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DOCTORAL DISSERTATION

Designing of grafted poly(ionic liquids) as potential drug delivery systems for antibacterial therapy

Promoter: prof. dr hab. inż. Dorota Neugebauer

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SUMMARY OF DOCTORAL DISSERTATION

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During studies, innovative polymer systems were developed as drug carriers for antibacterial therapy of lower respiratory tract diseases, using grafted copolymers containing units of choline ionic liquid, i.e. [2-(methacryloyloxy)ethyl]trimethylammonium chloride (TMAMA), which is known from biological activity. For this purpose, controlled atom transfer radical polymerization (ATRP) was used to obtain the well-defined copolymers. The presence of trimethylammonium groups with chloride counterions, allowed for the pharmaceutical ion introduction, through an ion exchange reaction. Sodium or potassium salts containing pharmaceutical anions used in the treatment of lower respiratory tract diseases, such as *p*-aminosalicylate, clavulanate, fusidate and piperacillin, were selected to modify the choline units, resulting in a ionic conjugates. These carriers showed satisfactory therapeutic amounts of incorporated pharmaceutical anions. Several tests were also conducted using analog linear polymers for comparative analysis.

The amphiphilic properties of graft copolymers and their conjugates, confirmed by critical micellization concentration (CMC), were suitable for encapsulation of selected antibacterial drugs, such as isoniazid, rifampicin and tazobactam. It has been proven that the hydrophobic-hydrophilic balance, the amount of drug contained in the matrix and the ability to nanoparticles forming can be regulated by the structure of the copolymer, as well as by the structure and nature of the drug. An encapsulation of non-ionic drugs in conjugates allowed for obtaining co-delivery systems containing two drugs with synergistic effects. Moreover, the presence of pharmaceutical anions had a positive effect on the encapsulation efficiency of the non-ionic drug in dual systems.

In vitro drug release experiments confirmed (co-)release of transported drugs. The release kinetics was influenced by the structure of the copolymer and the nature of the drug. An effective release process of the pharmaceutical anions was recorded for 4 hours, followed by a slower release lasting up to 24-48 hours. For comparison release of the ionic drug from the linear polymer matrix occurred in the first hour of the process, and then the release slowed down and lasted for approximately 3-4 hours. These observations showed that the release process from the systems based on graft copolymers was more controlled due to the greater stability of nonlinear nanostructures. In turn, the presence of the encapsulated drug in the nanoparticles based on graft copolymers caused a small limitation during pharmaceutical anion release as compared to single systems. *In vitro* cytotoxicity studies of the obtained polymer carriers showed a negligible effect on normal BEAS-2B cell lines and cancer cell A549 proliferation. Considering that an immunologically weakened body during disease is susceptible to the cancer, the effect of selective action of drug delivery systems is extremely desirable.

These findings highlight the potential of graft copolymers with pharmaceutical counterions as promising drug carriers based on the universal polymer matrix for single and dual systems, including drugs with synergistic action, in the treatment of respiratory diseases, such as tuberculosis. In the context of anti-tuberculosis treatment, their rapid action, completing a full cycle within four hours ensure an effective course of treatment.