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CASE STUDY

Department of Radiology and Nuclear Medicine, UMC Utrecht

Phenom Desktop SEM for the development of a radioablation device

A one-stop electron microscopy experience

Radioembolization is a type of internal radiation therapy developed for the treatment of liver tumors. The therapy selectively administers radioactive particles to the hepatic artery, which the tumors rely almost exclusively on for their blood supply. This leads to a selective accumulation of the particles around the tumor tissue, allowing it to be irradiated while the healthy liver tissue is spared.

Since the mid-nineties, research has been carried out at the Department of Radiology and Nuclear Medicine of the University Medical Center Utrecht (UMC Utrecht) on holmium-166 poly (L-lactic acid) microspheres (166HoPLLAMS). These microspheres are currently under clinical investigation in patients with unresectable liver malignancies.

Holmium microspheres, approximately 30 µm in diameter, are prepared in a non-radioactive manner by direct solvent evaporation, and are then made sufficiently radioactive by neutron activation in a nuclear reactor. The amount of radioactivity obtained per milligram of microspheres can be increased by extending the neutron irradiation time. Conversely, longer neutron irradiation times may lead to structural damage of the microspheres. Electron microscopy has proven to be a crucial tool in the determination of the maximum neutron irradiation time by assessing the structural integrity of these particles. The Thermo Scientific™ Phenom Desktop Scanning Electron Microscope (SEM), with its high resolution and fast image processing, allows for high throughput screening of a large number of samples in a short amount of time.

More recently, Dr. Frank Nijsen (Department of Radiology and Nuclear Medicine, UMC Utrecht) initiated the development of a radioablation device for direct intratumoral injection into solid malignancies, so-called ”tumor radioablation.” A thorough understanding of the particles’ shape, size and surface before and after neutron irradiation is required to ascertain the suitability of these particles for intratumoral administration. Based on the Phenom Desktop SEM images, the process characteristics have been optimized to further improve the microspheres.

In another study, the particle stability was investigated to ascertain their suitability as radioablation devices. The particles’ integrity after suspension in a buffer can be used as a surrogate test for particle stability *in vivo*. In addition to holmium measurements in the buffer, electron microscopy was used to determine particle integrity. Since the Phenom desktop microscope can handle magnifications from the millimeter to the micrometer range, it was possible to acquire high-resolution images of microsphere aggregates, as well as of single microspheres.

Why Phenom Desktop SEM

High-resolution scanning electron microscopy is very valuable for determining the microspheres’ quality. The Phenom Desktop SEM has proven to be the ideal solution for determining these factors. The intuitive controls allowed for high-resolution imaging by students and technicians with minimum training, thereby further improving the workflow. In addition, the storage of data on a USB drive is ideal, since the scientist can take the micrographs to their workplace after image acquisition. The Phenom Desktop SEM offers a ”one-stop electron microscopy experience,” allowing fast, yet high-resolution, image acquisition.

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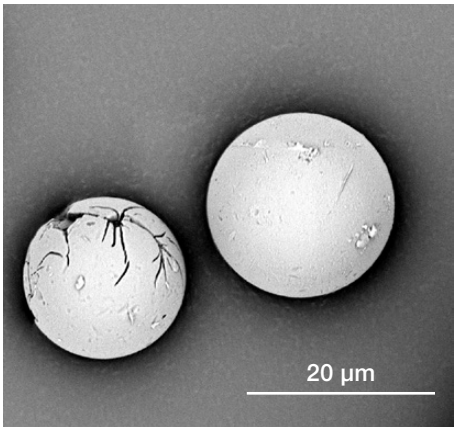
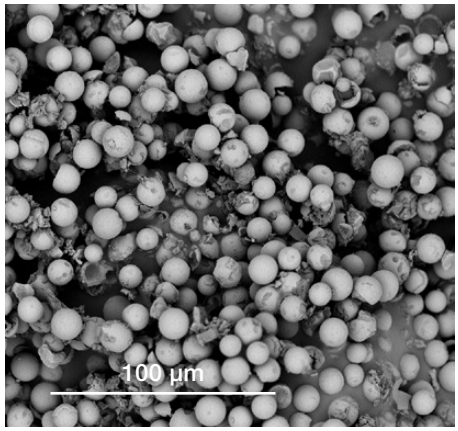
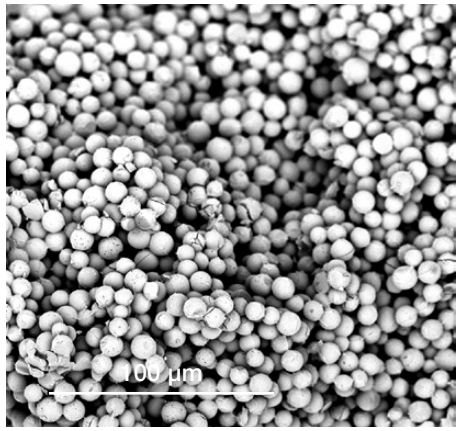
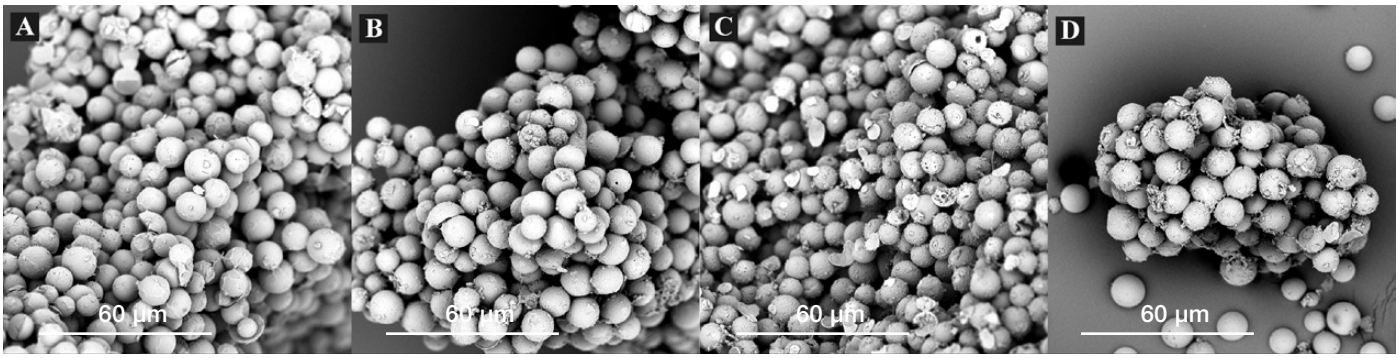


Cracked particle surface as a result of rapid solvent evaporation.

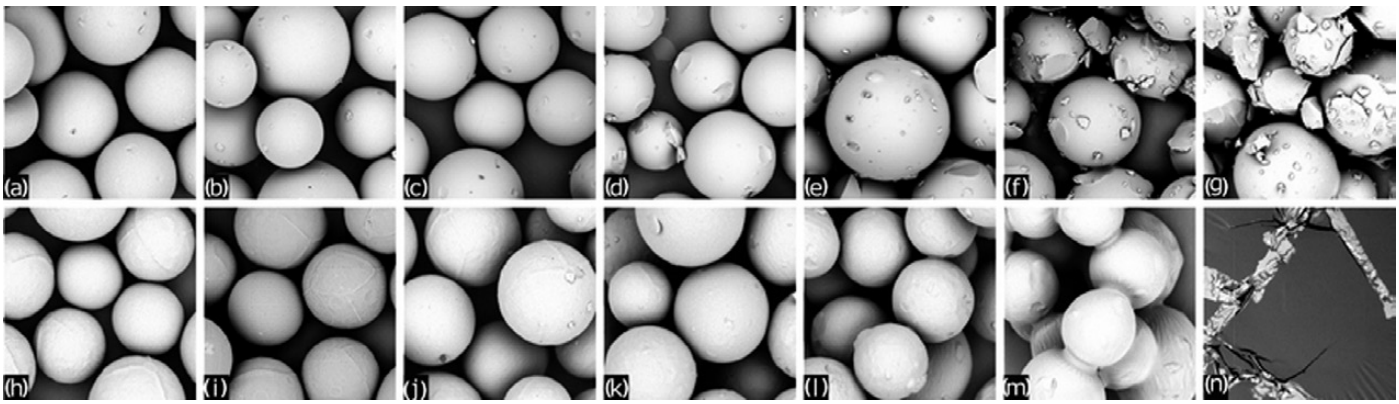




Surface of holmium acetylacetonate microspheres after suspension in human serum for two weeks as a surrogate marker for the short term stability of the microspheres before neutron irradiation.



Electron micrographs showing the surface of holmium acetylacetonate microspheres after suspension in phosphate buffer for a) one day, b) one week, c) one month and d) six months.



Scanning electron micrographs of Ho-PLLA-MS, either non-irradiated or neutron-irradiated for 2, 4, 6, 7, 8, or 10 hours (a-g). Damage is absent or minor in samples irradiated up to 7 hours (a- e). Small microsphere fragments are seen on the dented surface of the 8-hour irradiated microspheres (f). Disintegration has progressed in the 10-hour irradiated microspheres, with many microspheres actually having been broken into several large chunks, while many smaller fragments are visible as well (g). Scanning electron micrographs of PLLA-MS, either non-irradiated or neutron-irradiated for 2, 4, 6, 7, 8, or 10 hours (h-n). Damage is absent in samples irradiated up to 6 hours (h-k). A tendency to interfusion is observed in the 7-hour irradiated samples (l). Microsphere fusion is more frequently seen in the 8-hour irradiated samples (m). In the 10-hour irradiated samples, the microspheres had completely melted and non-identifiable remnants of microspheres were found (n). *Figure courtesy of Vente et al.,* Biomed Microdevices*, 2009 Aug;11(4):763-72*

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