



SILVER ATOMS ENCAPSULATED IN G4 PAMAM (POLYAMIDOAMINE) DENDRIMERS AS A MODEL FOR THEIR USE IN NANOMEDICINE FOR PHOTOTHERAPY

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The main goals of the research are to study the drug delivery nanoparticle, G4 PAMAM (polyamidoamine) dendrimer, using spectroscopic and thermodynamic methods and, based on the unique properties of G4 PAMAM dendrimer, create new, stable nano-sized (~5 nm) metalorganic nanocomplexes with silver atoms, which have a strong absorption in visible area and it can be used as a phototherapeutic agent for the treatment of cancer cells.

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facilitated by the high permeability of tumor tissue (pore size of tumor tissue about 200 nm). It should be noted that the loading of tumor tissue with nanodrugs is much more effective than the loading of the same drugs with conventional diffusion.^{21,22} Some of them remain in the tumor tissue for quite a long time, which significantly increases the anti-neoplastic effect of these substances. On the other hand, the wide surface of nanomaterial facilitates the better treatment of the targeted structures by the therapeutic agents.

INTRODUCTION

In recent times, a major challenge in nanomedicine is to deliver medication in the local area of the disease or tumor. This can be achieved by using different nanosystems for drug delivery, which allows one to maximize clinical benefits and reduce the side effects of the drug.¹⁻¹¹ The organic nanoparticles must be non-toxicity. Further, the structure of the drug delivery complex should be maintained as much as possible before the delivery to the damaged tissue. In addition, after the complex is injected into the diseased cell, the drug must be released with the help of enzymes located in the cell.¹²⁻¹⁵ For the efficiency of drug delivery complex, the size of complex size is also important; due to clear reasons, it should be significantly smaller (at least by one order) than the size of the cell and at the same time, the amount of medicine located in the nanoparticles should be enough for cell treatment.¹⁶⁻²⁰

The main goals of nanomedicine is targeted delivery of therapeutic and diagnostic agents, their proper operation, and minimization of potential negative effects. Upon reaching the required places (perhaps using different mechanisms), therapeutic agents should selectively destroy or restore damaged cells, however, they should have little to no effect on the healthy tissue. Therefore, it should take into account the finest mechanisms to control the exact delivery of the agent. In oncology, nanomaterials are used for targeted delivery of therapeutic and diagnostic agents to tumor cells. Trapped in the bloodstream, specially treated nanomaterial accumulates in the tumor area, which is

In the case of organic nanoparticles, a single hollow nanoparticle can contain hundreds of drug molecules, the extraction and function of which is strictly purposeful. Extraction of nanoagents in tumor tissue often occurs as a result of the degradation of nanocarriers, although there are other mechanisms of actions of anticancer nanodrugs. This requires strict control over the degradation of nanoparticles, the degree of degradation of nanoparticles depends on the composition of its polymer coating. The polymer coating of medical therapeutic and diagnostic nanocarriers are necessary for the facilitation of their movement in the body, "clearing the way" and protecting the therapeutic/diagnostic agents.

Medical nanostructures, dendrimers, are synthetic branched polymers. Dendrimers have one starting atom, for example nitrogen, and as a result of a number of chemical reactions, it is linked to carbon and other elements. Each ending of the dendrimer contains reactive functional groups, so it easily attaches additional monomers, resulting in a dendrimer size increase. The dendrimer function is significantly related to its size, shape, and polarity.^{23,24} Specifically, the hollow and branch structure of dendrimer is well-suited to the targeted delivery of the drug, and in some cases the same dendrimer can find the damaged cells and influence them.²⁵⁻²⁷ For example, in the tumor, one branch of the dendrimer may be treated with tumor detection molecules (for example folic acid, as many receptors for folic acid are on tumor cells) and the neighboring branch with anti-tumor drug. Dendrimer may also have an effect on specific receptors of specific sites.²⁸⁻³⁰ As a consequence of their unique structural topology and chemical versatility,

dendrimers have found (or are likely to find) applications that include catalysis,³¹⁻³³ drug delivery,^{34,35} energy transfer,³⁶⁻³⁸ and molecular recognition.^{39,40}

In modern research, dendrimers are also used for synthesis of various metal nanoparticles. This means that the metal ions enter the existing hollow space in the structure of the dendrimer, and when the reductant (NaBH_4) is added, they reduce to atoms and form a nanoparticle. In this case, the distribution of nanoparticle sizes is narrow.⁴¹

Dendrimer types and their functional and synthesis conditions determine nanoparticle size, morphology and suspension stability.⁴² It should be noted that the reduction of some metal ions, for example silver, gold, platinum, palladium, is a complex process. At first, the copper ions are reduced and replaced with ions of other metals. With partial replacement, bimetallic nanoparticles can be formed.⁴³ Dendrimers encapsulated with metal nanoparticles are used as catalysts in some reactions: hydrogenations, hydroformylation, olefin metathesis, Heck reactions, Suzuki coupling, alkylation and oxidations.

As one of the prospective delivery agent, we consider G4 PAMAM (polyamidoamine) dendrimer (see Figure 1). Since the G4 PAMAM dendrimers satisfy all of the aforementioned qualities, they will satisfy the classification for drug delivery systems.^{9,10} In particular, dendrimers have advantages over other delivery agents. The unique and most important characteristics are chemical content, huge surface, spherical form, "pockets" full of water between the branches, which represent a kind of trap for the drug. In addition, they have certain molecular size and shape, they have a large number of functional groups on the surface and are characterized by high penetration in the cell.^{25,26,27,44}

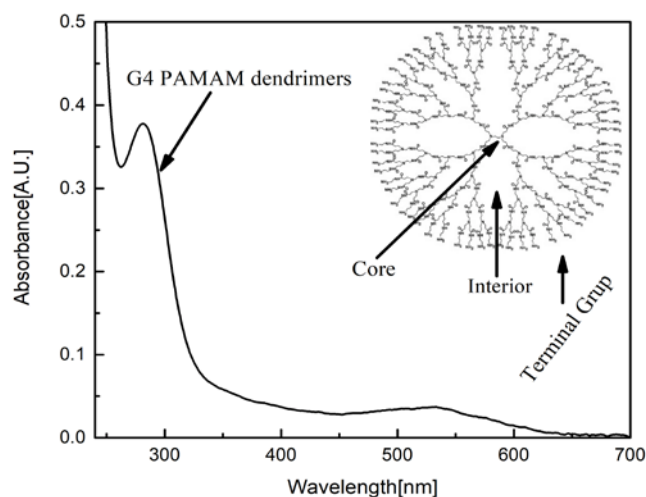


Figure 1. Absorption spectrum and structure of $\text{G4}(\text{NH}_2)_{64}$ PAMAM dendrimer.

These characteristics of G4 PAMAM dendrimers gives us the opportunity to prepare new stable nanocomplexes (metal encapsulated G4 PAMAM dendrimers) with high absorption properties in visible and near infrared areas of the spectrum, which makes it possible to use them in nanomedicine.

EXPERIMENTAL

In our tests, we have used the Calf thymus DNA (40 % GC) obtained from Sigma. The concentration of nucleic acids was determined by UV absorption using molar extinction coefficients ($\epsilon=6600 \text{ cm}^{-1} \text{ M}^{-1}$ at $\lambda=260 \text{ nm}$). The double helix structure of the polymers was proved by their hyperchromicity (>30 %) and their typical thermal denaturation transition (measured in 0.01 M NaNO_3 , $\text{pH} \cong 6.0$). The pH was checked by a pH-meter HANNA Instruments pH213. The $\text{G4}(\text{NH}_2)_{64}$ PAMAM dendrimer, with molecular sizes 4.5 nm, molecular weight 14215, was also purchased from Sigma ($\lambda = 280 \text{ nm}$). G4 PAMAM dendrimers were dissolved in a citrate buffer.

Double-distilled water served as a solvent. In tests with Ag^+ ions, chemically pure AgNO_3 was used and Tris buffer or NaNO_3 served as background electrolyte. For the reduction of silver ions, ascorbic acid (AA) was used. We have used molar extinction coefficient for silver atom $\epsilon=7160 \text{ cm}^{-1} \text{ M}^{-1}$ at $\lambda = 430 \text{ nm}$.

The measurement of absorption spectra was carried out by compact, precise, mobile, small-power consuming optical fiber spectrometer AvaSpec ULS 2048-USB2. As a source of light we used a deuterium lamp in the ultraviolet region and quartz halogen incandescent lamp in the visible region.

Data collection, processing and visualization were carried out by CCD, connected to a personal computer and special computer programs, experimental results were processed by Origin software.

RESULTS AND DISCUSSION

The Ag^+ ions reduction process in drug delivery nanoparticles, G4 PAMAM dendrimers, was studied. Figure 2 depicts absorption spectra of the silver atoms obtained from the reduction of silver ions in G4 PAMAM dendrimers, induced by ascorbic acid (AA).

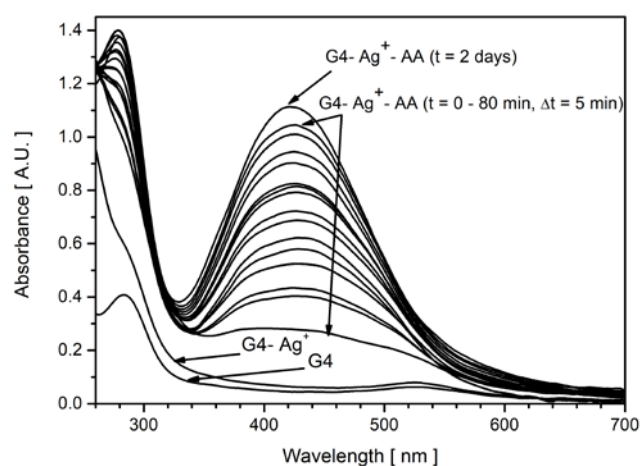


Figure 2. Time dependent absorption spectra of Ag^+ reduction in $\text{G4-Ag}^+-\text{AA}$ complex. $[\text{G4}] = 1.4 \times 10^{-4} \text{ M}$, $[\text{AgNO}_3] = 1.2 \times 10^{-4} \text{ M}$, $[\text{AA}] = 2.4 \times 10^{-4} \text{ M}$.

Therefore, using the unique features of G4 PAMAM dendrimers, new, stable, nanosized (~5 nm) complexes with 9-10 silver atoms, which have strong absorption in the visible area that make them eligible for use in nanomedicine, were created.

Figure 3 represents the kinetic curve of the reduction process of silver ions in G4 PAMAM dendrimers. The linear relationship shows that simple diffusion takes place (eqn. 1).

$$M_t/M_e = 2(Dt/\pi)^{1/2} [\text{cm/s}^{1/2}] \quad (1)$$

where M_t = the number of ions have been absorbed at t , M_e = the number of ions in equilibrium (saturation in optical absorption).

It also shows that G4 PAMAM dendrimer does not change conformation during the formation of a nanocomplex with silver atoms.

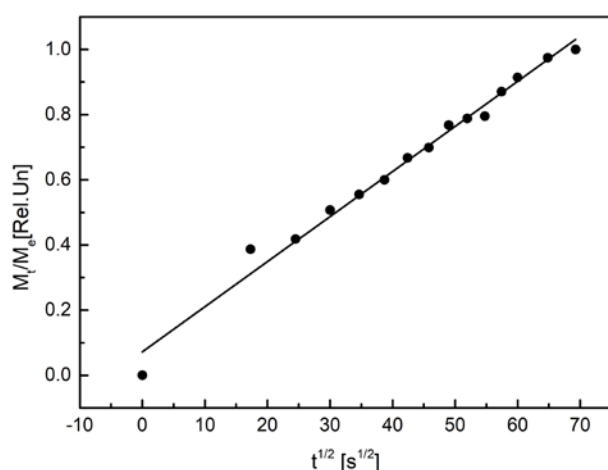


Figure 3. Kinetic curve of Ag^+ ions reduction in G4 dendrimers.

Figure 4 is a schematic representation of the model of the formation of the nanocomplex of G4 $(\text{NH}_2)_{64}$ PAMAM dendrimers with a silver atoms. The creation of nanocomplexes is a process consisting of two simple processes.

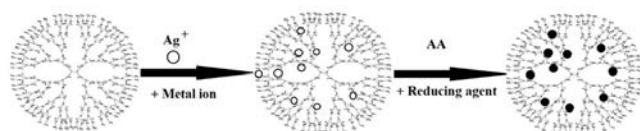


Figure 4. Model of creation of metal encapsulated G4 PAMAM dendrimers: reduction of silver ions to an atomic state in G4 PAMAM dendrimers.

It should be noted that the results presented in Figure 2 and 3 are of great spectroscopic interest. We have one G4 PAMAM dendrimer per 9-10 reduced silver atoms, and the absorption spectra show that the silver atom inside the dendrimer cavity is in the hydrated state. It should be noted that Ag^+ ions in solutions are in an octahedral complex.

Table 1. Wavelengths of the maximum and full width at half maximum of the of the absorption spectra of silver atoms in different conditions.

Material	λ_{max} , nm	Full width at half maximum, nm
AgNPs	431	140
AgNPs - DNA	425	133
Ag^+ -DNA-AA after 10	462	294
G4- Ag^+ -AA after 2 days	425	146

The location of the absorption maximum of silver atom ($\lambda = 425$ nm) indicates that the silver atom Ag^0 in G4 PAMAM dendrimer is in aqueous environment, i.e., that it is not connected to the polymer with a chemical or coordinate bond. This is the absorption maximum for the silver atom in a water environment with the shortest wavelength (Table 1). The diffusion of ascorbic acid molecule in G4 PAMAM dendrimer has a linear characteristic that indicates that the polymer molecule does not undergo the conformational changes.

Table 1 presents the wavelength of the maximum and full width at half maximum of the of the absorption spectra of silver atoms in AgNPs, AgNPs-DNA complex, Ag^+ -DNA complex after the reduction of Ag^+ by AA, and Ag^+ -G4 PAMAM dendrimer complex after the reduction of Ag^+ by AA. From the data presented in the table, it is clear that the shortest wavelength of absorption has the silver atoms incorporated into the G4 PAMAM dendrimer. The stronger the chromophore interacts with neighboring groups, the stronger the bathochromic shift.⁴⁵ Thus it may be concluded that the strongest interaction the silver atoms undergo are connected with the linear coordination between the DNA chains (inter strand croslink). It should be noted that linear coordination is characteristic of soft acids, namely Ag^+ , Ag^0 , Cu^+ , Pt^{2+} , Hg^{2+} . In an earlier work,⁴⁶ it was shown that the interaction of AgNPs with DNA leads to wetting of small-sized AgNPs with hydrated surface of DNA.

Figure 5 shows the scheme of irradiation of silver atoms encapsulated in dendrimers ($\lambda = 425$ nm) which will lead to excitation of silver atoms and the dissipation of energy on water molecules that will cause electrolytic dissociation of water molecules on H^+ and OH^- , which is the necessary condition for hydrolysis of amide groups (HNCO) of G4 PAMAM dendrimer.

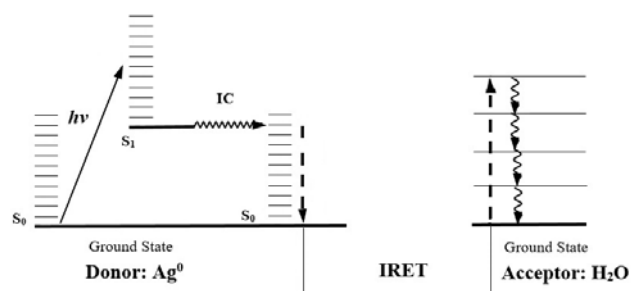


Figure 5. Scheme of energy levels corresponding to silver atom encapsulated in the G4 PAMAM dendrimer and high frequency vibration of water molecules (singlet-singlet energy transfer from donor to acceptor).

of cells and in case of cancer cells it can be a potential medication for photo chemotherapy (see Figure 9).

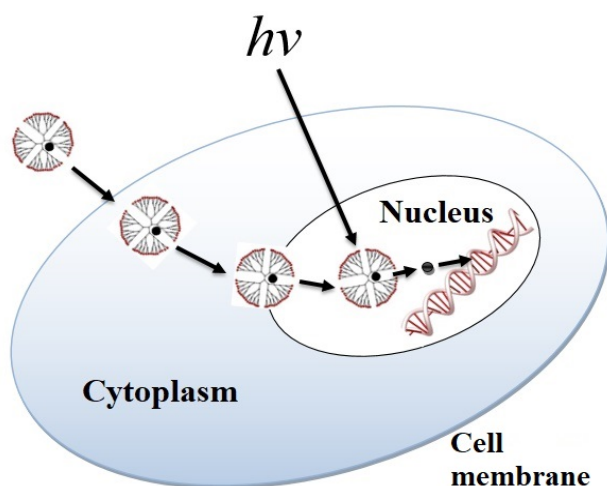


Figure 9. A schematic presentation of nanocomplex (silver atom encapsulated in G4 PAMAM dendrimer) entry in cell membrane through endocytosis, entry in nucleus from cytoplasm, irradiation of complex ($\lambda=425$ nm) and interaction of released silver atom with DNA.

It should be noted that the new potential medication proposed by us (silver atom encapsulated in G4 PAMAM dendrimer) has low toxicity to life, since the free silver atom is oxidized to a silver ion and silver ions form insoluble salts with chloride ions, the number of which is high in the body, and finally, the removal from the body occurs by fecal masses.⁵⁰ The irradiation of silver atom encapsulated in G4 PAMAM dendrimer and the influence of released silver atom on DNA will be studied experimentally in the future.

CONCLUSIONS

Silver ions reduction process in drug delivery nanoparticles, G4 PAMAM dendrimers, has been studied. Using the unique features of PAMAM dendrimers, new, stable, nanosized (~5 nm) complexes with 9-10 silver atoms in each dendrimer are created. Silver ions reduction process on DNA has been studied, and it has been shown that interaction of DNA with Ag⁰ atoms cause conformational changes, which in the living organism is the precondition for cell damage. For phototherapy, we suggest the nanocomplex of silver atoms encapsulated in the G4 PAMAM dendrimer, which should be able to overcome the cell membrane and cell nucleus, the size of pores in nucleus membrane is 8-9 nm.

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