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Synthesis and Functionalization of Radium-doped Barium Sulfate Nanoparticles

Objectives

The radionuclides radium-223 and radium-224 are two alpha-emitting radionuclides with suitable properties for the TAT. To this date, radium-223 in form of [223Ra]radium chloride (Xofigo) is the only EMA and FDA approved alpha-emitting radiopharmaceutical. Due to its calcimimetic behavior, the radium ion is a bone-seeking therapeutic. To extend the radiopharmaceutical potential of both radionuclides, novel carrier systems have to be developed. Therefore, it is appropriate to investigate different kinds of nanoparticles for their ability to transport radium. Especially, a barium sulfate matrix seems to be sufficient since the principle of co-precipitating the sulfates of radium and barium allows an easy and fast synthesis of radium-doped nanoparticles. Beyond the incorporation of alpha-emitting radionuclides like radium-223 and radium-224, the homologue radionuclide barium-131 can be incorporated as well. Barium-131 decays by electron capture and provides suitable properties for diagnostic applications in nuclear medicine. Radium-223/-224 and barium-131 form a matched pair for new theragnostic approaches. In our research group, we are developing simple methods for the synthesis of small radiolabeled radium/barium sulfate nanoparticles. Furthermore, we are investigating suitable surface functionalizations to attach biological targeting moieties.

Methods

Nanoparticles were synthesized by simple precipitation. Three different methods have been investigated: microemulsion systems, water/THF mixtures, and water/ethanol reaction systems. The reactions were performed under a variety of different parameters. Particle size distributions were determined initially by dynamic light scattering (DLS) and transmission electron microscopy (TEM), respectively. Using a one-pot method, the synthesis of alendronate-coated nanoparticles was achieved. The radiolabeling of the nanoparticles was performed using the water/ethanol reaction method. [224Ra]radium nitrate was separated from a Thorium-228 source by ion exchange chromatography. [133Ba]barium chloride was commercially obtained and used for test labeling instead of barium-131.

Results

The smallest nanoparticle sizes of around 150 nm (measured by DLS) were obtained by using the water/ethanol barium sulfate precipitation method. The functionalization with alendronate derivative was proven by infrared spectroscopy and the further reactivity of the alendronate functionalities was verified by active ester coupling with a dye and the performance of fluorescence spectroscopy measurements, respectively. The radiolabeling of the nanoparticles was successfully tested via co-precipitation of radium/barium sulfate by substituting equivalent amounts of non-radioactive Ba2+ by [133Ba]Ba2+ and [224Ra]Ra2+, respectively. TEM measurements showed that the actual average particle size is comparable to the DLS results.

Conclusions

The successful co-precipitation method can be a starting point for future therapeutic applications. The functionalization and reactivity showed that it is in principle possible to attach any targeting unit. Next steps will deal with the optimization of the particle size, the design of targeting moieties and the performance of first biological studies.

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Presentation Type

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