

Desktop SEM imaging in the development of a radioablation device

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Radioembolization is a type of internal radiation therapy developed for the treatment of liver tumors. Liver tumors rely almost exclusively on the hepatic artery for their blood supply. In radioembolization, radioactive particles are selectively administered to the hepatic artery, leading to a selective accumulation of these particles around the tumor. Consequently, the tumor tissue is irradiated, whilst sparing the healthy liver tissue. Since the mid-nineties, research has been carried out at the nuclear medicine department of the University Medical Center Utrecht (UMCU) on holmium-166 poly (L-lactic acid) microspheres (¹⁶⁶HoPLLAMS). These microspheres are currently under clinical investigation in patients with unresectable liver malignancies.



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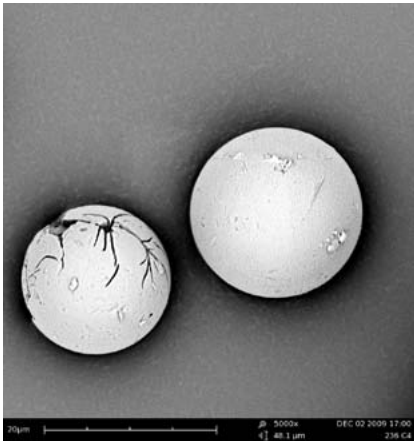
The Phenom offers a one stop electron microscopy experience"

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 a crucial tool in the determination of the maximum neutron irradiation time by assessing the structural integrity of these particles. The Phenom's high resolution and fast image processing allow for high throughput screening of a large number of samples in a short amount of time.

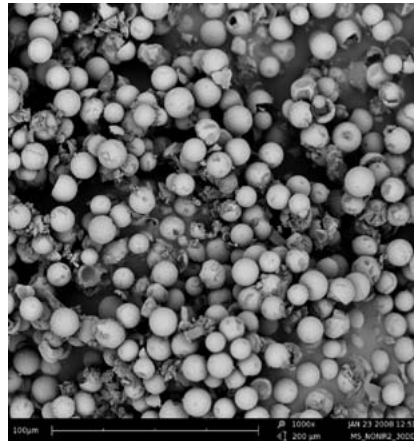
More recently, Dr. Frank Nijsen at the Department of Nuclear Medicine of the UMCU initiated the development of a radioablation device for direct intratumoral injection into solid malignancies, so-called "tumor radioablation". A thorough understanding of the particles' shape, size and surface before and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

In another study, the particle stability was investigated to ascertain the suitability of these novel particles 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.

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



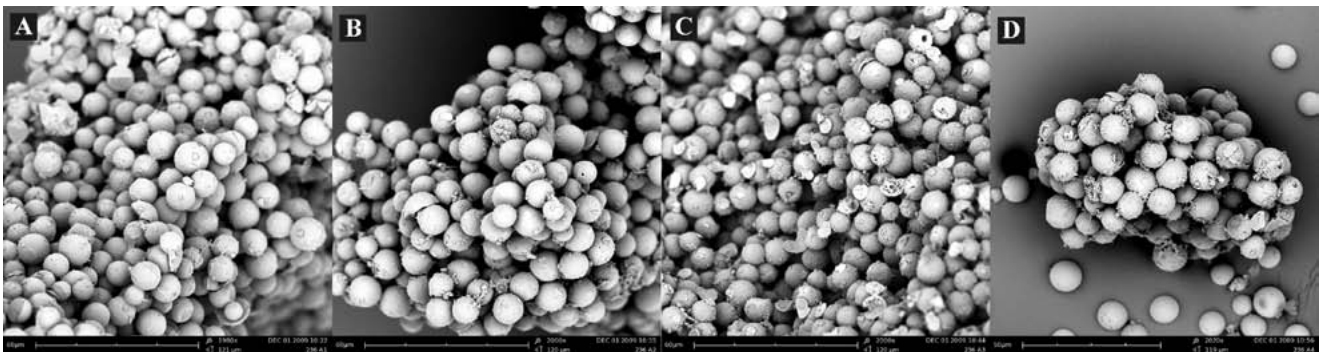
Cracked particle surface as a result of rapid solvent evaporation.



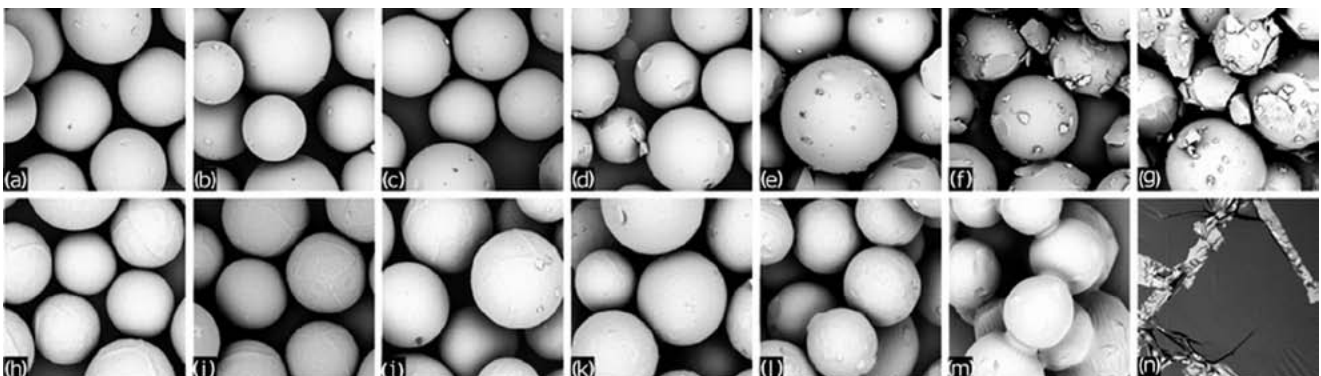
Surface of holmium acetylacetonate microspheres after suspension in human serum for two weeks as a surrogate marker for the short term stability of the microspheres before neutron irradiation.



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 after 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, non-irradiated, neutron-irradiated for 2, 4, 6, 7, 8, or 10-h. (a-g). Damage is absent or minor in samples irradiated up to 7-h (a-e). Small microsphere fragments are seen on the dented surface of the 8-h irradiated microspheres (f). Disintegration has progressed in the 10-h irradiated microspheres, with many microspheres actually having been broken into several large chunks, while many smaller fragments visible as well (g); Scanning electron micrographs of PLLA-MS, non-irradiated, neutron-irradiated for 2, 4, 6, 7, 8, or 10-h. (a-n). Damage is absent in samples irradiated up to 6 h (h-k). A tendency to interfusion is observed in the 7-h irradiated samples (l). Microsphere fusion is more frequently seen in the 8-h irradiated samples (m). In the 10-h irradiated samples, the microspheres had completely melted and no identifiable remnants of microspheres were found (n). Figure taken from Vente et al., *Biomed Microdevices*. 2009 Aug;11(4):763-72.