PREPARATIONS BASED ON THE MALEIC ACID COPOLYMERS CONTAINING SILVER NANOPARTICLES AND CATIONS AND FURAN-2-CARBOXYLIC ACID: SYNTHESIS AND ANTITUBERCULOSIS ACTIVITY

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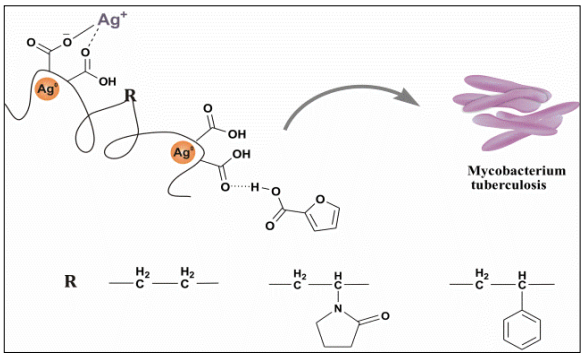
Abstract

The complexes of silver ions with furan-2-carboxylic acid (Fur-COOH) and the conjugates of polymer-stabilized silver nanoparticles with silver cations and Fur-COOH are synthesized. The silver nanoparticles are studied by transmission electron microscopy (TEM), while the resulting conjugates—by UV–vis spectroscopy. All the objects obtained display prominent *in vitro* activity against the H37Rv strain of *Mycobacterium tuberculosis*. A synergistic effect of the silver components is revealed for the conjugates based on maleic acid-*alt*-*N*-vinylpyrrolidone containing nano- and cationic forms of silver, as well as Fur-COOH.



Key words: maleic acid copolymers, silver nanoparticles, furan-2-carboxylic acid, antituberculosis activity.

Introduction

The polymer-containing conjugates of antibiotics and nanocomposites are promising candidates for the creation of effective antibacterial agents. Tuberculosis (TB) is one of the ancient diseases that annually claims millions of lives and still remains a serious threat for all humanity. Khabibullina *et al*. [1] estimated that about a quarter of the world population is infected with *Mycobacterium tuberculosis* (*Mtb*) and has latent tuberculosis infection (LTBI). It is emphasized that LTBI includes a broad spectrum of states and remains in the body in a persistent form. Furthermore, an immune response to LTBI cannot be detected. Recent years have witnessed significant advances in the investigation on LTBI. However, many biological and medical aspects of LTBI are still controversial. The appearance of the drug-resistant strains and, especially, a dormant form of tuberculosis infection that is insusceptible to medical treatment prompts the creation of principally new strategies to the construction of antituberculosis drugs. The rapid development of nanotechnologies opened up new opportunities for tuberculosis therapy, including treatment of dormant TB [2–12].

It is known that nanoparticles of some metals exhibit antimicrobial properties. For example, silver nanoparticles (AgNPs) are gaining increasing popularity as next generation antimicrobial agents owing to their prominent activity against many types of pathogens. The antibacterial properties of silver metal, ions (a salt form), and nanoparticles are well known, and pathogenic microorganisms, as a rule, cannot acquire resistance to them [13–16]. Upon contact with bacterial cells, silver nanoparticles form free radicals that can damage the cell membrane. Moreover, the nanoparticles can release silver ions; and these ions, in turn, can interact with the thiol groups of many vital enzymes and inactivate them, as well as destroy DNA, thus causing the death of a pathogen [17]. It was shown that the antibacterial activity of AgNPs was caused by the rapid release of Ag^+ ions that interact with the plasma membrane of gram-positive bacteria [15]. In addition to a broad spectrum of antimicrobial effects, silver features high thermal stability and low volatility. It is also not allergenic and well tolerated by patients.

One of the current trends in medicinal nanotechnologies is the production of AgNPs using green chemistry approaches. AgNPs can be formed upon enzymatic reduction of $AgNO_3$ under the action of two lignin-decomposing fungi: *Aspergillus flavus* (AfAg-NP) and *Emericella nidulans* (EnAg-NP). There is observed a synergistic antibacterial and antibiofilm activity of silver nanoparticles, biosynthesized by lignin-decomposing fungi, and an antibiotic (80–90% inhibition). Thus, a possibility of application of silver nanoparticles to improve the activity of antibiotics and other compounds was demonstrated. The high efficiency of biosynthesized AgNPs against bacterial films is of particular interest to fight multidrug-resistant TB [18]. However, this method of synthesis of nanosilver provides heterogeneous reaction medium, and the resulting preparation requires laborious purification. It was shown that *N*-acetylcysteine significantly enhances the effect of AgNPs on multidrug-resistant infectious agents (including, in the form of biofilms). All this created prerequisites for the construction of conjugates that would be effective against the forms of tuberculosis that are

insusceptible to modern drugs [19]. Chen *et al.* [4] showed that natural biopolymer alginate nanoparticles ALG-AgNPs are active both against the drug-resistant strains of *Mtb* and against dormant mycobacteria. The analysis of permeability of the bacterial cell membrane showed that the antibacterial action of ALG-AgNPs is caused by an increase in the cell permeability. The results obtained to date offer prospects for creating new types of conjugates that would be effective against *Mtb* and, more importantly, against the dormant form of tuberculosis. However, it should be noted that the resulting preparations can be stored only as colloidal solutions at 4 °C [4]. In a short review, Wanderley *et al.* [20] describe the silver complexes that were identified as antibacterial agents with promising activity against tuberculosis. The data on Ag(I) complexes with five different types of ligands connected with silver ions through N, O, P, and S donors are discussed. The metal complexes are presented as new drugs for tuberculosis treatment. The authors note that the interaction of silver with the cell wall/membrane, DNA, proteins, and enzymes of mycobacteria can lead to their death. A new paradigm in the creation of antituberculosis drugs using silver nanoparticles has enormous potential for addressing the issues of tuberculosis therapy [7].

The production of polymer-containing conjugates of antibiotics and nanocomposites is one of the promising directions of investigations aimed at overcoming challenges in tuberculosis treatment faced by modern medicine [21]. Soluble polymers can promote binding of silver nanoparticles with pathogen cells. This binding is caused by the high affinity between the polymer units and surface multivalent contacts of bacteria. It is also well known that the toxicity of both silver ions and silver nanoparticles reduces on passing from an inorganic silver salt to an organic one and further to polymer-stabilized forms of nanosilver [22, 23].

In this work, the readily available and cheap nontoxic water-soluble synthetic biocompatible anionic polymers, namely, the alternating copolymers of maleic acid with a range of comonomers were chosen as the initial polymers. Earlier it was shown that some copolymers of maleic anhydride (acid) with vinyl or acrylic monomers are biocompatible and have important pharmaceutical and medicinal applications [24–27]. Thus, the copolymers of maleic acid with *N*-vinylpyrrolidone were among the first synthetic polymers suggested as a basis for covalent binding of drugs [25]. The copolymers of maleic anhydride (acid) on their own do not cause teratogenic effects as well as do not lead to acute or toxic effects; they can reduce the drug toxicity [28] and even serve as nutrients [29].

An advantage of this type of polymers in the form of maleic acid copolymers is their high propensity to form different ionic and coordination bonds with organic compounds of various natures as well as easy chemical modification in the form of maleic anhydride copolymers. We have great experience in the synthesis of the polymer-stabilized silver nanoparticles [30] and showed their potential as antimicrobial agents against opportunistic pathogenic microbial flora both independently [31] and in a combination with conventional antibiotics [32–34]. The preparations were obtained that contained specific markers of lectins on the surface of the pathogen cells [35].

Furan-2-carboxylic acid (Fur-COOH) was chosen as a component for the production of a silver salt and conjugates with different types of polymeric nanosilver in order to study their antituberculosis activity. Fur-COOH is one of the organic compounds that, being inactive against *Mtb*, acquires prominent efficiency against the H37 Rv and smegmatis mycobacteria upon complexation with metals [36–38]. However, in this case, the process of complex formation is rather time-consuming and often unpredictable. In contrast, there are data on the ease of formation of Fur-COOH conjugates with glycine. These conjugates can provide new types of nanoconjugates with silver nanoparticles [39].

The goal of the present work was to obtain silver-containing derivatives, both low-molecular (a silver salt of furan-2-carboxylic acid) and polymer conjugates, based on the maleic acid copolymers bearing silver cations and nanoparticles as well as furan-2-carboxylic acid. Particular attention was drawn to the investigation of the activity of the resulting preparations against *Mtb*.

Results and discussion

The production of polymer-stabilized nanoforms of silver based on the alternating copolymers of maleic acid with *N*-vinylpyrrolidone (VM/Ag^0), ethylene (EM/Ag^0), or styrene (SM/Ag^0) was reported by our reserach group earlier [30]. In this work, the syntheses were performed at the molar ratio of the maleic acid polymer unit to a silver cation equal to 1/1 and double molar excess of a reducing agent (sodium borohydride). This range of ratios ensured the production of colloidal solutions that were stable for a long time (no less than a month). According to the results of TEM analysis, the shape of AgNPs in the sol samples was close to the spherical one. The diameter of the silver particles was 2.0 ± 0.5 nm (Fig. 1).

The copolymers form stable water-soluble polymer salts with silver cations both on their own and as a part of complexes with nanosilver.

The specific complexation of maleic acid residues with silver cations was revealed. According to the results of X-ray photoelectron and IR spectroscopic studies, the interaction of the dicarboxylic acid copolymers with ionic silver in the equimolar ratio affords the complexes of equimolar compositions, containing seven-membered rings. Ag^+ ions are bound with both carboxy groups of the monomer unit of the maleic acid residue by the coordination bonds. The silver coordination number is equal to two [34].

The low-molecular salt of ionic silver and furan-2-carboxylic acid as well the polymer conjugates containing cationic form of silver along with nanosilver and Fur-COOH were synthesized (Scheme 1).

The resulting derivatives based on the maleic acid copolymers appeared to be soluble in water. The most promising compounds are those derived from the maleic acid copolymer with *N*-vinylpyrrolidone, which are highly soluble in a wide range of pH, both in the acidic and alkaline media.

As an example, Fig. 2 depicts the optical spectra of the samples of the polymer nanosilver conjugates with furan-2-carboxylic acid.

The spectra of the resulting conjugates confirm the presence of the mentioned components in their structures. According to the optical microscopic studies, a plasmon surface resonance peak of AgNPs in the samples corresponds to 400–420 nm; a characteristic band of Fur-COOH is observed at *ca.* 240 nm.

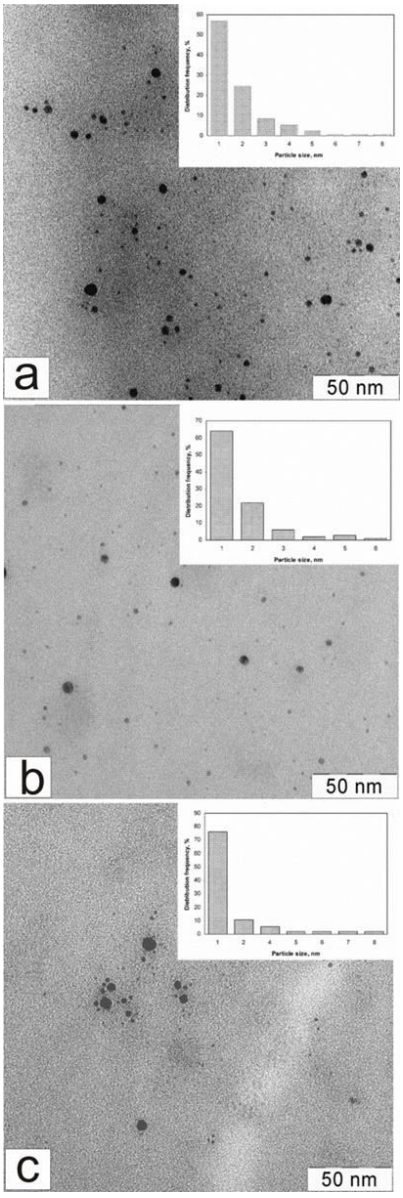
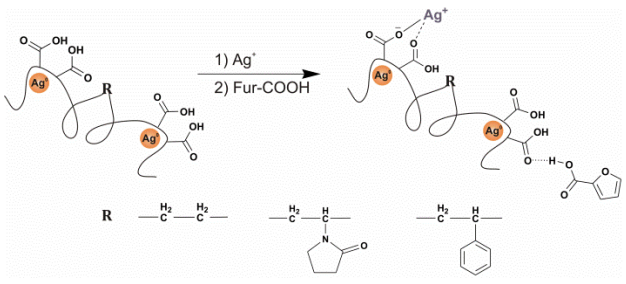


Figure 1. TEM micrographs of the VM/Ag^0 (***a***), EM/Ag^0 (***b***), and SM/Ag^0 (***c***) particles.



Scheme 1. Synthesis of the polymer conjugates containing nano- and cationic silver and furan-2-carboxylic acid.

The biological activity of the resulting preparations was tested against the H37Rv strain of *Mtb*. The results are summarized in Table 1.

The minimum inhibitory concentration (MIC) was defined as a range between the lowest concentration of the preparation

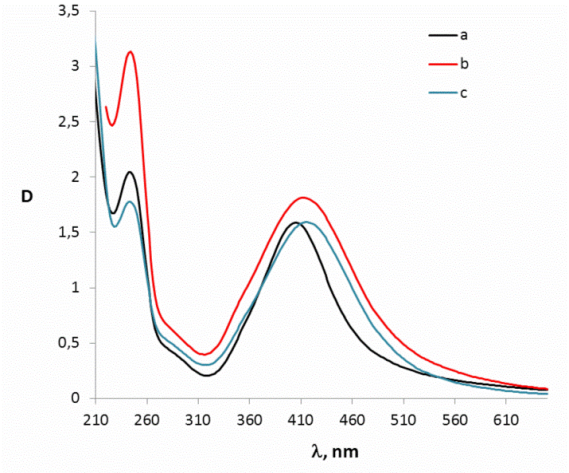


Figure 2. Optical spectra of the VM/Ag^0/Fur-COOH (***a***), EM/Ag^0/Fur-COOH (***b***), and SM/Ag^0/Fur-COOH (***c***) samples.

that completely suppresses the growth of mycobacteria and the highest concentration at which the growth of mycobacteria is detected; this explains why the activity values are presented as certain ranges. The MIC values for particular active components of the complex system were calculated based on the MIC values of the composite and the contents of Ag^0 and Ag^+ in the sample. The performed investigation showed that all the compounds obtained exhibit activity against the tested strain. The prominent efficiency was characteristic of the preparation bearing silver cations, in particular, Fur-$COOAg^+$, while the free acid itself, Fur-COOH, did not display any activity. However, it should be noted that this low-molecular silver salt of Fur-COOH almost did not dissolve in water, which can adversely affect the bioavailability of the preparation.

The results obtained are in good agreement with the earlier reported data on the activity of silver nanoparticles prepared by other methods against *Mtb*. Thus, the MIC value for AgNPs obtained using an extract from *Rhizopus* fungi composed 12.5 μg/mL [9], whereas the most effective concentration of the nanoparticles from the viewpoint of antibacterial activity for AgNPs derived electrochemically in the presence of ammonium citrate appeared to be 5 μg/mL, which provided the inhibition of mycobacterial growth in 78.8% of cases [40]. The previously obtained conjugates of nanosilver with a natural polymer, namely, alginic acid were active against a series of pathogenic tuberculosis strains (MIC < 20 μg/mL). However, it should be noted that the resulting preparations can be stored as colloidal solutions at 4 °C [4].

The nanoconjugates obtained based on the copolymer containing *N*-vinylpyrrolidone residues exhibited higher antibacterial activity in terms of the MIC values of AgNPs than their ethylene- and styrene-containing analogs, presumably, due to the higher copolymer hydrophilicity.

To estimate the mutual effect of the antimicrobial components—silver cations (A) and nanoparticles (B) stabilized with the copolymers of *N*-vinylpyrrolidone and maleic acid—in their conjugates, the fractional inhibitory concentrations (FICs) and fractional inhibitory concentration indices (FICIs) were calculated:

Table 1 Contents of the components in the resulting conjugates and their antibacterial activity

Sample	Component content in the sample (%)		MIC[a] (μg/mL)			FIC		FICI
	Ag^0	Ag^+	Sample	Ag^0	Ag^+	FIC Ag^0	FIC Ag^+	
$AgNO_3$	–	63.5	20[b]	–	12.7	–	–	–
Fur-$COOAg^+$	–	44.8	1.48–4.44	–	0.66–1.99	–	–	–
VM/Ag^0/Fur-COOH	23.0	–	4.44–13.3	1.02–3.06	–	–	–	–
EM/Ag^0/Fur-COOH	28.0	–	13.3–40.0	3.72–11.19	–	–	–	–
SM/Ag^0/Fur-COOH	23.4	–	4.44–13.3	1.28–3.86	–	–	–	–
VM/Ag^0	32.0	–	4.44–13.3	1.42–4.20	–	–	–	–
VM/Ag^+	–	32.0	1.48–4.44	–	0.47–1.42	–	0.04–0.11	-
VM/Ag^0/Ag^+	24.0	24.0	4.44–13.3	1.06–3.19	1.06–3.19	0.75–0.75	0.08–0.25	0.83–1.00
VM/Ag^0/Ag^+/Fur-COOH	18.7	18.7	4.44–13.3	0.27–0.83	0.27–0.83	0.19–0.19	0.02–0.06	0.21–0.24

[a] MIC was defined as a range between the lowest concentration of the compound that provides 99% inhibition of mycobacterial growth and the highest concentration at which the growth of mycobacteria was detected; FIC is the fractional inhibitory concentration; FICI is the fractional inhibitory concentration index;
[b] data from Ref. [7].

FIC (A) = MIC (A in combination with B)/MIC (A alone)
FIC (B) = MIC (A in combination with B)/MIC (B alone)
FICI = FIC (A) + FIC (B)

where MIC (A in combination with B) is the minimum inhibitory concentration of the complex conjugates containing polymer-stabilized nanosilver and silver cations, MIC (A alone) is the MIC value of the polymer-stabilized nanosilver (MIC Ag^0 in VM/Ag^0), and MIC (B alone) is the MIC value of silver cations (in $AgNO_3$). The interaction was determined as synergistic in the case when the FICI value was less or equal to 0.5. The FICI values above 2.0 indicated the antagonistic effects; the values between 0.5 and 2.0 pointed to the additive effects [41, 42].

From the data presented in Table 1, it follows that the introduction of silver cations into the polymer complex with AgNPs (VM/Ag^0/Ag^+) leads to the enhanced activity of nanosilver (MIC Ag^0) compared to the MIC value of Ag^0 in VM/Ag^0 and the enhanced activity of silver cations (MIC Ag^+) compared to the MIC value of Ag^+ in $AgNO_3$. This implies the existence of an additive effect of nanosilver and ionic silver in the conjugate composition (FICI $\leq$ 1). Earlier we have shown that the polymer composites of AgNPs with antibiotic components display the activity against a broad spectrum of potentially pathogenic microorganisms: gram-positive and gram-negative microorganisms and yeast-like fungi; the additive and synergistic effects were observed [31–35]. In the case of the application of AgNPs and Ag^+ in the composition of the conjugates, the calculated values of FICI for all the composites under consideration towards all the microorganisms explored ranged within 0.5–1.0, which indicates the additive interaction between the antimicrobial components in the system. Silver cations introduced into the systems with AgNPs reduce a charge of the polymer matrix and potentiate the activity of nanosilver, serving as an adjuvant. The presence of silver cations in the complex with silver nanoparticles shifts the dissociation equilibrium of nanoparticles towards its retardation, which promotes their prolonged action [34]. The VM/Ag^0/Ag^+/Fur-COOH conjugate displayed the FICI value below 0.5, which testifies the synergistic participation of the silver-containing components of the system. The introduction of Fur-COOH into the complex with the polymeric silver conjugates is likely to affect the conformational availability of the silver-containing components of the system.

Experimental

Materials

The copolymers of *N*-vinylpyrrolidone (VM), styrene (SM), and ethylene (EM) with maleic acid were obtained by the hydrolysis (through dissolution in deionized water followed by lyophilization) of the corresponding alternating copolymers of maleic anhydride. The following reagents were purchased from commercial sources: EM (Monsanto, USA, $M_w = 2.5 \times 10^4$), SM (Sterlitamak Chemical Plant, $M_w = 5.0 \times 10^4$), $AgNO_3$, $NaBH_4$, and furan-2-carboxylic acid (all from Sigma-Aldrich, USA), and NaOH (Reakhim, Russia). VM ($M_w = 4.0 \times 10^4$) was obtained according to the published procedure [43]. The elemental analyses were performed at the Laboratory of Microanalysis of INEOS RAS. The bioactivity studies were carried out with the H37Rv (Pasteur) strain of tuberculosis mycobacteria, which is sustained at the Department of Immunology of Central Research Institute of Tuberculosis.

Methods

Methods for analysis of the samples. The TEM images of AgNPs were obtained on a LEO 912 AB (OMEGA, KarlZeiss, Germany) transmission electron microscope equipped with a magnetic omega spectrometer with an energy filter integrated directly into an optical system of the unit. The electron accelerating voltage was E = 100 kV; the magnification ranged from 80× to 500000×; the image resolution was 0.2–0.34 nm. For investigations, a drop of the tested solution was placed on a 3 mm copper grid coated with formvar and dried under vacuum. The size distribution of AgNPs was calculated from the analysis of the images using at least 100 particles. The value of medium pH was determined with a Fisher Scientific 300 403.1 (USA) pH-meter. The optical spectra were registered on a Hitachi U-5100 (Japan) spectrophotometer using glassy cuvettes with the optical path length of 0.2 and 1 cm.

Synthesis of the polymer-stabilized NPs. Nanoscale silver was obtained according to the earlier published procedure [30]. The freshly prepared solutions of $AgNO_3$ (0.1 M) and maleic

acid copolymer (0.01 M, here the molar concentration of the copolymer refers to the monomer units of maleic acid) in water at pH = 7 (titration with 5% aq. NaOH) were mixed in equimolar amounts under vigorous stirring. In 5–10 min, a freshly prepared aqueous solution of $NaBH_4$ (0.1 M, double excess relative to the silver ions) was added to the resulting polymer salt under vigorous stirring. The reaction mixture was left at room temperature for 24 h. The dried samples of the polymer derivatives VM/Ag^0, EM/Ag^0, and SM/Ag^0 were obtained after ultrafiltration (YM5 membrane, Diaflo, Amicon Corp.) and lyophilization. The component contents in the samples were estimated based on the elemental analyses.

Synthesis of the silver salts

(a) Synthesis of the silver salt of furan-2-carboxylic acid (Fur-COOAg^+). Fur-COOH (561 mg, 5 mmol) was added to a solution of NaOH (200 mg, 5 mmol) in water (3.5 mL). The mixture was stirred for 15 min and adjusted to a neutral reaction. The resulting mixture was filtered. Then a solution of silver nitrate (849 mg, 5 mmol) in water (3 mL) was added dropwise to the stirred filtrate. The resulting precipitate was filtered off, rinsed with water (5 mL), and dried in a vacuum desiccator over phosphorus pentoxide. Yield: 875 mg (80%).

(b) Synthesis of the polymer salts VM/Ag^+ and VM/Ag^0/Ag^+. The polymer salts of silver cations in 1:1 ratio (molar ratio relative to the maleic acid units) were prepared according to the following procedure. To obtain VM/Ag^+, VM (100 mg, 0.44 mmol) and $AgNO_3$ (75 mg, 0.44 mmol) were dissolved in water (5 mL). The mixture was stirred until complete dissolution of the system components and left for 1 h at room temperature.

VM/Ag^0/Ag^+ was obtained by mixing the aqueous solutions of the components: 0.22 mL of the solution of $AgNO_3$ (0.044 mmol, 0.1 M) and 5 mL of the solution of VM/Ag^0 (0.044 mmol, 0.01 M). The reaction mixture was stirred at room temperature for 1 h. The dried samples of the polymer derivatives VM/Ag^+ and VM/Ag^0/Ag^+ were obtained after dialysis (YM5 membrane, Diaflo, Amicon Corp.) and lyophilization (–55 °C, 0.05 mbar). The compositions of the salts were confirmed by the Ag elemental analyses.

Synthesis of the polymer conjugates of Fur-COOH. All the Fur-COOH conjugates were prepared at 1/1/1/1 molar ratios (copolymer unit/silver in the form of nanoparticles/ionic silver/Fur-COOH). The synthetic procedure for VM/Ag^0/Ag^+/Fur-COOH used as a representative example was as follows. A solution of $AgNO_3$ (0.19 mL; 0.019 mmol, 0.1 M) was added to a solution of VM/Ag^0 (4.4 mL; 0.019 mmol, 0.0044 mmol/mL). Then Fur-COOH (2.5 mg) was added. The reaction mixture was stirred at room temperature until complete dissolution of Fur-COOH and left for 1 h. The dried samples were obtained after dialysis (YM5 membrane, Diaflo, Amicon Corp.) and lyophilization (–55 °C, 0.05 mbar). The samples of VM/Ag^0/Fur-COOH, EM/Ag^0/Fur-COOH, and SM/Ag^0/Fur-COOH were obtained analogously.

***In vitro* activity of the resulting conjugates against mycobacterial culture.** The antituberculosis activity of the compounds obtained was tested *in vitro* in 96-well plates. Tuberculosis mycobacteria were seeded in the Dubos medium at the amount of 180 μL per a well on separate plates at the initial concentration of 500 KOE/well. The samples were dissolved in DMSO; then their double dilutions were prepared in a 96-well plate using the Dubos medium. In 2 days, the diluted preparations were added to the mycobacterial culture in the amount of 20 μL per a well in serial dilutions. The growth of tuberculosis mycobacteria in the cells was registered as visually observed compact formations in the form of beads which sizes depended on the duration of the mycobacterial growth and activity of the potential antituberculosis agents [44]. When required, the growth area of mycobacteria was measured under the microscope. The minimum inhibitory concentration of the preparations was defined as a range between its lowest concentration that fully suppressed the growth of mycobacteria and the highest concentration at which the growth of mycobacteria was detected.

Conclusions

The facile and reproducible methods for synthesizing both low-molecular silver salt of furan-2-carboxylic acid and the polymer conjugates bearing nano- and ionic forms of silver and furan-2-carboxylic acid were suggested. The resulting preparations after purification and drying can be kept in a dry form for a long period of time without any loss in properties.

The performed investigations showed that all the prepared low-molecular and polymer compounds appeared to be active against H37Rv *Mycobacterium tuberculosis.* The silver salt of Fur-COOH demonstrated significant activity; however, it was almost insoluble in water. The nanocomposite based on the copolymer bearing *N*-vinylpyrrolidone residues displayed the highest bactericidal activity in terms of the MIC values calculated for AgNPs.

It was shown that the introduction of silver ions into the composition of the polymer complex with AgNPs leads to an additive effect. Furthermore, the most active compound appeared to the polymer conjugate containing nano- and cationic forms of silver as well as furan-2-carboxylic acid: the values of MIC ranged within 1.48–4.44 μg/mL. In this case, the calculated fractional inhibitory concentration index appeared to be below 0.5, which indicates the synergistic combined participation of the silver-containing system components. The presence of furan-2-carboxylic acid in the polymer conjugate at the same activity of the composites reduces the weight content of nano- and ionic silver. The results obtained render further bioactivity studies of the conjugates of polymer-stabilized silver nanoparticles bearing silver cations and furan-2-carboxilic acid as well as polymer complexes with other bactericides against dormant tuberculosis mycobacteria very promising.

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