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Dimensional and spectral characteristics of daunomycin/erythromycin complexes with dexrtan-stabilized silver nanoparticles

Albert I. Kipper,* Anna V. Plushenko, Alexander A. Kutin and Irina S. Garkushina

Institute of Macromolecular Compounds, Branch of B. P. Konstantinov Petersburg Nuclear Physics Institute of National Research Centre 'Kurchatov Institute', 199004, St. Petersburg, Russian Federation. Fax: +7 812 328 6869; e-mail: kipper@imc.macro.ru

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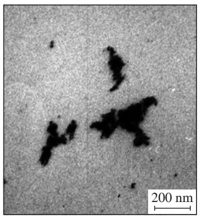
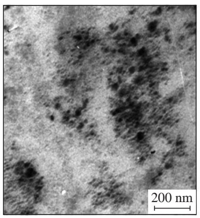
The conditions for the production and stabilization of silver nanoparticles with dextran with the formation of complexes with daunomycin and erythromycin antibiotics were determined. Using UV-visible spectroscopy and dynamic light scattering methods, the spectral and dimensional characteristics of the synthesized systems were established.



(Dextran + Ag) + Daunomycin



(Daunomycin + Dextran) + Ag

Keywords: daunomycin, erythromycin, dextran, modification of nanoparticles, silver, UV and visible spectra, dynamic light scattering, nanocomplexes.

Antibiotics are widely used in medical practice to eliminate pathogenic microorganisms and the consequences of their exposure in the form of various diseases.[1,2] However, the practical use of antibiotics is often limited by their toxicity and the development of resistance of microorganisms to the antibacterial drugs used. Therefore, when developing new drugs, much attention is paid to solving these problems. One of the approaches in this direction is the complexation of an antibiotic with various nanoparticles of biogenic elements and biocompatible polymers.[3–6] Antibiotic daunomycin (DM) has antibacterial activity and antitumor effects and is used in cancer chemotherapy.[7,8] Erythromycin (EM) has significant biological activity against intracellular infections, it does not cause serious adverse reactions, and is often used as an alternative drug for patients with an allergic reaction to other antibiotics. On the other hand, silver nanoparticles (AgNPs) exhibit antibacterial activity and are capable of increasing the effectiveness of anti-carcinogenic drugs.[7,8] However, AgNPs would easily aggregate and precipitate. One of the ways to obtain aggregation-stable dispersions of silver NPs is to synthesize them in the presence of polymers of various natures as a stabilizer.[9,10]

In this work involving DM and EM antibiotics, natural polymer dextran (Dex) was used as a stabilizer for AgNPs. Solutions of Dex are often used for medical purposes as multifunctional plasma replacement solutions and for normalizing blood counts (in particular, dextran reduces the aggregation of blood elements).[11] The purpose of this work is to synthesize and to study the size and spectral characteristics of supramolecular complexes of AgNP–DM/EM–Dex types.

The AgNPs were obtained in the course of reduction of silver nitrate with sodium borohydride in the presence of a polymer stabilizer at 4 °C and atmospheric pressure. Dextran samples with molecular weights (MWs) of 15000, 40000, 70000, and 110000 (hereinafter referred to as Dex15, Dex40, Dex70, and Dex110, respectively) were used. Complexes of dextran-stabilized AgNPs with antibiotics were prepared in two ways. The first method involved the synthesis of AgNPs in the presence of a mixture of dextran and antibiotic; such complexes are thereafter assigned as (/Dex + antibiotic/+ Ag). The second method involved the synthesis of AgNPs in the presence of dextran, and the antibiotic was added on the next day; such complexes are assigned as (/Ag + Dex/+ antibiotic).[†]

The absorption spectra of solutions of the obtained DM complexes obtained by the second method had an absorption band in the region $\lambda \sim 400$ nm, corresponding to the surface plasmon resonance (SPR) of the resulting AgNPs.[‡] The use of Dex of various molecular weights in the range $(15–110) \times 10^3$ as stabilizers for AgNPs was practically not accompanied by a change in the position of this SPR absorption band (Figure 1).

Measurements of the hydrodynamic radius (R_h) of the nanocomplex (NPs–Ag + Dex) for different MW Dex using the DLS method showed that the dimensions of the complex starting from Dex 40 practically did not change (Figure 2).[§] It can be assumed that the higher R_h value during Dex15 stabilization is due to the aggregation of the resulting AgNPs.

[†] The concentrations of the components were as follows: AgNPs, 0.005 wt%; polymer, 0.1 wt%; and antibiotic, 0.005 wt%. The sedimentation and aggregation stability of aqueous dispersions of AgNPs stabilized with Dex of different MWs was studied. With increasing the MW of Dex, the color of transparent solutions changed from dark brown to light yellow and was stable for ~30 days. In the absence of Dex, a precipitate formed already on the second day after the synthesis.

[‡] The optical density of the obtained dispersed solutions was measured using a Shimadzu 1900i spectrophotometer (Japan) in the wavelength range of 220–900 nm in 1 × 1 cm quartz cuvettes.

[§] The values of hydrodynamic radii R_h for the nanostructures were obtained by dynamic light scattering (DLS) using the Photocor Complex setup with a light source He–Ne laser with a wavelength of $\lambda = 632.8$ nm and a power of ~20 mV and a Photocor-FC correlator with 288 channels (Antex, Russia). The results of recording and the correlation functions of scattered light intensity fluctuations were processed using the DynaLS program (Helios, Russia).

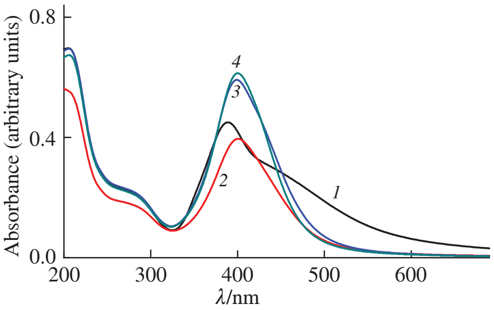


Figure 1 Absorption spectra of dispersions of complexes (*1*) (/Ag + Dex15-20/+ DM), (*2*) (/Ag + Dex40/+ DM), (*3*) (/Ag + Dex70/+ DM), and (*4*) (/Ag + Dex110/+ DM) synthesized by the second method.

In this case the formation of a continuous ‘shell’ of AgNPs did not occur, which caused the aggregation of these dispersions. With an increase in the MW of Dex, the situation was improved: already with Dex40, the solution became noticeably lighter, and with a further increase in the MW of Dex, the solution became light and transparent, and its appearance did not change for 30 days.

As for ternary systems, the first synthesis method toward (/Dex + DM/+ Ag)AgNPs afforded sedimentation-stable dark brown dispersions for Dex samples with MWs of all the range studied, and their color did not change within 22 days. With the employment of the second method toward (/Ag + Dex/+ DM), dark solution was formed only in the case of Dex15. At higher MWs of the Dex samples, all the systems obtained were transparent yellowish solutions. Apparently, in the ternary system (/Dex + DM/+ Ag) the initial binding of Dex to DM led to a decrease in the number of degrees of freedom of the Dex chains, an increase in their rigidity, and, as a consequence, to a decrease in the ability of the (Dex + DM) system to envelop AgNPs. Stabilization of the resulting AgNPs is carried out by a small part of the near-surface layer of the complex (Dex + DM). This stabilization left part of the surface of silver NPs free from the polymer, which led to their aggregation with each other and manifested itself in the dark color of the solutions. The second synthesis method led to the production of dark solutions only when using the low molecular weight stabilizer, Dex15. At the same time, the sizes of the nanocomplex coincided with the sizes of the nanocomplex obtained by the first method with Dex of the same MW (Figure 3). An increase in the MW of Dex to 40 000 did not lead to stabilization of the resulting silver nanoparticles, and only when using Dex with MW > 40 000 the stabilization began at an early stage of the formation of AgNPs and was not accompanied by aggregation of the resulting AgNPs (see Figure 3).

The TEM data for ternary systems (Dex/DM/Ag), when the complexation was carried out using both methods with Dex40, completely correlates with the DLS data. In TEM photographs for the first synthesis method, a significant aggregation of the resulting NPs (/Dex + DM/+ Ag) is observed [Figure 4(*a*)]. In the case of the second synthesis method, the aggregation does not stop and does not lead to the formation of large aggregates, so the formation of clusters of small NPs (/Ag + Dex/+ DM) and Dex macromolecules occurs [Figure 4(*b*)].

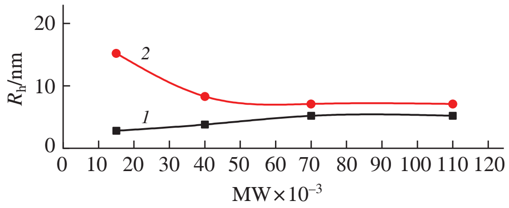


Figure 2 Dependence of the hydrodynamic radius (*1*) R_h Dex and (2) (Dex + Ag) on the molecular weight of Dex.

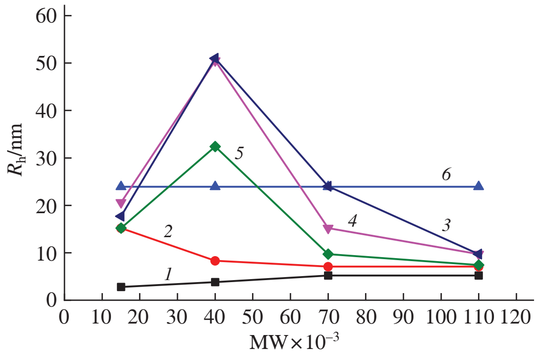


Figure 3 Dependence of hydrodynamic radii (R_h) on the MW of Dex (c = 2% in water): (*1*) Dex, (*2*) (Dex + Ag), (*3*) (/Dex + DM/+ Ag), (*4*) (/Ag + Dex/+ DM), (*5*) (/Dex + EM /+ Ag), and (*6*) (/Ag + Dex/+ EM).

Complexation in the Ag/Dex/EM system was also carried out in two ways using Dex of different MWs. With the using of the first method, complexes (/Dex15-20 + EM/+ Ag), (/Dex40 + EM/+ Ag), (/Dex70 + EM/+ Ag), (/Dex110 + EM/+ Ag) were prepared; with the use of the second method, (/Ag + Dex15-20/ + EM), (/Ag + Dex40/+ EM), (/Ag + Dex70/+ EM) and (/Ag + Dex110/+ EM) were obtained. The incorporation of EM into dextran-stabilized AgNP dispersions in the course of the both methods did not affect the sedimentation stability of the resulting systems. They appeared as transparent solutions, the color of which in both cases changed with increasing MM of Dex from dark brown to light yellow and persisted during observation for about a month, indicating a stable stabilization of AgNPs by the system (Dex:EM).

Analysis of the absorption spectra showed that there was no difference between the spectra of the systems obtained by method 1 and method 2. The magnitude of the hyperchromic effect for these systems was also maintained.

The dimensional characteristics of dispersed solutions of Ag/Dex/EM complexes stabilized by Dex of various molecular weights were obtained by the DLS method. Figure 3 shows that the dependences of the hydrodynamic sizes on the MW of Dex for the Ag/Dex/EM complexes synthesized by methods 1 and 2 were similar; *i.e.*, the presence of EM did not principally affect (in distinction to DM) the process of stabilization of AgNPs by Dex macromolecules. In fact, the dependence $R_h = f(\mathrm{MW}_{\mathrm{Dex}})$ for the system with EM repeated the dependence for the system with DM (method 2), which indicates the similarity of the stabilization mechanisms in these cases.

In summary, the conditions for the complex formation of the daunomycin (DM) and erythromycin (EM) antibiotics with silver nanoparticles and the biopolymer dextran were determined by two synthesis methods. The dependences of the sizes of nanocomplexes with DM and EM on the MW of dextran in the

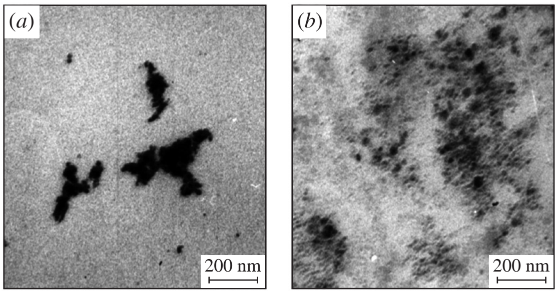


Figure 4 TEM photographs for ternary systems (Dex/DM/Ag): (*a*) (/Dex40 + DM/+ Ag) obtained by the first method and (*b*) (/Ag + Dex40/+ DM) obtained by the second method.

range (15–110) × 10^3, obtained with preliminary stabilization of AgNPs with dextran, have a similar character in the size range of 5–50 nm. In this case, for complexes with EM obtained by synthesis of the complex without preliminary preparation and stabilization of silver nanoparticles, the maximum size decreases to 30 nm, but the nature of the dependence remains the same. The obtained results may be useful in the future to improve the efficiency and sustainability of DM and EM used in therapy.

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