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SYNTHESIS AND STUDY OF A PHARMACEUTICAL COMPOSITION WITH SILVER NANOPARTICLES, PRODUCED BY ELECTRON BEAM EVAPORATION

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ABSTRACT

A technological scheme for generating and forming a directed atomic and molecular flow of silver in the process of electron beam evaporation and condensation for the synthesis of nanocomposites is considered. The influence of the initial mass of silver, beam current, evaporation time, and evaporation rate on the mass of evaporated silver was evaluated. The distribution of the average size of silver nanoparticles depending on the evaporated silver velocity was estimated. The obtained results make it possible to synthesize nanocomposites with a predetermined most probable average size of silver nanoparticles. The structure of the PVP–Ag composite and of the H_2O–PVP–Ag and Ethanol–PVP–Ag colloidal systems was investigated by TEM and photon correlation spectroscopy (PCS). The results of the study of glucosamine substance with PVP and nanosilver in the form of a gel with antimicrobial (antistaphylococcal, antipseudomonal), wound healing and antiinflammatory effects, which has low toxicity and can be used for the local treatment of infected wounds and purulent inflammatory skin lesions, are presented.

KEYWORDS: composite powders, nanostructured coatings, electron beam evaporation and condensation (EB–PVD), evaporator design, directed vapor flow in vacuum, deposition, colloidal systems, polyvinylpyrrolidone, photon correlation spectroscopy

INTRODUCTION

With active development of nanotechnology research on creation of new nanomaterials and their application as active pharmaceutical ingredients in medicines is growing [1]. Of great interest in this area are nanoparticles (NP) of metals, having antimicrobial properties. This is due to the fact that at present the issue of combating the increasing resistance of microorganisms to chemotherapeutic antimicrobial drugs is extremely acute in medicine [2, 3].

Introduction into medical practice of antibiotics of various origin, chemical structure, spectrum of antimicrobial activity, and mechanism of action promoted improvement of the effectiveness of treatment of many infectious diseases, and at the same time posed new, difficult-to-solve problems for theoretical and clinical medicine, which concern the correct choice of the necessary drug and prevention of side effects. Development of the acquired microorganism resistance is one of the complex issues of modern antibiotic therapy. Antimicrobial agents of new chemical groups are introduced, and combination drugs are used in order to overcome this complication. However, microorganism resistance is growing many times faster than the new antimicrobial agents are created. Against the background of a significant increase in the acquired bacterial resistance a very limited number of new antibacterial drugs have been introduced into the clinical practice in recent years.

Numerous literature data of the last years are indicative of the effectiveness of the action of metal nanoparticles, in particular, silver, against a wide range of aerobic, anaerobic, gram-positive and gram-negative bacteria, yeast fungi, filamentous fungi and viruses, absence of resistance to them on the part of microorganisms and the relevance of using silver nanoparticles as an antimicrobial agent for treatment of infectious diseases [1, 5–8].

Silver has been approved for use as an antimicrobial agent for the first time in the 20s of the previous century, but its usage has decreased with the beginning of application of antibiotics for treatment of bacterial infections since the 40s of the previous century. Recently, silver has become popular again, particularly in treatment of open wounds with the spreading of methicillin-resistant Staphylococcus aureus [6]. Silver is regarded as an element, required for normal functioning of internal organs and systems, as well as a powerful remedy that improves immunity.

Increasing use of silver for local treatment leads to increased problems associated with studying its antimicrobial action [6]. Since the time, when it was first established that the destruction of pathogenic microorganisms ceases, when penicillin concentration in the plasma drops below the minimal inhibitory concentration (MIC), determination of the pharma-

cological index became the main parameter during comparison of antimicrobial agents and development of optimal dosing regimens. Silver MIC is actively studied in various areas of its application [6]. MIC_{50} and MIC_{90} values, most often studied during evaluation of microorganism sensitivity to antibiotics, are not adapted to studying the action of silver-containing agents. According to literature data, silver MIC relative to *St*. *aureus* (close to 100 strains) is in the range from 8 to 80 mg/l, relative to Ps. Aeruginosa (close to 100 strains) it is in the range of 8–70 mg/l [6].

To summarize the above-said, there is no doubt that development of new medicines based on silver NPs, is a relevant and in-demand area of research.

The objective of the work was studying the possibility and evaluation of the prospects for application of the process of vacuum electron beam evaporation to produce silver nanoparticles; investigation of the dependence of the evaporated silver weight on the initial weight of the silver sample, current of the beam heating the reactor for oriented deposition of the vapor flow on the powder, evaporation rate and duration of the process of silver evaporation to produce silver nanoparticles on the surface of a powderlike carrier; providing recommendations on practical application of the technological parameters of silver evaporation for assessment of the preset average size of silver NPs; using the technology of silver deposition on the surface of a powderlike carrier, synthesizing a nanomaterial of PVP–Ag composition; using the produced material of PVP–Ag composition to develop a new medicine with bactericidal action.

INVESTIGATION MATERIALS AND PROCEDURES

At present, local antiseptic agents, in particular, silver preparations, are used to treat purulent wounds. Dermasin, Sulfargin, Argedin Bosnaliek creams contain 1 % of silver sulfadiazine, Argosulfan cream contains 2 % of sulfatiazole [9]. A disadvantage of these drugs is the fact the silver is in an ionized shape in their composition, which increases the toxicity risk. For instance, at topical application of silver sulfadiazine agents (Dermasin, Argosulfan, Sulfargin) up to 1 % of silver ions and up to 10 % of sulfadiazine can penetrate into the systemic blood circulation from the damaged surface. Thus, long-term application of these preparations can result in side effects, characteristic for sulfanilamides: allergic reactions, circulatory problems, digestive disorders, hepatite, etc.

A task was set to expand the range of drugs for the treatment of purulent wounds and purulent-inflammatory lesions through development of an original pharmaceutical composition in gel form, which contains a combination of active and additional substances, exhibits a wide spectrum of antimicrobial activity and at the same time has antiinflammatory, reparative and detoxication properties. The posed task is solved so that the pharmaceutical composition in the gel form for treatment of purulent wounds and purulent-inflammatory lesions contains silver nanoparticles as the active substance, produced by electron beam vacuum evaporation and condensation of silver on the carrier material — polyvinylpyrrolidone (PVP) and glucosamine and has carbopol, glycerin and water in the composition of the hydrophilic gel base. Addition of glucosamine allows expanding the spectrum of pharmacological action of the drug and revealing the antiinflammatory and reparative activity. It inhibits the formation of peroxide radicals and the activation of proteolytic enzymes in the area of inflammation, which damage the tissue, reduces the manifestations of inflammation, inhibits the formation of antiinflammatory cytokines, and exerts an endothelium-protective effect. Glucosamine also has analgesic effect. PVP promotes adsorption and removal of toxins from the wound. The gel hydrophilic base does not dry out or irritate the skin. Active components and drug base components are approved for use in the pharmaceutical industry. Introduction of the nanotechnologies allows reducing the toxicity of silver preparations. It is known that PVP stabilized silver nanoparticles, unlike the ionized species, do not exhibit any toxic properties in the human body and have unique physicochemical and biological properties, which ensure their high antibacterial, antifungal and antiviral activity, and additionally demonstrate antioxidant properties, stimulate the healing processes in the skin, and increase local immunity. Therefore, the problem of searching for and development of new preparations with silver nanoparticles for treatment of wounds is relevant for modern pharmaceutical medicine.

Polymers of PVP–Ag system were synthesized using Plasdon® (PVP) K-15 and Plasdon® K-17 polymers with the molecular weight 8000 and 10000 from the series of synthetic homopolymers, which have surfactant properties, are highly soluble in water, alcohol (ethanol) [10] and a number of organic solvents.

Works [11–13] highlight the technological capabilities for realization of the process of oriented deposition of the vapour flow on the powder surface. This method allows dosing the amount of silver in its vapour flow and ensuring deposition of the required amount on the carrier particle surface to produce a composite of the specified composition and structure. Surfactants (SA) in the powderlike form were predominantly used, when the material dispersion and its mixing can ensure a uniform distribution of silver

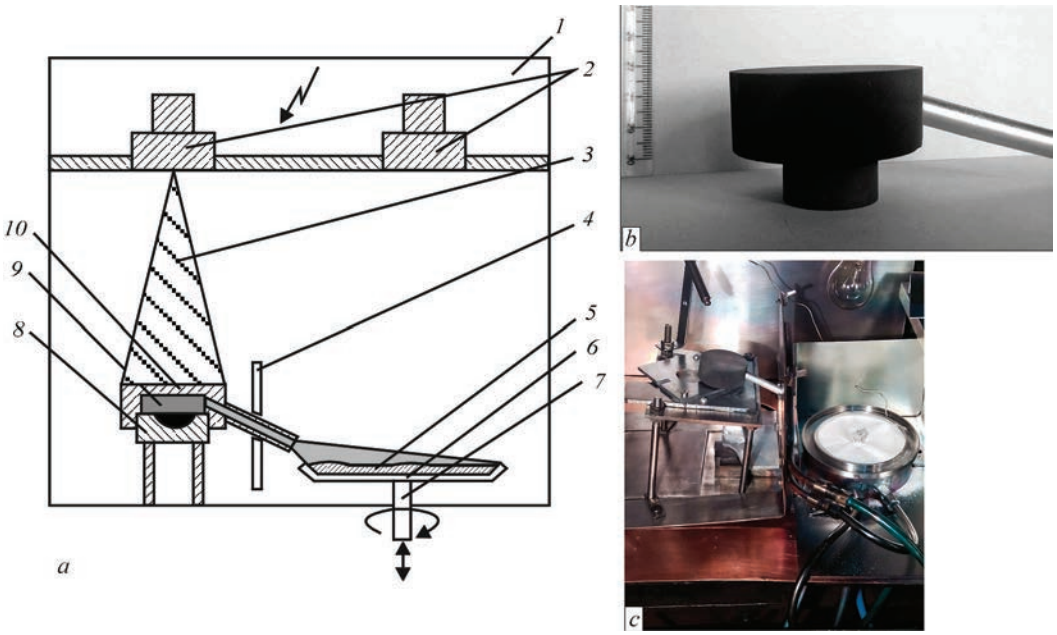

Figure 1. Scheme (*a*), and appearance of the evaporator (reactor) (*b*) for oriented deposition of the vapour flow on the powder and general view inside the process chamber of EBU UE-142 with the reactor and container with powder for silver deposition (*c*): *1* — vacuum chamber; *2* — electron beam gun; *3* — electron beam; *4* — water-cooled screen; *5* — powder; *6* — powder container; *7* — device for rotation and vibration of the powder container; *8* — lower part of evaporator (reactor); *9* — evaporation material; *10* — upper part of the evaporator with a hole and nozzle for directed vapour flow outlet [12]

particles on the carrier granule surface. Selection of a carrier from such SA, which are capable of stabilizing silver particles in the dispersed medium of a colloidal solution, allows obtaining a colloidal solution by dissolution of the nanocomposite directly in the dispersed medium without preliminary releasing of the silver nanoparticles from the nanocomposite by the carrier dissolution in the intermediate fluid. Such carriers can be SA soluble in water and/or other liquids, selected from a group which includes: polyvinylpyrrolidone, polyethylene oxide, polyacrylamide, dextran, and starch. PVP was used as the carrier material.

Figure 1, *a* shows the technological scheme of the process of vacuum electron beam evaporation and condensation of Ag molecular beams, in order to produce Ag nanoparticles, and the general view from the inside of the process chamber of an electron beam unit (*c*) with application of a reactor (*b*) which is used for generation and formation of a directed atomic-molecular Ag flow. Synthesis of nanocomposites from silver NPs was performed in UE-142 unit. In the presented variant of the technological scheme the graphite evaporator consists of the upper and lower parts, forming a closed volume. The evaporation material is located in the evaporator lower part, its upper part has an opening for the molybdenum tip. During heating of the evaporator by the electron beam, the material (silver), which is in its lower part, is brought to melting, evaporated and a molecular silver flow directed to the container with the powder is formed by the tip. At contact of the silver vapours with the carrier powder silver condensation occurs on the surface of its granules and a nanocomposite with Ag NPs is formed.

In the conducted experiments the powders were placed into flat copper cooled containers, and stirred with simultaneous deposition of the vapour flow. Produced Ag–PVP nanocomposites were used to prepare colloidal systems (CS) based on water and ethyl alcohol. Particle distribution by size in PVP–Ag–H_2O CS was determined by the method of photon-correlation spectroscopy (PCS) in the laser correlation spectrometer Zeta Sizer-3 (Malvern, Great Britain). A feature of the PCS method consists in that the results of separate measurement can be calculated both as monomodal, and as a polymodal approximation (in our case, using the Contin program). The monomodal approximation allows obtaining the average size of all the particles present in the solution, while the polymodal approximation shows the average size and quantity of each type of particles in the case of a polydisperse suspension. The method of transmission electron microscopy (TEM) was used to study in the transmission mode in HITACHI H-800 microscope at 150 kV accelerating voltage the precipitates obtained after removal of PVP and water from PVP–Ag–H_2O colloid. Mathematical processing of the obtained results was performed using Microsoft Excel statistical analysis programs.

Water, other polar, as well as nonpolar fluids: aliphatic and aromatic carbohydrates, their derivatives, etc., can be used to produce colloidal solutions. PVP application as the silver particle carrier, in which the

silver particles are fixed, allows producing by a simple and effective method the silver nanocomposite, which already contains a stabilizer, preventing silver particle aggregation during dissolution directly in the disperse medium of a target colloidal solution or in another intermediate liquid. This way, the process simplification is achieved both at the stage of silver nanoparticle synthesis, and at the stage of preparation of the colloidal solutions with provision of their aggregative resistance.

Colloidal solutions based on PVP with water are traditionally used in medicine as plasma substitutes. In order to prepare a CS of silver in water, a sample of powder of PVP–Ag nanocomposite (PVP of K-17 grade) is placed into a clean dry glass, 20 ml of deionized distilled water are added, the glass is capped, and placed into a water bath with 50–60 °C temperature to accelerate dissolution. After a ten minute soaking with mixing and ultrasonic treatment, a transparent colloidal solution of silver of a light-brown colour is produced.

PVP readily dissolves in ethyl alcohol. Therefore, CS of Ethanol-2 % PVP–Ag composition were also prepared, in order to determine the size of the nanoparticles in PVP–Ag compositions produced in the technological modes. CS were prepared in 20 ml test tubes as follows: sample of PVP-Ag powder was poured into the tube, 15 ml of ethyl alcohol was added, and the tube was capped. Stirring the tube contents, we tried to produce a transparent colloidal solution of silver of a light-brown colour. After that, the tubes (without the cap) with their contents were placed into an ultrasonic bath, heated up to 55 °C, and subjected to US treatment in "SWEEP" mode for 30 min. Twenty hours after preparation particle distribution was measured by PCS method.

The produced samples were studied at O.V. Palladin Institute of Biochemistry of the NAS of Ukraine. Investigations of antimicrobial activity of medicinal forms with silver nanoparticles were conducted at the National University of Pharmacy (NUPh, Kharkiv).

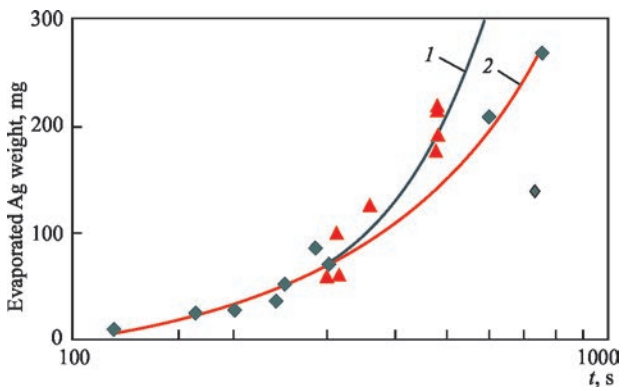

Figure 2. Dependence of the evaporated silver weight on the initial weight of silver, reactor heating current and evaporation time: *1* — 1230–1470; *2* — 900–1000 mg; graphite reactor, reactor heating current – 0.19–0.20 A (*1*); 0.15–0.17 (*2*)

INVESTIGATION RESULTS

To assess the possibility of practical application of the electron beam technology for synthesis of silver NPs of the specified size, first the dynamics of evaporation of a silver sample of 900 mg and greater weight placed into the reactor, was studied. Figure 2 shows examples of the dynamics of silver evaporation during the evaporation process, depending on the evaporation process parameters. Following the evaporation dynamics in time, as will be shown below, will allow determination of the average size of silver nanoparticles by the average rate of silver evaporation.

However, as shown by the first series of experiments, it turned out to be problematic to evaporate a precisely specified amount of silver, using a sample of a weight much greater than the amount required for evaporation. If you need to evaporate, for instance, 100 mg of silver, and load 900 or 1500 mg of silver into the reactor, it is a difficult task. In order to conduct the experiments, the weight of the loaded sample was close to the required mass of evaporated material. Figure 3 gives the results of such numerical experiments, conducted in order to determine the dependence of the evaporated silver weight on the duration of the evaporation process. The technological parameters of the process of silver evaporation from the reactor were varied, namely: initial weight of silver, current of the reactor heating beam, silver evaporation rate and angle of the reactor tip inclination. The work does not give the results of using the reactor with the vertically directed reactor tip. It should be noted that the efficiency factor of the reactor increases with increase of the angle of the tip inclination up to the maximum at the angle of 90°, reaching 30 % and more, depending on the size of the container for the powder and the distance from the tip outlet to the surface of the powder in the container. Results given in Figure 3 allow determining the silver evaporation rate, and, as shown by further studies, the silver evaporation rate determines the average size of NPs. The initial weight of silver samples, the current

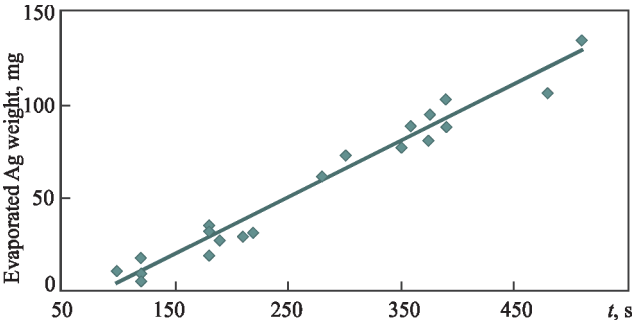

Figure 3. Dependence of the evaporated silver weight on the evaporation process duration

Table 1. Technological parameters of the processes of silver evaporation from a graphite reactor

Initial weight of Ag, mg	Evaporated Ag, mg	Beam current, A	Evaporation time, s	Average evaporation rate, mg/min
53.8	10.0	0.20–0.21	100	5.8
120.6	18.3	0.18–0.19	120	9.15
135.1	8.7	–»–	–»–	4.35
172.1	4.0	0.19...0.20	–»–	2.0
50.1	26.0	0.20	150	10.0
48.7	35.	0.21	180	13.0
49.8	30.8	0.210–0.215	–»–	10.3
54.70	18.3	0.23–0.21	–»–	6.1
31.7	27.7	0.18	190	8.8
51.0	28.0	0.21	210	8.0
39.8	31.3	0.21–0.22	220	8.5
75.9	61.4	–»–	280	13.2
83.6	73.5	0.20	300	14.7
80.0	77.2	–»–	350	12.9
136.4	87.9	0.21...23.0	360	13.5
79.3	79.3	0.19...0.20	375	12.2
98.0	95.6	0.20	–»–	14.7
98.0	95.6	–»–	–»–	–»–
115.6	87.4	0.20–22.0	390	13.4
148.4	103.7	0.21–0.23	–»–	16.0
116.4	105.0	0.20–22.0	480	13.1
142.0	136.2	–»–	510	16.0

Table 2. Fractional composition of silver NPs in H_2O–5 % PVP–Ag CS

Ag NPs	Most probable particle size, nm	Polymodal distribution		
		Fraction size, nm	Total particle weight, %	Total quantity of particles, %
First fraction	5.7	2–20	99.9	99.9
Second fraction	161	50–500	0.1	Less than 0.1

of the reactor heating beam, and the silver evaporation rate are shown in Table 1.

The average size of silver NPs was determined by the method of PCS of H_2O–1.4 % PVP–Ag H_2O–5 % PVP–Ag and Ethanol-2 % PVP–Ag colloidal systems. It was established earlier that the intensity of light scattering in colloidal solutions of H_2O–PVP and Ethanol-PVP systems is by 2 orders of magnitude lower on average, than that in H_2O–PVP–Ag and Ethanol–PVP–Ag systems. Given below are the results of investigation of the fractional composition and average size of silver NPs of the above CS.

The results of studying a sample of H_2O–5 % PVP–Ag CS (silver concentration in the CS was approximately 0.06 wt.%) one day after preparation are shown in Table 2 and in Figure 4.

Figure 5 gives the results of PCS-measurement of silver particle distribution in H_2O–14 % PVP–Ag CS (PVP

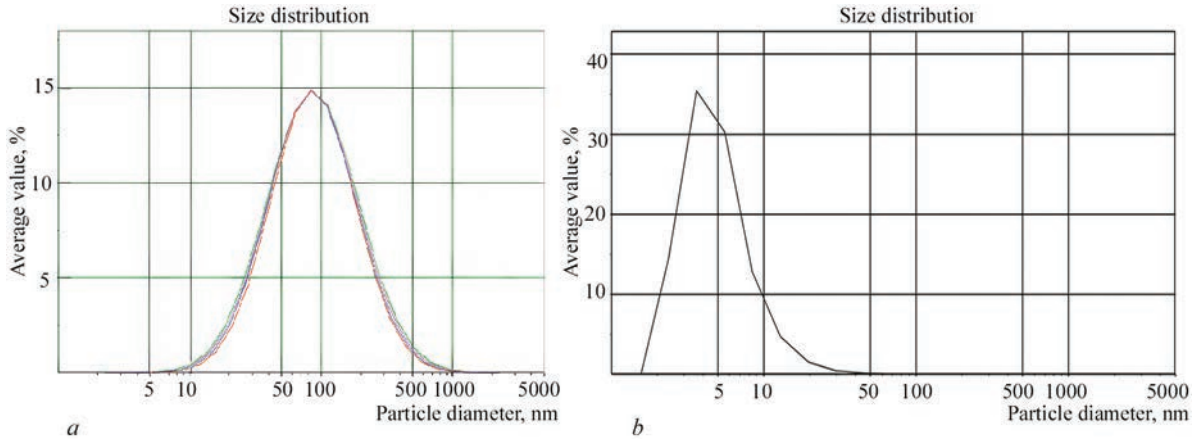

Figure 4. Laser correlation spectrum of H_2O–5 % PVP–Ag CS (*a*); particle size distribution by in CS (volume), 1 day after preparation

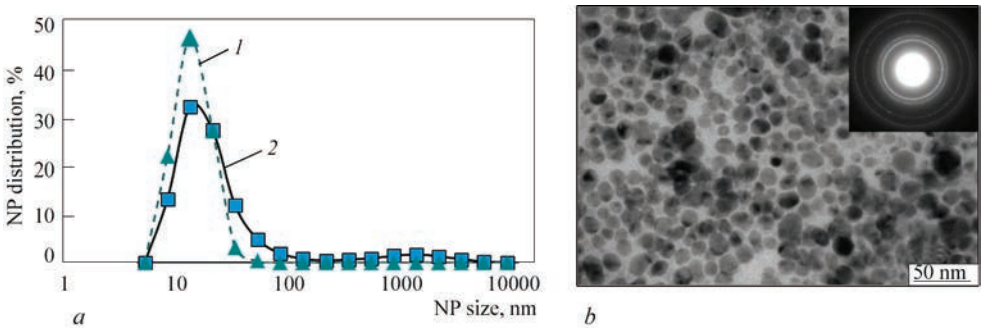

Figure 5. Silver particle size distribution in H_2O–1,4 % PVP–Ag CS determined by PCS measurement method: *1* — quantity; *2* — volume (*a*); silver particles (*b*)

Table 3. Composition of gels containing silver nanoparticles

Gel	Active ingredients	Base
1	Glucosamine (1.0 %) + PVP (2.0 %)	Hydrophylic: carbopol Ultrez — 2.0 %, glycerin — 5.0 %, purified water — up to 100 %
2	PVP (Ag 0.164 % - 0.1%) + PVP (2.0%)	
3	PVP (2.0 %)	
4	Glucosamine (1.0 % + PVP (Ag 0.164 % — 0.1 %) + PVP (up to 2.0%)	
5	Glucosamine (Ag 0.175 % — 0.1 %) + glucosamine (up to 1.0 %) + PVP	
6	Glucosamine (Ag 0.175 % — 0.01 %) + glucosamine (up to 1.0 %) + PVP	

Plasdon® K-15, molecular weight 8000) (*a*) and TEM of silver particles (*b*); molecular weight; average rate of silver evaporation was equal to 14.4 mg/min.

Figure 6 gives the dependence of average particle size in Ethanol-2 % PVP–Ag CS on silver evaporation rate, during obtaining of PVP–Ag composition according to the results of experiments and PCS measurements. As one can see, the average size of silver NPs depends on silver evaporation rate and with increase of the evaporation rate the general trend of the change of NP average size is directed towards decreasing of their size.

RESULTS OF STUDYING THE ANTIMICROBIAL ACTIVITY OF DRUG FORMS WITH SILVER NANOPARTICLES

As an example of practical application of PVP–Ag composition for development of medicinal substances with antimicrobial activity based on Ag nanoparticles we can cite investigation of antimicrobial activity of drug forms with silver nanoparticles of the average size of 10–12 nm in gel form. Six gels were developed at the Department of Plant Technology of Drugs of the National University of Pharmacy (NUPh, Kharkiv) (Table 3). Acute toxicity of the substances of glucosamine with nanosilver and PVP with nanosilver, as well as the gels, which were administered intragastrically, was studied using express-method on mice. Based on the results of previous studies of antimicrobial activity in vitro four promising samples of the gels were selected: 1, 2, 4 and 6 (Table 3). Reparative activity was studied in parallel with antimicrobial activity under in vivo conditions on a rat wound model. This model was selected as it allows studying not only the antibacterial activity of the drug, but also its reparative properties, as it reproduces three phases of the wound healing process at once: purulent-necrotic, granulation and epithelialization. Based on their composition, the studied gels should be the most active exactly in the first phase, demonstrating antibacterial (nanosilver), antiinflammatory and analgesic properties (glucosamine). As it is known, adequate therapy of the first phase of the wound process determines the speed of further reparative processes in the wound. The reference drug (Dermazin cream) was selected based on the fact that it contains 1 % sulphadiasine and is indicated for treatment of purulent wounds, that is compares well with the studied gels by its composition and indications. Treatment was begun three days after the wound infection, and the gels were applied once a

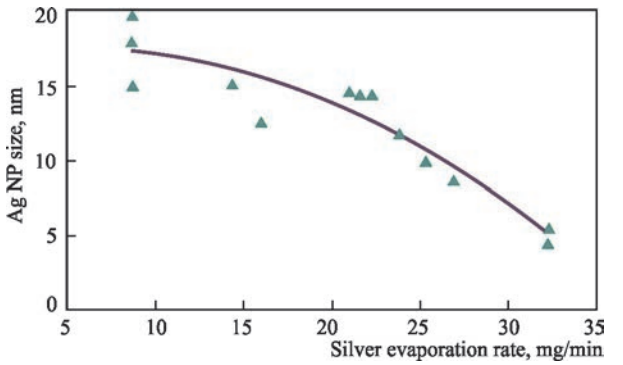

Figure 6. Average size distribution of silver NPs depending on silver evaporation rate. Measurements performed in Ethanol-2 % PVP–Ag CS

day in a thin layer in an empirical dose of 20 mg/cm^2. Wound suppuration was observed dynamically on the 1, 3, 5, 7, 9th day of the experiment. For an objective assessment of the therapeutic effect of the studied gels a morphological investigation of the wound surface zone was performed, and individual internal organs were examined for verification of the systemic action. Histological examination was performed on samples of the skin, heart, liver, and kidneys of the rats, for which the model pathology was reproduced — infected wounds, which healed naturally (control pathology), as well as samples of similar organs of the rats with infected wounds, which were treated with one of the gels with nanosilver (1, 2, 4 and 6) or with comparison drug — Dermazin ointment. Treatment with the studied gels with nanosilver and with the comparison drug was conducted for 9 days, beginning with the 3rd day after pathogen infection.

Based on the results of the conducted investigations, it was established that test-samples of gels 1, 2, 4, 5, 6 showed antimicrobial activity against gram-positive microorganisms (S. aureus). In relation to representatives of gram-negative microorganisms the following results were obtained: test-sample 1, 2, 3, 4 showed antimicrobial activity to P.aeruginosa; samples 2, 3 — to Kl.pneumoniae; sample 6 — to E.coli, respectively. Test-samples 2, 6 demonstrated moderate fungistatic activity. Investigations showed that the widest spectrum of selectively expressed antibacterial properties against the appropriately specified test strains is inherent in test samples 2, 6, 4. Considering the features of the composition of test-sample 2 (PVP (Ag 0.164 % — 0.1 %) + PVP (2.0 %) and the level of antimicrobial activity of test sample 6, it should be noted that the studied test-sample 4 is positively characterized by a pronounced bactericidal action against gram-positive (S.aureus) and gram-negative (P.a-eruginosa) microorganisms.

At application of the gel with glucosamine and silver nanoparticles, the wound area decreased by 51 %, that of the gel with glucosamine — by 13 %, that of the gel with silver nanoparticles — by 49 %, and that of Dermazin cream — by 32 %. On the 9th day the speed of reduction in the wound area of the declared sample was at the same level as the comparison drug. By epithelialization parameter already on the 9th day of the experiment in the group treated with helium with glucosamine and silver nanoparticles, complete healing of the wound had occurred in 40 % of the animals. While in the rest of the experimental samples epithelialization was observed only on the 11th day of treatment and was equal to 60 %, and in the group of officinal cream Dermazin it was 40 %.

Proceeding from the results of experimental planimetric studies we can conclude that the gel with glucosamine and silver nanoparticles contributes most to the acceleration of the regeneration and epithelialization processes, and by the expressiveness of the therapeutic effect it exceeds other gel samples and the reference drug. Analysis of the results of biochemical blood tests shows that wound treatment in animals with the declared gel helps reduce systemic manifestations of inflammation and destruction of the tissues.

CONCLUSIONS

1. Electron beam technology of evaporation and condensation in vacuum using a reactor for evaporation of Ag elements allowed synthesizing nanomaterials of PVP–Ag composition.

2. Dependence of the evaporated silver weight on the initial weight of silver, reactor heating current and process duration and average size distribution of silver NPs, depending on silver evaporation rate was established.

3. Obtained nanomaterial of PVP–Ag composition was used at the National University of Pharmacy (Kharkiv) to develop medicinal gels based on glucosamine with a low toxicity, wound healing ability and expressed bactericidal action under the conditions of purulent-necrotic wound process.

4. The best wound heating ability by the parameters of reliable normalization of biochemical, immunobiochemical and hematologic parameters during treatment was demonstrated by the gel of the following composition: glucosamine + 1.0 %; PVP + 0.164 % Ag, recalculated to silver it is 0.10; PVP — up to 2.0 %; carbopol Ultrez — 10–2.0 %; triethanolamine — up to pH 6.4; glycerin — 5.0 %; purified water — up to 100%, which exceeded the reference drug — Dermazin ointment by the epithelialization rate.

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