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In vitro study of the dynamics in elution of antibacterial drugs impregnated into matrices based on polymer hydrogel

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Abstract

The objective was to explore the dynamics and duration of antibiotic elution in samples based on polymer hydrogel and PMMA. **Material and methods** The samples impregnated with vancomycin, rifampicin and cefazolin at various concentrations were placed in phosphate-buffered saline and incubated at 37 °C. The medium was completely replaced at 1, 3, 7, 14, 21 and 28 days. Spectrophotometry was used to measure concentration of drugs in solution and the release profiles. The median and 95 % CI were employed to statistically describe data obtained from 5 parallel studies. **Results** Concentrations of the antibiotics eluted from the polymer hydrogel were 7 times greater than those released from PMMA on day 1; 15 times greater on days 2 and 3; 6.6 times greater on day 7 and 3 times or more in the following days of observation. The rate of antibiotic release from hydrogel volumes also differed markedly. **Discussion** The drug release was more than 70% of the total amount for all hydrogel samples in contrast to PMMA with elution not exceeding 10 %. Despite the fact that a burst release was observed with 80 % of the antibiotic released in the first 5 days as seen in the case of bone cement, the concentration of the drug eluted from hydrogels was several times higher and exceeded the MIC throughout the observation period. The release of the antimicrobial agent from hydrogels was caused by diffusion of the particles from the entire volume of the matrix demonstrating an important advantage over PMMA with the potential being limited by surface depletion. **Conclusion** At this point, we have shown the possibility of creating potential depot systems based on unsaturated PVA derivatives with controlled release of antibiotics and characteristics being superior to PMMA.

Keywords: antibiotic elution, antibiotic release, controlled release of antibiotics, biodegradable polymeric hydrogel, bone cement, polymethyl methacrylate (PMMA), orthopaedic infection, *in vitro* study

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INTRODUCTION

Orthopedic infection, which includes chronic osteomyelitis and periprosthetic joint infection (PJI), is a devastating complication. The treatment of PJI or chronic osteomyelitis of long bones would be dependent on the etiology with the common multimodality, which implies thorough surgical debridement, adequate wound drainage, local and systemic antibiotic therapy [1, 2]. Bone cement based on polymethyl methacrylate (PMMA) is widely used in clinical practice as a carrier depot matrix for local delivery of antibiotics [3]. However, PMMA cannot be considered an optimal delivery system antimicrobial agent due to incomplete release of antibiotics from the volume of the matrix [3, 4] (up to 10 % of the total amount of the impregnated drug) [5-7] due to its hydrophobic nature [1, 8, 9]. Various studies have shown that the concentrations of antibiotics released from bone cement exceed the minimum inhibitory concentrations (MICs) for most strains of microorganisms only in the first few hours or days after implantation [2]. The uncontrolled release of the drug from PMMA still remains one of the main problems in traumatology and orthopaedics and does not have a unanimous solution [10]. An ideal depot system should have the required pharmacokinetic properties that can ensure the elution of antibiotics over a long period of time, providing the high concentrations, being many times higher than the MIC to provide continuous infection arrest and prevent the emergence of new multidrug-resistant bacterial strains [4]. For this purpose, numerous in vitro and in vivo studies are being carried out to search for substances as additives to bone cements and create new local transport systems based on biodegradable materials [10].

The purpose of the study was to explore and compare the rate and duration of elution of antibacterial drugs from samples based on polymer hydrogel and bone cement.

MATERIAL AND METHODS

Optimal local transport systems were produced as part of the research work at the department of the consequences of musculoskeletal injuries and osteoarticular infection, Federal State Budgetary Institution 'The N.N. Priorov National Medical Research Center for Trauma and Orthopaedics' together

with the Department of Biomaterials of the Russian D.I. Mendeleev Chemical Technical University. Samples were made from pre-prepared and purified material based on unsaturated polyvinyl alcohol (PVA) derivatives in the form of aqueous solutions with a concentration of 8 g/100 ml. Modification of polyvinyl alcohol was carried out in accordance with previously developed methods [11, 12]. Solutions of modified PVA, ammonium peroxydisulfate (APS) (Aldrich, United States), and Mohr's salt (SM, ammonium-iron (II) sulfate) (Khimmed, Russia) were used to obtain samples. A weighed portion of an antibacterial drug was added to 5 ml of PVA solution in various concentrations, thoroughly mixed until the agent was completely dissolved. The resulting solution was poured into a three-component 20 ml Plastipack BD syringe with a pre-cut cone-tip. 0.2 ml of 8 % Mohr's salt solution and 0.2 ml of 10 % PSA solution were successively added and thoroughly mixed. Cylinders of 2 cm and a diameter of 19 mm were formed upon completion of the gelation process. Commercially available bone cement (Synicem 1, France) was used to obtain PMMA samples. Various concentrations of antibiotics were added to 5 g of powdered polymer, thoroughly mixed for better distribution of the impregnated drug. Then curing was produced according to the manufacturer's instructions (liquid monomer (2.5 ml) was added to a weighed amount of polymethyl methacrylate), and the mixture was stirred by hand for 30-50 s. The plastic bone cement achieved with a spatula was loaded into a three-component 20 ml Plastipack BD syringe with a pre-cut cone-tip. Cylindrical samples were formed, equal to the volume of samples based on polymer hydrogel.

The penetration method of a spherical indenter was used to determine the shear modulus of hydrogels. The measurement was carried out as follows: a stainless steel ball with a radius of 1.9 or 3.4 mm was pressed into the flat upper base of the sample and the indentation depth h was measured (equation 1) after relaxation, which usually took 10-15 s. The indentation depth increased during the first few seconds of observation and then became constant, which indicated that the equilibrium value of the deformation had been reached and that the equilibrium modulus of elasticity had been measured. With a stepwise increase in the impact force of the ball on the gel f ranging between 0.0001 and 0.01 N, the dependence h(f) was determined (10–15 points). The deformation region h where the measurements were made did not exceed 0.2R. The experimental data were processed using the elastic contact problem and the ratio between the ball indentation depth h and the force f should have the form (the gel is much softer than the steel ball):

$$h = h_0 + bf^{2/3}, \quad (1)$$

where the coefficient b depends on the shear modulus G and the ball radius R as $b = [3/(16GR^{1/2})]^{2/3}$.

The shear modulus was calculated from the slope value using the formula $G = 3/(16b^{3/2}R^{1/2})$. The range in the modulus values averaged to ± 6 % for polymer hydrogel samples.

Spectrophotometric method was used to obtain variations of the optical density of solutions on the concentration of antibiotics for quantification of biologically active substances in solutions.

The dynamics in the release of administered antibacterial drugs from the volume of the samples was produced under static conditions. To do this, 5 cm^3 cylindrical samples containing an antibiotic were placed in a 10-fold excess of phosphate buffer solution and incubated at 37 °C. The concentrations of antibiotics in the solution were determined using spectrophotometry. The absorption intensity was measured at a characteristic wavelength according to the variations of the absorption intensity on concentration preliminarily plotted for each preparation. The saline solution was replaced after 1 hour and at 1, 3, 7, 14, 21 and 28 days. The experiment was designed based on publications on this topic in order to be able to compare our data with findings of other authors [1, 13]. At least 5 samples of each composition were examined in parallel manner. The data were averaged. statistical functions of the Microsoft Excel program were used for statistical analysis of Median (Me) and confidence interval (95 % CI). Impregnation of antimicrobial agents to saturate the samples of carrier matrices was performed with rifampicin, cefazolin, and vancomycin. The choice of the antibiotics was based on the wide availability, prevalence of use in clinical practice and various physicochemical properties.

RESULTS

Polymer hydrogels and bone cement samples were formed through free-radical polymerization, and antibiotics impregnated during sample formation could affect this process due to the transfer and termination of the kinetic and material chain, and due to the interaction with components of the redox initiating systems. Because of this, the maximum concentration of the antibiotic in the samples was assessed at the first stage. The data are selectively shown in Table 1. Depending on the type, the maximum concentration of the antibiotic at which it was possible to obtain hydrogel polymer systems with sufficient mechanical properties (elastic modulus close to the soft tissue modulus) varied from 60 to 80 mg/cm^3. Similar preliminary experiments were carried out for bone cement. The fact of obtaining a monolithic block of hardened cement served the criterion there.

Table 1

Effect of the concentration of the antibiotic introduced into the composition on the process of sample formation

Antibiotic	Concentration, mg/cm³	Hydrogel	Bone cement
		Modulus of elasticity, kPa	linking
Cefazolin	20	27.6 ± 1.5	AFF
	40	23.6 ± 2.6	AFF
	60	18.4 ± 1.8	AFF
	80	10.2 ± 2.7	AFF
	100	–	NONE
Vancomycin	20	28.3 ± 1.9	AFF
	40	25.6 ± 1.7	AFF
	60	22.4 ± 2.3	AFF
	80	15.3 ± 2.8	AFF
	100	7.3 ± 1.9	AFF
Rifampicin	20	23.2 ± 1.6	AFF
	40	20.2 ± 2.3	AFF
	60	18.6 ± 2.1	AFF
	80	9.7 ± 1.4	NONE
	100	–	NONE

The concentration of antibiotics released from most PMMA-based samples, regardless of the type of drug and the volume impregnated did not exceed 400 mg/L after the first day. There was a noticeable decrease in the amount of the drug released further on. The concentration of the drug in case of vancomycin was approximately 6 times on day 2, rifampicin – 8.5 times and cefazolin – 7 times lower compared to the first day (see Table 2 and Fig. 1a; Fig. 2a; Fig. 3a). Subsequently, the decrease in the rate of drug release occurred more smoothly, however, the drug concentrations recorded in the eluate were lower than the MIC after 14 days. The concentrations of drugs released reached 3000 mg/L or more in samples based on polymer hydrogels on day 1 (Table 3). The reduction in release rate was not as pronounced as compared to PMMA. So, the elution rate decreased by 2 times on average on day 3 in the case of vancomycin, by 3.3 times for rifampicin and cefazolin (Fig. 1b; Fig. 2b; Fig. 3b). Because of this, concentrations of the drug above the MIC were recorded during the entire observation period. Data from 5 parallel examinations for bone cement samples are presented as mean values (Me) and 95 % CI in Table 2 and for polymer hydrogel in Table 3.

Table 2

Concentrations of antibiotics eluted from PMMA-based samples on control days of the study. Data are presented as Me (95 % CI)

Time point, days	Drug concentration, mg/l, Me (95 % CI)								
	Vancomycin			Cefazolin			Rifampicin		
	40 mg/cm³	60 mg/cm³	80 mg/cm³	20 mg/cm³	40 mg/cm³	60 mg/cm³	20 mg/cm³	40 mg/cm³	60 mg/cm³
1	264 (255; 273)	373 (361; 385)	433 (414; 452)	111 (106; 116)	212 (202; 222)	294 (276; 312)	160 (158; 162)	282 (265; 299)	372 (342; 402)
3	79.6 (75.6; 83.6)	102.6 (95.2; 110)	129.4 (122.5; 136.3)	29 (28.5; 29.5)	52.4 (51.8; 53)	71 (66.8; 75.2)	29 (28.5; 29.5)	43.2 (40.5; 45,.)	67.4 (31.4; 103.4)
7	64.4 (63.3; 65.5)	84.6 (79.9; 89.3)	107.6 (99.8; 115.4)	26 (25; 27)	46.2 (44; 48.4)	61 (58.9; 63.1)	26 (24.9; 27.1)	38.6 (36.9; 40.3)	55.4 (53.1; 57.7)
14	44.2 (42; 46.4)	57 (53.8; 60.2)	74.2 (68; 80.4)	18.3 (18; 18.6)	30.2 (28.6; 31.8)	48.8 (46.8; 50.8)	23,5 (22.3; 24.7)	35.9 (34.3; 37.5)	50.2 (49; 51.4)
21	27.2 (25; 29.4)	34.6 (32.5; 36.7)	45 (42.7; 47.3)	10.8 (9.9; 11.7)	18.6 (17.7; 19.5)	27.1 (26; 28.2)	18,4 (17.5; 19.3)	26.6 (26; 27.2)	40.4 (38.8; 42)
28	18.8 (16.6; 21)	22.4 (20.7; 24.1)	31.6 (30.5; 32.7)	7.5 (7.2; 7.8)	13.4 (12.9; 13.9)	17.6 (17; 18.2)	12,8 (12.3; 13.3)	19.4 (18.8; 20)	26.7 (25.2; 28.2)

Table 3

Concentrations of antibiotics eluted from polymer hydrogel samples on control days of the study. Data are presented as Me (95 % CI)

Time point, days	Drug concentration, mg/l, Me (95 % CI)								
	Vancomycin			Cefazolin			Rifampicin		
	40 mg/cm³	60 mg/cm³	80 mg/cm³	20 mg/cm³	40 mg/cm³	60 mg/cm³	20 mg/cm³	40 mg/cm³	60 mg/cm³
1	1613 (1556; 1670)	2491 (2391; 2591)	3235 (3010; 3460)	933 (868; 998)	1742 (1618; 1866)	2224 (1954; 2494)	936 (852; 1020)	1642 (1588; 1696)	2354 (2227; 2481)
3	1024 (962; 1086)	1501 (1435; 1567)	2001 (1942; 2060)	407 (388; 426)	833 (755; 911)	1060 (974; 1146)	408 (386; 430)	826 (783; 869)	1090 (1047; 1133)
7	124 (115; 133)	176 (168; 185)	224 (214; 234)	184 (177; 191)	402 (388; 416)	634 (593; 675)	180 (164; 196)	395 (377; 413)	622 (586; 658)
14	61 (57; 65)	101 (97; 105)	132 (129; 135)	86 (80; 92)	142 (135; 149)	218 (204; 232)	88 (86; 90)	135 (130; 140)	224 (219; 229)
21	42 (40; 44)	63 (57; 69)	78 (75; 81)	68 (64; 72)	94 (91; 97)	127 (122; 132)	66 (64; 68)	89 (86; 92)	129 (126; 132)
28	32 (30; 34)	45 (42; 48)	54 (51; 57)	44 (41; 47)	66 (62; 70)	77 (75; 79)	43 (41; 45)	64 (62; 66)	78 (72; 84)

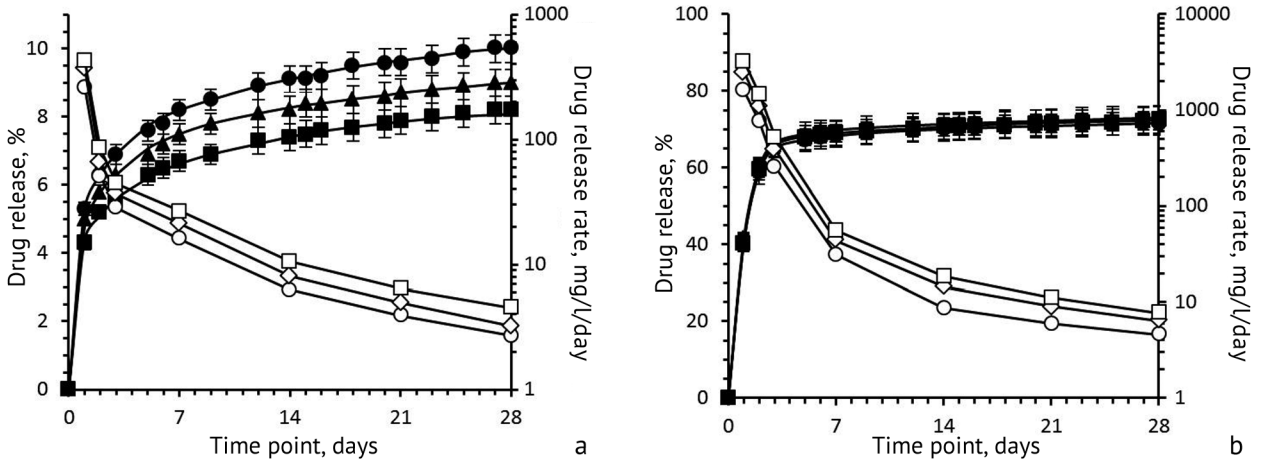

Fig. 1 Vancomycin. Samples based on PMMA (a) and polymer hydrogel (b). Amount of the drug released (●, ▲, ■) and the dynamics in the release (○, ◊, □) at different initial concentrations of the drug in the samples. Initial drug concentration: (●, ○) – 40, (▲, ◊) – 60, (■, □) – 80 mg/cm^3

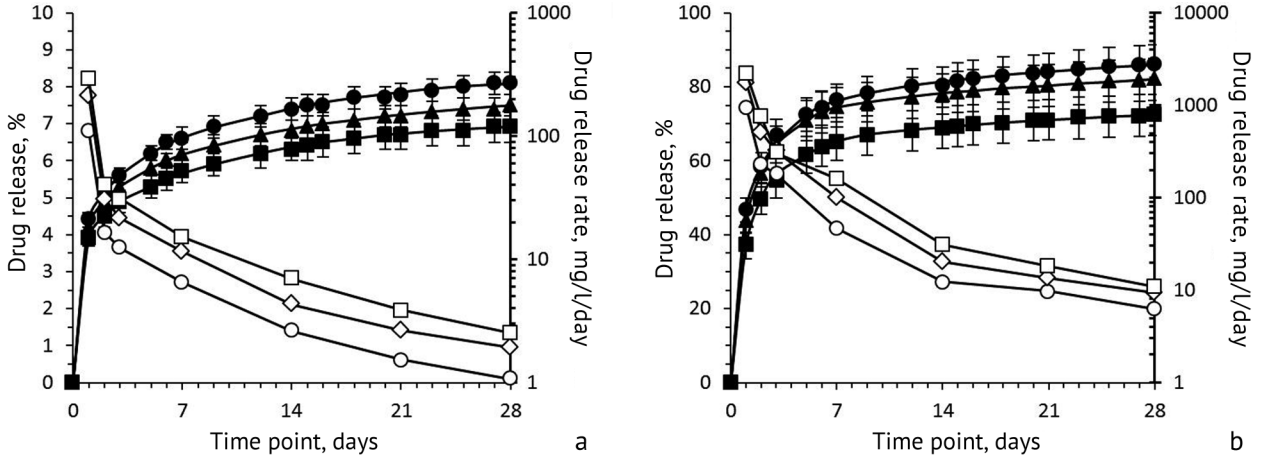

Fig. 2 Cefazolin. Samples based on PMMA (a) and polymer hydrogel (b). Amount of the drug released (●, ▲, ■) and the dynamics in the release (○, ◊, □) at different initial concentrations of the drug in the samples. Initial drug concentration: (●, ○) – 20, (▲, ◊) – 40, (■, □) – 60 mg/cm^3

The total amount of the drug released from the samples during the observation period in the case of PMMA was 8.2-10 % for vancomycin, 8.1-10.8 % for rifampicin, and 6.9-8.1 % for cefazolin (Fig. 1a; Fig. 2a; Fig. 3a) of the mass introduced at the formation stage. Up to 80 % of this small share released on days 4-5. Up to 73 % of the drug released from hydrogel samples in the case of vancomycin and up to about 86 % in the case of rifampicin and cefazolin. Greater release (up to 90 %) occurred in the first week of the study.

Using vancomycin as an example (Fig. 4), we demonstrated the ratio of drug release rates from polymer hydrogel and bone cement at different concentrations depending on the duration of incubation. This ratio was similar for other drugs.

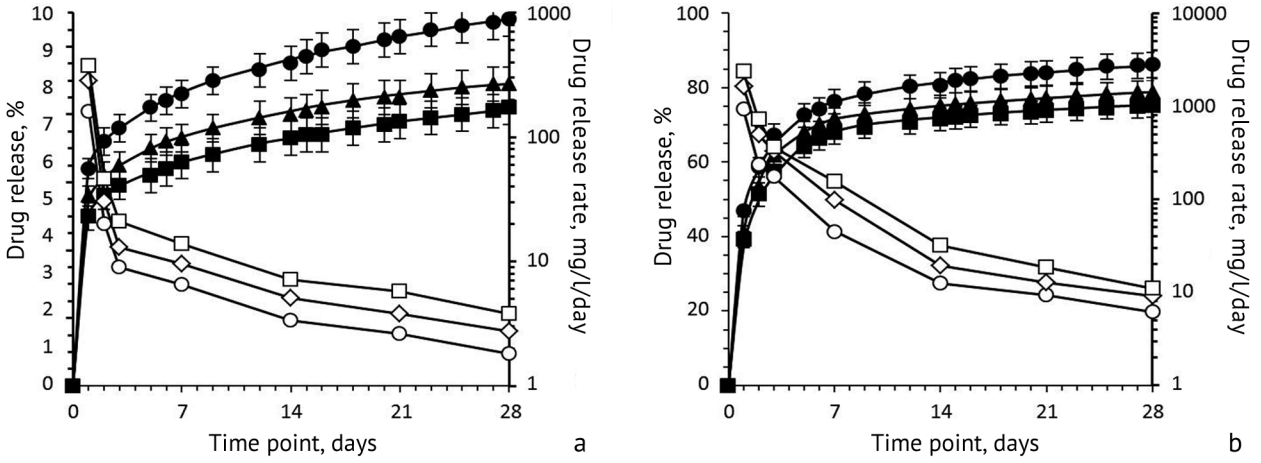

Fig. 3 Rifampicin. Samples based on PMMA (a) and polymer hydrogel (b). The amount of the drug released (●, ▲, ■) and the dynamics in the release (○, ◊, □) at different initial concentrations of the drug in the samples. Initial drug concentration: (●,○) – 20, (▲, ◊) – 40, (■, □) – 60 mg/cm^3

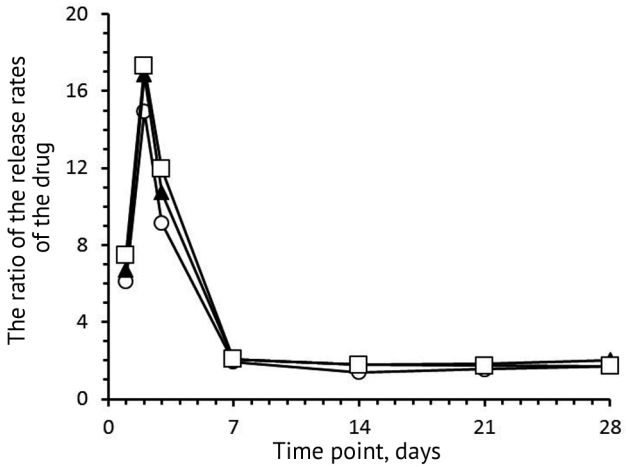

Fig. 4 Vancomycin. The ratio of the release rates of the drug from samples based on polymer hydrogel and PMMA at different initial concentrations of the drug in the samples. Initial drug concentration: (○) – 40, (▲) – 60, (□) – 80 mg/cm^3

DISCUSSION

Although volumes of the drug that can be impregnated in both types of materials are comparable, the values are higher in the case of bone cement for the drugs examined. the data obtained for PMMA correlate with the data reported in works devoted to the elution characteristics of bone cements impregnated with an antibiotic [4, 13, 14]. They demonstrated that the maximum allowable concentration of antimicrobial agent impregnated for most of the substances does not exceed 5 % of the weight of the bone cement sample. Despite their different physicochemical properties (molecular weight, solubility in water, etc.) the antibiotics examined with PMMA-based samples showed similar parameters (Table 2 and Fig. 1-3). There was a low proportion of the release of the drug impregnated not exceeding 10 % with the release of the drug from the superficial layers of the sample only (about 2-3 mm) (Fig. 1a; Fig. 2a; Fig. 3a). Greater elution (up to 80 %) from this small fraction of the drug was recorded during the first few days. The rate of antibiotic release from bone cement decreased by an order of magnitude or more after 3-4 days and the content of the drug eluted in the solution became lower than the MIC for most concentrations used after 14 days (Table 2, Fig. 1a; Fig. 2a; Fig. 3a). Our results are comparable with the data of other scientific works reporting the release of other types of antibiotics from PMMA [5, 8, 9, 14-19].

Moojen et al. reported the release of subtherapeutic concentrations of gentamicin and tobramycin from PMMA-based spacers as early as 1 week after implantation [17]. The elution potential of various groups of antibacterial drugs from bone cement ranged from 0.05 to 9.7 % [1, 4, 7, 8, 15, 20-22] regardless of their physicochemical properties reaching 17 % [5, 23].

The antibiotics exhibited a biphasic elution from PMMA, which is common for bone cements [6, 7, 9, 10, 24] consisting in explosive release [1, 19, 22, 25] (< 96 h) [2] (burst release) due to the elution of predominantly surface-bound particles of the drug [15] (50-100 μm from the surface) [26, 27] followed by a short-term 2-5 times slower release of the antimicrobial agent due to their hindered diffusion from the matrix [16, 21]. The release of concentrations below the MIC is known to be fraught with the emergence of resistant strains of microorganisms [17, 21] and their ability to seed the surface of PMMA [6, 18, 26, 28] and form microbial biofilms [2, 24] due to the hydrophobicity of cement [25] leads to recurrent orthopaedic infection [5, 10, 29] and poor treatment outcomes. An increase in the weight of the drug impregnated into the composition of bone cement slightly increases the release of the antibacterial drug [24], since it mainly contributes to the appearance of near-surface areas, which explains the bioavailability of a small amount of the drug when it is repeatedly loaded into the PMMA volume [15]. An increased weight of the drug impregnated into the bone cement slightly increases the release of the antibacterial drug [24], and contributes to the appearance of near-surface areas, which explains the bioavailability of a small amount of the drug when it is repeatedly loaded into the PMMA [15]. The rate of release of vancomycin with a relatively large molecular weight [6, 10, 15], cefazolin [30] and rifampicin with a low molecular weight eluted from PMMA showed no differences in our series. Similar results were described by other authors who compared the elution rates of vancomycin from bone cement and other antibiotics with low molecular weight including tobramycin and gentamicin [15, 25, 31].

Differences were observed for hydrophilic polymeric hydrogels. Much greater release of the impregnated drug was observed for all samples of this type, reaching 70 % or more as can be seen from the variations shown (Table 3, Fig. 1b; Fig. 2b; Fig. 3b). Despite the fact that a burst release was observed with bone cement, and most of the drug was released in the

first 5-7 days of observations, the concentration of the antibiotic eluted from the hydrogels was several times higher and exceeded the MIC throughout the entire period of observation (Table 3). The release of such a volume of an antimicrobial agent from hydrophilic hydrogels was due to the diffusion of particles from the entire volume of the matrix, which is an important advantage compared to bone cement having minimal potential for drug release from the internal volume of the material [15, 25]. The rate of antibiotic elution differed markedly. For example, for vancomycin in case of hydrogels, the release rate was approximately 7 times on the first day of observation, 17 times on the second day, 12 on the third day and 2 times higher on subsequent days as compared to samples based on bone cement (Fig. 4). A similar picture was observed for other antibiotics examined.

The dynamics in the release of cefazolin with a much smaller molecule is different from that of vancomycin as shown in Fig. 1 and Fig. 2, with the moduli of elasticity and the cross-linking frequency of the polymer network for all samples showing slight differences (Table 1). It can be concluded that the solubility and molecular weight of the drug impregnated into a polymer hydrogel and the dynamics of the desorption are interrelated, in contrast to bone cement. J. Slane et al. reported the release of 1.08 mg of tobramycin with molecular weight being much less than that of cefazolin, from PMMA [25]. Based on our results presented in the form of graphs for each group of antibiotics with the polymer hydrogel, we can conclude that the interaction between the hydrogel matrix and the molecules of the substances immobilized would allow for systems to be created with the required profile of the release of impregnated drug through modifications.

CONCLUSION

Therefore, we have shown the fundamental possibility of creating systems based on unsaturated PVA derivatives with controlled release of antibiotics which would potentially outperform the current depot systems based on bone cement.

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