THE EFFECT OF ENCAPSULATED AMOUNT OF CAFFEINE ON THE MECHANISM OF ITS RELEASE FROM HYDROGELS BASED ON POLY(METHACRYLIC ACID) AND CASEIN

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Abstract

Researchers are making everyday efforts to develop new drugs or improve present ones in order to enhance therapies of various diseases, especially serious ones like cancer. Drug delivery systems (DDS) are one of the solutions for safer and more efficient therapy. Hydrogels based on poly(methacrylic acid) (PMAA) are extensively investigated as DDS due to their non-toxicity, biocompatibility and pH sensitivity. Many chemotherapeutics are poorly water-soluble, so it is quite challenging to encapsulate them into highly hydrophilic PMAA. In our previous study we overcome this limitation by modifying PMAA with amphiphilic casein and demonstrated that poorly water-soluble model drug – caffeine can be successfully encapsulated and released in control manner from these samples (H hydrogels). In present study we go step forward and investigated how the change in the amount of encapsulated caffeine affect the mechanism of caffeine release from the H hydrogels in medium with pH of 6.8 (which simulates the environment in human intestines). Commonly used models for the analysis of kinetics of drug release from hydrogels: Ritger-Peppas, Higuchi and Kopcha model are employed for the analysis of the mechanism of caffeine release. Presented results indicate that it is possible to adjust the manner and mechanism of drug release by changing the amount of encapsulated drug, due to which the H hydrogels can adapt to the unique requirements of the therapy.

Introduction

Everyday struggle of humanity with various problems such as global warming and huge number of diseases urge researches to develop new innovative solutions, which are safe and effective and in the accordance with the principles of green chemistry. One of the promising tools for the therapies of various diseases are drug delivery systems. These systems are able to deliver drug to the site of action in human body and release it in control manner. Drug bioavailability can be improved, side effects reduced, the number of therapeutic doses can be decreased and therefore, overall therapy would be enhanced. Hydrogels are polymer materials which are recognized as promising systems for drug delivery due to the large number of their tremendous properties [1, 2]. Their 3D network can absorb and retain large amount of water and/or other physiological fluids due to which they have soft structure similar to the living tissue. One interesting group of hydrogels are those based on poly(methacrylic acid) (PMAA) [3]. PMAA hydrogels are non-toxic, biocompatible, highly hydrophilic and pH sensitive because of which they are extensively investigated for drug delivery. Namely, PMAA hydrogels are able to swell in the environments with pH higher than pKa of PMAA and therefore release encapsulated drug in the process [4]. In order to overcome their poor mechanical properties and enable encapsulation of poorly water-soluble drugs (like large number of chemotherapeutics) in our previous research we modified PMAA with amphiphilic casein (H hydrogels) [5]. It was investigated how the change of various synthesis parameters (such as crosslinker amount,

neutralization degree, pH of external medium, the amount of encapsulated active substance etc.) affect the release rate of poorly water-soluble model drug caffeine [4]. The obtained results showed that encapsulation and controlled release of poorly water-soluble active substance was successful and its release rate can be fine-tuned only by changing one of the synthesis parameters [6]. In present study we further deepened our research and employed several models (Ritger-Peppas [7], Higuchi [8] and Kopcha model [9]) to analyze how the change of encapsulated amount of caffeine affected the mechanism of its release from the H hydrogels in phosphate buffer with pH of 6.8 at 37 ºC (PB 6.8).

Experimental

The H hydrogels were synthetized by free-radical polymerization in aqueous solution and all samples had 4 mL of MAA, 4 g of casein, 0.4 mol% of crosslinker - methylenebisacrylamide (MBA) (with respect to the amount of methacrylic acid) and 0.9 ml of 1 wt% aqueous solution of initiator (2,2'-azobis-[2-(2-imidazolin-2-yl)propane] dihydrochloride). 1.859 g of NaOH was added to the reaction mixture of the samples with total neutralization degree of methacrylic acid. 1 g or 2 g of caffeine was encapsulated in both groups of the samples: with non-neutralized and neutralized MAA. The synthesis, the list of used chemicals and the feed composition are presented in our previous research [6]. The prepared samples were denoted as H/xN-y, where xN represented the neutralization degree of MAA (0N – 0% of neutralization degree of MAA or 100N – 100% of neutralization degree of MAA) and y showed the mass of encapsulated caffeine 1 g or 2 g.

In order to better understand the mechanism of caffeine release from the H hydrogels and how the change of caffeine amount affects it, the caffeine release profiles were analysed with three 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 release of active substance and t is the time of the process of active substance release (min). In Eq. (1) the parameter k shows the speed of active substance release (min^{-1}) and parameter n represents the type of the mechanism of active substance release (diffusion and/or relaxation of polymer's chains). In Eq. (2) the k_H parameter represents the speed of active substance diffusion from the carrier (min^{-1}). In Eq. (3) the k_1 parameter shows the speed of active substance release governed by diffusion (min^{-1}), whereas the k_2 parameter represent the speed of active substance 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 applied on the caffeine release data ($\frac{M_t}{M_\infty} - t$). The symbol adopted for the "fields of applicability" of applied models was Δα (%).

Results and discussion

The curves of caffeine release in PB were fitted to Ritger-Peppas (R-P), Higuchi and Kopcha model and are presented in Fig. 1., Fig. 2. and Fig. 3., respectively. Determined values of kinetics parameters of chosen models and their fields of applicability are presented in Table 1. The kinetics of caffeine release from H/0N-1 and H/100N-1 were analyzed in our previous

research [4], and only the obtained values of kinetics parameter are presented in Table 1. in order to facilitate the analysis of the results obtained in present study.

R-P model showed that diffusion governed caffeine release from the H/0N-1 sample (n<0.5), whereas polymer chains relaxation was the main mechanism of caffeine release from the H/100N-1 sample (n>1). Both mechanisms (diffusion and relaxation of polymer chains) were involved into the process of caffeine release from the H/0N-2 and H/100N-2 samples. The values of R^2 were between 0.954-0.999 which means that fitting of the R-P model to the data of caffeine release from the H samples was good. The field of applicability of R-P model was relatively high (the values of Δα were between 50.7 % and 85.7 %) taking into account that this model can be applied to the first 60% of the drug release data. Both models R-P and Kopcha model predicted that caffeine was released by diffusion from H/0N-1 and that relaxation of polymer chains was the main mechanism of caffeine release from the H/100N-1 sample.

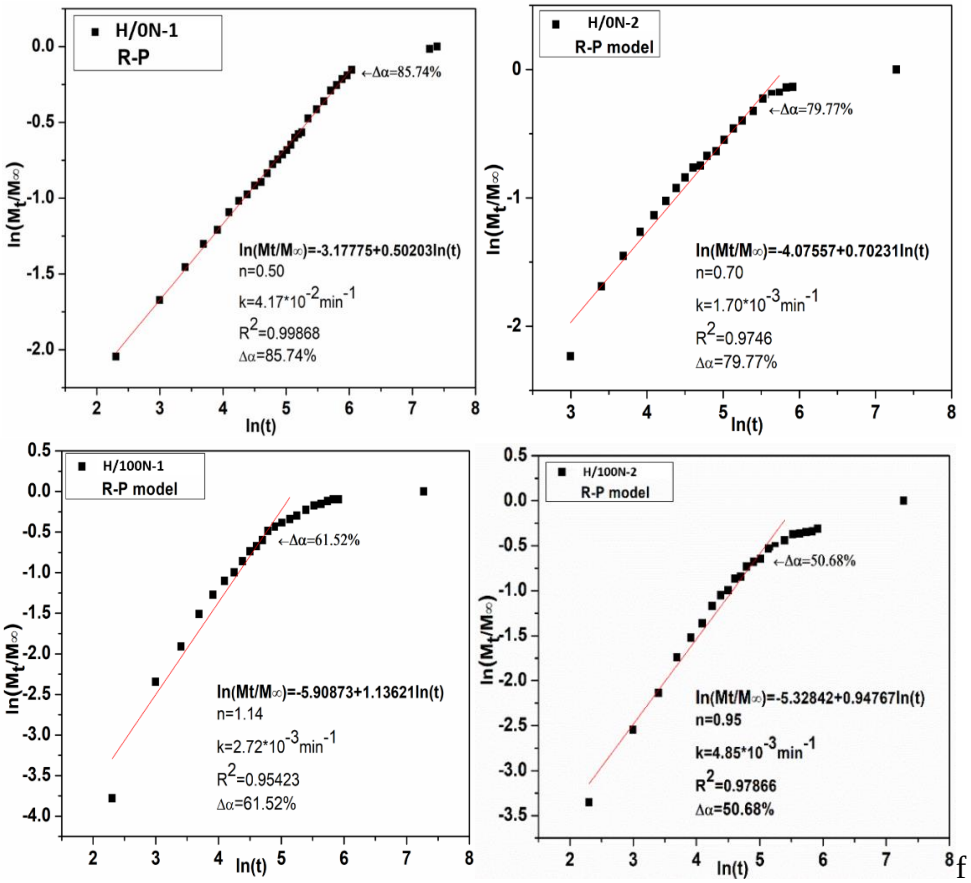

Figure 1. Fitting of the profiles of caffeine release from the H carriers in PB 6.8 with R-P model

It was possible to apply Higuchi model only to the curves of caffeine release from the H/0N-1 sample (R^2~0.999 and Δα was 85.7%). Obtained value of Higuchi parameter k_H was similar to the value of the R-P parameter k and Kopcha parameter k_1, which means that predictions of these three models that caffeine was released by diffusion from the H/0N-1 sample, were good.

The best fitting to the caffeine release data showed Kopcha model (the values of R^2 were between 0.975-0.998). The field of applicability of Kopcha model was between 50.7 % and 56.8%.

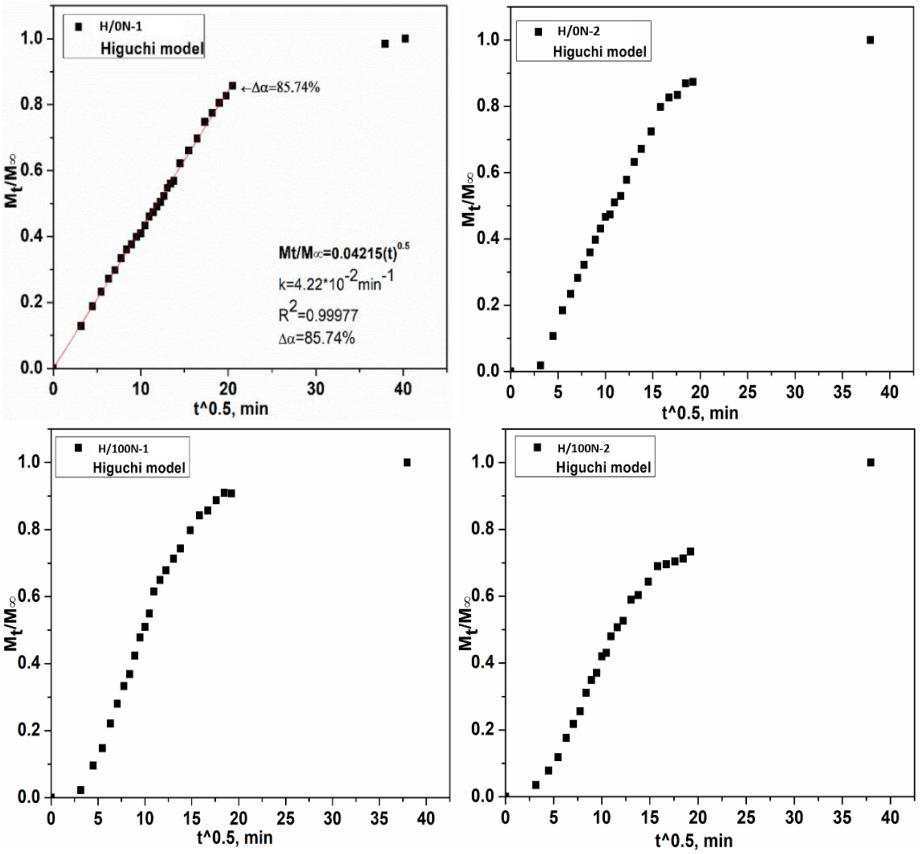

Figure 2. Fitting of the profiles of caffeine release from the H carriers in PB 6.8 with Higuchi model

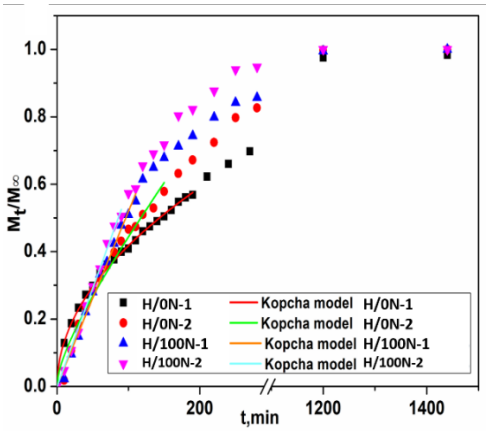

Figure 3. Fitting of the profiles of caffeine release from the H carriers in PB 6.8 with Kopcha model

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

Model	Sample	H/0N-1	H/0N-2	H/100N-1	H/100N-2
R-P	n	0.50	0.70	1.14	0.95
	$k*10^2$ (min^{-1})	4.17	1.70	0.272	0.485
	Δα(%)	85.7	79.8	61.5	50.7
	R^2	0.999	0.975	0.954	0.979
Higuchi	k_H*10^2	4.22	-	-	-
	Δα(%)	85.7	-	-	-
	R^2	0.999	-	-	-
Kopcha	k_1*10^2	4.18	2.27	0	5.80
	k_2*10^3	0	2.87	5.81	3.46
	Δα	56.8	60.6	56.1	50.7
	R^2	0.998	0.975	0.993	0.991

Conclusion

In our previous research we demonstrated that only by changing the amount of encapsulated caffeine it is possible to fine tune the manner of the H hydrogels swelling and caffeine release. In order to determine the type of mechanism of caffeine release from these hydrogels in PB 6.8, in present study we employed several models Ritger-Peppas, Higuchi and Kopcha. It was demonstrated that the Kopcha model showed the best fitting to the caffeine release curves and both mechanism (diffusion and relaxation of polymer's chains) governed the caffeine release from the H hydrogels.

Acknowledgements

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