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The *in vitro* antimicrobial activity of highly dispersed silica and polyhexamethylene guanidine hydrochloride composite for treating local infections

Antimicrobial drug resistance (ADR) is an urgent global problem for all countries; it has a negative effect on the treatment outcome of patients. The problem can be solved by creating and introducing new antimicrobial compounds and complex drugs. Development of the combined antimicrobial agent which would show the expressed antimicrobial action and sorption properties remains relevant. Polyhexamethylenguanidine hydrochloride (PHMG-HC), being a high-molecular cationic surfactant of the guanidine group, was chosen as an antimicrobial component.

Aim. To determine the antimicrobial activity of highly dispersed silica (HDS), a composite (code name CMU-211) of HDS and PHMG-HC, and PHMG-HC polymer solution.

Materials and methods. 5% suspension of HDS modified by PHMG-HC polymer, 5 % suspension of HDS and 20 % aqueous solution of polyhexamethyleneguanidine hydrochloride were used in the work. The antimicrobial activity of substances was studied using test-strains of such microorganisms as *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella enterica*, *Klebsiella pneumoniae*, and *Candida albicans*.

Results. The composite HDS/PHMG-HC has been shown to have a high activity against *C. albicans* and *S. aureus* with the minimum inhibitory concentration (MIC) of ~10 μg/mL (calculated with reference to HDS/PHMG-HC), as well as the marked effect against *E. coli* (MIC of ~20 μg/mL), *S. enterica* (MIC of MIC ~40 μg/mL) and *P. aeruginosa* (MIC ~40 μg/mL). The relatively low activity of CMU-211 was reported against *K. pneumoniae* (MIC ~ 80 μg/mL). The activity of the composite HDS/PHMG-HC was similar to those of PHMG-HC.

Conclusions. The composite HDS/PHMG-HC developed exhibits the marked antibacterial activity against gram-positive, gram-negative microorganisms, as well as *C. albicans*.

Key words: antibacterial activity; antibiotic resistance; antifungal action; polyhexamethyleneguanidine hydrochloride; silica nanoparticles

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Антимікробна активність in vitro нанодисперсного кремнезему і композиту полігексаметиленгуанідину гідрохлориду для лікування місцевих інфекцій

Резистентність до антимікробних препаратів є актуальною проблемою для всіх країн світу, що негативно впливає на результати лікування хворих. Вирішити поставлену проблему можна шляхом створення та впровадження нових антимікробних сполук та комплексних лікарських засобів. Актуальним залишається розробка комбінованого антимікробного засобу, який би проявляв виражену антимікробну дію та сорбційні властивості. В якості антимікробного компоненту було обрано полігексаметиленгуанідину гідрохлорид (ПГМГ-ГХ), що є високомолекулярною катіонною поверхнево-активною речовиною групи гуанідинів.

Мета. Визначити антимікробну активність суспензії нанодисперсного кремнезему (НДК), композиту НДК та ПГМГ-ГХ і розчину полімера ПГМГ-ГХ.

Матеріали та методи. В роботі була використана 5 % суспензія НДК, модифікована полімером ПГМГ-ГХ; 5 % суспензія НДК та 20 % водний розчин полігексаметиленгуанідину гідрохлориду. Дослідження антимікробної активності речовин проводили на мікроорганізмах: *Escherichia coli; Staphylococcus aureus; Pseudomonas aeruginosa; Salmonella enterica; Klebsiella pneumoniae; Candida albicans*.

Результати. Композит НДК/ПГМГ-ГХ має високу активність проти *C. albicans* і *S. aureus* з МІК ~10 мкг/мл (у перерахунку на ПГМГ-ГХ) і виражену активність проти *E. coli* (МІС ~20 мкг/мл), *S. enterica* (МІС ~40 мкг/мл) і *P. aeruginosa* (МІС ~40 мкг/мл). Відносно низьку активність композит НДК/ПГМГ-ГХ проявив щодо *K. pneumoniae* (МІС ~80 мкг/мл). Активність композиту НДК/ПГМГ-ГХ була подібна до такої ж у ПГМГ-ГХ.

Висновки. Розроблений композит НДК/ПГМГ-ГХ проявляє виражену антибактеріальну дію щодо грампозитивних, грамнегативних мікроорганізмів, а також *C. albicans*.

Ключові слова: антибактеріальна активність; антибіотикорезистентність; протигрибкова активність; полігексаметиленгуанідину гідрохлорид; наночастинки кремнезему

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Противомикробная активность in vitro нанодисперсного кремнезема и композита полигексаметиленгуанидина гидрохлорида для лечения местных инфекций

Резистентность к антимикробным препаратам является актуальной проблемой для всего мира, которая негативно влияет на результаты лечения больных. Решить поставленную проблему можно путем создания и внедрения новых антимикробных соединений и комплексных лекарственных средств. Актуальным остается разработка комбинированного антимикробного средства, которое бы проявляло выраженное антимикробное действие и сорбционные свойства. В качестве противомикробного компонента был избран полигексаметиленгуанидина гидрохлорид (ПГМГ-ГХ), который является высокомолекулярным катионным поверхностно-активным веществом группы гуанидина.

Цель. Определить противомикробную активность суспензии нанодисперсного кремнезема (НДК), композита НДК и ПГМГ-ГХ и раствора полимера ПГМГ-ГХ.

Материалы и методы. В работе были использованы 5 % суспензия НДК, модифицированная полимером ПГМГ-ГХ; 5 % суспензия НДК и 20 % водный раствор полигексаметиленгуанидина гидрохлорида. Исследование антимикробной активности веществ проводили на микроорганизмах: *Escherichia coli; Staphylococcus aureus; Pseudomonas aeruginosa; Salmonella enterica; Klebsiella pneumoniae; Candida albicans*.

Результаты. Композит НДК/ПГМГ-ГХ обладает высокой активностью против *C. albicans* и *S. aureus* с МИК ~10 мкг/мл (в пересчете на ПГМГ-ГХ) и выраженной активностью против *E. coli* (MIC ~20 мкг/мл), S. enterica (MIC ~40 мкг/мл) и P. aeruginosa (MIC ~40 мкг/мл). Относительно низкую активность композит НДК/ПГМГ-ГХ проявил к *K. pneumoniae* (MIC ~ 80 мкг/мл). Активность композита НДК/ПГМГ-ГХ была сходна с таковой у ПГМГ-ГХ.

Выводы. Разработанный композит НДК/ПГМГ-ГХ проявляет выраженное антибактериальное действие по отношению к грамположительным, грамотрицательным микроорганизмам, а также *C. albicans*.

Ключевые слова: антибактериальная активность; антибиотикорезистентность; противогрибковая активность; полигексаметиленгуанидина гидрохлорид; наночастицы кремнезема

Antimicrobial drug resistance (ADR) is an urgent global problem for all countries; it has a negative effect on the treatment outcome of patients. Currently, ADR is going beyond purely medical issues and becoming of great social and economic importance [1].

Staphylococcus aureus plays a leading role in development of nosocomial pyoinflammatory infections and, recently, there is an increase in its resistance to great part of antimicrobial drugs (AMD) used in clinical practice [2]. Furthermore, this prevalence of resistance has significant variations in different countries [3].

There is also an increase in AMD resistance of *Escherichia coli* strains [4], which are the leading cause of nosocomial pyoinflammatory infections [3, 5]. Other problematic drug-resistant pathogens encountered today include *Klebsiella pneumoniae*, *Pseudomonas aeruginosa, Salmonella enterica*, and *Candida albicans* [6].

The problem can be solved through development and implementation of novel antimicrobial compounds and combination drugs.

Cationic amphiphilic polymers, including polyhexamethylene guanidine hydrochloride (PHMG-HC), are among the promising antimicrobial agents for topical use [7]. Representatives of the polymeric guanidine family have a broad spectrum of activity against gram-positive, gram-negative bacteria, fungi, and yeast. PHMG-HC has received increasing attention in recent years since this compound can be developed as a highly effective disinfectant in combination with other substances and it can be bound to the substrate material to create covalently bound, nonleaching antimicrobial surfaces [8].

The bactericidal effect of PHMG-HC is based on binding of positively charged disinfectant molecules to the cytosolic membrane and lipopolysaccharides or murein of the cell wall. Bacterial cell death caused by critical changes in the areas being in contact with a disinfectant is followed by the cell wall destruction and cell lysis [9, 10].

As for a sorbent, over the past 15 years the research on the properties of highly dispersed silica (HDS) has been conducted at the Pharmacology Department of Bogomolets National Medical University (Kyiv, Ukraine) together with Chuiko Institute of Surface Chemistry of the National Academy of Sciences (NAS) of Ukraine. The HDS suspension has been found to possess pronounced absorption properties and reduce the toxicity of xenobiotics with different mechanisms of toxic action and chemical structure [11].

The development of a combined antimicrobial agent with the marked antimicrobial activity and absorption properties represents the continued scientific cooperation between the Pharmacology Department of Bogomolets National Medical University and Chuiko Institute of Surface Chemistry of the NAS of Ukraine. As a result of this cooperation, the composite of HDS+PHMG-HC have been developed.

The **aim** of the work was to determine the *in vitro* antimicrobial activity of highly dispersed silica (HDS, code name CMU-212), a composite (code

name CMU-211) of HDS + PHMG-HC, and PHMG-HC polymer solution as a reference against standard test-strains.

Materials and methods

Substances. The following substances were tested in the study:

- CMU-211, which is 5 % HDS suspension modified with PHMG-HC in the ratio of 200 mg of the polymer per 1 g of silica;
- CMU-212, which is 5 % HDS suspension;
- 1 % aqueous solution of PHMG-HC.

CMU-211 and CMU-212 were obtained at Chuiko Institute of Surface Chemistry of the NAS of Ukraine. CMU-212 is 5 % stabilized suspension of highly dispersed silica (i.e., 5 g of SiO_2 in 100 g of the suspension). CMU-211 is also the same 5 % suspension of highly dispersed silica, which additionally contains PHMG-HC in the ratio of 5:1 (i.e. 5 g of SiO_2 and 1 g of PHMG-HC per 100 g of the suspension). In the ratio of 200 mg of PHMG-HC per 1 g of silica a monolayer of adsorbed polymer is formed.

Microbial strains used. To assess the antimicrobial activity of the substances tested the following microbial strains were used: *Escherichia coli* UCM B-906, *Staphylococcus aureus* UCM B-918, *Pseudomonas aeruginosa* UCM B-900, *Salmonella enterica* UCM B-921, *Klebsiella pneumonia* UCM B-920, and *Candida albicans* UCM Y-1918. These strains were obtained from the Ukrainian Collection of Microorganisms (UCM) of D. K. Zabolotny Institute of Microbiology and Virology of the NAS of Ukraine. These microorganisms are the test strains to determine the antimicrobial activity of medicines [12].

Nutrient media. The LB liquid medium (Luria-Bertani broth, Merck, Germany) was used in preparation of the initial and working suspensions of microorganisms and test substances, as well as determination of the minimum inhibitory concentrations (MIC) of the test substances. The LB solid nutrient medium (Luria-Bertani medium, Merck, Germany) in Petri dishes was used to obtain twenty-four-hour cultures of microorganisms and determine the minimum bactericidal/fungicidal concentrations (MBC/MFC) when it was inoculated with aliquots of test and control suspensions.

The study of the antimicrobial activity of the test substances. For each species of microorganisms a line of 12 test-tubes was prepared. All test-tubes were filled with 0.5 ml of the LB medium. The first test-tube of each line was filled with 0.5 ml of the working solution of the corresponding substance (CMU-211, CMU-212 or PHMG-HC), and double serial dilutions were then prepared.

Twenty-four-hour cultures of microorganisms were obtained via cultivation on a slant solid LB medium at 37 °C for 18–24 h. Initial microbial suspensions with turbidity corresponding to 0.5 McFarland standard (1.5×10^8 CFU/ml) were prepared using 24-hour cultures. Working suspensions of microorganisms were obtained after dilution of the initial suspensions in the ratio of 1:5 (v/v).

After that 0.5 ml portions of each working suspension were transferred into test-tubes containing prepared double dilution of the corresponding test substance (CMU-211, CMU-212 or PHMG-HC). Therefore, the final volume of the solution in the experimental test-tubes was up to 1 mL. The titers of *S. aureus*, *E. coli*, *P. aeruginosa*, *S. enterica*, and *K. pneumoniae* were 10^7 CFU/mL, whereas the titer of *C. albicans* was 10^6 CFU/ml, which corresponded to the experimental procedure requirements.

The effect of CMU-211 on microorganisms was studied using 15 mg/mL as the initial concentration which corresponded to 12.5 mg of HDS and 2.5 mg of PHMG-HC per 1 mL of the suspension. For CMU-212 the initial concentration was 12.5 mg/mL of A-300 HDS suspension. Ultimately, as the starting concentration of PHMG-HC 2.5 mg/mL was used.

As for CMU-211, the final concentrations of HDS and PHMG-HC in the last (12^{th}) test-tube were 6.1 μg/mL and 1.22 μg/mL, respectively. For CMU-212 the final concentration of HDS was 6.1 μg/mL, whereas the final concentration of 1.22 μg/mL was used in the PHMG-HC series.

The experimental samples were compared with the negative controls of the microbial growth using the adjustments for suspension turbidity according to the negative controls of the substance purity. For each experimental series of test-tubes, the first concentration with no visible growth of microorganisms was determined. This concentration was denoted as the *minimum inhibitory (bacteriostatic) concentration* (MIC) of the corresponding substance with respect to a particular species of microorganisms.

The next step was to determine the *minimum bactericidal concentration* (MBC) of the substances. In this regard, 200 μL portions of the suspension taken from all experimental samples with no visible growth and from all control test-tubes were inoculated on Petri dishes with the solid LB medium. After uniform distribution of each suspension on the surface of agar and its drying plates were incubated at 37 °C for 24 h in a thermostat. Then in each area of the sample application colonies formed were counted, they indicated the number of viable microorganisms in the corresponding bacterial suspensions. This parameter was expressed as colony forming units (CFU). The minimum bactericidal (fungicidal) concentration of the corresponding substance in relation to the species of microorganisms studied was determined by the first concentration, in which the growth in the microbial suspension aliquots applied on the solid medium was less than 200 CFU. The above mentioned concentration for

Table

The antimicrobial activity of the composite of highly dispersed silica (HDS) and polyhexamethylene guanidine hydrochloride (PHMG-HC), as well as their components alone in relation to the test strains of microorganisms

Species of microorganisms	HDS and PHMG-HC (CMU-211)				PHMG-HC		HDS (CMU-212)
	MIC, μg/mL		MBC, μg/mL		MIC, μg/mL	MBC, μg/mL	MIC, μg/mL
	Substance	In relation to PHMG-HC	Substance	In relation to PHMG-HC	Substance	Substance	Substance
Escherichia coli UCM B-906	117.19	19.53	234.37	39.06	19.53	19.53	>12,500
Staphylococcus aureus UCM B-918	58.6	9.77	117.19	19.53	4.88	19.53	>12,500
Pseudomonas aeruginosa UCM B-900	234.37	39.06	468.76	78.13	39.06	78.13	>12,500
Salmonella enterica UCM B-921	234.37	39.06	234.37	39.06	19.53	19.53	>12,500
Klebsiella pneumoniae UCM B-920	468.76	78.13	468.76	78.13	39.06	39.06	>12,500
Candida albicans UCM Y-1918	58.6	9.77	117.19*	19.53*	4.88	9.77*	>12,500

Note. * The minimum fungicidal concentration (MFC) is denoted. HDS = highly dispersed silica; MIC = minimum inhibitory concentration; MBC = minimum bactericidal concentration; PHMG-HC = polyhexamethylene guanidine hydrochloride.

S. aureus, *E. coli*, *P. aeruginosa*, *S. enterica*, and *K. pneumoniae* were denoted as MBC. For *C. albicans*, the appropriate term 'minimum fungicidal concentration (MFC)' was used. The cultures from the positive and negative controls of growth were assessed on the presence of the confluent growth, and the cultures from the negative controls of the medium and purity of substances were assessed on the absence of the microbial growth. If these requirements for control samples were met, the experiment was considered to be conducted appropriately.

Results and discussion

The data obtained suggest that CMU-211, CMU-212 and PHMG-HC solution had different influence on the microorganisms tested (see Tab.).

The antimicrobial activity of CMU-211 (HDS suspension modified with PHMG-HC). MICs of CMU-211 against *S. aureus* and *C. albicans* were the lowest and were equal to 48.83/9.77 μg/mL. (Hereinafter, considering the content of CMU-211 the first figure denotes the actual concentration of HDS A-300 and the second figure stands for the actual concentration of PHMG-HC in the nutrient medium). However, MIC of CMU-211 against *E. coli* was slightly higher and in numerical terms was 97.66/19.53 μg/mL. Among other representatives of *Enterobacteriaceae* family *Escherichia* had the highest sensitivity to CMU-211. However, to achieve MIC for *S. enterica* the concentration of CMU-211 needs to be two times higher (195.31/39.06 μg/mL). *K. pneumoniae* appeared to be the most resistant, and it was required at least 390.63/78.13 μg/mL of CMU-211 to inhibit its multiplication. *P. aeruginosa* was also characterized by high resistance to the substance since its MIC was the same as that of *S. enterica* and was equal to 195.31/39.06 μg/mL. Thus, CMU-211 had the most prominent inhibitory effect against *S. aureus* and *C. albicans*, while the weakest effect was on *K. pneumoniae* (see Tab.).

The assessment of MBCs showed that bacteriostatic concentration of CMU-211 against *S. enterica* and *K. pneumoniae* was also proved to be bactericidal. However, the concentrations of the substance had to be twice as high as MICs to ensure the bactericidal (fungicidal) effect on other microorganisms studied. Therefore, for CMU-211, the lowest MBCs/MFCs of 97.66/19.53 μg/mL were proven to be against *S. aureus* and *C. albicans*. On the other hand, the highest MBCs of 390.63/78.13 μg/mL were found for *K. pneumoniae* and *P. aeruginosa* (see Tab.).

The antimicrobial activity of CMU-212 (HDS suspension). The antimicrobial properties of CMU-212, a suspension of HDS A-300 and one of the components of CMU-211, were also studied. It was found that CMU-212 failed to show the antimicrobial effect on

all microorganisms tested. Application of this substance in the maximum concentration of 12.500 μg/mL did not cause growth retardation in the test strains of microorganisms in the liquid medium. Plating of microorganisms incubated with the whole range of the test concentrations in test-tubes on the solid medium proved their viability since they demonstrated a confluent growth on the surface. Hence, it was concluded that CMU-212 failed to show the antimicrobial activity against the test strains (see Tab.).

The antimicrobial activity of PHMG-HC. The data obtained showed that PHMG-HC solution had a high level of the antimicrobial activity against the test strains studied. The indicators of MIC for this substance appeared to be the lowest for *S. aureus* and *C. albicans* (4.88 μg/mL). *E. coli* and *S. enterica* were less sensitive to PHMG-HC and demonstrated no growth in the presence of 19.53 μg PHMG-HC per 1 mL. Among the representatives of the *Enterobacteriaceae* family used in the study *K. pneumoniae* showed the highest resistance since the bacteriostatic effect was obvious only when the concentration of PHMG-HC was 39.06 μg/mL. *P. aeruginosa* appeared to have the similar level of resistance. Therefore, PHMG-HC was the most active in inhibiting the growth of *E. coli* and *S. enterica*, but it was 8 times less effective against *K. pneumoniae* and *P. aeruginosa* (see Tab.).

Summarizing the results of the antimicrobial activity assessment it should be noted that CMU-211 has a high activity against *C. albicans* and *S. aureus* and a marked effect on *E. coli* and *S. enterica*. The relatively low activity of CMU-211 was reported against *K. pneumoniae* and *P. aeruginosa*, however, the effect on *P. aeruginosa* was consistent with the activity of PHMG-HC applied alone.

According to the multiplicity of difference between MICs and MBCs/MFC for individual species of microorganisms the activity of the HDS + PHMG-HC composite (i.e. CMU-211) is similar to that of PHMG-HC (see Tab.). Thus, a twofold increase in the concentration of both substances converts the bacteriostatic/fungistatic effect against *P. aeruginosa* and *C. albicans* into a bactericidal and fungicidal effect, respectively. PHMG-HC demonstrated more prominent growth-inhibiting effect against *S. aureus* (MIC of PHMG-HC was 4.88 μg/mL vs 9.77 μg/mL for CMU-211), but the MBC values were the same for both substances (19.53 μg/mL). The antimicrobial activity against *E. coli* was higher with PHMG-HC since the MBC/MIC ratio was equal to 1; however, the HDS+PHMG-HC composite gave the MBC/MIC ratio of 2. For other microorganisms, the MBC/MIC ratios were the same for both substances and were equal to 1.

As far as we know, no similar studies assessing the antimicrobial activity of the HDS + PHMG-HC composite were found in the available literature. Oulé et al. [9] studied the antimicrobial activity of PHMG-HC and showed that complete death of *E. coli* could be achieved when this substance was applied in the concentration of 0.005 %. According to Gregirchak et al. [13] MIC of PHMG-HC for *E. coli* and *S. aureus* was 19 μg/mL and 9 μg/mL, respectively, it was close to the estimates obtained in our study.

CONCLUSIONS

1. The 5 % suspension of HDS modified with PHMG-HC polymer added in the ratio of 5:1 (i.e. 200 mg of the polymer per 1 g of the suspension) developed at the Chuiko Institute of Surface Chemistry of the NAS of Ukraine, exhibits the marked antibacterial activity against gram-positive, gram-negative microorganisms, as well as *C. albicans.*

2. This HDS+PHMG-HC composite (CMU-211) has showed the highest activity against *S. aureus* and *C. albicans*. MIC and MBC/MFC are 9.77 μg/mL and 19.53 μg/mL, respectively, calculated with reference to PHMG-HC.

3. The composite has been found to have different activities against gram-positive and gram-negative bacteria. Gram-negative microorganisms, such as *E. coli*, *P. aeruginosa*, *S. enterica* and *K. pneumonia*, have been found to have slightly lower sensitivity to the composite compared to the gram-positive *S. aureus.* It is assumed that this difference may be associated with the peculiarities of the bacterial wall structure. However, these hypothesis needs further testing.

Conflict of interests: authors have no conflict of interests to declare.

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