ZONAL THERMOSENSITIVE STAR POLYMERS BASED ON STEROIDS AND SACCHARIDES AS MODERN DRUG DELIVERY SYSTEMS

The chemistry of natural products (NP) has had a huge impact on the development of many areas of life and scientific disciplines. The use of compounds of plant and animal origin and their derivatives has directly contributed to the introduction of innovations in drug discovery, ecology and environment, toxicology, metabolomics, food science and industry, organic analysis and synthesis, biomedicine and many others. At present, the use of products based on their composition on NP or their derivatives constitutes the majority of currently used drugs or cosmetics. Natural products are inherently better tolerated in the body than their synthetic counterparts, which results from biological (biodegradability, biocompatibility), physicochemical (stability, availability of functional groups, spatial structure) and economic properties. It seems beyond debate that NPs in the face of global public health challenges play a key role in drug discovery and design.

Recent literature reports point to the great potential of cholesterol metabolites (bile acids) in pharmaceutical science. Bile acids are biosynthesized by cholesterol catabolism in the liver. The first stage involves the synthesis of primary bile acids (cholic acid and chenodeoxycholic acid), which are then metabolized in the colon by intestinal bacteria that perform dehydroxylation at position 7 to deoxycholic acid and lithocholic acid respectively. Bile acids are beneficial to the health and longevity of living organisms. Doxorubicin (DOX) is an anthracycline topoisomerase inhibitor that was approved by the FDA (Food and Drug Administration) in 1974. Because of its effectiveness, it is frequently used as a first-choice drug in cancer therapy. Unfortunately, DOX has highly undesirable side effects, in particular, cardiotoxicity, which, despite its clinical effectiveness, is limited. Therefore, it is important to minimize the dose of the drug being taken and that the drug is delivered in a controlled manner, preferably only in the affected area. Effective smart drug delivery systems (SDDS) are currently underway to minimize side effects associated with DOX toxicity.

Smart polymers that are sensitive to external stimuli (physical, chemical and biological) are used to synthesize SDDS. Such properties allow controlled release of drug molecules through phase transition caused by temperature changes, pH changes or the presence of specific enzymes or proteins. One of the most common and interesting are thermosensitive polymers, that change their physical properties with temperature. This phenomenon can be described as solubility in a change of temperature. The most widespread monomer used to synthesize temperature-sensitive polymers is *N*-isopropylacrylamide. Its popularity is caused by several factors, for example, Lower Critical Solution Temperature (LCST), which is close to body temperature, hydrophilicity, high susceptibility to polymerization and due to the use of modern techniques of controlled polymerization the product's molecular weight and dispersity can be controlled.

The overriding objective proposal is the synthesis of stimulus sensitive zonal star polymers based on natural products and encapsulation of biologically active compounds inside them. The incorporation of a hydrophobic steroid system into the polymer chain results in "hiding" this part in the micelle core, which limits its impact on the external environment. Star polymers should increase the impact of hydrophobic parts that would be on the arms' ends. An additional advantage provided by glucose and CD is the possibility of zonal building of star polymers. This is a new approach in the synthesis of drug delivery systems and in addition, they will be based on natural products, which allows us to claim that they will be safely metabolized in the body. The incorporation of a certain number of repeat units is possible due to the employment of controlled RAFT/MADIX polymerization technique.

Selected systems with the best physicochemical parameters will be tested to determine their biological properties. The most important biological studies are: examination of hemolytic activity, research on the interaction of obtained polymers with biological membranes and studies evaluating the survival of physiological and cancer cells of estrogen-dependent MCF-7 breast cancer.

We hope that the implementation of the project will expand knowledge about drug carriers containing steroid systems with a spatially developed structure. It will contribute to understanding the interaction with natural membranes and slowly explaining how the carrier works and establishing the activity-structure relationship.