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Antimicrobial effects of hydrogel implants incorporating gold nanoparticles and albucide and developed for reconstructive surgery in the orbit and periorbital area

Yu. M. Samchenko [1], S. M. Dybkova [1], A. P. Maletskyy [2], L. O. Kernosenko [1], T. G. Gruzina [1], N. O. Pasmurtseva [1], L. S. Rieznichenko [1], T. P. Poltoratska [1], O. B. Liutko [3], K. V. Vitrak [3], N. M. Bigun [5], P. V. Vorotytskyi [1], I. Ie. Mamyshev [4]

[1] F.D.Ovcharenko Institute of Biocolloidal Chemistry, NAS of Ukraine,
Kyiv (Ukraine)

[2] SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine"
Odesa (Ukraine)

[3] SI "The Institute of Traumatology and Orthopedics" by NAMS of Ukraine",
Kyiv (Ukraine)

[4] Institute of Geological Science of Ukraine National Science Academy,
Kyiv (Ukraine)

[5] Lviv Regional Clinical Hospital,
Lviv (Ukraine)

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Background: *It is important to develop orbital hydrogel implants capable of depositing drugs (particularly, antimicrobial and anticancer drugs).*
Purpose: *To assess antimicrobial effects of hybrid hydrogel implants containing gold nanoparticles and albucide and developed for reconstructive surgery in the orbit and periorbital area.*
Material and Methods: *A 30% aqueous solution of albucide was used in the study. Antimicrobial activity of synthesized hydrogels was determined using Escherichia coli ATCC 25922, Enterococcus faecalis ATCC 29213, Staphylococcus aureus ATCC 25923 and Pseudomonas aeruginosa ATCC 27853 strains.*
Results: *All the synthesized samples of orbital hydrogel implants were sterile. The synthesized hydrogels and hydrogel nanocomposites with incorporated Au nanoparticles demonstrated bacteriostatic effects against E. coli ATCC 25922, E. faecalis ATCC 29213, and S. aureus ATCC 25923 strains, and bactericidal effects against P. aeruginosa ATCC 27853 strain. This study also demonstrated marked bactericidal effects of hybrid hydrogel implants incorporating both Au nanoparticles and albucide.*
Conclusion: *Orbital hydrogel implants were found to be sterile after being sealed into polypropylene bags and steam sterilized at 121 °C for 20 minutes. Our findings of bacteriostatic and bactericidal effects of the synthesized hydrogels and hydrogel nanocomposites containing Au nanoparticles and albucide against bacterial strains of interest will allow for the absence of, or low probability of bacterial contamination in applications of these hydrogels in implants.*

Introduction

Aggressive cancer is a major cause of mortality worldwide and has a high risk of recurrence [1]. Most commonly, cancer is treated with surgery. However, it can be rather difficult to remove the infiltrating tumor completely [2]. Radiotherapy and chemotherapy are commonly used as adjuncts to surgery to remove residual malignant cells and reduce recurrence incidence. Traditional systemic chemotherapy and radiotherapy, however, have numerous limitations, which include, first and foremost, a low effect impact on the tumor and unavoidable adverse effects [3]. Targeted local drug delivery is advantageous over conventional drug intake as it has no aforementioned limitations [4–6]. Hydrogels are considered an ideal local drug delivery platform for postoperative recurrence prevention due to both their structural capacity to encapsulate drugs and similarity to soft tissues [7]. Another important problem to solve is endoprosthesis for maxillofacial and orbital reconstruction and for surgery for eye cancer. Craniofacial injuries represent 29% of all trauma cases [8], and are primarily caused by anthropogenic and criminal-related ocular and orbital trauma. In this connection, more and more patients

need to have their affected orbit, orbital adnexa, and periorbital area restored [9], in particular, after surgery for eye cancer.

Non-biological implants with a porous structure (first and foremost, cross-linked hybrid gels) capable of biological integration with the surrounding orbital tissue provide new opportunities to perform restorative surgery. Previously, our experimental in vivo studies [10–12] have demonstrated high biocompatibility and no resorption for our highly porous polyvinyl formal composite material, as well as ingrowth of adjacent tissue into implanted constructs. These findings showed that this was a promising material requiring further research aimed at an improvement in its performance. In addition, we have demonstrated [13] that gold nanoparticles have not only mild antimicrobial effects, but also marked wound healing and regenerative effects.

The purpose of the study was to assess antimicrobial effects of hybrid hydrogel implants containing gold nanoparticles and albucide and developed for reconstructive surgery in the orbit and periorbital area.

Material and Methods

The reagents used for hydrogel synthesis were as follows: N-Isopropylacrylamide (NIPAM; Merck, 97%) from hexane and dried overnight under vacuum; acrylic acid (AK; Merck, 97%) was vacuum distilled with 1 ml concentrated sulfuric acid to remove hydroquinone, a polymerization inhibitor, and purified by fractional crystallization; acrylamide (AA, Merck, 99%), N,N′- methylene bisacrylamide (MBA; Merck, 98%), ammonium persulfate (APS; $(NH_4)_2S_2O_8$, Sigma, 98%); potassium persulfate (PPS; $K_2S_2O_8$, Sigma, 98%); N,N,N',N'-tetramethylethylenediamine (TEMED; Merck, 99%), linear polyvinyl alcohol (PVA; 98 %; AppliChem GmbH, Darmstadt, Germany; 72 kDa), formaldehyde (37%; LAB-SCAN); concentrated sulfuric acid H_2SO_4; and Triton X-100 (AppliChem GmbH). Bi-distilled water was used as an eluent in all experiments.

Sodium sulfacyl 30% (Albucide, Farmak JSC, Kyiv, Ukraine) was used without additional purification.

Gold nanoparticle synthesis

Gold nanoparticles that are ~30 nm in diameter were synthesized by hydrothermal synthesis: hydrogen-tetrachloroaurate (III) trihydrate ($HAuCl_4 \cdot 3H_2O$; ≥99.9% trace metals basis, Sigma-Aldrich) was reduced by adding aqueous sodium citrate in the presence of potassium carbonate at 121ºC and 1.04 atm pressure. End gold concentration was C_{Au}=38.6 μg/ml.

Hydrogel synthesis and incorporating gold nanoparticles into hydrogels

PolyNIPAM (PNIPAM)-based hydrogels were synthesized by radical polymerization of aqueous NIPAM monomer and bifunctional MBA monomer at 10 °C. The polymerization was initiated by APS and TEMED redox system. The hydrogel synthesis procedure was as follows. The reaction mixture (the aqueous solution of monomer and cross-linking agent) was purged with Ar before adding the redox system. The mixture was stirred, and the composite was cast into a mold (consisting of two microscope slides separated by a 1 mm thick Teflon spacer) and kept at room temperature for about 60 min. Acrylic acid and acrylamide were copolymerized in a way similar to above, but at a higher temperature (60°C) and using PPS as a thermal initiator. To incorporate gold nanoparticles into hydrogel, the calculated amount of suspension at an Au concentration of 38.6 μg/ml was added to the gel-forming composite while stirring with a mixer before being cast in glass molds. In about 4 hours, the hydrogels were removed from the molds and washed with room temperature distilled water to remove the residue from the starting materials that did not react. The water was changed twice a day for 5 days, and a spectrophotometer (Specord M40, Carl Zeiss, Jena, Germany) was used to control the washing process. Hydrogel disc samples of diameter 10 mm were cut from swollen hydrogel films and dried to a constant weight at 25°C. Table 1 shows detailed compositions of the synthesized hydrogels.

To perform acetylation of linear polyvinyl alcohol, it was condensed with formaldehyde in the presence of strong acid with addition of a proper amount of preliminary synthesized Au nanoparticles. Details of polyvinyl formaldehyde (PVF) synthesis have been reported previously [13], and Table 2 shows detailed compositions of the synthesized PVFs.

Fig. 1 shows PNIPAM-based hydrogel discs.

Fourier transform infrared spectroscopy (FTIR) analysis was conducted using a Shimadzu IRAffinity-1S instrument equipped with a Specac Quest Attenuated Total Reflectance (ATR) in the 400–4000 cm−1 wavenumber range, during 25-40 scans, with a resolution of 4 cm−1. The spectroscopic data analysis was completed using LabSolutions IR Ver. 2.26 software.

Incorporating albucide within the implant

Orbital hydrogel implants were saturated with albucide as follows. The hydrogel samples dried to a constant weight were immersed in 30% albucide solution at 20°C for 24 hours. Thereafter, they were transferred to an Erlenmeyer flask with a ground stopper sealed with Parafilm and stored for further studies.

In order to test the sterility of orbital hydrogel implants, 6-8-mm hydrogel discs were placed onto Muller–Hinton agar surface in Petri dishes. After incubation at 37°C for 24 h, the test for bacterial growth was performed to conclude on hydrogel sterility. Orbital hydrogel implant samples were found to be sterile after being sealed into polypropylene bags and steam sterilized (BMT ECOSTERI sterilizer, BMT, Brno, Czech Republic) at 121°C for 20 minutes

Antimicrobial activity of synthesized hydrogels was determined at the Microbiology and Chemotherapy Laboratory at the Institute for Traumatology and Orthopedics, NAMS of Ukraine, using *Escherichia coli* ATCC 25922, *Enterococcus faecalis* ATCC 29213,

Table 1. Compositions of PNIPAM-based hydrogels and acrylamide/acrylic acid based hydrogels

Component	Component content (weight percent) in samples Nos. 1 to 8							
	1	2	3	4	5	6	7	8
Acrylamide	-	-	-	-	19.8	19.8	19.8	19.8
Acrylic acid	-	-	-	-	1.0	1.0	1.0	1.0
N-Isopropylacrylamide (NIPAM)	20.8	20.8	20.8	20.8	-	-	-	-
N,N'-methylene bisacrylamide (MBA)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Ammonium persulfate (APS)	0.5	0.5	0.5	0.5	1.0	1.0	1.0	1.0
N,N,N',N'-tetramethylethylene-diamine (TEMED)	0.5	0.5	0.5	0.5	-	-	-	-
Distilled water	78.1	78.1	78.1	78.1	78.1	78.1	78.1	78.1
Au nanoparticles, μg/g	-	4.02	8.04	12.06	-	4.02	8.04	12.06

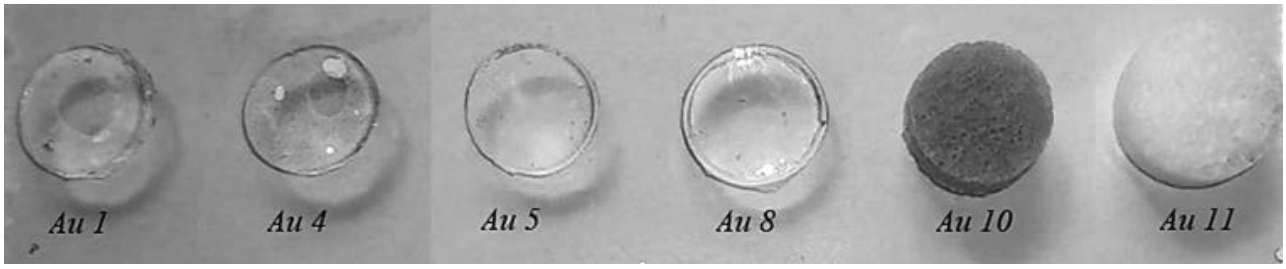

Fig. 1. Photographs of N-isopropylacrylamide (NIPAM)-based (Au1, Au4), copolymeric acrylamide/acrylic acid based (Au5, Au8) and polyvinyl alcohol-based (Au10, Au11) hydrogel discs. Note: C_{Au}=12.06 μg/g (Au4, Au8), C_{Au}=24.12 μg/g (Au10); C_{Au}=0 (Au1, Au5, and Au11)

Table 2. Composition of porous polyvinyl alcohol-based hydrogels

Component	Component content (weight percent) in samples Nos. 9 to 11		
	9	10	11
Polyvinyl alcohol	9.1	9.1	9.1
Formalin	3.5	3.5	3.5
Triton X-100	0.3	0.3	0.3
Sulfuric acid	3.2	3.2	3.2
Distilled water	83.9	83.9	83.9
Au nanoparticles, μg/g	12.06	24.12	-

Staphylococcus aureus ATCC 25923 and *Pseudomonas aeruginosa* ATCC 27853 strains from the collection of the laboratory. Antimicrobial effects of hydrogels were examined as follows. Bacterial cultures were grown in meat infusion broth at 37°C for 18-20 h. The inoculum density was adjusted to a 0.5 McFarland standard. To each Mueller-Hinton agar-containing Petri dish, 100 μL of organism suspension was added and spread homogeneously. 6-8-mm hydrogel discs were picked with a sterile forceps and placed onto Muller–Hinton agar-containing Petri dishes. Thereafter, the dishes were incubated for 24 h at 37°C. After completion of incubation, the dishes were placed upside down onto the dark dull surface, and inhibition zone diameters (mm) of bacteria were measured. All experiments were conducted in duplicate. Twenty-two hydrogel samples (particularly, samples of non-filled hydrogels and hydrogels with incorporated Au nanoparticles and albucide) were examined in this study.

Results

Fourier transform infrared spectroscopy (FTIR) analysis

The IR spectra of the synthesized nanocomposite hydrogels are considered below. The FTIR spectra of PNIPAM-based hydrogels (Fig. 2) showed characteristic vibrations at 3433 cm-1 and 3275 cm-1, asymmetric stretching vibrations and symmetric stretching vibrations of primary amine (NH_2); 2875 cm-1 – 2972 cm-1, asymmetric stretching vibrations and symmetric stretching vibrations of vibrations of the C–H functional group; 1541 cm-1, deformation vibrations of the N-H group; 1458 cm-1, deformation vibrations of the C-H group; and 1230 cm-1, vibrations of the C-N group. Vibrations at 1170 cm-1 and 1145 cm-1 correspond to skeletal vibrations of the methyl group, which is confirmed by a doublet of 1386 cm-1 and 1367 cm-1 deformation vibrations of the gem-dimethyl group H_3C - C - CH_3 [14, 15].

Figure 3 shows the IR spectra of the acrylamide/acrylic acid based hydrogels. The characteristic absorption bands of the IR spectra of copolymeric acrylamide/acrylic acid based hydrogels (Fig. 3a) are as follows: 3340 cm-1 and 3190 cm-1, asymmetric stretching vibrations and symmetric stretching vibrations of primary amine (NH_2); 2980 cm-1, 2860 cm-1 and 2780 cm-1 , asymmetric stretching vibrations and symmetric stretching vibrations

of vibrations of the C–H functional group; 1650 cm-1 and 1605 cm-1 correspond to asymmetric stretching vibrations and symmetric stretching vibrations vibrations of the acrylamide amid 1 C=O group, with these vibrations superimposed on acrylic-acid carboxyl group and C=C double bond vibrations; 1456 cm-1 and 1417 cm-1 bands correspond to amide II NH2; a band at 1320 cm-1 is caused by absorption of the C-N bond, and a 1192 cm-1 band corresponds to the deformation vibrations of C-H bonds and C-C stretching vibrations of carbon atoms; and 1120 cm-1 corresponds to deformation vibrations of the C-N group [15, 16].

The spectra of porous PVF hydrogels (Figure 3b) showed characteristic stretching and deformation vibrations of the methyl groups, with peaks at (2770 cm-1 and 2940 cm-1) and (1365 cm-1 and 1431cm-1), respectively. An intense 1006 cm-1 band corresponds to stretching vibrations of the C-O-C bond of the polyvinyl formal group. A broad absorption at 3470 cm-1 was attributed to stretching vibrations of the O-H group of the unreacted polyvinyl alcohol residue [16], and could be also due to atmospheric water adsorbed by the porous PVF hydrogel. Bands with absorption peaks at 1006 cm-1, 1066 cm-1, 1130 cm-1 and 1172 cm-1 reflect a cyclic sequence of bonds (–C-O-C-O-C-) in the polymer structure [15]. Deformation vibrations of the O-H group of the unreacted C-O-H group could also contribute to the peak at 1066 cm-1 [16].

On completion of the saturation of hydrogel nanocomposites with albucide, their IR spectra showed the absorption bands of the relevant functional groups Alb: 3344 cm-1 and 3244 cm-1, stretching vibrations of primary amine (NH2); 1635 cm-1, attributed to the C=O group in the amide I band; 1600 cm-1, 1570 cm-1 and 1502 cm-1, typical for the 1.4- substituted benzene ring of albucide; 1373 cm-1, 1321 cm-1 and 1236 cm-1, the C-H in-plane deformation vibrations superimposed on amide (II) N-H band, amide (III) C-N band and sulfuryl amide C-S-N group; and 1128 cm-1 and 1083 cm-1, stretching vibrations of the SO2 group [15]. Au nanoparticles were not identified in the IR spectra of hydrogel nanocomposites, and thermal processing of composites during their sterilization did not affect their spectral characteristics.

Examination of sterility and antimicrobial effects of orbital hydrogel implants

All hydrogel samples used in the study were found to be sterile: no bacterial growth was found on Muller–Hinton agar surface in Petri dishes after hydrogel discs were placed onto the surface. A reduction in disc size and change in the color from transparent to white were seen in hydrogel samples Nos. 1-4 (with and without Au nanoparticles) due to collapse of PNIPAM-based thermosensitive hydrogels at temperatures above a lower critical solution temperature (LCST) of 32–34ºC for the aforementioned gydrogels [17]. The results of tests for antibacterial effects of hydrogel samples against *E. coli* ATCC 25922, *E. faecalis* ATCC 29213, *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853 strains are presented in Tables 3 and 4.

Mild bacterial growth was noted at the site of disc application in tests for antibacterial effects of hydrogel samples and hydrogel nanocomposite samples with incorporated Au nanoparticles against *E. coli* ATCC 25922, *E. faecalis* ATCC 29213, and *S. aureus* ATCC 25923 strains. *P. aeruginosa* implant-associated infection is one of the most difficult-to-treat implant-associated infections, with a strong impact on the prognosis of the surgical strategy [18]. In the current study, beneath the hydrogel disc sample, we observed bactericidal effects of hydrogel samples and hydrogel nanocomposite samples with incorporated Au nanoparticles against *P. aeruginosa* ATCC 27853. This study also demonstrated marked bactericidal effects of hybrid hydrogel implants containing both Au nanoparticles and albucide (Table 4).

Samples 5-11 showed most prominent antibacterial effects against *E. coli* ATCC 25922 and *S. aureus* ATCC 25923 strains (Fig. 4A, B), and no bacterial growth beneath the sample and bacteriostatic effects within an area as large as 25 mm with regard to *E. faecalis* ATCC 29213 and *P. aeruginosa* ATCC 27853 (Fig. 4C).

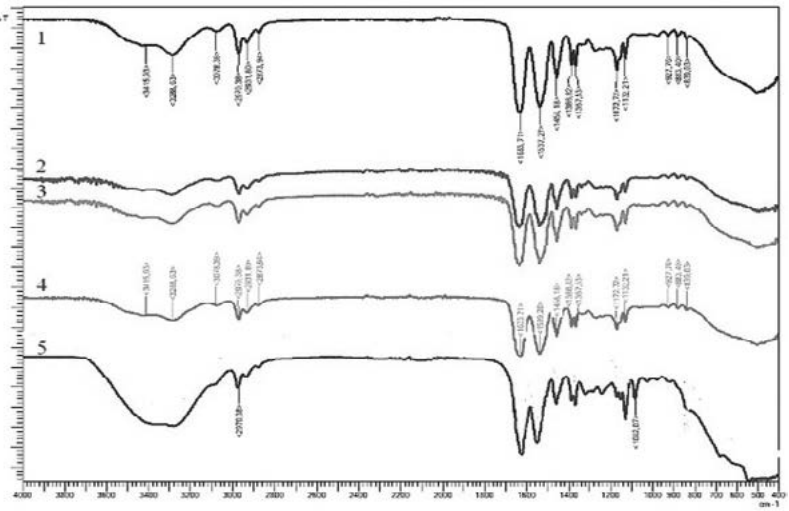

Fig. 2. Infrared spectra of (1) N-isopropylacrylamide (NIPAM)-only, (2) NIPAM +4.02 μg/g Au, (3) NIPAM +8.04 μg/g Au, (4) NIPAM +12.06 μg/g Au, and (5) NIPAM +12.06 μg/g Au + albucide based hydrogels

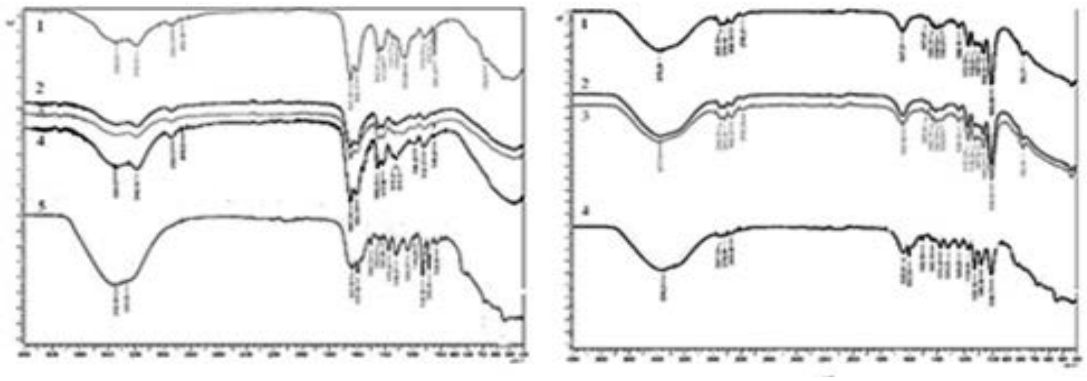

Fig. 3. Infrared spectra of (a) (1) copolymeric acrylamide/acrylic acid-only, (2) copolymeric acrylamide/acrylic acid +4.02 μg/g Au, (3) copolymeric acrylamide/acrylic acid +8.04 μg/g Au, (4) copolymeric acrylamide/acrylic acid +12.06 μg/g Au, and (5) NIPAM +12.06 μg/g Au + albucide based hydrogels and (b) (1) polyvinyl formaldehyde (PVF)-only, (2) PVF +12.06 μg/g Au, (3) PVF +24.12 μg/g Au, and (4) PVF +24.12 μg/g Au matrices

Therefore, there was no increase in bactericidal activity of hydrogel samples with an increase in the concentration of Au nanoparticles. Au nanoparticles and albucide showed no synergistic bactericidal effects. Our findings of bacteriostatic and bactericidal effects of the synthesized hydrogels and hydrogel nanocomposites containing Au nanoparticles will allow for the absence of, or low probability of bacterial contamination in applications of these hydrogels in implants. All the synthesized hydrogel samples were sterile, which is required for conformance with implant-related sanitary regulations [19].

Further research will be aimed at developing hybride hydrogel implants (particularly, orbital hybride hydrogel implants) with antimicrobial and anti-cancer effects for filling postoperative cavities to prevent wound infection and tumor recurrence.

Conclusion

First, we developed the techniques for the synthesis and characterized the chemical composition of orbital hydrogel implants on the basis of a wide number of functional hydrogels with incorporated Au nanoparticles. In addition, we improved the methods for removing the residue from the starting materials that did not react.

Second, we found that acrylamide/acrylic acid based hydrogels and PVA-based hydrogels showed better antibacterial effects compared to PNIPAM-based hydrogels. In addition, hydrogels and hydrogel nanocomposites with incorporated Au nanoparticles demonstrated bacteriostatic effects against *E. coli* ATCC 25922, *E. faecalis* ATCC 29213, and *S. aureus* ATCC 25923 strains, and antibacterial effects against *P. aeruginosa* ATCC 27853 strain.

Third, hybrid samples and samples of hydrogel nanocomposites containing Au nanoparticles and albucide exerted markedly improved bactericidal effects.

Finally, our findings of bacteriostatic and bactericidal effects of the synthesized hydrogels and hydrogel nanocomposites containing Au nanoparticles and albucide against bacterial strains of interest will allow for the absence of, or low probability of bacterial contamination in applications of these hydrogels in implants.

Table 3. Assessment of antimicrobial effects of orbital hydrogel implants incorporating Au nanopartucles

Test strains of bacterial patho-gens and opportunistic pathogens	Effect of hydrogel samples and hydrogel nanocomposites samples on bacterial growth										
	1 NIPAM	2 NIPAM + 4.02 μg/g Au	3 NIPAM + 8.04 μg/g Au	4 NIPAM + 12.06 μg/g Au	5 AA-AK	6 AA-AK + 4.02 μg/g Au	7 AA-AK + 8.04 μg/g Au	8 AA-AK + 12.06 μg/g Au	9 PVF + 12.06 μg/g Au	10 PVF + 24.12 μg/g Au	11 PVF
E. coli ATCC 25922	Mild bacterial growth beneath the disc										
E. faecalis ATCC 29213	Significant growth							Mild bacterial growth beneath the disc			
S. aureus ATCC 25923	Mild bacterial growth beneath the disc										
P. aeruginosa ATCC 27853	No bacterial growth beneath the disc										

Note: AA-AK, copolymeric acrylamide/acrylic acid based hydrogel; NIPAM, N-isopropylacrylamide; PVF, polyvinyl formaldehyde

Table 4. Assessment of antimicrobial effects of orbital hydrogel implants incorporating Au nanopartucles and impregnated with 30% aqueous solution of albucide

Test strains of bacterial pathogens and opportunistic pathogens	Effects of hydrogel samples and hydrogel nanocomposites samples impregnated with 30% aqueous solution of albucide on bacterial growth										
	1A NIPAM	2A NIPAM + 4.02 μg/g Au	3A NIPAM + 8.04 μg/g Au	4A NIPAM + 12.06 μg/g Au	5A AA-AK	6A AA-AK + 4.02 μg/g Au	7A AA-AK + 8.04 μg/g Au	8A AA-AK + 12.06 μg/g Au	9A PVF + 12.06 μg/g Au	10A PVF + 24.12 μg/g Au	11A PVF
E. coli ATCC 25922	Mild bacterial growth beneath the disc				Bactericidal effects, 22 mm						
E. faecalis ATCC 29213	No bacterial growth beneath the disc and mild bacteriostatic effects within an area as large as 15 mm				No bacterial growth beneath the disc and bacteriostatic effects within an area as large as 25 mm						
S. aureus ATCC 25923	No bacterial growth beneath the disc and bacteriostatic effects within an area as large as 15 mm		Growth	No bacterial growth beneath the disc and bacteriostatic effects within an area as large as 15 mm	Bactericidal effects, 25 mm						
P. aeruginosa ATCC 27853	No bacterial growth beneath the disc and bacteriostatic effects within an area as large as 15 mm				No bacterial growth beneath the disc and bacteriostatic effects within an area as large as 25 mm						

Note: AA-AK, copolymeric acrylamide/acrylic acid based hydrogel; NIPAM, N-isopropylacrylamide; PVF, polyvinyl formaldehyde

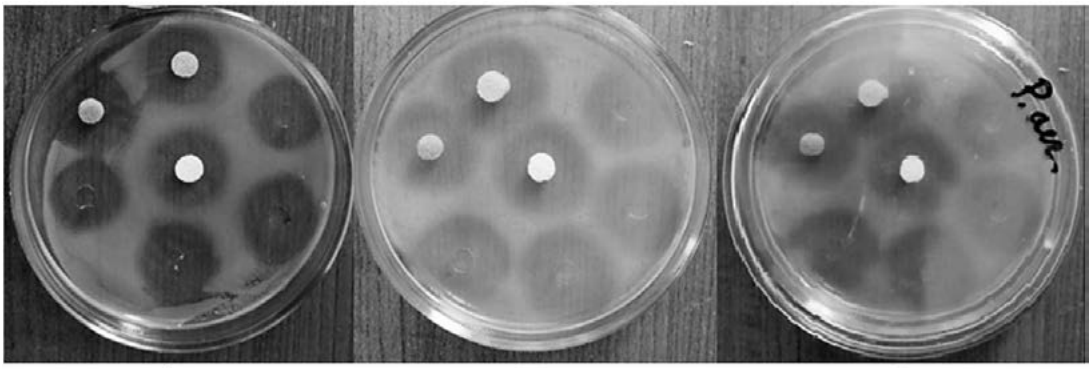

Fig. 4. Studies of antimicrobial effects of hydrogels against *Escherichia coli* ATCC 25922 (A), *Staphylococcus aureus* ATCC 25923 (B), *Pseudomonas aeruginosa* ATCC 27853 (C) for the development of orbital hydrogel implants. Hydrogel and nanocomposite samples (5A-11A) impregnated with a 30% aqueous solution of albucide

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Disclosures

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Corresponding Author: *Yurii M. Samchenko, Ovcharenko Institute of Biocolloid Chemistry, NAS of Ukraine, Kyiv. E-mail: yu1sam@yahoo.com*

Author Contributions: *YuMS: Conceptualization, Design of the Experiment for the Development of Techniques for the Synthesis of Orbital Hydrogel Implants, Methodology, Writing-original draft, Writing-review & editing; SMD: Design of the Experiment for the Assessment of Sterility and Antimicrobial Effects of Hydrogels and Hydrogel Nanocomposites, Studies on the Assessment of Sterility and Antimicrobial Effects of Hydrogels, Writing-original draft, Writing-review & editing; APM: Conceptualization, Writing-review & editing; LOK: Writing-original draft, Formal Analysis, Writing-review & editing; TGG: Studies on the Assessment of Sterility and Antimicrobial Effects of Hydrogels and Hydrogel Nanocomposites, Writing-original draft, Writing-review & editing; NOP: Monomer Clearance, Synthesis and Clearance of Orbital Implants; LSR: Studies on the Assessment of Sterility and Antimicrobial Effects of Hydrogels and Hydrogel Nanocomposites, Writing-review & editing; TPP: Functional Hydrogel Synthesis; OBL: Studies on the Assessment of Sterility and Antimicrobial Effects of Hydrogels and Hydrogel Nanocomposites; KVV: Studies on the Assessment of Sterility and Antimicrobial Effects of Hydrogels and Hydrogel Nanocomposites; NMB: Conceptualization, Writing-review & editing; PVV: FTIR Studies of Hydrogels and Hydrogel Nanocomposites, Interpretation of Study Results; IIeM: Spectroscopy for the Clearance of Synthesized Orbital Implants from Toxic Residue from the Starting Materials that did not React, Graphic Processing of the Results. All authors reviewed the results and approved the final version of the manuscript.*

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