



# Synthesis and characterization of holmium phosphate microspheres applied to radioembolization studies in the treatment of hepatocellular carcinoma

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## 1. Introduction

Liver cancer is receiving increasing attention, as it is estimated that by 2025 more than 1 million people will be affected. As hepatocellular carcinoma (HCC) accounts for 90% of primary cases of liver cancer [1]. Currently, available treatments have been employed according to the disease stage. One promising treatment is radioembolization, where microspheres are introduced through the hepatic artery and locally irradiate the tumor. This involves a procedure in which radioactive microspheres, with a diameter close to the caliber of the vessels that supply the tumor, are introduced through the femoral artery, reducing blood supply to the tumor and irradiating it with high-energy  $\beta$ - particles. Thus, the synthesis of phosphate microspheres containing the holmium-166 radioisotope was utilized. This is advantageous for imaging by Single Photon Emission Computed Tomography (SPECT) [2].

For these microspheres to be used in radionuclide therapy, they must strictly meet the following properties: mechanical stability to support transport through blood capillaries; chemical stability to resist elution of radioactive elements and not undergo radiolysis; narrow and adequate size distribution (between 20  $\mu\text{m}$  and 60  $\mu\text{m}$ ) to lodge in tumor arterioles; adequate density to prevent sedimentation and facilitate labeling with radionuclides; emission of high-energy beta particles and intermediate physical half-life (days) [3].

## 2. Methodology

$\text{HoPO}_{4(s)}$  microspheres were obtained from 1g, previously synthesized  $\text{Ho}_2\text{Acac}_{3(s)}$  microspheres, which were dispersed in a  $0.58 \text{ mol.L}^{-1}$  monobasic sodium phosphate solution. The dispersion was kept under stirring at 500 rpm for 2 h at room temperature. Then separated by centrifugation, washed in deionized water three times, vacuum filtered and dried under reduced pressure for 24 hours at room temperature [4]. After drying, the microspheres were characterized regarding their elemental composition, microstructure, thermal behavior and density.

## 3. Results and Discussion

Regarding composition, data obtained using the ray fluorescence spectroscopy technique showed that

microspheres were obtained with 81.74 % holmium oxide, 17.11 % phosphorus pentoxide and 1.16 % silicon oxide contaminant. The synthesized  $\text{HoPO}_4(\text{s})$  microspheres were characterized and tested for microstructure using the X-ray diffraction technique, in which characteristic of amorphous material was observed, Fig. 1. Assessment by scanning electron microscopy showed that the microspheres formed maintain homogeneous morphology and distribution within the appropriate distribution range, Fig. 2a. After characterization, the microspheres underwent neutron activation of the radionuclide  $^{166}\text{Ho}$  for 8 h under a neutron flux of  $1.54 \times 10^{12} \text{ n.cm}^{-2}.\text{s}^{-1}$  and, subsequently, evaluated by scanning electron microscopy, showing that the microspheres remained intact, Fig. 2b.

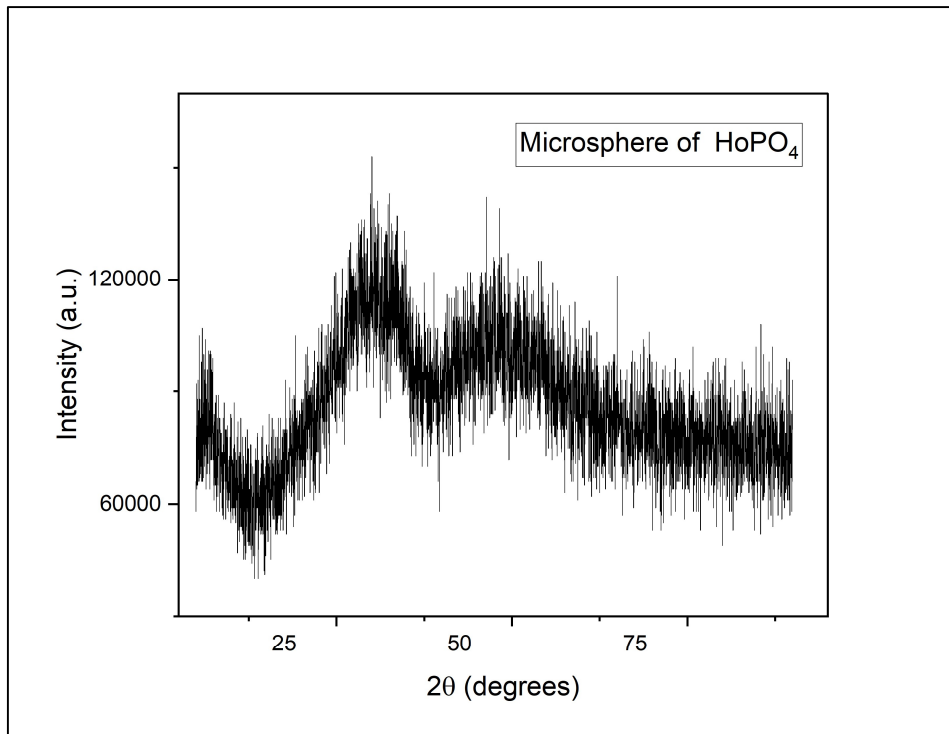


Figure 1. X-ray diffraction diagram of  $\text{HoPO}_4(\text{s})$  microspheres, showing that it is an amorphous structure.

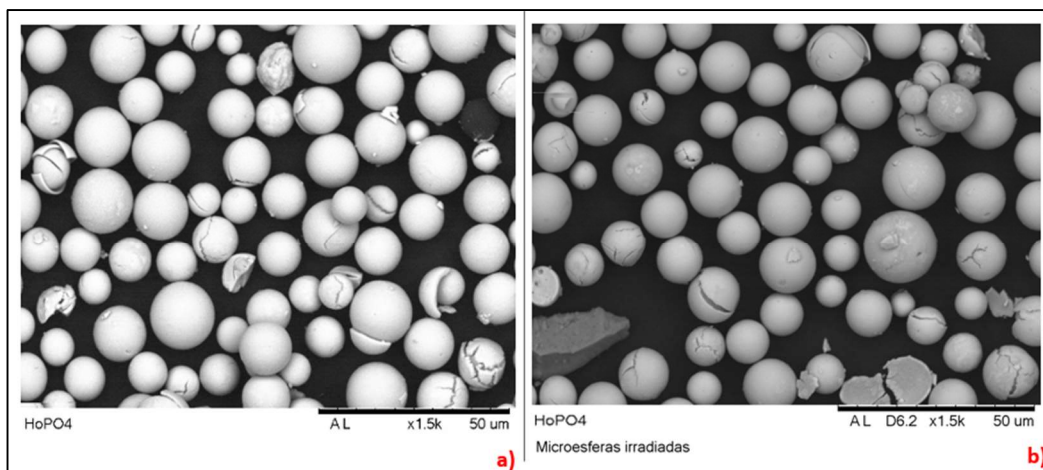


Figure 2. a) Micrograph of  $\text{HoPO}_4(\text{s})$  microspheres. b) Micrograph of  $\text{HoPO}_4(\text{s})$  irradiated microspheres.

#### 4. Conclusions

Based on the preliminary results obtained, it can be stated that  $\text{HoPO}_4$  microspheres are promising for continuing studies aimed at treating HCC by radioembolization.

### Acknowledgements

The authors would like to thank IPEN's Inter-Centers Program for funding Project 2018.05.IPEN.07 and CNPq for the Ana Paula Curcio Master's Scholarship.

### References

- [1] J.M. Llovet, et al., "Hepatocellular carcinoma," *Nature Reviews Disease Primers*, vol.7, no. 6, pp. 1–28 (2021).
- [2] M.T.M. Reinders, et al., "Holmium-166 Microsphere Radioembolization of Hepatic Malignancies," *Seminars in Nuclear Medicine*, vol. 49, pp. 232–240 (2019).
- [3] E.B.F. Cordeiro, "Desenvolvimento de microesferas de vidro fosfato contendo hólmio para uso em radioterapia interna seletiva," 2016, 189 f., Tese de Doutorado em Tecnologia Nuclear, Instituto de Pesquisas Energéticas e Nucleares, Universidade de São Paulo, São Paulo, 2016.
- [4] A.G. Arranja, et al., "Radioactive holmium phosphate microspheres for cancer treatment," *International Journal of Pharmaceutics*, vol. 548, pp. 73–81 (2018).