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SYNTHESIS AND STUDY ON ANTIMICROBIAL PROPERTIES OF HYDROGEL MATERIALS FOR MAXILLO-FACIAL SURGERY

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Artificial implants are a favorable environment for bacterial adhesion and subsequent biofilm formation, thereby accelerating the development of infection in the area of implant incorporation. Despite significant progress in the development of various endoprostheses over the past decades, bacterial periprosthetic infection is one of the main factors leading to complications in their use, prolongation of rehabilitation, and significant economic losses. The present work is devoted to the creation of hybrid hydrogel nanocomposites with complex antimicrobial action for endoprosthetics in the maxillofacial region and for filling postoperative cavities (primarily after tumor removal). These nanocomposites were created on the basis of pre-synthesized spongy polyvinylformal with encapsulated gold nanoparticles, the pore space of which was partially filled with pH-sensitive hydrogels based on acrylic acid (or copolymers based on acrylamide and acrylic acid) with sorbed Albucid. The structure of the synthesized hybrid hydrogel materials was confirmed by IR spectroscopy. Studies of the kinetics of hydrogel swelling in buffer solutions with different pH values have shown that the sample filled with a copolymer of acrylamide and acrylic acid with their ratio 95:5 has the optimal properties for preserving the geometric dimensions of the material for endoprosthetics, while in the case of incorporation of 100 % acrylic acid, the degree of swelling of the material (and, respectively, its dimensions) can vary significantly with a change of pH. Antimicrobial effect of the developed hybrid hydrogel materials was investigated using the following bacterial cultures: Escherichia coli ATCC 25922, Enterococcus faecalis ATCC 29213, Staphylococcus aureus ATCC 25923, and Pseudomonas aeruginosa ATCC 27853. The antibacterial effect of polyvinylformal-based composites with incorporated gold nanoparticles that were saturated with Albucid on all test microorganisms was demonstrated (growth inhibition zones ranged from 15 to 35 mm), which will prevent microbial contamination of the developed hybrid hydrogel material when it is used in endoprosthesis.

***Keywords**: pH-sensitive hydrogels, endoprosthesis, gold nanoparticles, antibacterial properties, polyvinylformal, acrylic acid, hydrogel implants, Albucid*

INTRODUCTION

Artificial implants are a favorable environment for bacterial adhesion and further biofilm formation, thereby accelerating the development of infection in the implant area [1]. Despite significant progress in the development of various implants (primarily for bone) over the past decades, bacterial peri-prosthetic infection is one of the main factors leading to implant failure. When a bacterial infection occurs around a prosthesis, bone regeneration and integration are inhibited by an inflammatory reaction, leading to implant failure. Infection of endoprostheses is the main factor causing the ineffectiveness of this treatment option [2]. Every year, about 6 million fracture fixation devices are implanted worldwide [3], and about 5 % of these procedures (112.000 in the United States only) are accompanied by the development of infection (66 % of staphylococcal) with economic losses of more than $2 billion. Implant reinfection occurs through three pathways: direct contamination of the implant, spread of infection from a nearby source to the implant, which leads to colonization of the implant. The current treatment of orthopedic implant infections is limited to a combination of aggressive surgical treatment, device removal, and long-term treatment with systemic antibiotics, which can lead to the development of opportunistic infections due to disruption of the intestinal microbiota, development of antibiotic resistance, and the formation of bacterial biofilms [4], which increases the resistance of bacteria to antibiotics

by three orders of magnitude. To prevent bacterial colonization of implanted biomaterials, various antibacterial surface coatings have been proposed, but current technologies are far from being used on a large scale due to various limitations, including doubtful long-term effects on bacterial resistance, unresolved regulatory issues, and significant economic costs [5].

In general, bacterial infections associated with biomedical devices and implants have created a serious problem for the global healthcare system. These infections are mainly caused by bacterial biofilms that form on the surface of biomaterials, protecting encapsulated bacteria from traditional antibiotic therapy [6].

Complications from implant-associated infection (IAI) pose a significant threat to the use of implants in clinical practice and are accompanied by additional economic costs, significantly prolonging hospitalization [7]. As an alternative to the use of antibiotic therapy with all its inherent disadvantages, antimicrobial hydrogel coatings for implants and medical devices are proposed [8], including those that prevent endoprosthesis fouling (namely, bacterial adhesion), thus hindering further biofilm formation on the surface of endoprostheses [9].

Another alternative to the use of antibiotics for IAI is numerous sulfonamide drugs [10]. Sulfonamide drugs were the first widely used effective antibacterial drugs, systemically used since the 1930s, and are still widely used. They are also attracting attention as medical remedies for the treatment of infections caused by bacteria resistant to other antibiotics [11].

In recent years, hydrogels, spatially cross-linked hydrophilic polymers, which have proven themselves in other biomedical fields (in particular, as nanocarriers for controlled drug delivery [12], anti-burn coatings with immobilized stem cells [13], artificial soils for micropropagation of valuable plants [14]) have been used to prevent implant infection.

To impart antibacterial properties to hydrogel coatings and implants, nanoparticles of heavy metals (silver, gold, copper, zinc) are introduced into their structure. Among these metals, silver is the most widely used due to its good antibacterial properties and relatively low toxicity. However, other metals, primarily gold, have their own advantages [15]. Gold nanoparticles can attach to the bacterial cell membrane wall, causing leakage of the cell cytoplasm and its structural deformation, which leads to cell death [16]. The conjugate of gold nanoparticles with ampicillin has been successfully used to kill numerous drug-resistant bacteria, including methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa*, *Enterobacter aerogenes*, and *E. coli* [17]. Gold nanoclusters with incorporated antiseptic cetylpyridinium chloride can effectively kill multidrug-resistant (MDR) Gram-positive bacteria by several mechanisms, including induction of bacterial aggregation, disruption of bacterial membrane integrity and potential, and generation of reactive oxygen species. Moreover, the combination of the optimized gold nanocluster with conventional antibiotics can significantly increase the antibacterial activity against MDR bacteria, which has been proven in both *in vitro* and animal models of skin infections [18].

In the previous study [19], we examined the bactericidal capability of acrylic hydrogels and polyvinylformal (PVF), and the present study is devoted to the synthesis and study of the antimicrobial properties of hybrid materials with a complex structure based on a PVF sponge matrix and incorporated into their pore space pH-sensitive hydrogels based on Acrylic acid, additionally enriched by gold nanoparticles and the sulfonamide drug Albucid.

MATERIALS AND METHODS

Acrylic acid (AAc), (Merck, 99 %) was distilled under vacuum with the addition of 1 ml of concentrated sulfuric acid to remove the polymerization inhibitor (hydroquinone) and purified by fractional crystallization. Acrylamide (AA), (Merck, 99 %); N,N′-methyle-nebisacrylamide (MBA); (Merck, 98 %); ammonium persulfate (PSA); $(NH_4)_2S_2O_8$, (Sigma, 98 %); linear polyvinyl alcohol (PVA), (AppliChem GmbH, 98 %; molecular weight 72 kDa); formaldehyde (LAB-SCAN, 37 %); concentrated sulfuric acid H_2SO_4; Triton X-100 (AppliChem GmbH), Sodium sulfacyl (Albucid) – 30 % aqueous solution (PJSC Farmak, Ukraine) was used as received without additional purification. Distilled water was used as a solvent in all experiments.

Spherical gold nanoparticles with an average size of 30 nm were synthesized by the method of hydrothermal synthesis: the reduction of gold hydrochloric acid ($HAuCl_4 \cdot 3H_2O$) (≥99.9 % trace metals basis, Sigma-Aldrich) with sodium citrate in the presence of potassium carbonate was

carried out at the temperature of 121 °C, pressure of 1.04 atm for 15 min. Initial concentration of C_{Au} = 38.6 μg/ml by metal.

Acetalization of PVA was carried out by its condensation with formaldehyde in the presence of a strong acid and with the addition of an appropriate amount of pre-synthesized gold nanoparticles according to the scheme (Fig. 1). The details of the synthesis of polyvinyl formaldehyde (PVF) were discussed in our previous works [20], and the chemical composition is given in Table 1. Content of gold nanoparticles in sample Au 1 is 12.06 μg/g, in sample Au 2 – 24.12 μg/g and sample Au 0 does not contain gold nanoparticles.

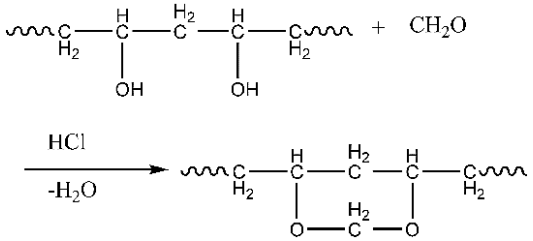

Fig. 1. Scheme of polyvinylformal synthesis by acetalization of polyvinyl alcohol [21]

Hydrogels based on AAc and hydrogel copolymers based on AA and AAc were synthesized by radical polymerization of an aqueous solution of the monomer(s) in the presence of a covalent crosslinker, the bifunctional monomer MBA The synthesis was carried out as follows. Argon was bubbled through the reaction mixture (an aqueous solution of the mixture of monomer(s) and crosslinker) before adding the heat-initiating agent ammonium persulfate. After mixing of components, the composition was thoroughly agitated and transferred to a mold consisting of two parallel glass plates separated by 1 mm thick spacers and kept for 1 hour at 60 °C. After about four hours, the hydrogels were removed from the molds and intensively washed with distilled water at room temperature to remove unreacted residues. The water was changed 2 times a day, and the washing process was monitored using a UV spectrometer (SPECORD M40, Carl Zeiss, Germany). Gel samples in the form of disks were cut out of swollen hydrogel films using a punch (d = 10 mm) and dried to a constant weight at 25 °C. The detailed composition of the synthesized hydrogels is shown in the Tables 2 and 3.

Dry sponges (Samples Au 1, Au 2, Au 0) were soaked in distilled water during 1 hour. Then they were squeezed in a syringe, and the volume of squeezed water was determined. Next, a volume of gel equal to the volume of squeezed water was poured into the syringe with the squeezed sponge. 50 or 75% of the gel was squeezed out of the total volume. Argon was passed into the syringe with the squeezed sponge for 30 seconds, then the syringe was closed and placed in a drying oven at 40–50 °C for polymerization (Fig. 2).

Table 1. Chemical content of the composition for synthesis of PVF-based sponges

Component	Content, % wt.
PVA	9.1
Formalin	3.5
Triton X-100	0.3
Hydrochloric acid	3.2
Distilled water	83.9
Gold nanoparticles	see text

Table 2. Composition of hydrogels based on AA-AAc and AAc

Component	Content, % in sample No	
	1–6; 8–13	7; 14
AA	8.0	–
AAc	0.44	9.9
MBA	0.10	0.2
PSA	35.0	34.7
Distilled water	Balance up to 100	Balance up to 100

Table 3. Chemical composition and squeezing rates of hybrid hydrogels based on PVF

Sample No	Hydrogel composition	Squeezing rate, %	Au NPs content, μg/g	Albucid impregnation
1	AA+AAc (95:5)	50	12.06	–
2	AA+AAc (95:5)	75	12.06	–
3	AA+AAc (95:5)	50	24.12	–
4	AA+AAc (95:5)	75	24.12	–
5	AA+AAc (95:5)	50	–	–
6	AA+AAc (95:5)	75	–	–
7	AAc (100 %)	75	24.12	–
8	AA+AAc (95:5)	50	12.06	+
9	AA+AAc (95:5)	75	12.06	+
10	AA+AAc (95:5)	50	24.12	+
11	AA+AAc (95:5)	75	24.12	+
12	AA+AAc (95:5)	50	–	+
13	AA+AAc (95:5)	75	–	+
14	AAc (100 %)	75	24.12	+

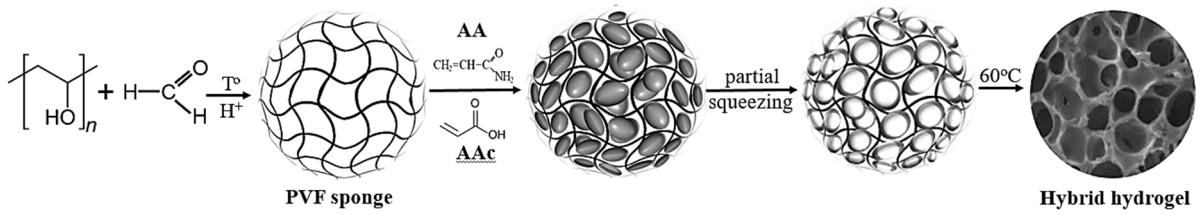

Fig. 2. Scheme of hybrid hydrogels synthesis

a *b*

Fig. 3. Appearance of PVF-based sponges without gold nanoparticles (*a)* and PVF sponges filled with pH-sensitive hydrogels based on AAc (*b*) – C_{Au} = 12.06 μg/g (squeezing rate 75 %)

The appearance of PVF sponges filled with pH-sensitive hydrogels based on AAc is shown in Fig. 3.

The FTIR spectra were recorded in the range of 400–4000 cm^{-1} at room temperature (internal reflection spectroscopy, with resolution of 4 cm^{-1}, accumulations of 40 scans which were combined to average out random absorption artifacts) using a Shimadzu IRAffinity-1S spectrometer equipped with GS10800-X Quest ATR Diamond Accessory.

The equilibrium degree of swelling of hydrogels in distilled water, W, was calculated using the formula $W = (m_s - m_d)/m_d$, where m_s is the mass of the swollen hydrogel in the equilibrium state after 24 hours of swelling, and m_d is the mass of the completely dried xerogel after water evaporation. The hydrogel samples

were incubated in a TS-1/80 SPN thermostat and weighed with an accuracy of 10^{-4} g on an AXIS analytical balance (Poland). Data are presented as mean standard deviation of three to five independent experiments. ANOVA was used for statistical data processing, $p < 0.05$ was considered reliable.

The sterility of the PVF-based composites with incorporated gold nanoparticles was checked on a solid nutrient medium (Muller-Hinton agar) in Petri dishes by applying 6–8 mm hydrogel disks to the surface of the medium and incubating the dishes at a temperature of 37 °C for 24 hours. After 24 hours of incubation, the presence of bacterial growth was checked and conclusions were drawn about the sterility of the hydrogels.

Antimicrobial activity of the synthesized hybrid hydrogels was determined in the Laboratory of Microbiology and Chemotherapy of SI "The Institute of Traumatology and Orthopedics" NAMS of Ukraine, with the involvement of 4 test strains from the collection of the Laboratory of Microbiology and Chemotherapy: *Escherichia coli* ATCC 25922*, Enterococcus faecalis* ATCC 29213*, Staphylococcus aureus* ATCC 25923 *and Pseudomonas aeruginosa* ATCC 27853. Studies of antimicrobial activity were carried out in the following way. Cultures of microorganisms were grown in a liquid nutrient medium for 18–20 hours at a temperature of 37 °C. Standard inoculum corresponding to 0.5 according to the McFarland standard was used. 0.1 ml of a suspension of microorganisms was applied and distributed with a spatula over entire surface of a Petri dish with a solid nutrient medium (Muller-Hinton agar). After that, 6–8 mm disks of PVF-based composites were placed on the Petri dish. After applying of the discs, Petri dishes were placed in a thermostat and incubated at a temperature of 37 °C for 24 hours. After the end of the incubation period, to record the results, the Petri dishes were placed upside down on a dark matte surface and the growth was characterized and the diameter of the zones of inhibition was measured with an accuracy of 1 mm. Experiments were performed twice. 14 samples of PVF-based composites with incorporated gold nanoparticles, half of which impregnated by Albucid, were studied.

RESULTS AND DISCUSSION

FTIR spectra studies of the synthesized PVP-based hybrid hydrogels with incorporated AAc-based hydrogels impregnated with Albucid have fully confirmed their structure, contain characteristic bands corresponding to the sponge matrix (2770–2940 cm^{-1}, 1365–1431 cm^{-1}, 1006 cm^{-1}, 3470 cm^{-1} (explained by the valence vibrations of the O-H group of the unreacted polyvinyl alcohol residue), hydrogel filler (3340, 3190, 2860, 1650, 1456, 1320, 1192, 1120 cm^{-1}), and incorporated antibacterial drug (3344, 1635, 1570, 1321 cm^{-1}) and are in agreement with the IR spectra of their components described by us earlier [19].

The fundamental characteristic of hydrogels, which determines their consistency state, as well as a set of their inherent physicochemical and exploitation characteristics, is their degree of swelling. This parameter becomes especially important in relation to the so-called "smart" hydrogels (in particular, pH- and temperature-sensitive hydrogels) whose parameters change dramatically [12] in response to minor changes in their surrounding environment. In contrast to PVF-based sponges impregnated by hydrogel based on 100 % AAc, PVF sponges filled by a mixture of AA and AAc (95:5) are practically devoid of polyelectrolyte properties (Fig. 4), which is probably due to the low content of AAc and its copolymerization constant with AA, whose at a pH close to neutral is significantly lower than that of the latter, leading to an even greater increase in the content of AA links in the copolymer hydrogel [22]. Taking into account that the hybrid polymeric material developed by us is intended for endoprosthetics in the maxillofacial region, as well as for filling postoperative cavities, in particular, after tumor resection, based on the swelling data we can come to the conclusion that it is preferable to use a gel, the dimensions of products made of which are not subject to significant changes when the pH varies.

It was shown that all the samples of PVF-based composites after steam sterilization (121 °C, 1.04 atm, 15 min) in the sealed polypropylene bags turned out sterile. Bacterial growth was absent under the discs after application on the surface of Muller-Hinton agar. Results of antimicrobial action studies of samples using test strains of microorganisms *E. coli* ATCC 25922*, E. faecalis* ATCC 29213*, S. aureus* ATCC 25923*, P. aeruginosa* ATCC 27853 are demonstrated in Table 4 and Fig. 5.

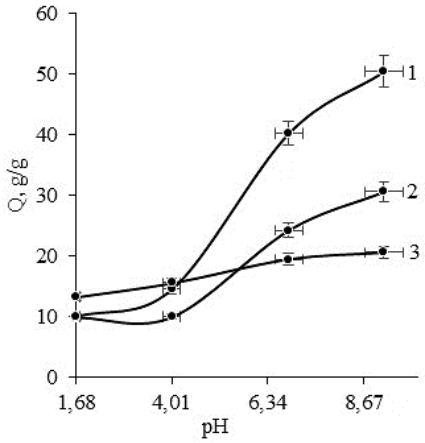

Fig. 4. Comparison of the swelling kinetics of PVF-based sponges filled with 100 % AAc (*1* – CAu = 12.06 μg/g; *2* – CAu = 24.12 μg/g) and with AA+AAc in a 95:5 ratio (*3*, squeezing rate 75 %)

Table 4. Evaluation on the antimicrobial effect of PVF-based composites (1–7 without Albucid; 8–14 saturated with Albucid)

Test strains	Characteristics of growth under the influence of samples of PVF-based composites, Samples No													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8***	**9***	**10***	**11***	**12***	**13***	**14***
E. coli ATCC 25922	+	+	+	+	–	–	+	23	24	24	24	26	26	15
E. faecalis ATCC 29213	–	–	–	–	–	–	–	25	28	35	28	32	28	20
S. aureus ATCC 25923	+	+	–	–	+	+	+	32	34	35	33	33	35	20
P. aeruginosa ATCC 27853	+	+	–	–	–	–	–	35	25	32	35	32	35	20

Notes: * – Diameter of growth inhibition zone for samples 8–14 , mm
"+" – Bacterial Growth
"– " – Growth inhibition under the disk

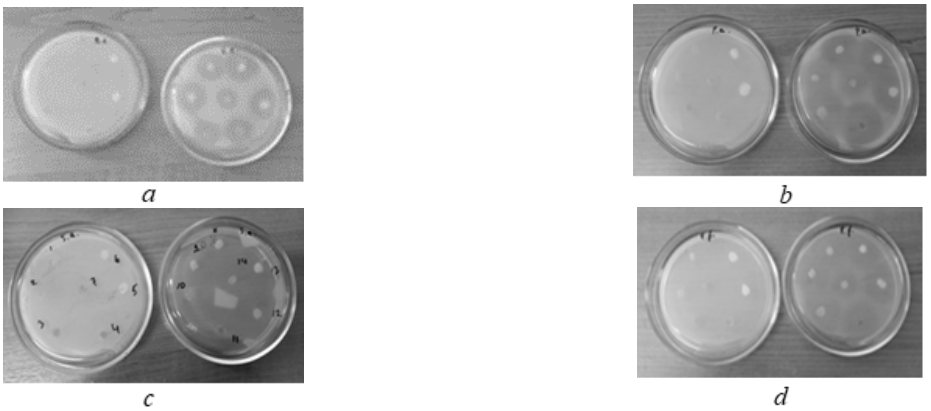

Fig. 5. Study on the antimicrobial effect of PVF-based composites (1–7 without Albucid; 8–14 saturated with Albucid) against strains: *a* – *E. coli* ATCC 25922, *b* – *P. aeruginosa* ATCC 27853, *c* – *S. aureus* ATCC 25923, *d* – *E. faecalis* ATCC 29213. On the left on each picture are samples 1–7, on the right – samples 8–14

The antimicrobial effect of PVF-based composites with incorporated gold nanoparticles that were not saturated with Albucid (samples 1–7) on *E. coli* ATCC 25922, *E. faecalis* ATCC 29213, *S. aureus* ATCC 25923, *P. aeruginosa* ATCC 27853 was not observed. However, in most cases, growth inhibition under the disk at the sites of their application was recorded (Table 4, Fig. 5, images *a–d*, on the left). Incorporation of gold nanoparticles into the composition of hydrogels was not intended to increase the antimicrobial effect, but to provide such hydrogels with regenerative and anti-inflammatory potential. However, the absence of bacterial growth in the places of application of hydrogels with incorporated gold nanoparticles indicates that such hydrogels do not have the potential to form biofilms. This confirms the compliance of hydrogels with incorporated gold nanoparticles to the requirements for implants [23].

The Albucid saturation of samples of PVF-based composites (samples 8–14) resulted in the antimicrobial effect observed for all test microorganisms. Growth inhibition zones were 20–35 mm (Table 4, Fig. 5, images *a–d*, on the right).

Thus, the antibacterial effect of PVF-based composites is due to the saturation of such composites with Albucid as a widely used medical antimicrobial agent.

CONCLUSION

Methods for the synthesis of a hybrid hydrogels based on polyvinylformal, acrylamide, acrylic acid, and gold nanoparticles saturated with antibacterial preparation Albucid have been developed. Obtained experimental results serve as a basis for the creation of a sponge material for endoprosthesis in the maxillofacial area.

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Синтез та дослідження антимікробних властивостей гідрогелевих матеріалів для щелепно-лицевої хірургії

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Штучні імплантати є сприятливим середовищем для адгезії бактерій і подальшого формування біоплівки, тим самим прискорюючи розвиток інфекції в області інкорпорування імплантату. Незважаючи на значний прогрес у розробці різноманітних ендопротезів за останні десятиліття, бактеріальна перипротезна інфекція є одним з основних факторів, що призводять до ускладнень при їх застосуванні, подовження терміну лікування, значних економічних втрат. Дана робота присвячена створенню гібридних гідрогелевих нанокомпозитів з комплексною антимікробною дією для ендопротезування в щелепно-лицевій ділянці та для заповнення післяопераційних порожнин (насамперед, після видалення пухлин). Вказані нанокомпозити було створено на основі попередньо синтезованого губчатого полівінілформалю з інкопорованими наночастинками золота, поровий простір якого був частково заповнений pH-чутливими гідрогелями на основі акрилової кислоти (чи співполімерів на основі акриламіду та акрилової кислоти) з сорбованим антимікробним препаратом Альбуцидом. Структура синтезованих гібридних гідрогелевих матеріалів була підтверджена з використанням методу ІЧ-спектроскопії. Проведені дослідження кінетики набухання гідрогелів у буферних розчинах з різною величиною pH засвідчили, що оптимальні властивості щодо збереження геометричних розмірів матеріалу для ендопротезування має зразок, наповнений співполімером акриламіду та акрилової кислоти при їхньому

співвідношенні 95:5, тоді як у випадку інкорпорування 100 % акрилової кислоти ступінь набухання матеріалу (і відповідно його розміри) може змінюватися у рази при зміні величини pH. Антимікробну дію розроблених гібридних гідрогелевих матеріалів було досліджено із використанням бактеріальних культур Escherichia coli ATCC 25922, Enterococcus faecalis ATCC 29213, Staphylococcus aureus ATCC 25923 та Pseudomonas aeruginosa ATCC 27853. Продемонстровано антимікробну дію гідрогелевих нанокомпозитів на основі полівінілформалю з інкопорованими наночастинками золота, просочених Альбуцидом, стосовно усіх тестових мікроорганізмів (зони затримки росту становили від 15 до 35 мм), що забезпечуватиме запобігання мікробної контамінації розробленого гібридного гідрогелевого матеріалу при його використанні у ендопротезуванні.

***Ключові слова**: pH-чутливі гідрогелі, ендопротези, наночастинки золота, антибактеріальні властивості, полівінілформаль, акрилова кислота, гідрогелеві імплантати, Альбуцид*

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