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pH-responsive delivery of doxorubicin from citrate–apatite nanocrystals with tailored carbonate content

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Abstract-

In this work, the efficiency of bioinspired citrate-functionalized nanocrystalline apatites as nanocarriers for delivery of doxorubicin (DOXO) has been assessed. The nanoparticles were synthesized by thermal decomplexing of metastable calcium/citrate/phosphate solutions both in the absence (Ap) and in the presence (cAp) of carbonate ions. The presence of citrate and carbonate ions in the solution allowed us to tailor the size, shape, carbonate content, and surface chemistry of the nanoparticles. The drug-loading efficiency of the two types of apatite was evaluated by means of the adsorption isotherms, which were found to fit a Langmuir–Freundlich behavior. A model describing the interaction between apatite surface and DOXO is proposed from adsorption isotherms and ζ-potential measurements. DOXO is adsorbed as a dimer by means of a positively charged amino group that electrostatically interacts with negatively charged surface groups of nanoparticles. The drug-release profiles were explored at pHs 7.4 and 5.0, mimicking the physiological pH in the blood circulation and the more acidic pH in the endosome-lysosome intracellular compartment, respectively. After 7 days at pH 7.4, cAp-DOXO released around 42% less drug than Ap-DOXO. However, at acidic pH, both nanoassemblies released similar amounts of DOXO. In vitro assays analyzed by confocal microscopy showed that both drug-loaded apatites were internalized within GTL-16 human carcinoma cells and could release DOXO, which accumulated in the nucleus in short times and exerted cytotoxic activity with the same efficiency. cAp are thus expected to be a more promising nanocarrier for experiments in vivo, in situations where intravenous injection of nanoparticles are required to reach the targeted tumor, after circulating in the bloodstream.

Index Terms-

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