Synthesis of positron emitter labeled metal oxide nanoparticles for biodistribution studies by direct activation with high energy protons

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Nanoparticles (NPs) are widely used and have potential applications in different areas like health care, electronics, manufacturing, food industry, etc. The widespread use of NPs raises several issues regarding their possible toxicological end points. A key issue regarding the study of the possible toxicological effects of NPs is to determine their biological fate and biodistribution. For this, the use of animal models and the application of techniques such as Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) become highly necessary. There is, therefore, an increasing interest for the development of radiolabeling strategies of such NPs, either to determine their pharmacokinetic properties or to assess potential toxicological effects related to long term exposure.

The objectives of the present work are:

1. To develop a new strategy for the introduction of a radioactive atom (positron emitter) in the core of metal oxide NPs.
2. To characterize NPs before and after irradiation to evaluate the effects of activation in the physic-chemical properties.
3. To perform preliminary in vivo biodistribution studies in rodents.

Aluminum oxide NPs incorporating Oxygen-18 in their crystalline structure (which can be activated to the positron emitter Fluorine-18, half-life = 110 min) were synthesized by dissolving an aluminum salt ($AlCl_3$, $Al_2(SO_4)_3$) in [^{18}O]H_2O in the presence of a base (NH_4OH, Urea). NPs were irradiated with 18 MeV protons in an IBA cyclone 18/9 cyclotron. The activated NPs were introduced in a specifically designed phantom and measured with a PET camera (eXplore Vista-CT, GE Healthcare) for 6 hours in 1-20 minutes frames. Time-Activity Curves were obtained and the percentage of the activity as ^{18}F was determined. In the best scenario ($AlCl_3$ / NH_4OH) up to 570 MBq/g of ^{18}F were produced in 6 minutes (Beam intensity on target: 5 μA, beam current: 0.5 μAh). Characterization by means of TEM, light Scattering and X-Ray showed no significant changes in crystal structure, crystal size and NP size after irradiation. In vivo studies were performed using PET after administration of the radioactive NPs to mice and rats (I.V. and oral). Images were co-registered with MRI to localize anatomically regions of interest (ROIs) and Time-Activity curves were determined for liver, kidneys, brain, lungs, stomach, intestine and bladder.

In conclusion, metal oxide NPs containing ^{18}O could be synthesized and activated by bombardment with high energy protons. The irradiation process did not introduce significant changes in particle size and crystal structure. Final amount of radioactivity was sufficient to perform whole body in vivo biodistribution studies in rodents.