ISSN 1064-2269, Journal of Communications Technology and Electronics, 2016, Vol. 61, No. 1, pp. 56–60. © Pleiades Publishing, Inc., 2016.
Original Russian Text © Yu.V. Gulyaev, V.A. Cherepenin, I.V. Taranov, V.A. Vdovin, A.A. Yaroslavov, V.P. Kim, G.B. Khomutov, 2016, published in Radiotekhnika i Elektronika, 2016, Vol. 61, No. 1, pp. 61–65.

APPLICATIONS OF RADIOTECHNOLOGY AND ELECTRONICS IN BIOLOGY AND MEDICINE

Remote Decapsulation of Nanocomposite Liposomal Capsules Containing Gold Nanorods by Ultrashort Electric Pulses

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Received August 9, 2015

Abstract—The decapsulation effect of nanocomposite liposomal capsules containing anisotropic gold nanoparticles (nanorods), which is caused by the action of ultrashort electric pulses on these capsules, is discovered. The mechanism of destruction of liposomal shells of the capsules near poles of conducting gold nanorods under the pulse electric action is described. An expression for the critical intensity of the pulse electric field, which determines the threshold of initiation of this effect, is obtained. Its numerical value is in agreement with the obtained experimental data. It is shown experimentally that the discovered decapsulation effect is caused by the presence of gold nanorods connected to the liposomal shell of the capsules and does not arise in the absence of nanorods.

DOI: 10.1134/S1064226915120104

INTRODUCTION

The possibility of carrying out the controlled address delivery of drugs occupies an important place among modern investigations in the area of nanotechnologies. One of promising approaches to solution of this problem is the development of systems for encapsulation, address delivery, and controlled liberation of drugs at a specified point of the organism [1–4].

The problem of the effective and, at the same time, safe (for surrounding biological structures) liberation of the encapsulated substance from the container is the most complex and urgent. Works on changes in the permeability of container shells with the use of laser radiation, microwave fields, alternating magnetic field, and changes in the chemical composition of the environment are devoted to solution of this problem [5–11]. One of the most promising approaches to creation of the drug containers sensitive to external electromagnetic action is the use of inorganic particles in its nanocomposite structure. As a rule, inorganic nanoparticles having different nature and composition (metal, magnetic, and semiconducting) possess a set of physical and chemical properties, which differ substantially from the properties of corresponding macrovolumetric materials. This quality makes such nanoparticles unique and interesting objects of basic research and important functional components of promising devices and technologies. For example, the single-electron tunnel transistor operating at the room temperature was for first developed with the use of metal nanoclusters [12–14]. Metal and magnetic nanoparticles are widely used in nanobiomedical technologies for diagnostics and therapy [15, 16]. Inclusion of magnetic nanoparticles into the structure of polyelectrolyte capsules has made these capsules sensitive to the external microwave action, which can controllably change the structure and permeability of the shells of these capsules [9–11].

Metal and semiconductor nanoparticles with a substantially elongated shape (nanorods) and their organized ensembles possess anisotropic optical properties. Using DNA molecules as an adsorbing matrix, quasilinear structures of semiconductor CdSe nanorods were created. Fluorescence of these structures was polarized [13, 17].

In this study, liposomal nanocomposite capsules containing gold nanorods sensitive to the external pulse electric action were synthesized using the technique from [18]. The duration of the applied electric action was about 8 ns. In accordance with [19], pulses of this duration will be called ultrashort pulses. The effect of decapsulation of the synthesized capsules caused by the action of the ultrashort electric pulses was discovered.

1. OBTAINING LIPOSOMAL NANOCOMPOSITE CAPSULES

Amphiphilic compounds of phosphatidylcholine and stearylspermine (SS) were used for the synthesis of

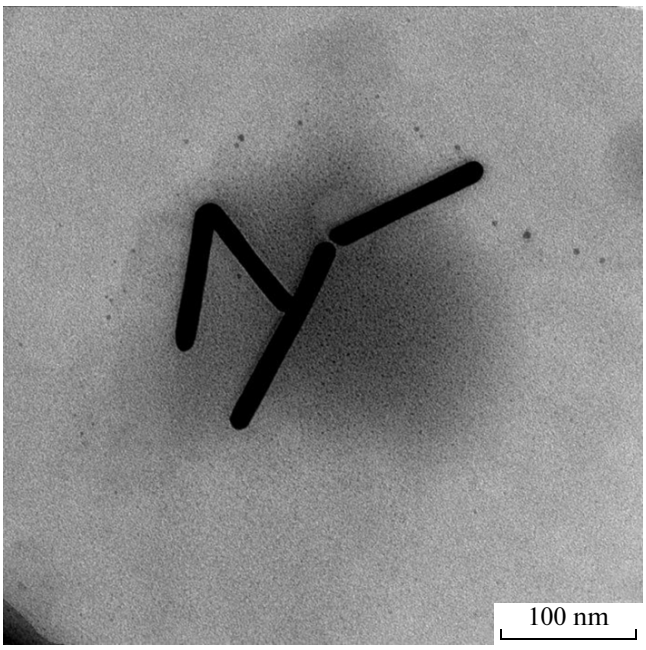

Fig. 1. Electron-microscopic image of the nanocomposite liposomal capsule containing gold nanorods.

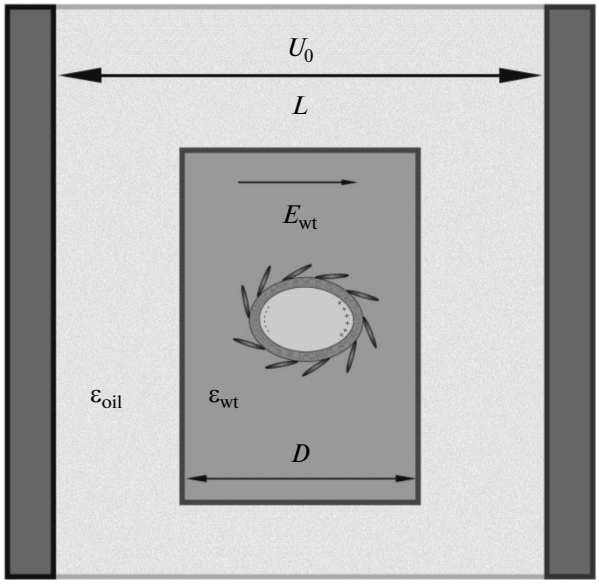

Fig. 2. Scheme of the action of ultrashort electromagnetic pulses on the aqueous suspension of liposomal nanocomposite capsules.

the capsules. In this case, the portion of the SS molecules in the shell of the obtained liposomal capsules was 1/5. The aqueous suspension of the gold nanorods with typical dimensions (the average length is 90 nm and the average diameter is 10 nm) was bought from Sigma-Aldrich Corp. To ensure colloidal stability of the nanorods (for preventing their aggregation), a cationic surface-active substance (cetyltrimethylammonium bromide) was added to the nanorod suspension. Gold nanorods were connected with the shells of preliminarily obtained (by a standard ultrasonic method) liposomes consisting of biogenic lipid molecules (phosphatidylcholine) and amphiphilic SS compound in a ratio of 4 : 1. The internal volume of the capsule was filled with a solution of NaCl salt by a standard method using the dialysis procedure. The structure of the synthesized liposomal nanocomposite capsules was studied by the methods of transmission electron microscopy (TEM). A typical image of the liposomal capsule containing gold nanorods is shown in Fig. 1.

2. EFFECT OF ULTRASHORT ELECTRIC PULSES ON LIPOSOMAL NANOCOMPOSITE CAPSULES

Possibilities of the remote activation of nanocomposite liposomal capsules containing gold nanorods, were studied using ultrashort electric pulses. The pulse action of the electric field on the water suspension of the synthesized liposomal capsules was carried out as follows (Fig. 2). A transformer oil with relative dielectric permittivity $\varepsilon_{oil} = 2.2$ was placed between flat electrodes with gap $L = 1$ cm. A cylindrical container with thickness $D = 5$ mm with an aqueous suspension of the liposomal capsules with typical dimensions $l \cong 200$ nm was in the oil. Shells of liposomal membranes were connected to conducting gold nanorods with a typical length of 90 nm and average diameter of 10 nm and the internal volume of the containers contained the conducting solution of NaCl. Voltage pulses $U_0 = 150$ kV with duration $\tau = 8$ ns were applied to the electrodes.

The effect of decapsulation of the nanocomposite liposomal capsules containing gold nanorods was recorded by the conductometry method from changes in the conductivity of the aqueous limosome suspension. During the decapsulation, the NaCl salt contained inside liposomal capsules was liberated into the ambient medium, thus increasing the specific conductivity of the suspension. Before the action of ultrashort electric pulses, the specific conductivity of the suspension was 104 μS/cm and, after the action, it was 115 μS/cm. The specific conductivity of the suspension corresponding to the decapsulation of all liposomal capsules (which was attained by adding the triton X100 detergent) was 129 μS/cm. Incomplete decapsulation of the suspension is attributed to the fact that not all liposomal capsules are connected to the gold nanorods. A similar action on the aqueous suspension of liposomal capsules not containing gold nanorods did not result in noticeable changes in its specific conductivity.

The effect of decapsulation of the nanocomposite liposomal capsules containing gold nanorods was confirmed independently by the TEM method. Figure 3 shows typical image of the nanocomposite liposomal capsules after the action of ultrashort electromagnetic

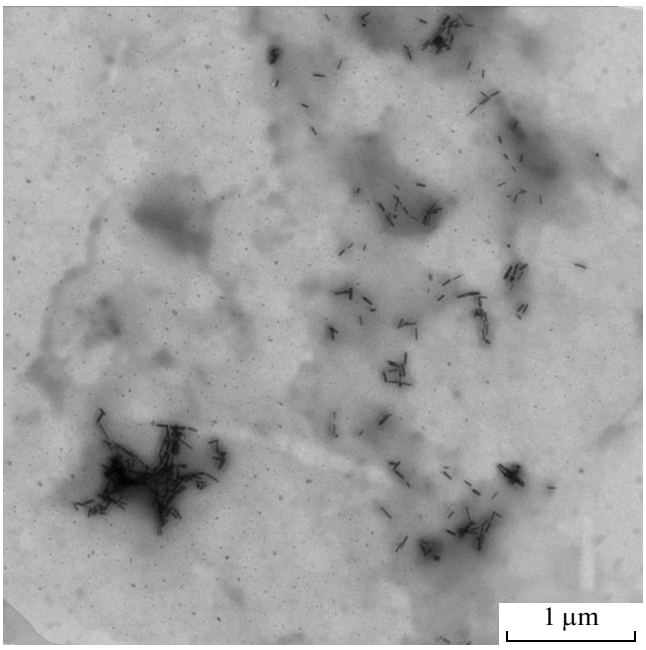

Fig. 3. Electron-microscopic image of the nanocomposite liposomal capsules after the action of ultrashort electromagnetic pulses.

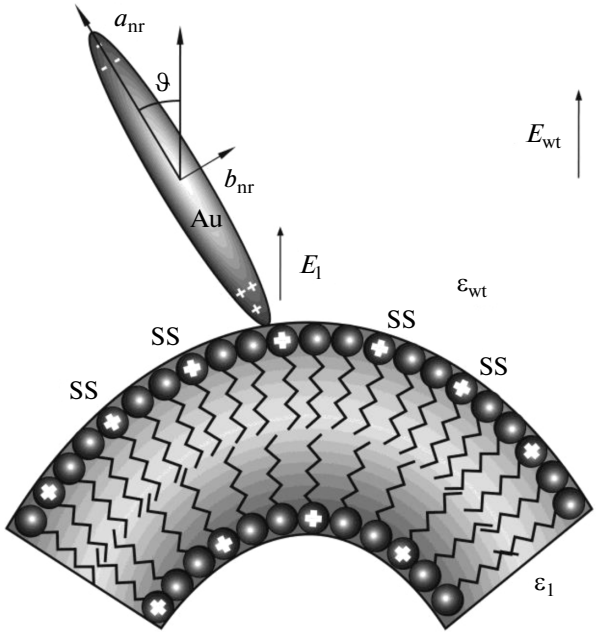

Fig. 4. Scheme of interaction between protonated molecules of stearylspermine (SS) and the polarized nanorod.

pulses. Destroyed liposomes, fragments of their membranes, and aggregations of the gold nanorods can be seen in the image. After a similar action, changes in the structure of liposomal capsules not containing gold nanorods were not detected by the TEM methods.

To determine the critical intensity of the electric field leading to decapsulation of the nanocomposite liposomal capsules whose shells are connected to the conducting gold nanorods, we consider possible mechanism of destruction of their shells, which is initiated by the external electric field.

The quasi-stationarity condition of the electromagnetic field $c\tau \gg l$ (c is the speed of light) is met for the above values of l and τ [20]. The duration of the electric pulse meets also the conditions:

$$\sigma_{ext}^{-1} \gg \tau \gg \sigma_{int}^{-1}, \quad (1)$$

where $\sigma_{ext,\,int}$ are the specific conductivities of aqueous salt solutions outside and inside the capsules. In this case, the internal solution of the capsule can be considered conducting and the external solution can be assumed dielectric.

In the aqueous medium, the capsules in the shell of the SS molecule can acquire positive charge q equal to the value of the electron charge. The capsule shell is a dielectric with permittivity $\varepsilon_1 = 2.7$. Gold nanorods with a strongly elongated shape are connected to the shell. During the action of the electric pulse, this liposomal capsule, surrounded by water, is in external electric field E_{wt}. Field E_{wt} can be found as a solution to the Laplace equation for a dielectric cylinder with the permittivity equal to permittivity of water $\varepsilon_{wt} = 80$, which is surrounded by the dielectric medium with permittivity $\varepsilon_{oil} = 2.2$ and placed into the external uniform electric field (Fig. 4):

$$E_{wt} = \frac{2\varepsilon_{oil}}{\varepsilon_{oil} + \varepsilon_{wt} - (\varepsilon_{wt} - \varepsilon_{oil})\dfrac{D^2}{L^2}} \frac{U_0}{L} = 6 \times 10^5 \ \frac{\text{V}}{\text{m}}. \quad (2)$$

Earlier it was shown [19, 21] that the shape of the liposomal capsule could change under the action of the external electric field from spherical to ellipsoidal. Using the solution to the problem of the distribution of the electric field in a layered ellipsoidal medium [19–21], we find the electric field intensity near the polar region of the elongated liposomal capsule:

$$E_l = \frac{\varepsilon_1 + 2n_1\dfrac{\Delta R}{R}(\varepsilon_{wt} - \varepsilon_1)}{\varepsilon_1 + 2\dfrac{\Delta R}{R}(\varepsilon_{wt} - \varepsilon_1)} \frac{E_{wt}}{n_1}, \quad (3)$$

where

$$n_1 = \frac{1 - e_1^2}{e_1^2}\left(\frac{1}{2e_1}\ln\frac{1 + e_1}{1 - e_1} - 1\right)$$

is the depolarization coefficient, $e_1 = \sqrt{1 - a_1^2/b_1^2}$ is the eccentricity, $a_1 > b_1$ are the major semi-axes of the ellipsoid, ΔR is the thickness of the liposomal membrane, and R is the radius of the ball with the volume equal to the liposome volume.

The conducting gold nanorod is located on the surface of the liposome (Fig. 4). It is polarized in field E_1 (3) and locally changes the electric field in its proximity. We assume that its shape is close to an elongated ellipsoid of revolution with major semi-axes $a_{nr} > b_{nr}$. For a conducting ellipsoid of revolution placed into an external electric field, the electric intensity near the pole of the nanorod located in the polar region of the liposomal capsule is determined by the following expression:

$$E_{nr} = \frac{\varepsilon_1 + 2n_1\frac{\Delta R}{R}(\varepsilon_{wt} - \varepsilon_1)}{\varepsilon_1 + 2\frac{\Delta R}{R}(\varepsilon_{wt} - \varepsilon_1)}\frac{1}{n_1}\left(\frac{a_{nr}^2}{b_{nr}^2} - 1\right) \times \left(\frac{a_{nr}}{\sqrt{a_{nr}^2 - b_{nr}^2}}\ln\frac{a_{nr} + \sqrt{a_{nr}^2 - b_{nr}^2}}{b_{nr}} - 1\right)^{-1} E_{wt}\cos\vartheta, \quad (4)$$

where $e_{nr} = \sqrt{1 - a_{nr}^2/b_{nr}^2}$ is the eccentricity of the ellipsoidal nanorod and ϑ is the angle between the longer major semi-axis of the ellipsoid and the normal to the liposome surface.

Protonated SS molecules of the liposomal bilayer with unit positive change q are located in local field (4) near the nanorod pole [22]. Interaction of the polarized nanorod with the charged SS molecules can lead to local destruction of the shell of the liposomal capsule if external field E_{wt} exceeds critical value E_{cr}:

$$E_{wt} > E_{cr}. \quad (5)$$

Critical electric field E_{cr} can be found from the condition of the equality of the work of movement of the SS molecule in the local field of the nanorod beyond the bounds of the liposomal bilayer $\epsilon_{nr} = qE_{cr}\Delta R$ and the portion of surface energy $\epsilon_{surf} = \alpha S_0$ per one SS molecule, where S_0 is the area occupied by one SS molecule and α is the surface tension coefficient of the shell of the liposomal capsule. For a weakly elongated liposomal capsule ($(e_1 \ll 1)$), strongly elongated nanorod ($a_{nr} \gg b_{nr}$), and $\vartheta \ll 1$, we obtain the expression for the critical field:

$$E_{cr} = \frac{3a_{nr}^2}{b_{nr}^2}\left(\ln\frac{2a_{nr}}{b_{nr}} - 1\right)^{-1} \times \frac{\varepsilon_1 + 2\frac{\Delta R}{R}(\varepsilon_{wt} - \varepsilon_1)}{\varepsilon_1 + \frac{2}{3}\frac{\Delta R}{R}(\varepsilon_{wt} - \varepsilon_1)}\frac{\alpha S_0}{q\Delta R}, \quad (6)$$

which assumes the value $E_{cr} = 1.1 \times 10^5$ V/m for parameters of the considered case: $\alpha = 25$ dyn/cm, $S_0 = 30$ Å^2 [22], $R = 100$ nm, $\Delta R = 4$ nm, $\varepsilon_1 = 2.7$, $\varepsilon_{wt} = 8$, and $a_{nr}/b_{nr} = 9$.

In the performed experiment, the value of the electric field in the aqueous suspension of liposomal capsules was $E_{wt} = 6 \times 10^5$ V/m and, hence, condition (5) was met. Thus, in this case, the effect of decapsulation of nanocomposite liposomal capsules due to local destruction of their shells near poles of elongated conducting nanorods was implemented.

CONCLUSIONS

The effect of decapsulation of nanocomposite liposomal capsules containing gold nanoparticles, which is caused by the action of ultrashort electric pulses, has been discovered. The mechanism of destructing the shells of the liposomal capsules near the pole of the elongated conducting nanorod under the pulse electric action has been described. The expression for the critical value of the electric field intensity, which determines the initiation threshold of this effect, has been obtained. The critical field value is in good agreement with the experimental data. It has been shown that the detected decapsulation effect is attributed to the presence of conducting gold nanorods in the capsule shell and does not arise in the absence of the nanorods. This circumstance points to the selectivity of the used action. This selectivity of the action is very important for practical applications related to the controlled delivery of drugs in an organism, since it allows one to avoid damages of cell membranes of the organism and ensure changes in the structure only near the shells of nanocomposite liposomal capsules.

ACKNOWLEDGMENTS

This work was supported by the Russian Scientific Foundation, project no. 14-12-01379.

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Translated by N. Pakhomova

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