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Development of the Technology for Remote Controlled Decapsulation of Nanostructured Liposomal Capsules, based on Non-thermal Impact by Ultrashort Electrical Pulses

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Abstract

The results regarding the development of the Technology for remote controlled decapsulation of nanostructured liposomal capsules, based on non-thermal impact by ultrashort electrical pulses are presented. The mechanism of destruction of liposomal shells of the capsules under the pulse electric impact was investigated. The series of the experiments were made with using of the laboratory equipment developed at the Kotelnikov IRE RAS, including pulse generator system provided voltage equal to 150 kW/cm and pulse duration up to 5 ns.

1. Introduction

At present, the further progress in solution of the targeted drag delivery problem depends on the creation of novel functional biocompatible and bioactive materials, efficient systems for capsulation and targeted delivery of various functional active compounds. The success in mentioned directions is determined by solution of correlated physical, chemical, biological and nanotechnological tasks and becomes now an important and challenging interdisciplinary problem.

The main questions that have to be solved in the frameworks of that problem are the following:

i. how the drug could be capsulated by the carrier and then delivered to definite local areas of the organism?
ii. how the drug could be delivered and removed from the carrier by a controlled way?
iii. how to decrease potential toxicity of the used materials and compounds to minimize their possible negative effects on the organism?

Proposed by the authors approach is especially relevant and in demand because in all industrially developed countries the active research are being conducted in the field of targeted drug delivery. In available sources the results by Capsules of different composition type and structure are being tested, different ways for control of capsule movement in bloodstream are under consideration, but the problem of decapsulation control remains the open.

2. Technology for remote decapsulation of nanostructured liposomal capsules

The authors make investigations in the field of capsulation and controlled targeted delivery of various compounds in aqueous media based on the colloid nanocomposite vesicles and capsules representing hybrid constructions formed by polymers (including biopolymers and inter-polyelectrolyte complexes), lipids and amphiphiles, inorganic nanoparticles and other functional components.

The nanocomposite membranous vesicles were prepared successfully by sequential adsorption of colloid cationic ligand-free magnetite nanoparticles and polyanions onto the cationic surface of mixed phosphatidylcholine/ stearoylspermine liposomes preliminarily formed using conventional ultrasound method. The formed vesicles were characterized by transmission electron microscopy, AFM, electron magnetic resonance technique, laser light scattering and electrophoresis techniques.

The electric pulses impacts on the nanocomposite capsules have been studied by the authors as well as the remote non-thermal activation of capsules.

The series of the experiments were made with using of the laboratory equipment developed by the authors at the Kotelnikov Institute of Radio-engineering and Electronics RAS, including pulse generator system provided voltage equal to 150 kW/cm and pulse duration up to 5 ns [1, 2, 4].

The analysis of the mechanisms for nonthermal impact by ultrashort electrical pulses (not more than 10 nanoseconds duration) on nanostructured liposomal capsules containing in the membrane the conducting quasi-spherical or anisotropic nanoparticles, for targeted drug delivery problems and controlled decapsulation was made. The critical parameter values for the external electric field leading to the decapsulation were investigated.

The effect of threshold value reducing for the external electric field due to the presence of significantly anisotropic gold nanoparticles (nanorods) in the liposomal capsule membrane is confirmed by the executed tests [3, 5].

This effect is responsible for selectivity of the external pulse impact under that only nanostructured liposomal capsules are activated, while the surrounding cells that do not contain nanoparticles are not damaged. This selectivity of the impact is very significant for practical applications related to controlled drug delivery in the human body, since it allow to avoid the damage of the body's cellular

membranes, providing structural changes only in the membranes of nanocomposite liposomal capsules.
Criteria that allow predicting and selecting the optimal sizes and shape of nanocomposite liposomal capsules, as well as the optimal size and shape of conducting nanoparticles immobilized in the membrane of such capsules, in order to achieve the minimum values of the critical electric field leading to its decapsulation, were investigated.
Obtained by the authors results confirm the possibility to form hybrid nanocomposite magnetic vesicles and capsules composed of lipids, polymers and nanoparticles whose spatial localization, structure and permeability could be changed remotely by a controllable way through corresponding electromagnetic pulses. Such colloid nanosystems could be the base for development of novel efficient tools for capsulation, targeted controlled delivery of various compounds in aqueous media that is perspective for biomedical and other related applications.
To confirm the absence of the negative effects because of impact by ultrashort electrical pulses on biological objects, the tests of a series with 10 and 50 pulses were executed with Mus Musculus. Voltage pulses U0=1,5x105 V with duration T= 10-8 s were applied to flat electrodes with a gap of L = 3 cm, between that the container with Mus Musculus was placed. No negative consequences regarding mouse's health, activity and mood were detected.
At Figure 1 common view of the experimental system used for tests is presented.

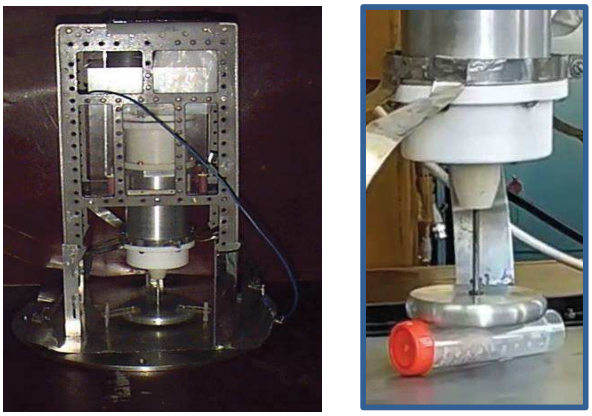

Figure 1. Common view of pulse generator system.

Container with Mus Musculus is placed between flat electrodes with a gap equal 3 cm.

3. Conclusions

1. The synthesized stable biocompatible nanocomposite magnetic liposomal vesicles can be useful in development of novel efficient systems for capsulation, targeted transport, controlled spatial localization and physical stimuli-addressed drug and DNA delivery.
2. The effective release of encapsulated substances can be provided by external ultrashort pulsed electrical effects. The essential feature of such an impact is its non-thermal character. It was confirmed also that impact duration is significant parameter because of ultrashort pulse impact with duration up to 50 ns has direct effect on intracellular structures. It opens new possibilities for the gene delivery to cell nucleus, inducing apoptosis and controlling intracellular processes.
3. Developing technology has the great scientific and practical significance for solution of targeted drug delivery problems, for the development of new effective and safe methods for remote non-thermal activation of nanocomposite capsules by external electromagnetic impact.

4. Acknowledgements

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5. References

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