KINETIC ASPECTS OF SILVER IONS RELEASE FROM Ag-POLY(*N*-ISOPROPYLACRYLAMIDE/ITACONIC ACID) HYDROGEL NANOCOMPOSITES

Jelena Spasojević[1], Ivana Vukoje[1], Nikolina Nikolić[1], Milica Milošević[1], Dragan Ranković[2], Aleksandra Radosavljević[1]

[1]Vinča Institute of Nuclear Sciences, National Institute of the Republic of Serbia, University of Belgrade, Mike Petrovića Alasa 12-14, 11351 Vinča, Belgrade, Serbia
[2]Faculty of Physical Chemistry, University of Belgrade, Studentski trg 12-16, 11000 Belgrade, Serbia
e-mail: jelenas@vin.bg.ac.rs

Abstract

In recent years, drug delivery systems have been one of the most investigated solutions for safer and more efficient therapy. Among many investigated materials, hydrogels with incorporated drugs and/or active substances can be produced in different ways to meet the criteria of biocompatibility, non-toxicity, continuous drug delivery, etc. In our previous work, the Ag-P(NiPAAm/IA) hydrogel nanocomposites were produced by radiolytic method, which enabled the synthesis and sterilization of materials in one technological step. Because of silver ions release, these hydrogel nanocomposites showed good antibacterial potential against both gram-positive and gram-negative bacteria. In this study, we go a step forward and investigate the silver release mechanism by fitting experimentally obtained data with several commonly used kinetics models of drug release.

Introduction

During the past decades, hydrogels have gained considerable interest because of their unique properties and versatile applications. Their 3D network can absorb and retain large amounts of water and/or other physiological fluids, giving them a soft structure similar to living tissue. Such types of materials are recognized as promising systems for drug and/or active compound delivery. Nanocomposite materials based on polymer hydrogels with embedded metal nanoparticles have attracted tremendous attention due to an extremely wide range of applications, especially in biomedicine [1, 2]. In a previous study, novel multifunctional silver-poli(*N*-isopropylacrylamide/itaconic acid) (Ag-P(NiPAAm/IA)) hydrogel nanocomposites were prepared by gamma irradiation induced synthesis. This "green" technique uses biologically harmless and biocompatible radiolytic products of water, enabling the production of crosslinked nanocomposites without the use of any additional substances, which can be harmful, toxic, or difficult to remove from the system. Moreover, this method also enables simultaneous synthesis and sterilization of materials, which is a very important prerequisite for their use in the field of biomedicine [3, 4]. Among the numerous nanoparticles, probably the most investigated and the most promising have become the silver nanoparticles (AgNPs) due to their ability to prevent the growth and development of single-celled organisms and therefore can be used as a therapeutic agent against Gram-positive and Gram-negative bacteria, fungus or viruses. Furthermore, AgNPs also possess strong anti-septic and anti-inflammatory properties, with low systemic cytotoxicity effects [5]. Nowdays, great emphasis has been placed on the development of suitable wound dressing, with appropriate antibacterial effects, which could be able to protect the injury site from further insult, contamination, and infection [6].

In this study, the Ag^+ ions release from Ag-P(NiPAAm/IA) hydrogel nanocomposites was investigated in a physiological simulated condition. To evaluate the mechanism of silver release, the experimentally obtained data were fitted using zero-order, first-order, Ritger-

Peppas, Higuchi, Kopcha, and Makoid-Banakar models. Moreover, the diffusion coefficients of silver release from hydrogel nanocomposites were determined.

Experimental

Series of P(NiPAAm/IA) hydrogels were prepared by adding the IA into NiPAAm solutions (10 wt%) to obtain comonomer mixtures with the weight ratios 100/0, 98.5/1.5, 97/3 and 95.5/4.5. Those mixtures were saturated with argon for 30 min, poured into specially designed glass molds, and exposed to γ-irradiation (absorbed dose of 50 kGy; dose rate 0.5 kGy/h). The obtained hydrogels were cut into discs (diameter ≈ 10 mm, thickness ≈ 4 mm) and immersed in distilled water (changed daily for one week) to remove unreacted residues. Furthermore, the P(NiPAAm/IA) hydrogel discs were swelled in the solution of $AgNO_3$ (1.0×10^{-2} mol/dm^3) and 2-propanol (0.2 mol/dm^3), and then exposed to γ-irradiation to perform reduction of Ag^+ ions (absorbed dose of 18 kGy; dose rate 17 kGy/h). As a result, the formation of AgNPs was confirmed by obtaining yellow-colored Ag-P(NiPAAm/IA) hydrogel nanocomposites.

The release of Ag^+ ions from the Ag-P(NiPAAm/IA) hydrogel nanocomposites was monitored in phosphate buffer solution (PBS, pH 7) at 37ºC. Nanocomposite samples were immersed in 10 ml of PBS, which was changed at predetermined time intervals with new 10 ml, to maintain the perfect sink condition. The total content of silver within the Ag-P(NiPAAm/IA) hydrogel nanocomposites was determined upon treatment in HNO_3 (1:1 v/v) to induce the oxidation of all AgNPs into Ag^+ ions. The Ag^+ ions concentration was determined by atomic absorption spectrometry, and the results represent the mean of three measurements.

Results and discussion

The release of Ag^+ ions from Ag-P(NiPAAm/IA) hydrogel nanocomposites was monitored in PBS at 37ºC in order to simulate the physiological condition. The obtained results for cumulative silver release indicate that after 4 days of monitoring, the Ag-P(NiPAAm/IA) (100/0) hydrogel nanocomposite released the smallest amount of initial concentration of silver (59.9 %), whereas samples with 1.5 wt%, 3 wt% and 4.5 wt% of IA in copolymer network released 73.8 %, 71.1 % and 78.2 % of initial concentration of silver, respectively. Moreover, it is obvious that the initial burst release of Ag^+ ions is followed by the slower release in the middle and later phases.

To evaluate the kinetics and to determine the mechanism of release, the experimental data were fitted and compared with several commonly used kinetics models of the drug release process. The cumulative Ag^+ ions release profiles were analyzed by zero-order (Eq. (1)), first-order (Eq. (2)), Ritger-Peppas (Eq. (3)), Higuchi (Eq. (4)), Kopcha (Eq. (5)) and Makoid-Banakar (Eq. (6)) models [2, 7, 8]:

$$M_t = M_0 + k_0\, t, \tag{1}$$

$$ln(M_\infty - M_t) = lnM_0 - k_1\, t, \tag{2}$$

$$\frac{M_t}{M_\infty} = k_{\mathrm{RP}}\, t^n, \tag{3}$$

$$\frac{M_t}{M_\infty} = k_H\, t^{1/2}, \tag{4}$$

$$\frac{M_t}{M_\infty} = A\, t^{1/2} + B\, t, \tag{5}$$

$$\frac{M_t}{M_\infty} = k_{MB}\, t^n \exp(-Ct), \tag{6}$$

where M_t is the amount of silver released in time t, M_0 is the amount of silver released in time t=0 (M_0=0), M_∞ is the initial amount of silver in hydrogel nanocomposites, while M_t/M_∞ is the fraction of silver released at each time point; k_0 is a zero-order rate constant, k_1 is the first-order

rate constant, k_{RP} is constant dependent on the polymer network properties, n is the diffusional exponent which indicates the transport mechanism during the release, k_H is the Higuchi dissolution rate constant, A and B are the Kopcha constants indicating the dominant process during the release, k_{MB} is the Makoid-Banakar constant and C is an empirical parameter. The mathematical modeling of Ag^+ ions released from hydrogel nanocomposites is presented in Fig. 1, while the obtained fitting parameters are summarized in Table 1.

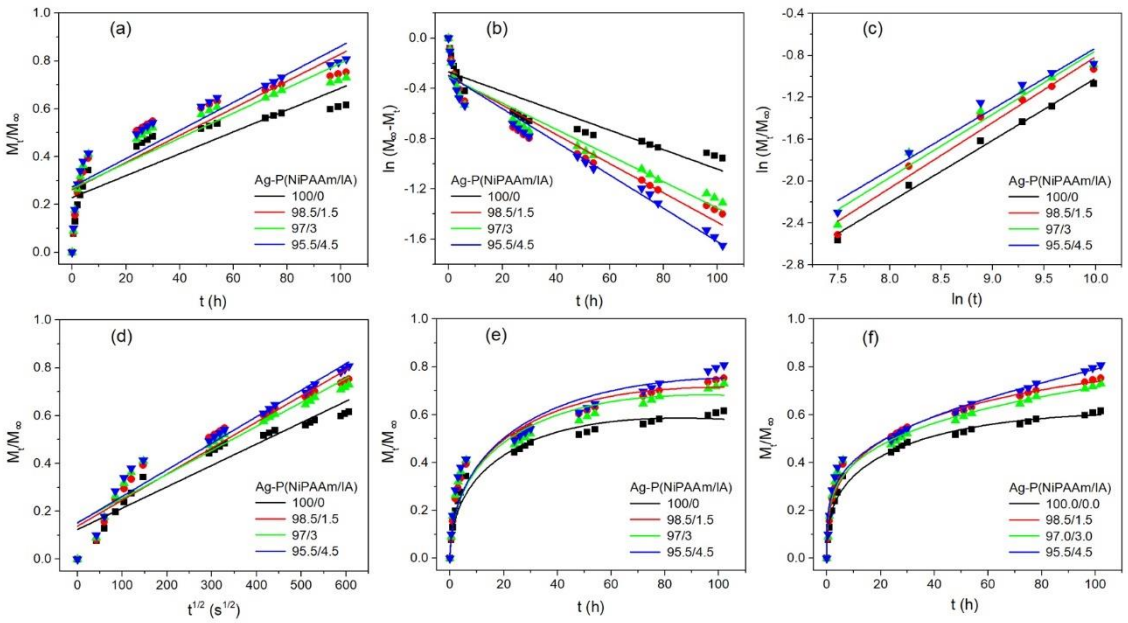

Figure 1. Mathematical modeling of cumulative Ag^+ ions release from Ag-P(NiPAAm/IA) hydrogel nanocomposites: (a) zero-order model, (b) first-order model, (c) Ritger-Peppas model, (d) Higuchi model, (e) Kopcha model and (f) Makoid-Banakar model.

The curvilinear nature of cumulative release profiles suggests that silver release from the hydrogel nanocomposites follows neither the zero-order nor first-order kinetics. This observation is supported by the lowest values of correlation coefficients (R^2). The Ritger-Peppas model showed that silver release from investigated samples follows anomalous or non-Fickian diffusion ($n \approx 0.58$-0.61) when both mechanisms (diffusion and relaxation of polymer chains) influence the release process. The high values of R^2 (0.95-0.99) indicate the good fitting between the model and experimentally obtained data, but only at an early stage of releasing ($M_t/M_\infty < 0.6$). In this case, that is the stage of the initial burst release of Ag^+ ions. As expected, the values of Higuchi dissolution rate constants are higher for systems with improved swellability (higher IA content). The formation of a concentration gradient is the main trigger for the diffusion of Ag^+ ions from the polymer matrix into the surrounding medium. The Higuchi model shows a good fit with silver release data ($R^2 \approx 0.97$-0.98), as well as the Kopcha model, but with slightly lower R^2 (0.95-0.98). The Kopcha model can be used to quantify the relative contributions of diffusion and polymer relaxation to drug release. The data in Table 1. clearly show that the values of the diffusional constant (A) are far greater than that for the relaxation constant (B), suggesting that Ag^+ ions release from the Ag-P(NiPAAm/IA) hydrogel nanocomposites is primarily controlled by a Fickian diffusion process. However, the mathematical model that best describes Ag^+ ions release is the Makoid-Banakar model in which the R^2 values are the highest (0.98-0.99). Makoid-Banakar model provided a slightly better fit for the experimental data, compared to the Ritger-Peppas model. When the value of parameter $C \rightarrow 0$, the Makoid-Banakar model becomes equal to Ritger-Peppas. The values of C are low

but not equal to zero, so the introduction of an exponential parameter in the model, related to the dissolution of AgNPs, evidently provides a better correlation with the experimental data.

Table 1. Kinetic parameters of Ag^+ ions released from hydrogel nanocomposites obtained by different models, and diffusion coefficients determined by Etters approximation.

Model	Parameters	Sample Ag-P(NiPAAm/IA)			
		100/0	98.5/1.5	97/3	95.5/4.5
Zero-order	$k_0 \times 10^6$ (1/s)	1.27	1.57	1.46	1.63
	R^2	0.74	0.78	0.77	0.81
First-order	$k_1 \times 10^6$ (1/s)	2.15	3.24	2.90	3.68
	R^2	0.83	0.85	0.85	0.84
Ritger-Peppas	$k_{RP} \times 10^4$ (1/s^n)	9.64	8.34	10.95	14.24
	n	0.59	0.60	0.61	0.58
	R^2	0.99	0.96	0.95	0.95
Higuchi	$k_H \times 10^3$ (1/s$^{1/2}$)	0.89	1.09	1.00	1.11
	R^2	0.97	0.98	0.98	0.97
Kopcha	$A \times 10^3$ (1/s$^{1/2}$)	2.11	2.37	2.34	2.37
	$B \times 10^6$ (1/s)	-1.90	-1.97	-2.00	-1.85
	R^2	0.98	0.97	0.95	0.95
Makoid-Banakar	$k_{MB} \times 10^3$ (1/s^n)	9.35	14.40	24.16	28.40
	n	0.35	0.32	0.27	0.25
	$C \times 10^4$	7.38	3.18	0.37	-2.62
	R^2	0.99	0.99	0.98	0.98
Diffusion coefficient	$D_E \times 10^3$ (cm^2/s)	3.34	6.44	6.66	11.60
	R^2	0.90	0.97	0.97	0.99

Finally, the diffusion coefficients of Ag^+ ions from the polymer matrix were determined by the Etters approximation, using the following equation:

$$\frac{M_t}{M_\infty} = \left[1 - exp\left(-K\left(\frac{D_E\, t}{\delta^2}\right)^a\right)\right]^{1/b}, \qquad (7)$$

where D_E is the diffusion coefficient of silver for the entire range of releasing ($0 < M_t/M_\infty < 1$), t is the time and δ is the thickness of the xerogel, while a = 1.3390, b = 2.6001 and K = 10.5449 are the constants [9]. As can be seen from Table 1, the diffusion coefficients of Ag^+ ions release increase with increasing IA content in a polymer matrix, which is expected. Namely, with increasing IA content, the swelling capacity of hydrogel nanocomposites increases because of increased porosity, leading to the faster diffusion of the medium into the hydrogel nanocomposites. Therefore, the higher content of the swelling medium enables easier and faster dissolution of silver and its diffusion from the hydrogel nanocomposites. According to the values of R^2, the least fit is observed for the homopolymer network (100/0) probably due to the initial burst release of Ag^+ ions.

Conclusion

In order to evaluate the kinetics and to determine the mechanism of Ag^+ ions release from the Ag-P(NiPAAm/IA) hydrogel nanocomposites the several drug delivery models were employed. It was demonstrated that the Makoid-Banakar showed the best fitting to the silver release

profiles, indicating that diffusion is the dominant mechanism. This was supported by the Kopcha model, while the Higuchi model confirms that the dissolution of AgNPs and the formation of a concentration gradient play a key role in the release process. In addition, diffusion coefficients of silver release increase when the hydrogel nanocomposites are in more hydrated form (more porous network).

Acknowledgements

This work was supported by the Ministry of Science, Technological Development and Innovations of the Republic of Serbia (Contract No. 451-03-47/2023-01/200017).

References

[1] J. Spasojević, A. Radosavljević, J. Krstić, D. Jovanović, V. Spasojević, M. Kalagasidis Krušić, Z. Kačarević-Popović, Dual responsive antibacterial Ag-poly(N-isopropylacrylamide/itaconic acid) hydrogel nanocomposites synthesized by gamma irradiation, Europen Polymer Journal 215 (69) 168-185.

[2] J. Krstić, J. Spasojević, A. Radosavljević, A. Perić-Grujić, M. Đurić, Z. Kačarević-Popović, S. Popović, *In Vitro* Silver Ion Release Kinetics from Nanosilver/Poly(vinyl alcohol) Hydrogels Synthesized by Gamma Irradiation, Journal of Applied Polymer Science 131 (2014) 40321.

[3] M.T.S. Alcantara, N. Lincopan, P.M. Santos, P.A. Ramirez, A.J.C. Brant, H.G. Riella, A.B. Lugao, Simultaneous hydrogel crosslinking and silver nanoparticle formation by using ionizing radiation to obtain antimicrobial hydrogels, Radiation Physics and Chemistry 165 (2019) 108369.

[4] N. Nikolić, J. Spasojević, A. Radosavljević, M. Milošević, T. Barudžija, L. Rakočević, Z. Kačarević-Popović, Influence of poly(vinyl alcohol)/poly(N-vinyl-2-pyrrolidone) polymer matrix composition on the bonding environment and characteristics of Ag nanoparticles produced by gamma irradiation. Radiation Physics and Chemistry 202 (2023) 110564.

[5] S. Bhowmick, V. Koul, Assessment of PVA/silver nanocomposite hydrogel patch as antimicrobial dressing scaffold: Synthesis, characterization and biological evaluation, Materials Science and Engineering: C 59 (2016) 109-119.

[6] Y. Xie, X. Liao, J. Zhang, F. Yang, Z. Fan, Novel chitosan hydrogels reinforced by silver nanoparticles with ultrahigh mechanical and high antibacterial properties for accelerating wound healing, International Journal of Biological Macromolecules 119 (2018) 402-412.

[7] M. Askarizadeh, N. Esfandiari, B. Honarvar, S. Ali Sajadian, A. Azdarpour, Kinetic Modeling to Explain the Release of Medicine from Drug Delivery Systems, ChemBioEng Reviews, https://doi.org/10.1002/cben.202300027.

[8] K. Nešović, A. Janković, V. Kojić, M. Vukašinović-Sekulić, A. Perić-Grujić, K. Yop Rhee, V. Mišković-Stanković, Silver/poly(vinyl alcohol)/chitosan/graphene hydrogels – Synthesis, biological and physicochemical properties and silver release kinetics, Composites Part B: Engineering 154 (2018) 175-185.

[9] M.P. Mullarney, T.A.P. Seery, R.A. Weiss, Drug diffusion in hydrophobically modified N,N-dimethylacrylamide hydrogels. Polymer 47 (2006) 3845-3855.