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Drug Delivery Systems for Antibacterial and Antifibrotic Drugs Based on Lipid–Polymer Complexes

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To date, the pandemic of the new coronavirus infection has turned the world community's view of how to combat the pandemic and forced countries to take unprecedented measures to protect the population. According to Rospotrebnadzor in Russia, a million patients required intensive medical assistance, and then, probably, long-term rehabilitation will be required. Often, COVID-19 is complicated by a bacterial infection in the form of pneumonia, which is treated with antibacterial drugs such as fluoroquinolones. According to the "Algorithm for prescribing antibiotic therapy for SARS-Cov-2-associated lung injury in patients with COVID-19" (guidelines of the Moscow Department of Health), levofloxacin and moxifloxacin (fluoroquinolone-type drugs) are prescribed to a large patient: an allergy to penicillin who have taken other antibacterial drugs of the last 3 months who have somatic diseases (chronic kidney disease stage 3-5, liver cirrhosis, severe chronic lung pathology, congestive heart failure, etc.).

No less acute is the issue of preliminary rehabilitation of patients who have undergone severe COVID-19. The SARS-Cov-2 virus is known to trigger an immune response in the lungs, resulting in tissue fibrosis similar to idiopathic pulmonary fibrosis. This serious illness shows the quality of life of patients and requires therapy. Optimism is the possibility of using two FDA-approved antifibrotic drugs: pirfenidone and nintedanib. A promising approach to reducing the severity of side effects against the background of a sharply increasing number of people requiring antifibrotic therapy, the use of inhaled forms of drugs can reduce the dosage of drugs.

Thus, it is extremely important to develop new drug delivery forms for severe forms of pneumonia caused by a new coronavirus infection, as well as for the rehabilitation of patients with advanced pulmonary fibrosis.

To solve this problem, the approach proposed in our laboratory, based on the use of lipid-polymer submicron particles loaded with the target drug, can be used. As a polymer, it is proposed to use chitosan derivatives of various molecular weights with various substituents.

In this work, we have studied the physicochemical characteristics of the initial (unmodified) liposomal systems based on phosphatidylcholine with additions of cardiolipin and cholesterol, loaded with antibacterial or antifibrotic drugs, and investigated the molecular mechanisms of the interaction of drug molecules with the lipid membrane via FTIR-spectroscopy.

Complexes of liposomal forms with chitosan derivatives with molecular weights of 5 and 90 kDa with substituents mannose or PEG were obtained and investigated. The sites of binding of the polymer to the vesicle and the thermodynamic stability of such complexes have been investigated. The effect of the polymer shell on the slowing down of the release of the content is shown.

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Effect of Phosphatidylinositol, Ganglioside GM_1 and Carboxymethylated Oligoglycine Lipid Conjugate in a Fluid Phase Lipid Bilayer on Interactions with Albumin

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Liposomes are intended for intravenous injections thus interactions with proteins and blood cells are the first physiological barrier to cells and tissues. Albumin is the most abundant blood protein which is also often found in liposome protein coronas. We investigated albumin (BSA) binding to and effect on lipid bilayer by FTIR-spectroscopy. Liposomes were made of egg phosphatidylcholine (ePC) alone or with 10 mol.% of phosphatidylinositol (PI), ganglioside GM_1 or synthetic carboxymethylated oligoglycine lipid conjugate (CMG-PE) (Fig. 1.). We registered liposome spectra in PBS, then added BSA and incubated mixtures for 20 min at 37°C in a cell. Spectra were obtained every 5 min and then analyzed for changes in peaks positions.

Asymmetric stretching vibrations of lipid phosphate groups (1220–1260 cm^{-1}) respond to different molecules binding to liposome surface. Changes in bilayer microenvironment also affects lipid carbonyls absorption band (1715–1745 cm^{-1}). Asymmetric (2920 cm^{-1}) and symmetric (2850 cm^{-1}) methylene stretching vibrations reflect the order of lipid packaging in the bilayer. Changes in protein structure affect the shape of Amide I (1620–1680 cm^{-1}) and result in redistribution of protein structural elements contribution (α-helix, β-sheet and turn, random coil) into the peak form.

Albumin adsorption onto ePC liposomes does not change bilayer order: peak shifts for phosphate (1231 cm^{-1}) and choline (973 cm^{-1}) groups are small to negligible (<0.5 cm^{-1}), and for methylene peaks there are none (ν_{as} = 2924 cm^{-1} и ν_s = 2853 cm^{-1} const). There are no changes in BSA during incubation either, α-helix contribution to the structure remains about 60%. Uncharged liposome surface binds less protein and presumably creates „mild“ conditions for the interaction because there are no functional groups with significant charge which could trigger conformational changes upon binding.

When 10 mol.% of PI, ganglioside GM_1 or CMG-PE were added to the bilayer we detected changes in liposome-protein interactions. Phosphate groups in these liposomes respond to albumin adsorption.