

## DEVELOPMENT OF PHOSPHATE GLASS MICROSPHERES CONTAINING HOLMIUM FOR SELECTIVE INTERNAL RADIOTHERAPY

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**Abstract:** Selective internal radiotherapy is used to treat hepatocellular carcinoma. Glass microspheres containing  $\beta^-$  particle emitter radionuclides are introduced into the liver close to the tumor. The microspheres are trapped in the arterioles which feed the tumor. The irradiation with  $\beta^-$  particles can cause the death of cancer cells. In this work the development of phosphate glass microspheres containing holmium is proposed.  $^{165}\text{Ho}$  has a high cross section for neutron absorption enabling the production of  $^{166}\text{Ho}$  which decays to  $^{166}\text{Er}$  by emitting a  $\beta^-$  particle. The microspheres were produced using the flame method and characterized by different techniques to evaluate their potential use in radiotherapy. Microspheres with suitable morphology, size, density, and holmium concentration were obtained.

### Introduction

Cancer is one of the major causes of mortality among human beings due to its aggressiveness in the healthy tissues. Despite of all advances in technology in the early diagnostic, cancer still remains a hidden threat, and of unexpected occurrence <sup>(1)</sup>.

Hepatocellular carcinoma (HCC) or primary liver cancer is the fifth kind of cancer most commonly found worldwide. <sup>(2-5)</sup>

The treatment of HCC is considered a challenge and the only effective treatment is surgery followed by transplantation. Due the late diagnosis associated to the slow growth of the tumor, only 10 to 15% of patients are submitted to surgical procedures <sup>(3,6)</sup>. Selective internal radiotherapy or radioembolization can also be used as a treatment to HCC. This therapy consists of the use of microspheres containing  $\beta^-$  particle emitter radionuclides which are introduced in the liver through a catheter inserted in the hepatic artery. When the microspheres reach the liver they are trapped in the arterioles that feed the tumor. The emission of  $\beta^-$  particles by the microspheres delivers high doses directly in the tumor causing the death of the cancer cells. Usually aluminosilicate glass microspheres containing yttrium are used and commercially available (known as theraspheres<sup>®</sup> - MDS Nordion company).

Phosphate glasses were previously investigated as an alternative to be used in the selective internal radiotherapy <sup>(7)</sup>. In that case  $^{31}\text{P}$  was the  $\beta^-$  emitter. However, this approach is not suitable for the Brazilian conditions due to the relatively low cross section of  $^{31}\text{P}$  for neutron absorption and the low neutron flux of the nuclear reactors in Brazil. The  $^{165}\text{Ho}$  has an advantage to this application, especially considering its relatively high cross section to neutron capture and the fact that  $^{166}\text{Ho}$  is a  $\beta^-$  and  $\gamma$  ray emitter. Therefore,  $^{166}\text{Ho}$  could be easily produced in low neutron flux. In this work, the development of phosphate glass microspheres containing holmium is evaluated considering that phosphate glasses are good matrices of rare earth ions. Besides that, the preparation of phosphate glasses usually requires lower melting temperatures when compared to aluminosilicate glasses. Phosphate glass particles containing holmium were obtained through the traditional melting/cooling method and glass microspheres were produced by re-heating those particles. The density, final

chemical composition, crystalline phases, thermal properties, and materials morphology were determined.

### Experimental procedure

Glasses with composition  $25\text{Ho}_2\text{O}_3.75\text{P}_2\text{O}_5$  (%mol) were prepared after melting and cooling mixtures of  $(\text{NH}_4)_2\text{HPO}_4$  and  $\text{Ho}_2\text{O}_3$ . This composition was chosen based on the phase diagram of  $\text{P}_2\text{O}_5\text{-Al}_2\text{O}_3\text{-La}_2\text{O}_3$ <sup>(8)</sup>. The chemical compounds were mixed by using a porcelain pestle and a mortar during 20 minutes and the melting was performed in an electric furnace (Lindberg model Blue M) at  $1500^\circ\text{C}$  using an alumina crucible. The liquid was kept at this temperature during 2 hours, stirred each 30 min by using a silica rod for homogenization and fining. The liquid was cast in a stainless steel mold at room temperature; the material was milled using a vibratory ball mill (Pulverizette). Particles were separated in the range of  $45\mu\text{m} < \phi < 63\mu\text{m}$  by using stainless steel sieves. The glass microspheres were produced using the "flame method" as described elsewhere<sup>(9)</sup>. Microspheres samples were analyzed by X-rays diffraction (Rigaku model multiflex,  $\text{CuK}_\alpha$  radiation,  $10 - 90^\circ$  (step  $2^\circ / \text{min}$ )), Energy Dispersive X-rays Fluorescence Spectroscopy (Shimadzu model 720), Scanning Electron Microscopy (Philips model – XL30), and Differential Thermal Analyzes (Netzsch 404F3 Pegasus). The density was determined by He pycnometry.

### Results and discussion

#### X Ray Diffraction

The XRD patterns of glass powders before and after the spheroidization process are shown in the figures 1 and 2, respectively.

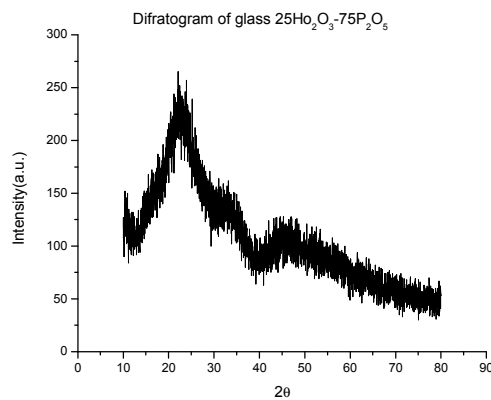


Fig. 1: XRD pattern of irregular shape powder

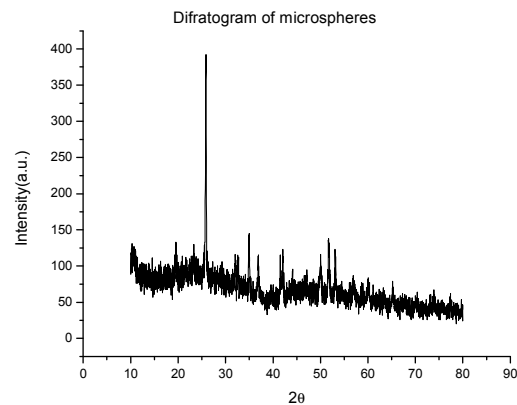


Fig. 2: XRD pattern of microspheres

It is noticed in Fig. 1 two halos located in the range of  $15^\circ - 40^\circ$  indicating the presence of amorphous phases. There is no evidence of crystalline phases. However, after the spheroidization process, the diffraction pattern (Fig. 2) shows sharp peaks which are related to the presence of crystalline phases. In principle, the presence of crystalline phases does not jeopardize the use of microspheres in the internal selective radiotherapy, but could affect mechanical properties, and the chemical durability.

### Energy Dispersive X-ray Fluorescence Spectroscopy

The chemical composition of the glass particles was determined by EDX and the results are presented in the Table 1:

Table 1: Chemical composition of glass particles (weight %)

<i>Chemical Composition [weight %]</i>		
<i>Component</i>	<i>Final composition</i>	<i>Nominal composition</i>
P <sub>2</sub> O <sub>5</sub>	46.91 ± 0.08	53
Ho <sub>2</sub> O <sub>3</sub>	41.62 ± 0.05	47
Na <sub>2</sub> O	6.65 ± 0.18	-
Al <sub>2</sub> O <sub>3</sub>	2.12 ± 0.07	-
SiO <sub>2</sub>	2.70 ± 0.03	-

The final composition contains some elements which were not initially predicted and they originated from the chemical compounds (impurities). Their presence should not represent a concern due to their low cross section for neutron absorption or, in the case they are activated during the neutron irradiation, they produce radioisotopes with relatively short half life.

### Differential Thermal Analyzes

The DTA curve for the 25.Ho<sub>2</sub>O<sub>3</sub>-75.P<sub>2</sub>O<sub>5</sub> glass particles is shown in Fig. 3:

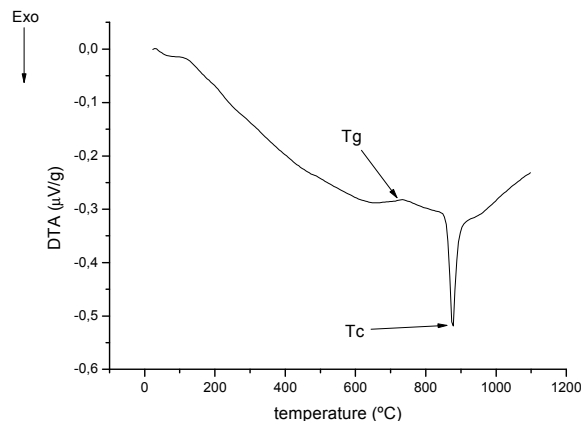


Fig. 3: DTA curve for 25.Ho<sub>2</sub>O<sub>3</sub>75.P<sub>2</sub>O<sub>5</sub> glass particles.

The glass transition temperature  $T_g = (721 \pm 1)^\circ\text{C}$  and the maximum crystallization temperature  $T_c = (878 \pm 1)^\circ\text{C}$  are indicated in the curve. During the spheroidization process the flame has a temperature around  $1200^\circ\text{C}$ , and consequently, the glass particles are initially heated above  $T_c$  and further cooled below  $T_c$ , when crystallization occurs. This effect can be confirmed by the XRD pattern presented in Figs. 2.

### Pycnometry

The density of glass microspheres containing holmium is  $(3.5 \pm 0.1)\text{g/cm}^3$ . This value is relatively large compared to the blood density, however, it is close to the one for commercial aluminosilicate glass microspheres containing yttrium ( $\sim 3.2\text{g/cm}^3$ ), which have been used for selective internal radiotherapy. Therefore, these microspheres can be considered suitable for that application concerning to this property.

### Scanning Electron Microscopy

Fig. 4 shows the microspheres observed in a scanning electron microscope.

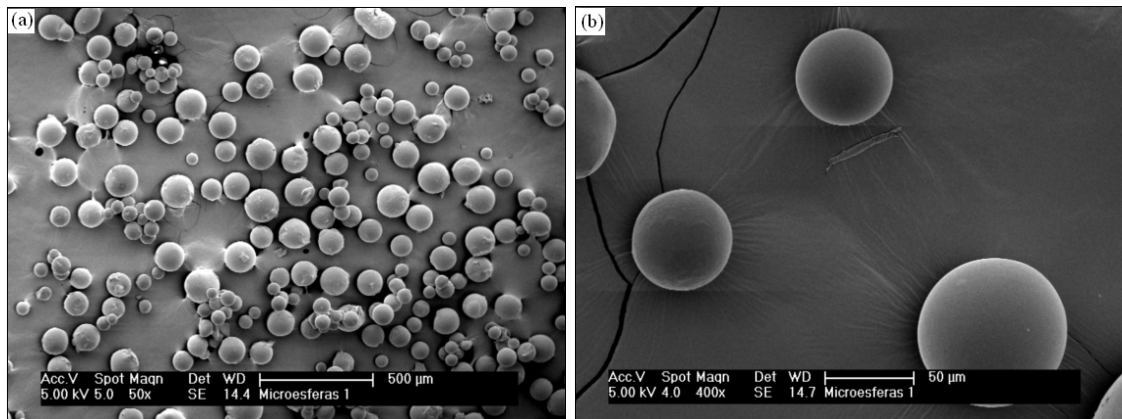


Fig. 4: Micrograph of microspheres: a) magnitude 50 X, and b) magnitude 400X.

It can be noticed that the spheroidization process was successful, and several microspheres with appropriate shape and size were produced which eventually could be used in the selective internal radiotherapy.

### Conclusions

Phosphate glasses microspheres containing holmium oxide were obtained by using the traditional method of melting/cooling followed by the flame method. The density, morphology, size and  $^{165}\text{Ho}$  concentration were considered suitable for the selective internal radiotherapy. Although the glasses contain some impurities, these elements do not make the material inappropriate for the targeted application. A partial crystallization of the glass microspheres was noticed which was attributed to the heating/cooling process during the spheroidization when the maximum crystallization temperature is reached. It is planned now to evaluate the chemical durability these glasses in water and SBF.

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