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APPLICATIONS OF RADIOTECHNOLOGY AND ELECTRONICS IN BIOLOGY AND MEDICINE

Effect of Gold Nanorods on the Remote Decapsulation of Liposomal Capsules Using Ultrashort Electric Pulses

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Abstract—Decapsulation of nanocomposite liposomal capsules due to the effect of ultrashort electric pulses is obtained when the liposomal sheaths of the capsules are bound to significantly anisotropic gold nanoparticles (nanorods). Destruction of the liposomal sheath is interpreted using the rotational displacement of gold nanorods in the presence of the pulsed electric field. Such an interpretation is used to derive an expression for the critical electric field that determines the threshold level of the effect. The calculated critical field is in agreement with the experimental results. It is shown that the decapsulation is related to the presence of the gold nanorods in the sheath of liposomal capsules and is not obtained in the absence of the nanorods.

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INTRODUCTION

Development of efficient biocompatible nanomaterials and capsulation systems based on such materials and target delivery and controlled release of biologically important compounds at the desired time moment are important topical problems of modern fundamental and applied science. The development of such systems necessitates the study of interdisciplinary physical, chemical, and biological problems in the leading research centers. The main problems are related to encapsulation and target delivery of drugs to the desired organ using a specific carrier and controlled separation of the drug and carrier. The study must be performed with allowance for toxicity of substances and materials to avoid undesired side effects. Modern nanocontainers and carriers of drugs under study are based on dendrimers, micelles, liposomes, fullerenes, and hydrogels. Note also a search for methods for controlled release of encapsulated substances using physical and chemical effects [1–4].

Hollow polyelectrolyte and nanocomposite microcapsules are promising microcontainers that can be fabricated with the aid of the layer-by-layer polyionic assembly [5–7]. Several specific advantages of such objects can be used in medicine, biology, chemistry, and technology. Changes of the permeability of the microcapsule walls may result from variations in the chemical parameters of the local environment or external physical effects. The permeability of the microcapsule sheath can be changed using variations in pH [8], optical radiation [9, 10], ac magnetic field [11], and microwave radiation [12, 13]. The sensitivity of nanocomposite polymer microcapsules to pulsed electromagnetic field [14, 15] can be used for remote-controlled target delivery of drugs. However, the polyelectrolyte microcapsules exhibit several disadvantages related to multistage labor-consuming technological procedure. Note also that several substances can hardly be encapsulated since the polyelectrolyte sheath has a relatively high permeability for low-molecular substances. Lipid biomimetic vesicles (liposomes) that are free of the above disadvantages are widely employed in model biophysical experiments and are promising for biomedical applications [16, 17]. Biocompatibility is an important distinctive feature of liposomes in the development of systems for encapsulation and target delivery of biologically important compounds. Such a feature is related to the fact that the liposome membranes are formed of molecules that are contained in biological membranes. Various substances (from inorganic ions to large proteins and nucleic acids) can be encapsulated in liposomal containers.

Efficient remote and safe (for biological environment) release of the encapsulated substance is a complicated topical problem. To solve such a problem, we must choose a method and fabricate a specific container that is sensitive to the corresponding external action. In particular, variations in the permeability of the container sheaths can be reached using optical radiation, microwave fields, ac magnetic field, and variations in the chemical composition of the medium

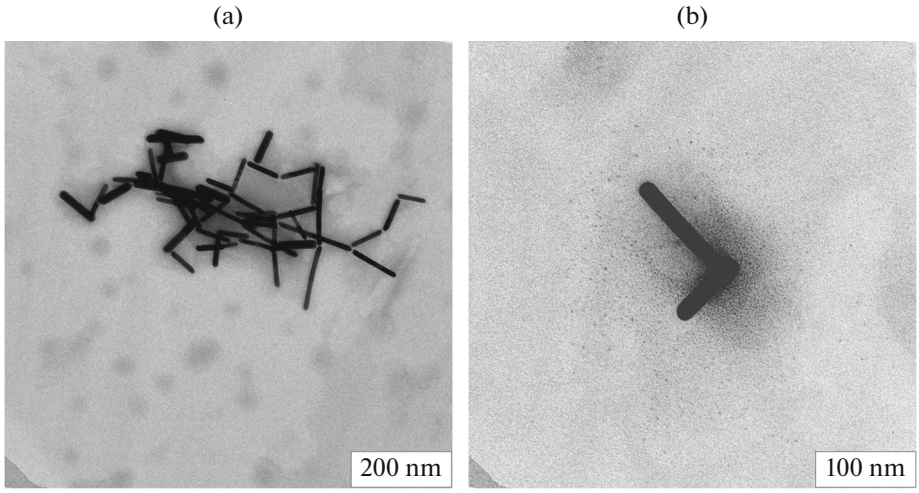

Fig. 1. TEM images of (a) group of liposomal capsules and (b) single liposome capsule containing gold nanorods.

[9–19]. A promising method for the selective action on the drug containers employs ultrashort electromagnetic pulses and nanostructured liposomal capsules containing inorganic nanoparticles (transportation containers).

Inorganic nanoparticles are specific objects for fundamental science and important functional components of promising technological devices. Metal nanoclusters have been used to construct a single-electron tunneling transistor working at room temperature [20–22]. Metal and magnetic nanoparticles are widely used in biomedical experiments for diagnostics and therapy [23, 24]. Significantly elongated semiconductor nanoparticles (nanorods) and ordered ensembles of such nanoparticles exhibit anisotropic optical properties. Significantly polarized fluorescence is typical of quasi-linear structures of the CdSe semiconductor nanorods bound to the DNA molecules as an adsorbing matrix [22, 25].

In this work, we study the selectivity of electromagnetic action on drug containers. Ultrashort high-intensity electric pulses are used for remote action. Liposomal capsules the membranes of which are bound to substantially anisotropic particles (gold nanorods) serve as containers that are sensitive to the electric field. The nanocomposite liposomal capsules containing gold nanorods are synthesized using the procedure of [26, 27]. The electric pulse duration is about 10 ns. Such pulses are classified as ultrashort [28].

1. FABRICATION OF NANOCOMPOSITE LIPOSOMAL CAPSULES CONTAINING GOLD NANORODS

For the fabrication of the nanocomposite liposomal capsules, we use single-layer liposomes that are synthesized with the aid of the conventional ultrasonic method from amphiphilic compounds of phosphatidylcholine (80%) and stearylspermine (SS) (20%). Gold nanorods with a diameter of 10 nm and a length of 100 nm serve as substantially anisotropic conducting nanoparticles. The gold nanorods are bound to the external surface of preliminary synthesized single-layer liposomes when aqueous suspension of gold nanorods (40 μL) and liposome solution (100 μL) are added to deionized water (800 μL) for the further incubation. Conventional dialysis is employed for filling of the internal volume of capsule with the NaCl solution. The structure of the synthesized liposomal nanocomposite capsules is examined using transmission electron microscopy (TEM). Figure 1 shows typical images of the liposomal capsules that contain gold nanorods.

2. DECAPSULATION OF LIPOSOMAL CAPSULES USING ULTRASHORT ELECTRIC PULSES

We experimentally study the decapsulation of the aforementioned nanocomposite liposomal capsules containing gold nanorods using ultrashort electric pulses (Fig. 2). Plane electrodes are located at a distance of $L = 1$ cm in transformer oil with a permittivity of $\varepsilon_{oil} = 2.2$. A cylindrical container with a diameter of $D = 5$ mm is filled with the aqueous suspension of preliminary synthesized nanocomposite liposomal capsules with a characteristic size of $l \cong 200$ nm and placed in the space between the electrodes. The outer surface of the liposomal membranes is bound to conducting gold nanorods with a characteristic length of 100 nm and a mean diameter of 10 nm. The internal volume of the vesicles contains conducting solution of NaCl. Electric pulses $U_0 = 1.5 \times 10^5$ V with a duration of $\tau = 10^{-8}$ s are fed to the plane electrodes.

Decapsulation of the liposomal containers in the suspension of nanocomposite liposomes takes place in

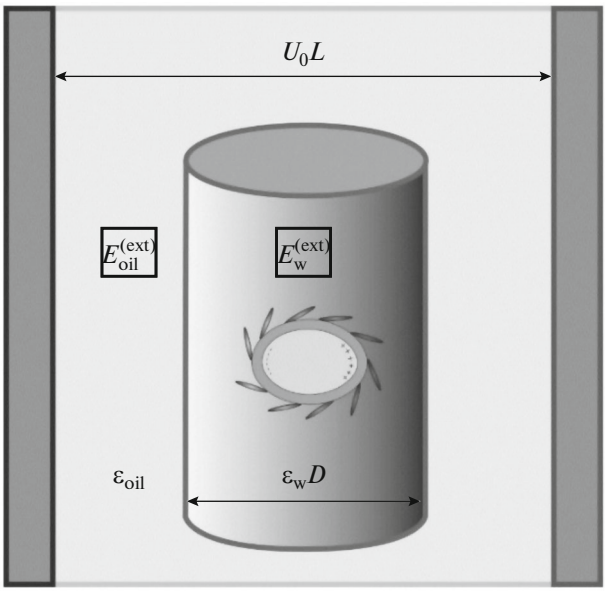

Fig. 2. Schematic drawing that illustrates the effect of ultrashort electric pulses on the aqueous suspension of nanocomposite liposomal capsules containing gold nanorods.

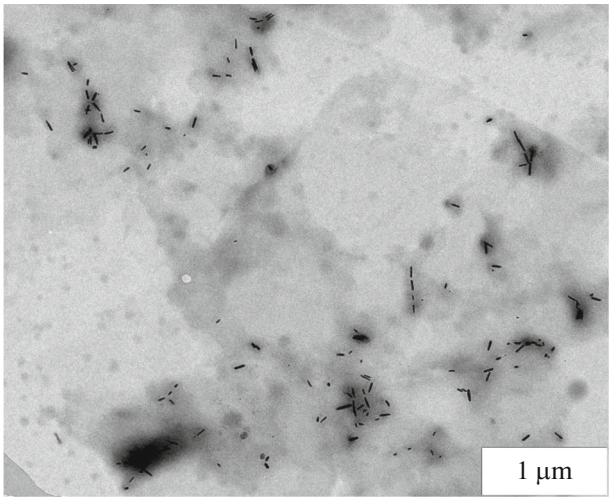

Fig. 3. TEM image of the nanocomposite liposomal capsules destroyed by ultrashort electromagnetic pulses.

the presence of ultrashort electric pulses. Salt (NaCl) that is contained in the liposomal capsules is released to surrounding water, so that the conductivity of the suspension increases. Thus, a variation in the conductivity of the suspension in the presence of the electric pulses indicates the decapsulation of liposomal containers.

The experiments show that ultrashort electric pulses cause an increase in the conductivity of the suspension of nanocomposite liposomal capsules from 103 to 114 μS/cm. Note that the complete decapsulation of the nanocomposite liposomes resulting from the chemical effect of the triton X100 detergent leads to a conductivity of 127 μS/cm. The experiments also show that the electric pulses do not cause noticeable variations in the conductivity of the suspension containing liposomal capsules that are not bound to gold nanorods. Thus, the conductivity measurements indicate the decapsulation of the nanocomposite liposomal capsules containing gold nanorods owing to the effect of ultrashort electric pulses.

The TEM measurements make it possible to independently prove such an effect. Figure 3 presents a typical image of the nanocomposite liposomal capsules affected by ultrashort electromagnetic pulses. We observe fragments of membranes of destroyed liposomes, clusters of nanorods, and the absence of whole liposomes. The TEM measurements of the liposomal capsules that do not contain gold nanorods show the absence of changes of the capsule structure.

We consider possible scenario of the destruction of the liposomal sheath due to the rotational displacement of the gold nanorods induced by pulsed electric field. Note that the condition for the quasi-stationary character of the electric field $c\tau \gg l$ (c is the speed of light) is satisfied for the parameters of the problem under study [29]. Electric pulse duration τ satisfies the conditions $\sigma_{ext}^{-1} \gg \tau \gg \sigma_{int}^{-1}$, where σ_{ext} and σ_{int} are the conductivities of the salt solutions outside and inside the capsule such that the internal and external media can be classified as a conductor and insulator, respectively. The capsule sheath is a dielectric material with a permittivity of $\varepsilon_l = 2.7$. Substantially elongated conducting gold nanorods are bound to the external surface of the sheath. The SS molecules in water acquire positive charge q that is equal to the magnitude of electron charge.

The results of [27] show that the following electric field is exerted on the liposomal capsules in the configuration of Fig. 2 in the presence of the electric pulse:

$$E_w^{(ext)} = \frac{2\varepsilon_{oil}}{\varepsilon_w + \varepsilon_{oil} - (\varepsilon_w - \varepsilon_{oil})\dfrac{D^2}{L^2}} \frac{U_0}{L}. \qquad (1)$$

The field is $E_w^{(ext)} = 10.5$ kV/cm for $D/L = 1/2$ and a water permittivity of $\varepsilon_w = 80$.

In the presence of external electric field $E_w^{(ext)}$ the spherical shape of the liposomal capsule is transformed into a prolate ellipsoid of revolution [27]. Using the approach of [27], we solve the problem of the distribution of electric field in the layered ellipsoidal medium and obtain the electric field strength in

the vicinity of the polar region of the elongated liposomal capsule:

$$E_{\rm l} = \frac{\varepsilon_{\rm l} + 2n_{\rm l}\dfrac{\Delta R}{R}(\varepsilon_{\rm w} - \varepsilon_{\rm l})}{\varepsilon_{\rm l} + 2\dfrac{\Delta R}{R}(\varepsilon_{\rm w} - 1)}\frac{E_{\rm w}^{(\rm ext)}}{n_{\rm l}}, \qquad (2)$$

where $n_{\rm l} = \dfrac{1-e_{\rm l}^2}{e_{\rm l}^2}\left(\dfrac{1}{2e_{\rm l}}\ln\dfrac{1+e_{\rm l}}{1-e_{\rm l}} - 1\right)$, $e_{\rm l} = \sqrt{1 - b_{\rm l}^2/a_{\rm l}^2}$ is the eccentricity of the ellipsoidal liposome, $a_{\rm l} > b_{\rm l}$ are the semimajor axes of the ellipsoid, ΔR is the thickness of the liposomal membrane, and R is the radius of the sphere the volume of which is equal to the liposome volume. The external surface of the liposomal membrane is bound to conducting gold nanorods (Fig. 4) the orientation of which can be changed in the presence of field $E_{\rm l}$ (2). We assume that the shape of the gold nanorods is close to the elongated ellipsoid of revolution with semimajor axes $a_r > b_r$. In this case, the torque of the conducting nanorod in the presence of field $E_{\rm l}$ is represented as

$$N_E = a_r b_r^2 \frac{3n_r - 1}{6n_r(1 - n_r)}\sin^2 2\vartheta E_{\rm l}^2, \qquad (3)$$

where $n_r = \dfrac{1-e_r^2}{e_r^2}\left(\dfrac{1}{2e_r}\ln\dfrac{1+e_r}{1-e_r} - 1\right)$, ϑ is the angle between $\vec{E}_{\rm l}$ and the greater semimajor axis of the gold nanorod, and $e_{\rm l} = \sqrt{1 - b_{\rm l}^2/a_{\rm l}^2}$ is the eccentricity of the ellipsoidal nanorod. The maximum torque is reached in the vicinity of the pole of the liposome and is given by the following expression for a significantly elongated rod ($a_r \gg b_r$) and weakly deformed liposome ($a_{\rm l} \cong b_{\rm l}$ and $\vartheta \cong \pi/4$)

$$N_E = \frac{3a_r^3}{2}\left(\frac{\varepsilon_{\rm l} + \dfrac{2}{3}\dfrac{\Delta R}{R}(\varepsilon_{\rm w} - \varepsilon_{\rm l})}{\varepsilon_{\rm l} + 2\dfrac{\Delta R}{R}(\varepsilon_{\rm w} - \varepsilon_{\rm l})}\right)^2 \times \left(\left(\ln\frac{2a_r}{b_r} - 1\right)^{-1} - 2\frac{b_r^2}{a_r^2}\right)\left(E_{\rm w}^{(\rm ext)}\right)^2. \qquad (4)$$

When torque (4) reaches a sufficient level, the rotational displacement of the gold nanorods may lead to extraction of the molecules that interact with the nanorod from the liposomal monolayer. Thus, the liposomal membrane can be destroyed. A condition for the extraction of molecules from the liposomal bilayer due to the rotational displacement of the nanorod is written as

$$N_E \geq N_{\rm s}, \qquad (5)$$

where

$$N_{\rm s} = 2\alpha\delta\sqrt{\pi S_0} \qquad (6)$$

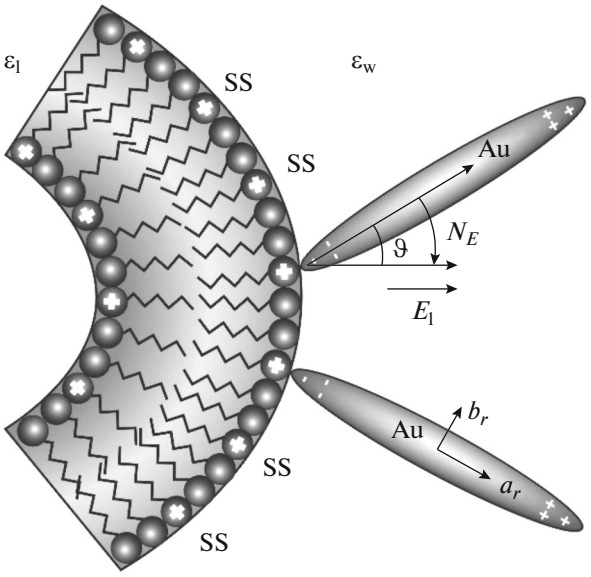

Fig. 4. Scheme of interaction of gold nanorods and liposomal membrane.

is the torque of the surface tension that is exerted upon the gold nanorod when the SS molecule is extracted from the lipsomal monolayer, α is the surface tension coefficient of the membrane, $\delta = b_r^2/a_r$ is the radius of curvature of the gold nanorod in the vicinity of the pole, and S_0 is the area per molecule in the liposome membrane.

Substituting expressions (4) and (6) in condition (5), we derive an expression for critical electric field $E_{\rm w}^{(\rm cr)}$ in the vicinity of the liposome that leads to the torque of the gold nanorod sufficient for the extraction of the SS molecules from the liposome membrane:

$$E_{\rm w}^{(\rm cr)} = \frac{2}{3}\frac{b_r}{a_r^2}\frac{\varepsilon_{\rm l} + 2\dfrac{\Delta R}{R}(\varepsilon_{\rm w} - \varepsilon_{\rm l})}{\varepsilon_{\rm l} + \dfrac{2}{3}\dfrac{\Delta R}{R}(\varepsilon_{\rm w} - \varepsilon_{\rm l})} \times \left(\frac{3\alpha\sqrt{\pi S_0}}{\left(\ln\dfrac{2a_r}{b_r} - 1\right)^{-1} - 2\dfrac{b_r^2}{a_r^2}}\right)^{1/2} \qquad (7)$$

for $a_r \gg b_r$, $a_{\rm l} \cong b_{\rm l}$, and $\vartheta = \pi/4$.

For the parameters $a_r = 120$ nm, $a_r/b_r \cong 10$, $S_0 = 30$ Å^2, $\alpha = 25$ dyn/cm [30], $\varepsilon_{\rm l} = 2.7$, $\varepsilon_{\rm w} = 80$, and $\Delta R/R \cong 1/50$, critical electric field (7)

$$E_{\rm w}^{(\rm cr)} = 9.8\ \text{kV/cm} \qquad (8)$$

is less than electric field $E_{\rm w}^{(\rm ext)}$ (1) that emerges in the experiments in the vicinity of the liposomal capsules in the presence of the electric pulses.

Thus, condition (5) for the extraction of the liposomal molecules from the liposomal bilayer due to the rotational displacement of the nanorod is satisfied in the experiments. The experiments show the destruction of liposomal capsules containing gold nanorods due to the effect of the pulsed electric field.

CONCLUSIONS

We have shown the decapsulation of the nanocomposite liposomal capsules in the presence of ultrashort electric pulses for the capsules the sheaths of which are bound to substantially anisotropic gold nanoparticles (nanorods). Note the selective character of such interaction. The decapsulation is observed for the liposomal capsules that contain the gold nanorods and is absent for the capsules that do not interact with the gold nanoparticles. The destruction of the liposomal sheath is interpreted using the rotational displacement of the gold nanorods in the presence of the pulsed electric field. The interpretation is used to derive an expression for the critical (threshold) electric field of the effect. The numerical value of the critical field is in agreement with the experimental results. The selectivity of the remote action is important for practical applications related to the target delivery of drugs, since such an effect makes it possible to avoid damage of the surrounding cells and provide decapsulation only for nanocomposite liposomal structures.

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