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EXPERIMENTAL APPROACH TO THE CREATION OF EFFICIENT MULTICOMPONENT NANOCOMPOSITES FOR ANTITUMOR THERAPY

UDC 539

Water-soluble polymers with special characteristics can be used as carriers in which the active ingredients are entrapped, encapsulated, adsorbed, or chemically attached. The understanding of the processes occurring during the formation of multicomponent nanosystems is the urgent task for the synthesis of antitumor nanocomposites. Gold nanoparticles (AuNPs), photosensitizer Chlorine e6 (Ce6), and Doxorubicin (Dox) are currently used for the photodynamic therapy and chemotherapy. We have been focused on the study of three-component nanosystems Polymer/AuNPs/Ce6, and four-component nanosystems Polymer/AuNPs/Ce6/Dox at physiological temperatures (37 °C). The star-like copolymer with Dextran core and grafted Polyacrylamide chains in nonionic and anionic forms are used as a matrix for the synthesis of nanocomposites. The nanosystems are characterized by the dynamic light scattering and transmission electron microscopy. The increasing of the aggregation processes for the four-component nanosystem Polymer/AuNPs/Ce6/Dox in comparison with the three-component one Polymer/AuNPs/Ce6 is registered. These nanosystems are tested in vitro against the subline of breast carcinoma MCF-7/S – sensitive to cytostatics. It is demonstrated that the increase of the aggregation process occurring in four-component systems leads to the loss of the antitumor activity of multicomponent drugs.

K e y w o r d s: polymer nanocarrier, gold nanoparticles, Chlorine e6, Doxorubicin, antitumor therapy.

1. Introduction

Over the past few decades, the drug delivery area has shown that nanoscale drug delivery systems offer an opportunity to achieve a more efficient drug action and minimize side effects [1].

Nanotechnology represents a strategic tool for the pharmaceutical industry and provides the improved stability and absorption of drugs [2]. Nanostructures can protect drugs from the hydrolytic and enzymatic degradations. They also prevent drugs from first-pass metabolism and increase the blood residence time. They can penetrate tissues efficiently due to their reduced size [3]. Drugs, which are water-insoluble and unstable in the biological environment, may be delivered properly with nanotechnology [4]. However, despite all possible advantages of nanosystems, they have some practical problems caused by possible aggregation processes, aging processes, *etc.*

Water-soluble polymers with special characteristics in a soluble state can be promising nanocarri-

ers for different nano-sized objects. These polymeric nanocarriers are generated to achieve the controlled drug release and targeting. Being biocompatible, they can be used therapeutically as adjuvant in vaccines or drug carriers in which the active ingredient is dissolved, entrapped, encapsulated, adsorbed or chemically attached [5].

Nanotechnology provides the opportunity to create novel multicomponent drug delivery systems, consisting of a few components, for example, metal nanoparticles (NPs), a photosensitizer, and anticancer substances. These components can be incorporated into the polymeric nanocarrier simultaneously. Polymeric nanocarriers are interesting options for the controlled drug delivery and drug targeting. However, the characteristics of nanosystems and their behavior should be fully understood before using in medicine and human health products.

The modern era of biological applications of metal nanoparticles was started in 1970, when Faulk and Taylor introduced the immunogold staining procedure [6, 7]. Gold nanoparticles can be used in almost all medical applications: diagnostics, therapy, prevention, and hygiene. The applications of AuNPs are based on their unique physical and chemical properties. In particular, the optical properties of AuNPs are determined by their plasmon resonance, which is associated with the collective excitation of conduction electrons, and is localized in the broad region from the visible to the infrared region depending on the particle size, shape, and structure [8]. The AuNPs have been used to deliver photosensitizer agents for the photodynamic therapy (PDT) of cancer. The gold surface enhances the singlet oxygen generation. AuNPs significantly increase the efficiency of traditional photosensitisers for both cancer therapies *in vitro* and *in vivo* [9].

Our recent study has proved that water-soluble star-like copolymers are efficient matrices for the synthesis of metal nanoparticles *in situ* [10] and can be a promising nanocarrier for the delivery of drugs. It was shown that star-like polymers are much more efficient for the stable nanosystem synthesis in comparison with their linear analog. It was clearly demonstrated that the water-soluble star-like copolymer with Dextran core and grafted poly-N-isopropylacrylamide chains loaded by Doxorubicin (Dox) sharply decreases the viability of HeLa cells at low concentrations (1.5–6 $\mu g \cdot mL^{-1}$) [11]. This result indicates the importance of Dextran-graft-PNIPAM copolymer as a universal platform for the drug delivery, and, in particular, the huge potential of Dextran-PNIPAM + Dox nanosystem as novel anticancer agents. It was shown the polymer Dextran-graft-(Polyacrylamide-co-Polyacrylic acid) loaded with cisplatin causes the cytotoxic effect in cell lines at 10 g/mL. The data of the cytotoxic studies of the nanosystem Dextran-graft-(Polyacrylamide-co-Polyacrylic acid)/Silver Nanoparticles indicate that nanosilver induces the toxicity in cells. However, when the copolymers were conjugated to both nanosilver and Cisplatin, such a nanosystem displayed a less cytotoxic effect compared to the conjugates of Dextran-graft-polyacrylamide and Cisplatin [12]. Such effect was caused by the aggregation in a multicomponent system [13].

It was reported that the *in vitro* experiments with a nanocomposite consisting of gold nanoparticles and photosensitizer Ce6 into a dextran-graft-polyacrylamide matrix demonstrated the twofold increase of the photodynamic efficacy compared to the free photosensitizer [14].

The aim of our present study is to study the processes occurring in the three-component nanosystem polymer/AuNPs/Ce6 and the four-component nanosystem polymer/AuNPs/Ce6/Dox at a physiological temperature of 37 °C. We have focused on the prediction of the antitumor efficacy of the multicomponent nanosystems prepared into polymer nanocarriers of various chemical nature.

2. Materials and Methods

2.1. Reagents

Tetrachloroauric acid and sodium borohydride ($NaBH_4$) were purchased from Sigma-Aldrich (USA) and used without a further purification. Hank's balanced salt solution (HBSS) and a photosensitizer Chlorin e6 (Ce6) were obtained, respectively, from Sigma-Aldrich (USA) and Santa Cruz Biotechnology (USA). Doxorubicin hydrochloride (Dox) was purchased from Sigma-Aldrich (USA). Dimethyl sulfoxide (DMSO) was obtained from Serva (Germany).

2.2. Polymeric nanocarrier

Copolymer dextran-graft-polyacrylamide (D-*g*-PAA) with dextran core ($M_w = 70 \times 10^5$ g/mol) and five grafted PAA chains in nonionic and anionic forms

were used as a polymer matrix for the synthesis of gold nanoparticles (AuNPs) and then for the fabrication of multicomponent nanosystems loaded by AuNPs, photosensitizer Ce6, and Dox. The synthesis, molecular parameters, and peculiarities of the macromolecular structure of star-like copolymer D-g-PAA were discussed in details in [15]. The average molecular weight of D-g-PAA (M_w) was equal to 2.15×10^6 g/mol, radius of gyration (R_g) = 85 nm, and polydispersity (M_w/M_n) = 1.75. The anionic form of this copolymer was obtained via alkaline hydrolysis of the initial D-g-PAA copolymer by treating with a NaOH solution for 30 min using sodium hydroxide. The fraction of carboxylate groups evaluated by the potentiometric titration was equal to approximately 37% [15]. The copolymer was purified, freeze-dried, and kept under vacuum for preventing it from the further hydrolysis. The copolymer in the anionic form was designed as D-g-PAAan.

2.3. Synthesis of gold nanoparticles

AuNPs were synthesized by the chemical reduction of an Au precursor (tetrachloroauric acid). The synthesized copolymer was thought to be a matrix capable to act as a nucleating, capping, and stabilizing agent simultaneously. A 0.05 ml aqueous tetrachloroauric acid solution (C = 0.1 M) was added to a 1 mL of aqueous polymer solution ($C = 1 \times 10^{-3}$ g/mL) and stirred for 20 min. Then, 0.1 mL of an aqueous $NaBH_4$ solution (0.1 M) was added. The final solution was stirred for 30 min. It was ruby red in color; thus, the formation of AuNPs was indicated. The reduction process was performed at $T = 25°$ C.

2.4. Synthesis of the nanosystem polymer/AuNPs/Ce6

A stock solution of Ce6 (0.182 mg/mL) was prepared in DMSO. Then 0.55 mL of a photosensitizer Ce6 solution was mixed with 0.27 mL of distilled water. Finally, this mixture was added to 1.15 mL of the polymer/AuNPs system under a constant stirring.

2.5. Synthesis of the nanosystem polymer/AuNPs/Ce6/Dox

0.27 mL Dox (0.147 mg/mL) and 0.55 mL Ce6 (0.182 mg/mL) solutions were added to 1.15 ml of the nanosystem Polymer/AuNPs under a constant stirring.

2.6. Transmission electron microscopy (TEM)

For the sample preparation, 400 mesh Cu grids with a plane carbon film were rendered hydrophilic by a glow discharge treatment (Elmo, Cordouan Technologies, Bordeaux, France). A 5 μl drop was deposited and let adsorbed for 1 min. Then the excess of the solution was removed with a piece of filter paper. The observations of the AgNPs were carried out employing two TEMs, Tecnai G2 or CM12 (FEI, Eindhoven, Netherlands), and the images were acquired with a ssCCD Eagle camera on the Tecnai and a Megaview SIS Camera on the CM12.

2.7. Dynamic Light Scattering (DLS)

DLS measurements were carried out using a Zetasizer Nano ZS90 (Malvern Instruments, UK). The apparatus contains a 4-mW He–Ne laser with a wavelength of 632.8 nm, and the scattered light is detected at an angle of 173° (back scattering). The nanosystems were studied at 37 °C. The temperature point was held for 5 min before measurements to equilibrate the sample. At least 10 correlations were treated by the CONTIN algorithm [16] that is known to be reliable for complicated systems [17] to get hydrodynamic diameter (DH) distributions.

2.8. In vitro study of the efficiency of nanosystems on malignant cells

Subline of breast carcinoma MCF-7/S – sensitive to cytostatics, was obtained from the culture bank of R.E. Kavetsky Institute for Experimental Pathology, Oncology and Radiobiology of the NAS of Ukraine. Cells were maintained in RPMI-1640 medium containing 10% fetal bovine serum at 37 °C in 95% air and 5% carbon dioxide (CO_2).

Cell suspensions in Hank's balanced salt solution were prepared from a culture of the malignant cell lines in a log phase of growth. The cells were incubated at 37 °C with the nanocomposite for 1.5 h. Then the cells were washed twice with fresh Hank's solution and were irradiated with red laser light (λ = 658 nm). The power density of a laser was equal to 1.1 mW/cm^2, and the dose was 1B J/cm^2. After the irradiation, the cells were placed to a growth medium and incubated at 37 °C for 18 h to complete the apoptosis process. The viability of cells was estimated by using the trypan blue dye exclusion test.

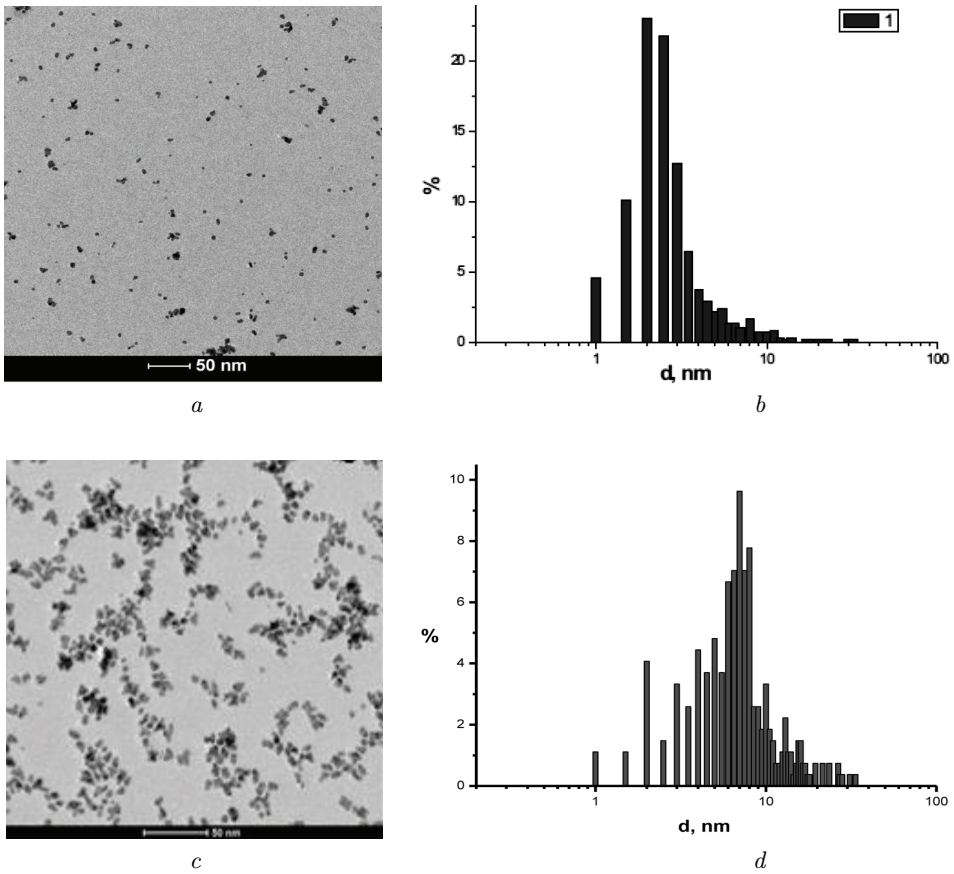


Fig. 1. TEM image of the nanoparticle size distribution for D-*g*-PAA (*a, b*) and D-*g*-PAAan (*c, d*)

The evaluation of the dark cytotoxicity of nanocomposites was determined by using the MTT test.

3. Results and Discussion

As was mentioned above, the nanocomposite D70-*g*-PAAan/AuNPs/Ce6 revealed a high photodynamic efficiency for malignant cell line MT-4 [14], and the high efficacy of star-like copolymer D70-*g*-PAAan as a nanocarrier for anticancer drug Cisplatin was demonstrated in [12].

Thus, the idea was to create a nanocomposite for the complex photodynamic and chemical therapy, namely, to synthesize a polymer-based nanocomposite in nonionic and anionic polymer nanocarriers. The both polymers were loaded by AuNPs, photosensitizer Ce6, and anticancer drugs Dox simultaneously. However, it is difficult to predict the behavior of multicomponent nanosystems, because the adding of any additional component or some temperature changes can provoke the aggregation. It can lead to the loss of a biological activity of the nanocomposite [18].

So, the aim of the present study was to analyze the behavior of multicomponent nanosystems at the physiological temperature (37 °C).

Multicomponent nanosystems containing Ce6 and Dox were prepared with the use of Au sol synthesized in the solution of both polymers.

TEM images of AuNPs synthesized in the solution of D-*g*-PAA and D-*g*-PAAan are represented in Fig. 1. It is seen that sols synthesized in nonionic and anionic polymer matrices differ in the size characteristics of AuNPs. The nanosystem obtained in the nonionic polymer matrix contains individual nanoparticles of 1–10 nm in size (Fig. 1, *a, b*) and some clusters of nanoparticles. It should be noted that the size

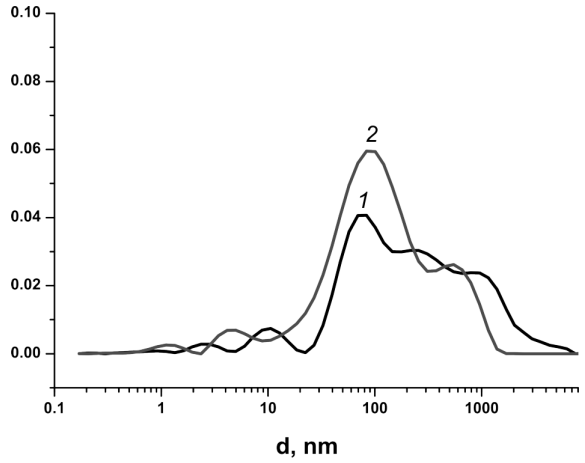


Fig. 2. Dependence of the normalized scattering intensity on the hydrodynamic radius of a scattering object for the nanosystems D-*g*-PAA/AuNPs/Ce6 (*1*) and D-*g*-PAA/AuNPs/Ce6/Dox (*2*) at 37 °C

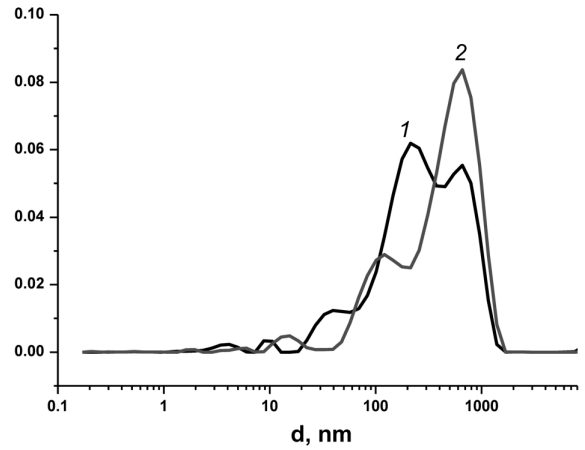


Fig. 3. Dependence of normalized scattering intensity on the hydrodynamic radius of a scattering object for the nanosystems D-*g*-PAAan/AuNPs/Ce6 (*1*) and D-*g*-PAAan/AuNPs/Ce6/Dox (*2*) at 37 °C

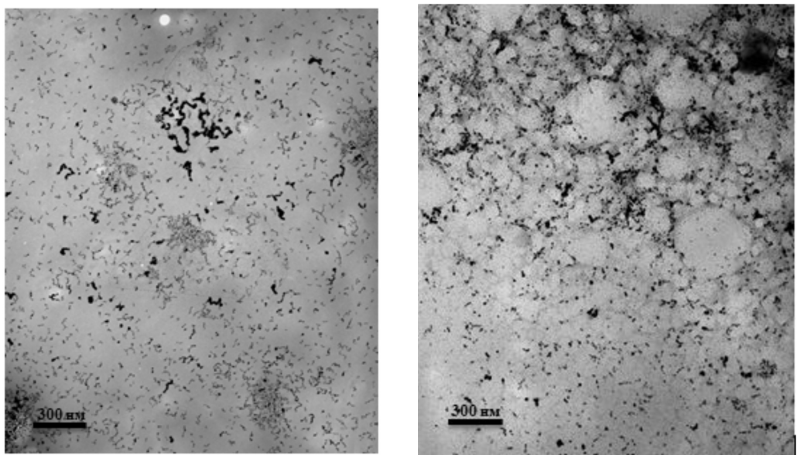
of nanoclusters corresponds to the size of individual polymer molecules in a solution (50–60 nm). The well-defined clusters are not observed for sol synthesized in the anionic polymer solution (Fig. 1, *c, d*). AuNPs prepared into D-*g*-PAAan solutions are of 1–12 nm in size. This nanosystem is less monodispersed in comparison with the previous one mentioned above.

The cause for the differences in the sols synthesized in the solutions of nonionic and anionic polymers may be found in the chemical nature of the polymer matrices. The interaction of an Au precursor with the anionic polymer matrix takes place with both carbamide (as in nonionic polymers) and carboxylate groups. Moreover, the interactions have different mechanisms: the ion-dipole interaction in the first case and the electrostatic one in the second case.

DLS was used to study the processes occurring in the multicomponent nanosystems at 37 °C. For the correct DLS result analysis, author's program for the data treatment was used [19]. The size distributions of scattering nanoobjects for the three-component nanosystem polymer/AuNPs/Ce6 and for the four-component nanosystem polymer/AuNPs/Ce6/Dox are shown in Fig. 2 for the nonionic polymer matrix and in Fig. 3 for the anionic one.

For the three-component nanosystem polymer/AuNPs/Ce6 at 37 °C (Figs. 2 and 3; curves *1*), DLS revealed several types of scattering nanoobjects in both nonionic and anionic polymer nanocarriers. The first maximum corresponds to AgNPs of about 2–10 nm in size. It is known that the scattering intensity of particles smaller than 10 nm is drastically lower in comparison with larger objects [20]. The second maximum can be attributed to the individual macromolecules of 60–70 nm in size with incorporated AgNPs. The third, fourth, and fifth maxima revealed the presence of various aggregates of macromolecules with AuNPs inside. The sizes of those nanoobjects are equal to 110-120 nm and 800–1000 nm, correspondingly. According to the normalized scattering intensity, the aggregation is more intense for the nanosystem synthesized in the anionic polymer. The analysis of the normalized scattering intensity for four-component nanosystems synthesized in the nonionic anionic polymer allows us to conclude that the four-component nanosystem in the anionic matrix provokes the formation of large aggregates, which can lead to the loss of a biological activity.

For the four-component nanosystem Polymer/AuNPs/Ce6/Dox at 37 °C (Figs. 2 and 3, curves *2*), AuNPs of abour 10 nm in size, the aggregates of 100–200 nm and 700–800 nm are observed. The individual macromolecules as for three-component nanosystems are not registered. Obviously, the drastic increase of the amount of big aggregates (70–800 nm) in these nanosystems compared to ones described above is a result of the additional component incorporated into the macromolecule of the polymer. This leads to a further change in the hydrophobic-hydrophilic bal-



a *b*

Fig. 4. TEM image of the nanosystems: Polymer/AuNPs/Ce6 (*a*); Polymer/AuNPs/ Ce6/Dox (*b*)

ance of the macromolecule. Macromolecules becomes more hydrophobic, since hydrophilic acrylamide and carboxylate groups are blocked both by Ce6 and Dox.

Thus, the increase of the aggregation ability in the four-component nanosystem in comparison with three-component one is evident. Figure 4, *a, b* presents TEM images for the three- and four-component nanosystems. These data confirm the results of DLS data analysis concerning the increase of the aggregation with the addition of Dox to the nanosystem polymer/AuNPs/Ce6.

Polymer/AuNP/Ce6 and polymer/AuNPs/Ce6/Dox nanosystems were tested for the PDT and dark cytotoxicity on MCF-7/S breast cancer cells. The compositions of the tested nanosystems are shown in Table. Nanocomposite 1 – D-*g*-PAA/AuNPs/Ce6; Nanocomposite 2 – D-*g*-PAA/AuNPs/Ce6/Dox; Nanocomposite 3 – D-*g*-PAAan/AuNPs/Ce6; Nanocomposite 4 – D-*g*-PAAan/AuNPs/Ce6/Dox were presynthesized and kept in a refrigerator.

In the "control" experiment, the cancer cells were subjected to the same manipulations, but without the addition of nanocomposites. It was shown that MCF-7/S cells were not sensitive to nanocomposites 1–4 without external irradiation (Fig. 5, black bars). The "dark" measurements demonstrated the same results on the survival of cells being incubated with the addition of the studied nanocomposites and in the "control" experiment.

A significant increase in the toxic properties of three-component nanocomposite 1 and nanocomposite 3 was registered after PDT (Fig. 5, gray bars). Nanocomposite 1 and nanocomposite 3 caused 72.8 and 68.4% cell deaths after the laser irradiation. However, the drastic decrease in the efficiency

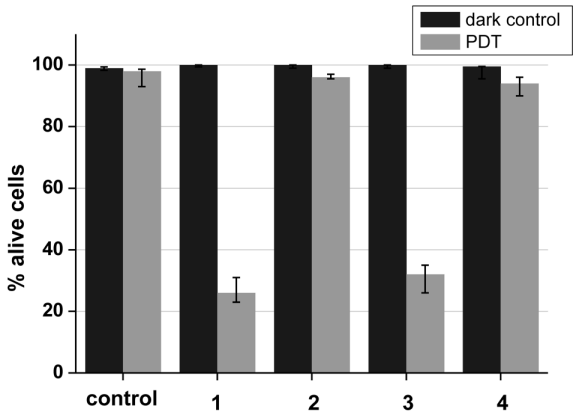


Fig. 5. The survival of MCF-7/S cells after the treatment with nanocomposites 1–4 and in the control experiment (black – "dark" measures, gray – after PDT)

Composition of the nanocomposites used for *in vitro* tests on MCF-7/S breast cancer cells

Sample	C_{polymer}, mkg/mL	C_{AuNPs}, mkg/mL	C_{Ce6}, mkg/mL	C_{Dox}, mkg/mL
Nanocomposite 1	508	500	50	–
Nanocomposite 2	508	500	50	20
Nanocomposite 3	508	500	50	–
Nanocomposite 4	508	500	50	20

of four-component nanocomposite 2 and nanocomposite 4 compared to three-component nanocomposite 1 may be a result of the increased aggregation in the nanosystems, as was demonstrated above.

Similar effects of decreasing the efficiency of polymer nanosystems loaded with active components toward a damage of cancer cells were revealed, when the number of these components increased [12, 18]. As was reported in [12], the water-soluble polymer nanocarriers such as dextran-graft-(polyacrylamide-co-polyacrylic acid) loaded with chemotherapeutic substances Cisplatin demonstrated a high toxicity to cancer cells. However, when the copolymers were conjugated with both AgNPs and Cisplatin, the three-component nanosystem showed a lower cytotoxic effect. As was shown, this effect was caused also by the aggregation in the multicomponent system.

4. Conclusions

The processes occurring during the formation of multicomponent nanosystems containing gold nanoparticles (AuNPs), photosensitizer Chlorine e6 (Ce6) and Doxorubicin (Dox) loaded into nonionic and anionic polymer nanocarriers revealed an increase in the aggregation for the four-component nanosystem in comparison with the three-component one.

These nanosystems are tested *in vitro* against the subline of breast carcinoma MCF-7/S – sensitive to cytostatics. It is demonstrated that an increase in the aggregation occurring in four-component systems leaded to the loss of the antitumor activity of multicomponent drugs. Thus, the four-component polymer/AuNPs/Ce6/Dox nanosystem cannot be recommended for *in vivo* antitumor efficacy tests.

This publication is supported in part by the Ministry of Education and Science of Ukraine: joint Ukrainian–Belarussian research and development projects "Design and physico-chemical properties of novel multicomponent nanosystems for the treatment and diagnostics of solid tumors" M/110 (2019-2020).

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Received 18.03.20

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ЕКСПЕРИМЕНТАЛЬНИЙ ПІДХІД
ДО СТВОРЕННЯ ЕФЕКТИВНОГО
БАГАТОКОМПОНЕНТНОГО НАНОКОМПОЗИТА
ДЛЯ ПРОТИПУХЛИННОЇ ТЕРАПІЇ

Р е з ю м е

Водорозчинні полімери з особливими характеристиками можуть використовуватися в ролі носіїв для інкапсульованих, адсорбованих або хімічно приєднаних активних компонентів. Розуміння процесів, що відбуваються при формуванні багатокомпонентних наносистем, є нагальним завданням для синтезу протипухлинних нанокомпозитів. Наночастинки золота (AuНЧ), фотосенсибілізатор Хлорин е6 (Се6) та Доксорубіцин (Докс) в даний час використовуються фотодинамічної терапії та хіміотерапії. Ми зосередились на дослідженні трикомпонентних наносистем Полімер/AuНЧ/Се6 та чотирикомпонентних наносистем Полімер/AuНЧ/Се6/Докс при фізіологічних температурах (37 °C). Зіркоподібний кополімер з декстрановим ядром та прищепленими поліакриламідними ланцюгами в неіонній та аніонній формах використовувався в ролі матриці для синтезу нанокомпозитів. Характеристики наносистеми визначалися методом динамічного світлорозсіювання та просвічуючою електронною мікроскопією. Було зафіксовано підвищення агрегаційних процесів у чотирикомпонентних наносистемах Полімер/AuНЧ/Се6/Докс у порівнянні з трикомпонентною системою Полімер/AuНЧ/Се6. Ці наносистеми були протестовані in vitro на клітинах карциноми молочної залози MCF-7/S – чутливої до цитостатиків. Було продемонстровано, що посилення процесу агрегації, яке відбувається в чотирикомпонентних системах, привело до втрати протипухлинної активності багатокомпонентних препаратів.