the PMAC samples without the caffeine was described in our previous work [4]. Compared to the FTIR spectrum of the PMAC carriers without the itaconic acid the FTIR spectrum of PMAC/IA carriers has more intensive peaks at 1540 cm^{-1} (symmetric stretching vibration of C(=O)–O^-) and at 1645 cm^{-1} (C(=O)–OH symmetric stretching vibrations) as a consequence of the presence of the higher number of the –COO^- and –COOH groups due to the presence of two carboxylic groups in the itaconic acid structure [8]. The presence of the caffeine was confirmed by the presence of the caffeine characteristic peaks: the peak at 973cm^{-1} (C-C stretching), 1357 cm^{-1} (C-H stretching) and at 1700 cm^{-1}(stretching of C=O) [9]. The shifts of the characteristic peaks of casein at 1235 cm^{-1} (saturated C–C stretching) and at 1452 cm^{-1} (C-C stretching of aromatic ring) to 1245 cm^{-1} and to 1442 cm^{-1}, respectively, suggested that hydrophobic interactions between the casein and caffeine were established [10]. Also, the shift of the characteristic peak of casein at 1398 cm^{-1} (C=O stretching of aspartic acid and glutamic acid residues) to 1408 cm^{-1} could be caused by the hydrogen bonds established between the casein and caffeine [10]. The FTIR spectra of the PMAC-100N-L and PMAC/IA-100N-L showed the shift of the characteristic peak of casein observed at 1398 cm^{-1} to 1388 cm^{-1} which could be caused by the hydrogen bonds established between the casein and the liposomes (carbonyl group or N-H group of amide II of protein and oxygen group of phospholipid nanoparticles). The hydrophobic bonds established between the casein and liposomes may cause the shifts of the casein characteristic peaks at 1235 cm^{-1} and at 1452 cm^{-1} to 1245cm^{-1} and to 1444cm^{-1}, respectively.

The SEM micrographs of synthesized PMAC carriers are presented in Fig. 2. The micrograph of PMAC-100N-0.2 (Fig. 2. a)) showed the regular porous structure. The PMAC-100N-L sample has the same structure as the PMAC-100N-0.2 and the micrograph confirmed the presence of the liposomes which were marked with the white circles (Fig. 2. b)). The micrograph of the PMAC/IA-100N-0.2 (Fig. 2. c)) showed a non-regular highly porous structure. This was expected due to the presence of the itaconic acid which caused higher value of swelling degree and higher swelling rate of the carrier compared to the samples without itaconic acid. The micrograph of the PMAC/IA-100N-L (Fig. 2. d)) showed the same structure as the analog sample without the liposomes. The liposomes are marked with white circles in Fig. 2. d).

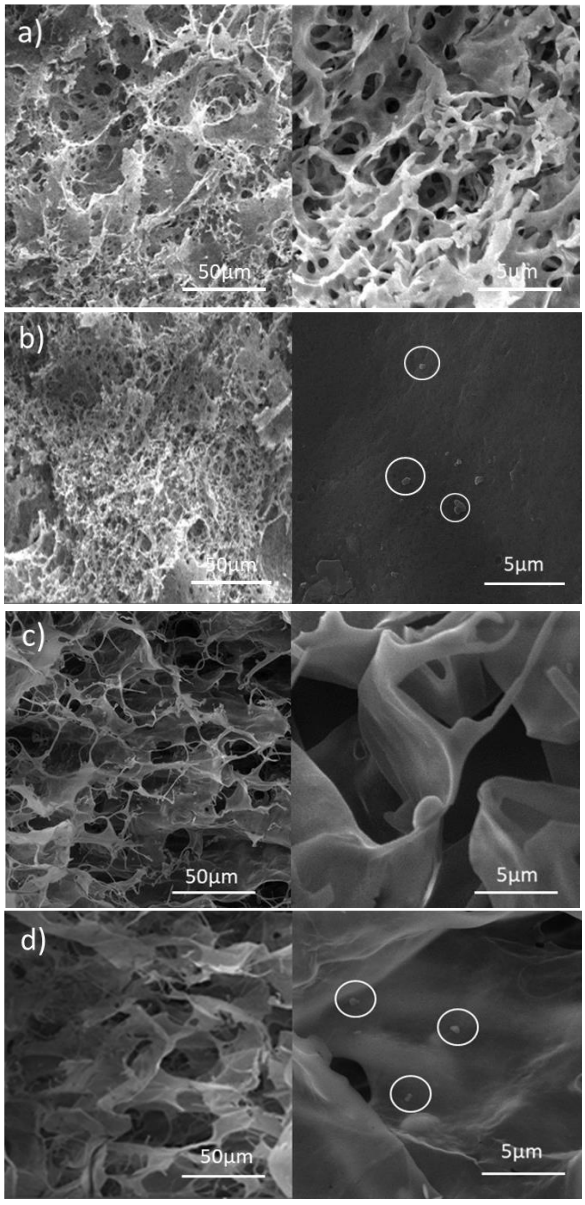

Fig. 2. The SEM micrographs of the carriers of the different formulation

The swelling curves of the synthesized carriers and caffeine release profiles in two media with different pH values are presented in Fig. 3. and in Fig. 4., respectively. From Fig. 3, it can be seen that the PMAC carriers with itaconic acid have higher equilibrium swelling degree and higher swelling rate than the analog samples without the itaconic acid (Table 2.) due to the presence of the higher number of carboxilyc groups. The values of the equilibrium swelling degree were higher in PB than in 0.1 M HCl for all samples (Table 2.) because the negative charges were generated on the carboxylic groups in PB medium which caused the repulsion between the polymer chains and the higher swelling rate of all carriers than the swelling rate of the carriers in 0.1M HCl. The presence of the liposomes in the carriers caused the decrease in the value of the swelling degree. The diffusion of the medium into the carriers could be slower due to the presence of the liposomes in the pores of the matrix of the carriers.

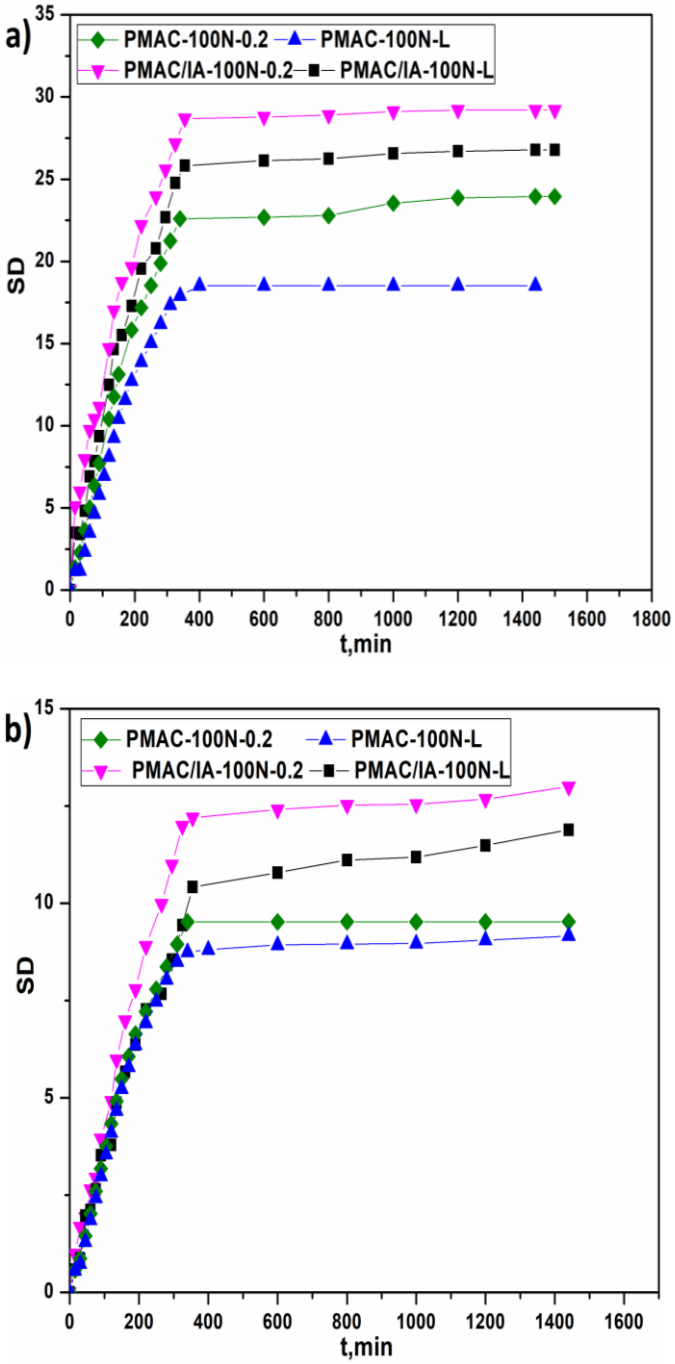

Fig. 3. The swelling curves of the carriers for: a) PB and b) 0.1 M HCl

The released caffeine concentration- c (mg/ml) during time- t (Fig. 4.) showed that the carriers with itaconic acid released caffeine faster than the carriers without it due to the presence of the higher number of carboxylic groups and higher swelling rate. All samples released higher concentration of caffeine in PB than in 0.1M HCl due to the aforementioned behavior of the samples in the PB medium. The caffeine was released more slowly from the samples with liposomes than from the samples without liposomes.

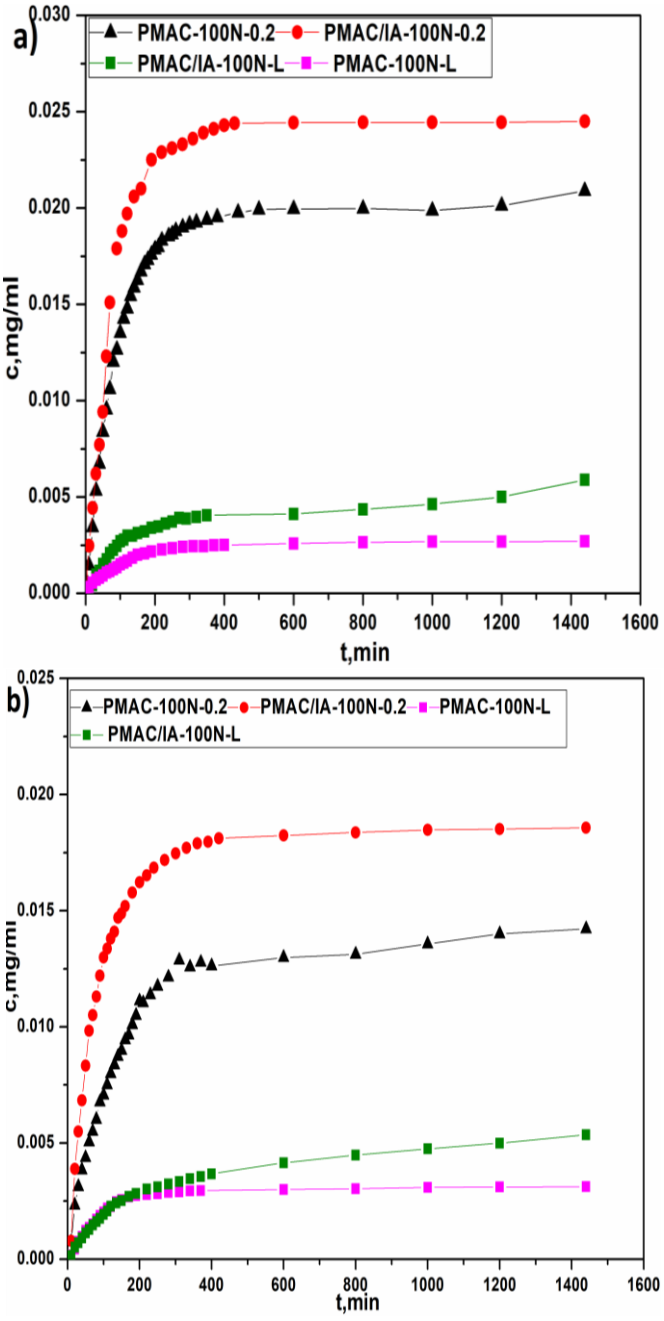

Fig. 4. The caffeine release profiles from the carriers in: a) PB and b) 0.1 M HCl

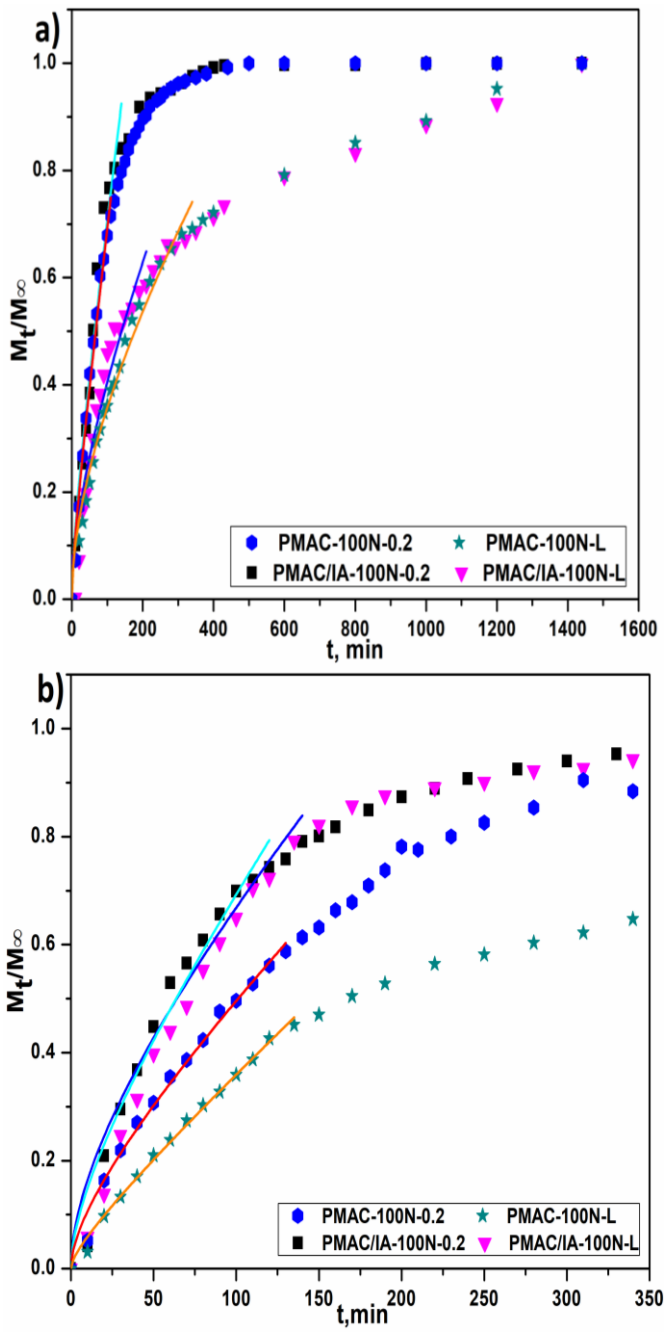

Fig. 5. The fractional caffeine release from the carriers in both media: the symbols represent the experimental data and the solid lines represent the Kopcha model

The fractional release data for PB and 0.1 M HCl to which the Kopcha model was applied is presented in Fig. 5. a) and b), respectively. The estimated values of the parameters of the Kopcha model, the field of applicability $\Delta\alpha$ and the values of R^2 are shown in Table 2. The first 60%-80% of release data fitted well to this model (R^2 ~0.980). The values of the Kopcha model parameter k_D were higher than the values of k_R for all samples, which suggested that the diffusion was the main mechanism of caffeine transport into the media.

TABLE 2.
THE VALUES OF THE EQUILIBRIUM SWELLING DEGREE AND THE KINETIC PARAMETERS OF THE KOPCHA MODEL

Sample	Media	The Kopcha model				SDeq
		k_D $*10^2$	k_R $*10^3$	Δα %	R^2	
PMAC-100N-0.2	HCl	2.62	2.34	58.78	0.991	9.5
	PB	2.40	4.52	71.53	0.989	23.95
PMAC/IA-100N-0.2	HCl	3.67	3.26	74.28	0.972	13.0
	PB	2.96	4.1	84.08	0.968	29.2
PMAC-100N-L	HCl	3.22	0.380	70.74	0.983	9.2
	PB	3.65	2.46	74.96	0.998	22.6
PMAC/IA-100N-L	HCl	2.65	3.65	79.24	0.986	11.9
	PB	3.09	0.96	57.53	0.939	26.8

IV. CONCLUSION

The PMAA based carriers of different formulations were synthesized for controlled and targeted delivery of a poorly water-soluble model drug-caffeine. The significance of these carriers is that they represent the fusion of hydrophilic polymers-PMAA and IA and one amphiphilic polymer-casein, which enabled bonding to poorly water-soluble substance. The FTIR spectra of these carriers showed that established interactions between the casein and caffeine were hydrophobic interactions and hydrogen bonds. The SEM micrographs showed the regular porous structure of the PMAC carriers without itaconic acid, whereas the PMAC carriers with itaconic acid had a non-regular structure with large voids. The presence of the liposomes in the carriers was confirmed by the SEM micrographs of the PMAC-L carriers, indicating that the degradation of the liposomes did not occur during the synthesis of the carriers.

The carriers with itaconic acid had higher equilibrium swelling degree and higher swelling rate than the samples without it. The presence of the liposomes caused a minor decrease in the values of the SDeq, which could be a consequence of the physical presence of the liposomes in the pores of the carriers which may cause the decrease in the diffusion speed of the media into the carriers. All carriers had higher swelling rate in the PB than in 0.1M HCl.

These pH sensitive drug delivery carriers were able to protect the model drug in 0.1M HCl at 37°C (as simulation of the pH condition in human stomach) and release higher caffeine concentration in a medium which simulated the conditions in human intestines- phosphate buffer pH=6.8 at 37°C. The carriers with itaconic acid released higher caffeine amount than the analog carriers without it due to the higher swelling rates. The mathematical model used for investigation of the release kinetics- the Kopcha model, fitted well to the experimental caffeine release data. The Kopcha model showed that the diffusion governed caffeine release from all samples and that the polymer chains relaxation was also present, but its influence on caffeine release was minor. The best control of caffeine release was achieved from the PMAC samples with incorporated liposomes. Incorporated liposomes in PMAC carriers decreased the speed of the caffeine release compared to the samples without them. Synthesized pH-sensitive PMAC carriers are promising candidates for controlled and targeted delivery of poorly water-soluble drugs.

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