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HAFNIUM OXIDE MODIFICATION FOR DRUG DELIVERY

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In this study synthesis of drug delivery nanoplatform for cancer treatment was developed. The purpose of the study was to formulate and characterize a new drug-delivery system based on hafnium oxide (Z=72).

Nowadays, cancer is one of the leading causes of the death worldwide. Smoking, obesity, poor diet, lack of physical activity, excessive drinking of alcohol along with certain infections, exposure to ionizing radiation and environmental pollutant lead to genetic changes in cells, and, therefore, their excessive growth [1]. There is a great variety of techniques to cause tumour death: chemotherapy, radiotherapy, surgery, immunotherapy. However, each of them has its own drawbacks, the main one being the death of the healthy tissue as well as of the malignant ones. To provide a more effective therapy, a combined approach may be a promising option. For example, nanoparticles of high-Z elements can be used as both radiosensitizers [2] and drug carriers, that bring therapy exactly to where it is needed because of the EPR effect [3, 4]. However, it is important to remember that nanoparticles without "stealth" coverage are attacked by the blood proteins and cleared from the organism through the reticuloendothelial system. One of the most widely used polymers to avoid the formation of protein corona is polyethylene glycol (PEG). The numerous studies have shown that the addition of PEG prolongate the blood circulation time allowing bigger accumulation of nanoparticles in the tumour [5, 6].

The nanoparticles obtained through a simple sol-gel route allowed us to provide radiotherapy and chemotherapy to malignant tissue. The controlled hydrolysis of hafnium n-butoxide was carried out in isopropanol (IPA) while the water for the reaction was produced in situ through esterification of IPA by acetic acid. The fluorescent mark was attached to the surface during sol step to enable the visibility in cells experiments. For that purpose, Rhodamine B was chosen because it contains carboxylic group which can interact with the surface of nanoparticles. As the nanoparticles were formed from aerogel, they possess a great surface area (SBET = 266 $m^2 \cdot g^{-1}$) which is beneficial for the absorption of various molecules. To enable drug delivery the layer of oleic acid was introduced allowing the encapsulation of water insoluble drugs such as doxorubicin (DOX) used in this study. The drug release proved to be pH dependent because the DOX molecule hydrophobic at pH=7 becomes hydrophilic at pH=4. The final step of functionalization is the coverage with amphiphilic block copolymer. mPEG-PCL was specially synthesized through a ring-opening polymerization of ε-caprolactone to enable both solubility in water and protection against protein corona which is usually formed in the blood stream. Unlike the oleic acid the polymer is not covalently bonded to the surface but its hydrophobic moiety is physically absorbed into the hydrophobic layer. As the application implies living organisms, tests on cell cultures HCT-116 and HPF were conducted to prove the absence of cytotoxicity without any irradiation.

The nitrogen sorption was used to describe the surface area and pore size of the initial HfO2. X-ray diffraction (XRD) confirmed the formation of amorphous hafnium oxide that is beneficial for the X-ray irradiation as the electron pathway through crystal structure is shorter. The nanoparticles have been characterized through transmission electron microscopy (TEM) and scanning electron microscopy (SEM) to establish the composition and nanoparticle size of the derived platform. Dynamic light scattering (DLS) helped to estimate the size of hydration shell around pure and modified nanoparticles in various media. Fourier transform infrared spectroscopy (FTIR) proved the appearance of oleic acid and mPEG-PCL on the surface. The structure of polymer was proved by 1H nuclear magnetic resonance spectrum (NMR) and FTIR. Gel permeation chromatography (GPC) established the size and polydispersity of the polymer. The effectiveness of DOX entrapment and the pH-dependent release were studied by UV-Vis spectroscopy.

To sum up, a new drug delivery platform was synthesized and characterized. The first biological tests have shown that our system is very promising and future investigations on living organisms are expected.

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