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Hyaluronan functionalized pH-responsive calcium carbonate nanoparticles for local treatment of breast cancer

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INTRODUCTION: Current radio- and chemotherapies are not efficient and many tumors remain resistant to conventional cancer treatments. Specific properties and signaling molecules from tumor microenvironment (TME) have been explored to increase treatment efficacy. An example is the acidic pH of the TME that has been explored to develop stimuli responsive release systems. Herein, we obtained biocompatible calcium carbonate ($CaCO_3$) nanoparticles that are stable at neutral pH but dissolve at acidic conditions and evaluated their potential as a drug carrier for local cancer treatment.
METHODS: $CaCO_3$ nanoparticles were produced by co-precipitation of calcium chloride ($CaCl_2$) and sodium carbonate (Na_2CO_3) in the presence of ethylene glycol [1]. Rhodamine was encapsulated as a model drug. The morphology and diameter of the nanoparticles were determined by scanning electron microscopy and dynamic laser scattering. The particles were coated by layer-by-layer (LbL) assembly of poly-L-lysine and hyaluronic acid (HA). The release was studied in phosphate buffered saline at pH 6.3 and 7.4. Cultures of two breast cancer cell lines (MDA-MB-231 and SK-BR-3) and a healthy epithelial cell line MCF10A (control) were observed under confocal laser scanning microscopy to assess particles internalization and their effect on cell viability (live/dead staining) and metabolic activity (Alamar Blue).
RESULTS: We obtained nanoparticles with a diameter of 560 nm and negative charge that allowed deposition of a LbL coating containing HA - a specific ligand for CD44 receptors overexpressed in cancer cells. The coating and the pH affected the kinetics and quantity of rhodamine release. The coating reduced the release at pH 6.3 two-fold, and three-fold at physiological pH 7.4. Significantly more nanoparticles were internalized after the coating by the cancer cells MDA-MB-231 and SK-BR-3, which inhibited their metabolic activity (48h). The nanoparticles had little effect on the healthy MCF10A cells.
DISCUSSION & CONCLUSIONS: $CaCO_3$ particles are advantageous encapsulation systems because therapeutics can be conveniently embedded during their production. Our results demonstrated a higher release at the pH found in the TME and a double role of the coating in tuning the release profile and internalization that was dependent on the expression of CD44. Keeping in mind the possibility to tailor the size and morphology of $CaCO_3$ nanoparticles as well as the thickness of the coating, we suggest that this system is an excellent candidate for local stimuli responsive cancer therapy.
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