ANALYSIS OF KINETICS OF POORLY WATER-SOLUBLE DRUG RELEASE FROM HYDROGELS BASED ON POLY(METHACRYLIC ACID) AND CASEIN WITH DIFFERENT CROSSLINKER AMOUNT

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Abstract

Nowadays, humanity are faced with many challenges which affect health of people all around the globe (such as climate change, new diseases and/or already present ones for which cure has not been found yet – cancer). The efforts of researchers on the field of drug delivery systems bring everyday novel tools for safer and more effective therapy. pH sensitive hydrogels based on poly(methacrylic acid) are recognized as materials with huge potential for controlled release of drugs. The encapsulation and controlled release of many chemotherapeutics is quite challenge due to their poorly water-solubility. In our previous research we overcome this problem by modifying hydrophilic pol(methacrylic acid) with amphiphilic casein and showed that prepared material have potential for encapsulation and controlled release of poorly water-soluble model drug – caffeine (PMAC carriers). In present study we deepened further our research and employed various models: Ritger-Peppas, Higuchi and Kopcha model to analyze how the change of crosslinker amount affect the mechanism of release kinetics of caffeine in medium with pH of 6.8 (which simulated the environment in human intestines). Obtained results showed that only by changing one parameter such as crosslinker amount it is possible to fine tune the type of drug release mechanism, due to which the PMAC carriers would be able to respond to the specific demands of therapy.

Introduction

Climate change and serious diseases are grate challenges of modern world. Researchers efforts in the field of medicine resulted in promising tools for safer and more effective therapy of serious diseases such as various types of cancer. One of these tools are certainly drug delivery systems which enable targeted delivery of a drug at specific place in human body and its controlled release due to which drug concentration remains constant. In that way bioavailability of drug is improved whereas side effects are reduced which further leads to the better therapy [1]. pH sensitive hydrogels based on poly(methacrylic acid) (PMAA) are materials with huge potential for controlled release of drugs. These hydrogels are non-toxic, biocompatible and are able to swell in environment with pH higher than pKa of PMAA and therefore release encapsulated drug in the process [2]. Due to the hydrophilicity of PMAA it is quate challenging to encapsulate poorly water-soluble drugs (such as many chemotherapeutics). We overcome this limitation by modifying PMAA with amphiphilic casein and demonstrated effectiveness of this carrier for encapsulation and controlled release of poorly water-soluble model drug – caffeine (PMAC carriers) [2-5]. In our previous research we also showed that only by changing one synthesis parameter such as crosslinker amount it was possible to tune caffeine release profiles [5].

In present study we further deepened our research and employed several models (Ritger-Peppas [6], Higuchi [7] and Kopcha model [8]) to analyze how the change of crosslinker amount affect the mechanism of caffeine release from the PMAC carriers in phosphate buffer with pH of 6.8 at 37ºC (PB 6.8).

Experimental

The PAMC carriers were synthetized by free-radical polymerization and all carriers had 4 ml of PMAA, 4 g of casein, 0.2 g caffeine and 0.9 ml of 1wt% aqueous solution of initatior (2,2'-azobis-[2-(2-imidazolin-2-yl)propane] dihydrochloride), whereas the amount of crosslinker - methylenebisacrylamide (MBA) was varried: 0.8mol%, 1.6mol% and 3.2mol% (with respect to the amount of methacrylic acid). The synthesis, the list of used chemicals and the feed composition are presented in our previous research [5]. The synthetized carriers were denoted as PMAC-xM, where xM represented the amount of crosslinker (M, 2M, 4M and 8M = 0.4 mol%, 0.8mol%, 1.6mol% and 3.2mol% of crosslinker, respectively).

In order to better understand the mechanism of caffeine release from the PMAC carriers and how the increase in the crosslinker amount affects it, caffeine release data were analyzed with the most commonly used models Ritger-Peppas (Eq. (1)), Higuchi (Eq. (2)) and Kopcha model (Eq. (3)):

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

$$\frac{M_t}{M_\infty} = k_H\sqrt{t} \quad (2)$$

$$\frac{M_t}{M_\infty} = k_1 t^{0.5} + k_2 t^1 \quad (3).$$

In all equations the $\frac{M_t}{M_\infty}$ represents the fractional drug release and t is the time of the drug release process (min). In Eq. (1) the coefficient k is the constant of the speed of drug release (min^{-1}) and exponent n shows the type of the mechanism of drug release (diffusion and/or relaxation of polymer's chains). In Eq. (2) the coefficient k_H represents the constant of the speed of drug diffusion from the carrier (min^{-1}). In Eq. (3) the coefficient k_1 is the constant of the speed of drug release governed by diffusion (min^{-1}), whereas the coefficient k_2 is the constant of the speed of drug release governed by relaxation of polymer's chains (min^{-1}).

The equations Eq. (1) and Eq. (2) were used in following forms: $\ln(\frac{M_t}{M_\infty}) = \ln(kt^n)$ and $\frac{M_t}{M_\infty} = k_H t^{0,5}$, respectively. The form of Eq. (3) was added into the OriginPro 8.5 program and then it was applayed on the caffeine release profiles ($\frac{M_t}{M_\infty} - t$). The "fields of applicability" of applied models were denoted as Δα (%).

Results and discussion

The profiles of caffeine release in PB 6.8 were fitted with Ritger-Peppas (R-P), Higuchi and Kopcha model and are presented in Fig. 1., Fig. 2. and Fig. 3., respectively. Calculated kinetics parameters of applied models and corresponding fields of applicability are presented in Table 1. The analysis of the kinetics of caffeine release from PMAC-M were presented in our previous research [2], and only obtained values of kinetics parameter are presented in Table 1. in order to compare with the results obtained in present study.

R-P model showed that caffeine release from PMAC-M and PMAC-2M was governed only by relaxation of polymer's chains of the carrier's network, whereas caffeine was released from PMAC-4M and PMAC-8M carriers by both mechanism – diffusion and relaxation of polymer's chains. The obtained values of Higuchi coefficient k_H for all the samples were higher than the values of corresponding Kopcha coefficient k_1, and the fields of applicability of these two

models were similar. However, Higuchi model does not consider the impact of the polymer's chains relaxation on the process of drug release. The increase in the crosslinker amount led to the decrease of the speed of caffeine release (decrease of the Kopcha coefficient k_2).

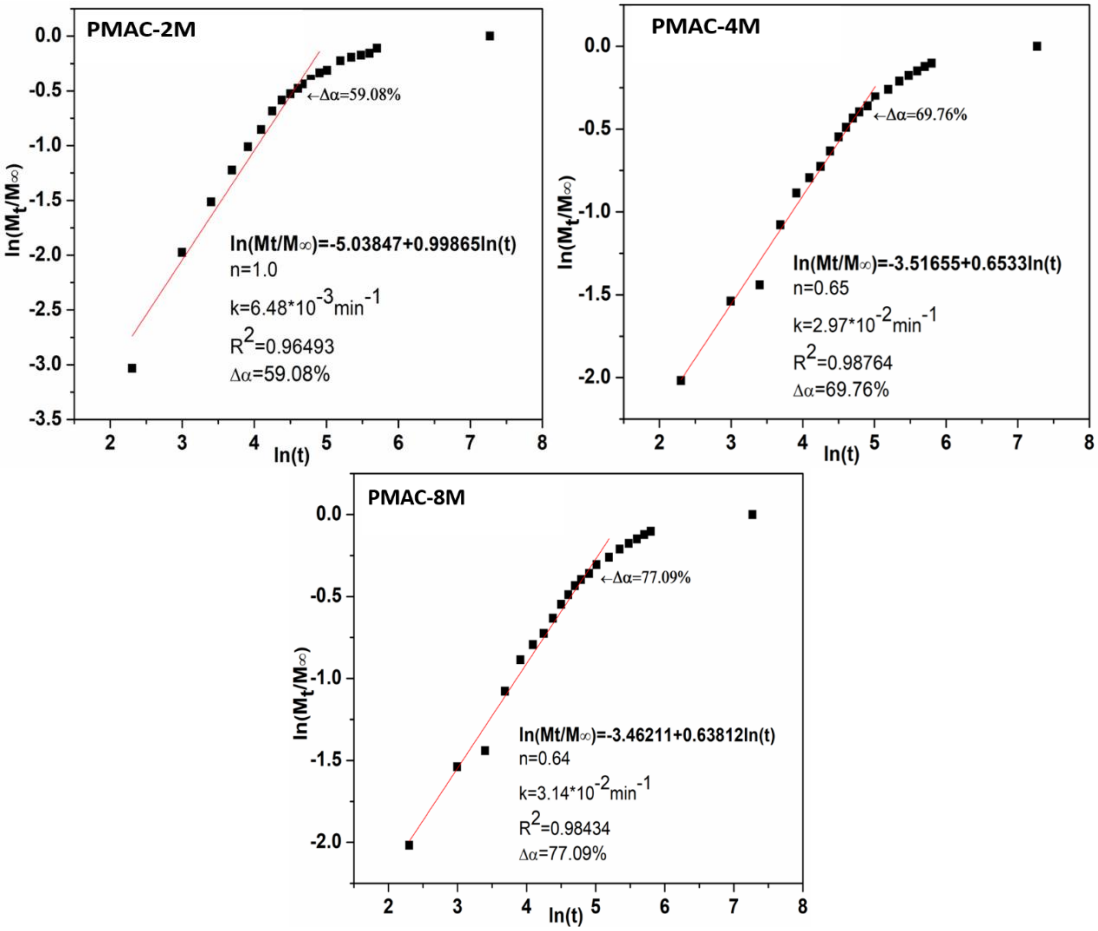
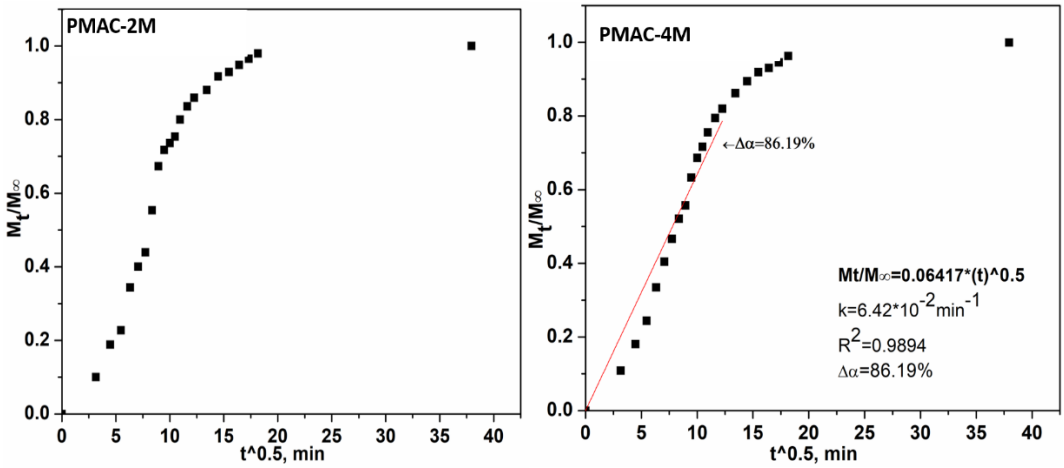


Figure 1. Fitting of the profiles of caffeine release from the PMAC carriers in PB 6.8 with R-P model



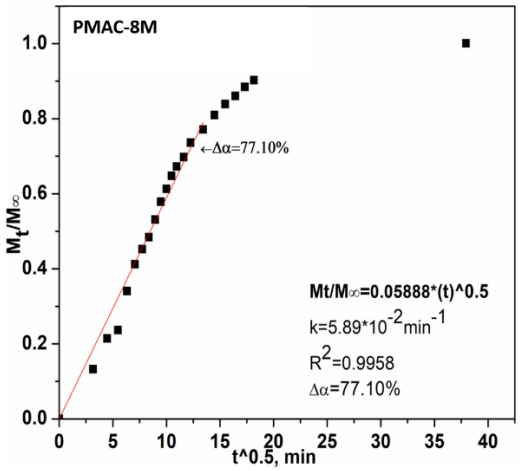


Figure 2. Fitting of the profiles of caffeine release from the PMAC carriers in PB 6.8 with Higuchi model

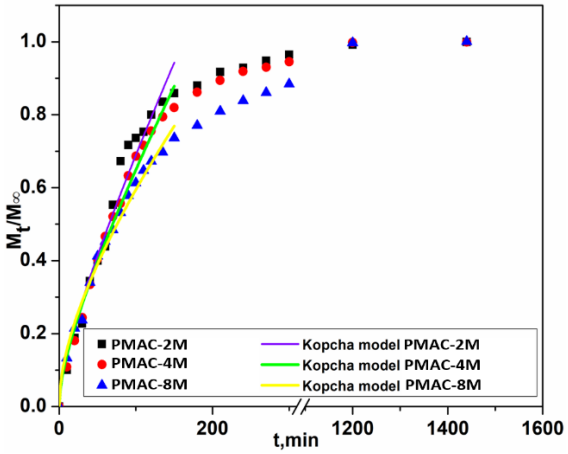


Figure 3. Fitting of the profiles of caffeine release from the PMAC carriers in PB 6.8 with Kopcha model

Table 1. Obtained kinetics parameters of chosen models for each PMAC carrier

Model	Sample	PMAC-M	PMAC-2M	PMAC-4M	PMAC-8M
R-P	n	1.0	1.0	0.65	0.64
	$k*10^2$ (min^{-1})	0.930	0.648	2.97	3.14
	Δα(%)	71.5	59.1	69.8	77.1
	R^2	0.911	0.965	0.988	0.984
Higuchi	k_H*10^2	5.13	6.48	6.42	5.89
	Δα(%)	90.5	55.3	86.2	77.1
	R^2	0.985	0.965	0.989	0.996
Kopcha	k_1*10^2	2.40	3.35	4.30	4.21
	k_2*10^3	4.52	3.55	2.07	1.81
	Δα	71.5	83.6	81.9	69.8
	R^2	0.989	0.969	0.977	0.990

The fitting of the caffeine release data was the best with Kopcha model, therefore it can be concluded that the caffeine release from PMAC carriers was governed by both mechanism - diffusion and polymer's chains relaxation.

Conclusion

In our previous research we synthetized PMAC carriers and investigated how the increase in the crosslinker amount affect the swelling of the carriers and release of poorly water model drug - caffeine. In present study we did step forward and analyzed the mechanism of caffeine release from PMAC carriers in PB 6.8 and investigated how the change in crosslinker amount affect the type of the drug release mechanism. Several models Ritger-Peppas, Higuchi and Kopcha model were used for the analysis of kinetics of caffeine release from PMAC carriers. Obtained results showed that the best fitting of the caffeine release data was with Kopcha model and both mechanism (diffusion and relaxation of polymer's chains) governed the caffeine release from the PMAC carriers.

Acknowledgements

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