Lanthanide nanoparticles as vascular contrast agents for preclinical computed tomography

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**Introduction:** Recent advances in nanotechnology have led to the development of vascular contrast agents for preclinical computed tomography (CT). The advantage of using nanoparticles is the ability to achieve prolonged residence times for preclinical CT, which can take tens of minutes; this is attained by polymer-coated nanoparticles exceeding 10 nm in size. Although long-circulating nanoparticle agents exist for preclinical CT, they are predominantly based on iodine, which has a low atomic number. Superior CT contrast can be achieved using lanthanides (i.e. erbium) that have higher atomic numbers, particularly at energies exceeding 72 kVp. While lanthanide-based contrast agents are used clinically in MRI, they are composed of small molecules (<1 nm) that exit the blood pool of small animals within seconds. Thus, the purpose of our work is to develop polymer-encapsulated erbium nanoparticles exceeding 10 nm in size into a vascular contrast agent for preclinical CT.

**Methods:** Nanoparticle synthesis- Erbium nanoparticles were synthesized by following a method reported by Zhao et al. Ten different encapsulations – each composed of 20 mg/mL of varying polymers – were prepared using 3.5 mg/mL of erbium. Large aggregates were removed by passing the samples through a 450 nm syringe filter. The encapsulations were freeze-dried followed by re-concentration in water, saline and a mouse blood pool mimic.

**Characterization-** Erbium contents were measured by inductively coupled plasma mass spectrometry using the Agilent 7700. The average hydrodynamic sizes were measured by dynamic light scattering (DLS) using the Malvern Zetasizer Nano ZS instrument. Transmission electron microscopy (TEM) was done using the Philips CM10 microscope.

**Optimization of the contrast agent-** From the series of polymers that were studied, the formulation that remained stable after re-concentration and had relatively higher erbium content than the others was studied further. Additional samples containing 10, 5 and 2.5 mg/mL of polymer were prepared using 3.5 mg/mL of erbium. The samples were filtered, re-concentrated and characterized as described above.

**Micro-CT of the contrast agent-** The optimized polymer-encapsulations were scanned with the GE Locus SpeCZT along with calibrators of known erbium content. Scans were acquired at 90 kVp, 40 mA (900 views, 16 ms per view) and the reconstructed images were rebinned at 2 × 2 for a voxel size of 100 × 100 × 100 µm. Images were analyzed using MicroView and linear regression was used to determine the relationship between Hounsfield Units (HU) and mg/mL of erbium.

**Results:** The synthesized erbium nanoparticles had an average hydrodynamic diameter of 49.9 ± 2.3 nm with a polydispersity index of 0.2, indicating a moderately polydisperse size distribution. The size of the polymer-encapsulations ranged from average sizes of 52.9 ± 1.1 nm up to 176.0 ± 3.8 nm, all of which were moderately polydisperse in size or better. The TEM images of the samples were in good agreement with the DLS-measured diameters. The optimized formulation was measured to encapsulate all the erbium that was used in their preparation, even at lower polymer content; all formulations of the optimized polymer were also stable in saline for up to a day and a mouse blood pool mimic for up to an hour. Finally, an attenuation of up to 3390 ± 13 HU was achieved by the contrast agent at 90 kVp, which corresponds to an erbium content of up to 113 mg/mL.

**Conclusion:** Moderately polydisperse erbium nanoparticles containing up to 113 mg/mL of erbium were successfully synthesized. The contrast agent was stable in saline and a mouse blood pool mimic for up to one hour, suggesting that it will circulate in the vasculature of mice during this time. This work represents the development of the first lanthanide-based contrast agent that is targeted for in vivo preclinical imaging. No such agent has been synthesized previously.

**References:**