**Development of molecular containers based on polyethylenimines, cyclodextrins, spermine and mannose for targeted delivery to alveolar macrophages of fluoroquinolone-based formulations combined with essential oils**

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The aim of the work is to develop and characterize molecular systems based on cyclodextrins (CDs), polyethylenimines (PEIs) and mannose – carriers for targeted delivery to alveolar macrophages of drugs for the treatment of a wide range of diseases, including postcovid pneumonia and tuberculosis. Biopharmaceutical properties of drugs loaded into molecular containers can be improved: increased solubility and bioavailability, slowing release in tissues, protection from destruction, concentration of drugs in the target organ, tissues – due to the complexation of fluoroquinolones with cyclodextrin derivatives, as well as their copolymers.

4 groups of conjugates with different molecular architecture and physicochemical parameters were synthesized: 1) mesh conjugates of cyclodextrins with a large hydrodynamic size 350-700 nm and a zeta potential of 3-5 mV; 2) linear polyethyleneimines of 35 kDa with grafted CDs - 55 nm, +5-10 mV; 3) star-shaped cyclodextrin conjugate with grafted mannose clusters on spermines - 150 nm, -6 mV; 4) star-shaped cyclodextrin conjugate with grafted branched light (2-10 kDa) chains of PEI – 70 and 370 nm, +4 mV. The variety of conjugate structures will make it possible in the future to select the best drug carriers for specific therapy tasks.

 The "targeting" of macrophage mannose receptors was confirmed by the high affinity binding of ligands with the model lectin concanavalin A due to the presence of mannose clusters on spermines or PEI in conjugates: by changes in the intensity and position of peaks of Amide I and II in the FTIR spectra, by quenching and polarization of tryptophan fluorescence in the protein *K*d ≈ 10-6-10-7 M, the affinity of the natural trimannoside ligand (1·10-5 M).

The inclusion of antibacterial levofloxacin and moxifloxacin molecules in the CD cavity and interaction with the conjugate polymer chains leads to a decrease in the intensity of "aromatic" peaks in the IR spectra and a shift in the maxima/minima of ellipticity in the near UV region in the circular dichroism spectra. Conjugates with high affinity bind from 10-15 to 70 drug molecules with constants of 103-105 M. To reduce the dose of the toxic main component double complexes of inclusion of levofloxacin (Lev) and the synergist eugenol were obtained, which showed a significant increase antibacterial activity: the minimum inhibitory growth of *E.coli* (NCIB 12210) levofloxacin concentration was reduced from 0.1-0.15 µg/ml to 0.02-0.03 due to the adjuvant effect.

The adjuvant apiol significantly enhances and accelerates the antibacterial effect of Lev in the star-shaped conjugate HPCD-spermine-Man in experiments on liquid media, therefore, the MIC of the antibiotic can potentially be reduced. Levofloxacin in conjugates acts more effectively than the free form. Moreover, the effect of prolonged action is observed (the decline of curves against the plateau in the case of Lev).

The advantage of the dosage forms in the composition of conjugates is a prolonged release from 1 hour, but more than 6-12 hours (up to several days), depending on the architecture of the conjugate – to reduce the dosage of the toxic agent, reduce the frequency of administration, increase the friendliness of therapy.

The conducted research has demonstrated a significant therapeutic potential of targeted delivery systems of combined drugs for the treatment of respiratory diseases.

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