

Antibacterial *in vitro* Study of Fe^{III}Cl-Tetraphenylporphyrin Incorporated into Poly-*N*-vinylpyrrolidone Polymeric Matrix

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The incorporating method of Fe^{III}Cl-tetraphenylporphyrin (FeCITPP) into the poly-N-vinylpyrrolidone (PVP) polymeric matrix is presented. A number of FeCITPP-PVP films with FeCITPP content varying by an order of magnitude were obtained and deposited on the inner surfaces of glass vessels. These vessels were used to simulate the surfaces of objects of veterinary and sanitary control that require periodic antibacterial treatment (disinfection). The antibacterial activity of indicated concentrations of FeCITPP-PVP against antibiotic-resistant gram-negative and gram-positive microorganisms - Escherichia coli (E. coli, strain 1257) and Staphylococcus aureus (S. aureus, strain 209 P) was demonstrated. As these microorganisms are also representatives of the most frequently encountered contaminants, we have studied the prepared bacterial suspensions from daily cultures of E. coli and S. aureus in dilutions from 10⁸ to 10⁴ CFU/mL. After that, the artificial contamination of the inner surfaces of the test objects was carried out. Antibacterial activity was determined by the degree of inhibition and was recorded visually and spectrophotometrically. The inhibitory effect on the growth of E. coli and S. aureus was directly proportional to the concentration of FeCITPP-PVP and inversely proportional to the degree of microorganism's dilution. The greatest effect (about 87% reduction in bacterial growth) was achieved by the influence of FeCITPP-PVP maximum concentration.

Keywords: Tetraphenylporphyrin, Fe^{III} complex, poly-*N*-vinylpyrrolidone, *Escherichia coli*, *Staphylococcus aureus*, antibacterial activity.

Антибактериальные исследования *in vitro* Fe^{III}Cl-тетрафенил-порфирина, включенного в полимерную матрицу поли-*N*-винилпирролидона

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В работе предложено включение $Fe^{III}Cl$ -тетрафенилпорфирина ($FeClTPP$) в полимерную пленку поли-*N*-винилпирролидона (ПВП). Получена серия пленок $FeClTPP$ -ПВП с содержанием $FeClTPP$, меняющимся на порядок, которые были нанесены на внутренние стенки стеклянных сосудов. Данные сосуды использовали для имитации поверхностей объектов ветеринарно-санитарного контроля, требующих периодической антибактериальной обработки (дезинфекции). Продемонстрирована антибактериальная активность пленок $FeClTPP$ -ПВП в отношении антибиотикорезистентных грамотрицательных и грамположительных микроорганизмов – *Escherichia coli* (*E. coli*, штамм 1257) и *Staphylococcus aureus* (*S. aureus*, штамм 209 P), которые являются представителями наиболее часто встречаемых контаминантов. Для проведения данного исследования из суточных культур *E. coli* и *S. aureus* были приготовлены бактериальные взвеси в разведениях от 10^8 до 10^4 м.к./мл. После чего была проведена искусственная контаминация внутренних поверхностей тест-объектов. Антибактериальная активность определялась по степени ингибирования и регистрировалась методом спектрофотометрии. Было показано ингибирующее действие на рост *E. coli* и *S. aureus*, прямо пропорциональное концентрации $FeClTPP$ -ПВП и обратно пропорциональное степени разведения микроорганизмов. Наибольший эффект (около 87% снижения бактериального роста) достигался при воздействии максимальной концентрации $FeClTPP$ в пленке.

Ключевые слова: Тетрафенилпорфирин, Fe^{III} комплекс, поли-*N*-винилпирролидон, *Escherichia coli*, *Staphylococcus aureus*, антибактериальная активность.

Introduction

The increase in the number of microorganisms strains with the resistance to anti-bacterial and disinfecting agents is getting more and more highly prevalent and has become an issue when treating the humans and animals diseases, and carrying out of measures for disinfection treatment of veterinary and sanitary supervision objects.^[1-8] Antimicrobial resistance poses a serious threat to human health worldwide. The solution to this problem is achieved by developing and incorporating new antibacterial drug systems that can overcome the resistibility of microorganisms. An alternative approach is the use of photodynamic (PDT) and light-independent (dark) therapy.^[1-3,9-13] Natural or synthetic chromophores^[14] and various metal complexes^[15] can act as sensitizers and photosensitizers for the formation of reactive radical particles and reactive oxygen species.

For many years, tetrapyrrole compounds, such as chlorins, phthalocyanines, porphyrins and their metal complexes have been successfully used in the field of antimicrobial therapy.^[16-18] It is known from literature sources, that metalloporphyrins have low toxicity to eukaryotic cells, which seems to be an advantage of their use both for therapeutic purposes and for conducting antibacterial treatment (disinfection) of various objects.^[1,16,19] According to works,^[16,19] the mechanism of the light-independent antibacterial action of metalloporphyrins is presumably based on their ability to inhibit some metabolic pathways, disrupt cellular

respiration, and also cause oxidative stress. These studies provide evidence that metalloporphyrins can penetrate into the bacterial cell in two ways: using heme receptors or passive diffusion through the outer membrane. Next, metalloporphyrins are incorporated into the heme binding sites of cytochromes, either directly into the periplasm (or extracellular space in Gram-positive bacteria), or after transport into the cytoplasm and export back to the periplasm using the cytochrome assembly mechanism. The incorporation of metalloporphyrins into cytochromes interrupts the transfer of electrons to oxygen, causing incomplete reduction of O_2 and the formation of reactive oxygen species (ROS).^[16,19]

However, the hydrophobicity of tetrapyrrole compounds and their high tendency to aggregate^[20] leads to the difficulty of developing drugs on their base. Nevertheless, it is possible to control the aggregation behavior of tetrapyrroles by immobilizing them on solid carriers,^[21,22] nanoparticles^[23] as well as incorporating them in biopolymer complexes and polymer matrices.^[24,25]

This paper presents the results of evaluating the antibacterial activity of a tetrapyrrole compounds group representative - $Fe^{III}Cl$ -tetraphenylporphyrin ($FeClTPP$), incorporated in the poly-*N*-vinylpyrrolidone (PVP) polymer matrix *in vitro* against gram-negative microorganisms illustrated by *Escherichia coli* usually presented in the intestines of humans and animals and gram-positive ones – illustrated by *Staphylococcus aureus* frequently founded in the human respiratory tract and on the skin. The choice of these microorganisms was made due to the fact, and as it is

known from the literature and practical data, these bacteria are one of the most common causes of antibiotic-resistant infections.^[1,26] A lot of nosocomial diseases (hospital-acquired infections) are mainly caused by these two common pathogens. Moreover, *E. coli* и *S. aureus* are widespread contaminants of many critical points in the production of pharmaceutical and food products.^[7-9]

Experimental

Fe^{III}Cl-Tetraphenylporphyrin (FeCITPP), kindly provided by colleagues from MIREA – Russian Technological University, poly-*N*-vinylpyrrolidone (PVP, 10 000 g/mol) were used. The structural formulas of these compounds are shown in Figure 1. The purity and identity of FeCITPP were confirmed by MALDI mass spectrometry on a Thermo DSQ II instrument. *N,N*-Dimethylformamide (DMF, Sigma) was subjected to double distillation.

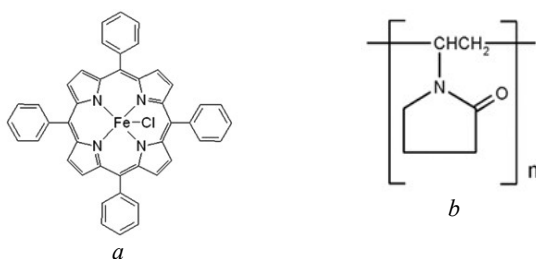


Figure 1. Structures of Fe^{III}Cl-tetraphenylporphyrin (a) and poly-*N*-vinylpyrrolidone (b).

The initial stock solution of FeCITPP with a concentration of 10⁻² mol/L was prepared by dissolving a dry sample of FeCITPP in DMF while vigorous stirring. After that a series of FeCITPP solutions in DMF with a concentration of 1, 2, 4, 6, 8, and 10 mM was obtained by dilution. Then PVP solution in distilled aqua (10 wt%) was prepared. To a series of 1 mL portions of this solution, 10 μL of FeCITPP in DMF solution was added to get final concentrations of FeCITPP of 10, 20, 40, 60, 80, and 100 μM, as well as 10 μL of pure DMF to obtain a control sample. The resulting mixtures were placed in cylindrical glass vessels with a volume of 10 mL, which were rotated in a horizontal position at a speed of 10 rpm until the mixtures were completely dry and films were obtained. The registration of electron absorption spectra (200-900 nm) of the pure FeCITPP solutions and FeCITPP in the presence of PVP solution was carried out in cuvettes with a width of 1 cm using a spectrophotometer DR/4000, Hach.

Germ cultures *Escherichia coli* (strain 1257) and *Staphylococcus aureus* (strain 209 P) were taken from the collection of cell cultures of the All-Russian Research Institute of Veterinary Sanitation, Hygiene and Ecology. For biological testing, sterile saline solution (0.9% NaCl), meat-peptone broth (MPB) and meat-peptone agar (MPA) purchased from the “SPC Khimikom” company were used, as well as the industrial turbidity standard to determine the total concentration of microorganisms (set BAK-10, Ltd. “Art-Medica”).

To obtain daily cultures *E. coli* and *S. aureus* they were reseeded in a Lamsystems laminar and further cultivated on a slanted MPA in a thermostat for 24 h at 37 °C. Suspensions of 10⁹ CFU/mL were prepared from daily cultures in sterile saline according to the turbidity standard. The obtained concentrations of suspensions were confirmed by spectrophotometry (λ = 600 nm) using a PE5400UF spectrophotometer (Ekroschem). Then, suspensions of

10⁸, 10⁷, 10⁶, 10⁵ and 10⁴ CFU/mL were prepared by sequential dilution in steps of 10 from suspensions of daily cultures of *E. coli* and *S. aureus* (10⁹ CFU/mL) using sterile saline. All dilutions were carried out in sterile tubes. To avoid impurity contamination, the tubes were sealed with sterile stoppers. To imitate a bacterial contamination of the surface of the veterinary supervision object, 5 mL of sterile MBP were placed into 5 cylindrical vessels with applied FeCITPP-PVP films with a certain content of FeCITPP, after which 50 μL of a bacterial suspension of *E. coli* and *S. aureus* of the described above dilutions were added. The vessels were closed with sterile stoppers and placed in a thermostat for 24 h at 37°C. A similar procedure was also carried out for films with other FeCITPP contents. The results obtained were taken into account by spectrophotometry method (λ = 600 nm, spectrophotometer PE5400UF). The results presented below are the average of six independent experiments.

Results and Discussion

At the initial stage of the experiment, aqueous solutions of PVP containing FeCITPP with different concentrations of 10, 20, 40, 60, 80, and 100 μM were obtained. The choice of PVP is explained by its water solubility, non-toxicity and wide application in pharmacology and medicine as a biocompatible polymer. Figure 2 shows the electronic spectra of these solutions.

The spectra (Figure 2a) show that the absorption bands of FeCITPP are broadened, which is due to the manifestation of coordination and other non-covalent interactions with polymer macromolecules and, possibly, local concentration of porphyrin molecules in the regions of binding to PVP macromolecules. At the same time, the intensity of the Soret band increases linearly with increasing concentration of FeCITPP (Figure 2b). In addition, no new bands characteristic of H- or J-aggregates of porphyrins appear in the spectra. This fact allows us to conclude that the formation of FeCITPP aggregates in aqueous solutions of PVP does not occur.^[18]

It was of interest to study the bactericidal effect of FeCITPP in combination with PVP on a solid surface. To achieve this goal, the resulting FeCITPP-PVP solutions were deposited on the inner surfaces of cylindrical glass vessels (volume of 10 mL), imitating the surfaces of veterinary and sanitary control objects. While FeCITPP-PVP was drying, a film of FeCITPP-PVP with different content of FeCITPP was formed on the treated surfaces. After that, artificial contamination of these objects with prepared suspensions of daily cultures of *E. coli* and *S. aureus* in dilutions from 10⁸ to 10⁴ CFU/mL was carried out.

The primary accounting results of the antibacterial activity were carried out by the visual registration of the turbidity of the MPB relatively to the control glass vessel, containing sterile MPB without the addition of the specimen and bacterial suspension. The increased turbidity depended on the increased intensity of microorganisms growth. A spectrophotometric study (λ = 600 nm) of the glass vessels contents was carried out to determine the inhibition degree of the microorganisms growth by FeCITPP in a polymer film. The results for different concentrations of FeCITPP and numbers of bacterial cells are shown in Figure 3.

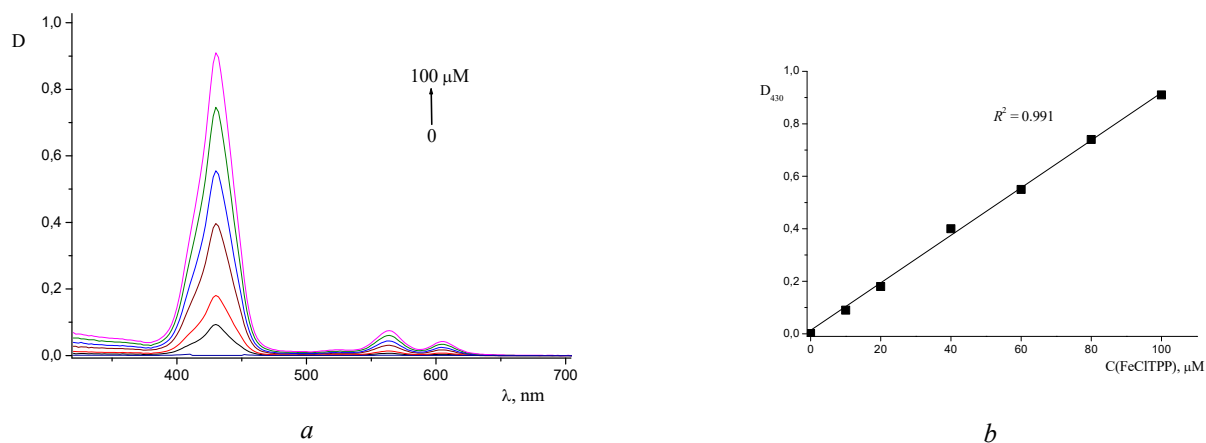


Figure 2. Electronic absorption spectra of FeCITPP (0, 10, 20, 40, 60, 80 and 100 μM) in aqueous solution of PVP (a) and a dependence of optical density on FeCITPP concentration (b).

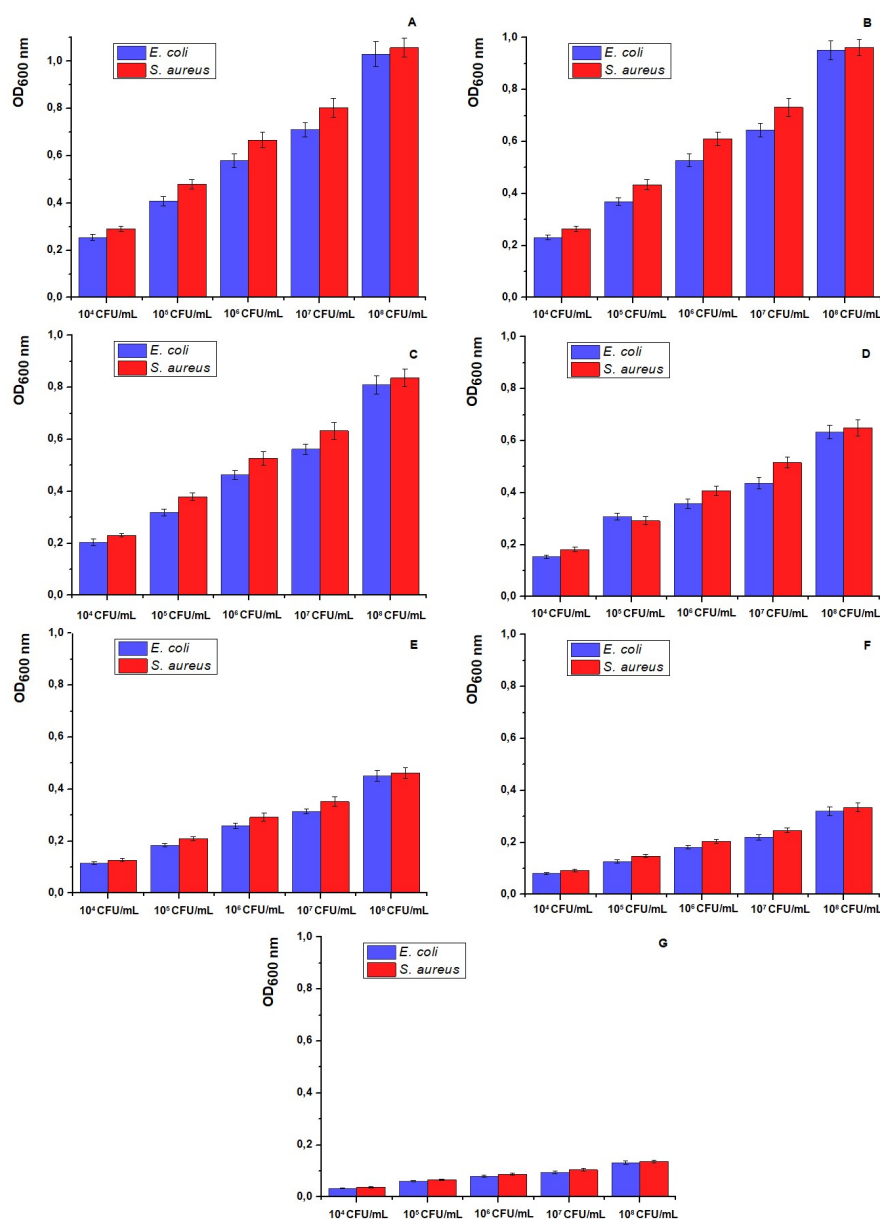


Figure 3. The inhibitory effect of PVP (a) and FeCITPP-PVP (b-g) on *E. coli* (strain 1257) and *S. aureus* (strain 209 P) with different initial content of cells. Initial concentrations of FeCITPP solutions for the FeCITPP-PVP films preparation 10 (b), 20 (c), 40 (d), 60 (e), 80 (f) and 100 μM (g).

When studying the number of cells by spectrometry, the appearance of characteristic absorption bands of porphyrin within 24 h was not noticed. It can be assumed that FeCITPP molecules fixed in the polymer matrix act as catalysts for reactive oxygen species and their bactericidal effect^[16,19] is carried out in the near-wall layer. The mechanism of oxygen activation is associated with the transfer of an electron from an iron(II) cation to an oxygen molecule. The resulting superoxide anion radical is further converted into other reactive oxygen species. Thus, the presence of reducing substances is required for the formation (regeneration) of iron(II) from iron(III). It is most likely that some components of the MPB broth exhibit restorative properties, for example, aminoacids and ascorbic acid.

According to the data obtained, we can state that the FeCITPP-PVP complex deposited on the glass surface has a comparable inhibitory effect on the growth of *E. coli* and *S. aureus*, which is directly proportional to the concentration of the drug and inversely proportional to the degree of dilution of the bacterial suspension (Figure 4).

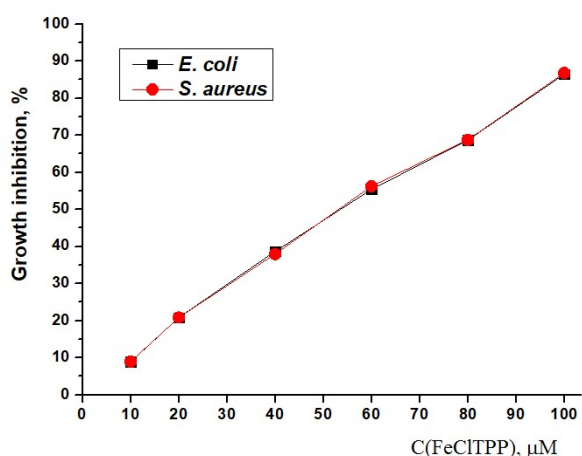


Figure 4. The relationship between FeCITPP initial concentrations and the inhibitory effect on *E. coli* and *S. aureus*.

In the case of a minimum drug concentration exposure (10 μM), the degree of growth inhibition was insignificant and amounted to 8.9 and 9.0%, respectively. Thus, the maximum initial concentration of FeCITPP (100 μM) reduces the growth of microorganisms on the treated surfaces by 86.5% and 86.8% for *E. coli* and *S. aureus*, respectively.

Conclusions

Based on the presented data, it may be said that that it is possible to solubilize FeCITPP in a non-aggregated form in an aqueous solution of PVP. Films obtained from these solutions can be deposited on solid surfaces. Molecules of FeCITPP in a PVP film have a significant inhibitory effect on the growth of *E. coli* and *S. aureus*. The effect of FeCITPP depends on the initial number of bacterial cells and the content of the metal complex in the polymer matrix. This study may be useful in the development of new drugs for the disinfection of veterinary and sanitary supervision

objects and control of antibiotic-resistant gram-negative and gram-positive microorganisms.

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