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Development and evaluation of holmium doped phosphate glass microspheres for selective internal radiotherapy

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ABSTRACT

Selective Internal Radiotherapy is used to treat hepatocellular carcinoma. In this treatment ^{90}Y –doped aluminosilicate glass microspheres are introduced in the hepatic artery and they migrate to the liver near to the tumor where they are trapped in the arterioles. The radiation β^- emitted by the decay of ^{90}Y annihilates the cancer cells. A macroaggregate of albumin containing technetium is previously used to monitor the lung shunt and to prevent the spreading of ^{90}Y during the treatment. In the present work, ^{165}Ho- doped phosphate glass microspheres were developed aiming that application. ^{165}Ho has high cross section for neutron capture (64 bars) and ^{166}Ho decays emitting β^- radiation with appropriate energy for killing cancer cells, and gamma rays with low energy which can be used to obtain images of the microspheres location and to check possible occurrence of lung shunt. Holmium also is highly paramagnetic and can be used to obtain images whereby NMR. The glass matrix consists of (P_2O_5) tetrahedrons and can be produced by a relatively lower melting temperature of chemical compounds. The ^{31}P decays by emitting β^- radiation and contributes to the absorbed dose, helping to annihilate the cancer cells. The microspheres were produced by using two methods: the flame and the gravitation falling methods to obtain microspheres with appropriate properties.

1. INTRODUCTION

The hepatocellular carcinoma (HCC) has an annually incidence rate close to 500.000 cases [1]. Although most of the cases are due to primary tumors, some metastases originated from other organs (gastro intestinal tract with incidence of one million new cases by year) are found [1-2]. Due to the late diagnosis just few patients overcome one year after the diagnosis. HCC can sometimes be attributed to the exposition to aflatoxins, cirrhosis, infections with B or C virus hepatitis and other factors. The treatment of HCC is a true challenge because the effective cure is the resection procedure followed by transplantation but this procedure

depends on the localization of the tumor, age of the patient, cirrhosis degree and other factors. Only 10 – 15 % of patients are able to be submitted to surgical procedures and only 7 % of the non elected patients have life expectation above 5 years. [1-2]. Novel therapy options are been investigated for inoperable patients and many of them are helping to save lives like R.F. ablation, TACE, target therapy, external radiotherapy, hyperthermia, and immunotherapy. However most of those therapies are not effective and cause side effects reducing the quality of life [3-4]. Selective internal radiotherapy uses microspheres containing a radionuclide that decays emitting β^- particles which are introduced in the liver through the hepatic artery. When the microspheres are delivered to the liver, they migrate preferentially to hypervascular regions where the cancerous tissue is located. The microspheres are trapped in the arterioles which feed the tumors, and the β^- particles annihilate the cancer cells. The selective internal radiotherapy has been used in several countries with outstanding results [5-7]. Glassy and polymeric microspheres are used for this purpose and both types contain ^{90}Y because this radioisotope decays by emitting β^- particles. For the success of this therapy it is necessary to know the characteristics of the tumor and the degree of the lung shunt. To monitor preventively the spreading of the microspheres albumin macroaggregate containing technetium is previously injected in the patient. If there is extensive lung shunt the selective internal radiotherapy should be discarded. This procedure is very important but false positives can occur [8,9]. Besides that the ^{89}Y $(n,\gamma)^{90}Y$ reaction can be effective only in nuclear reactors where the neutron flux is suitable because ^{89}Y has a relatively low cross section for neutron capture. At present Brazil does not have a nuclear reactor appropriate for that purpose, therefore the development of phosphate glass microspheres containing holmium might be an innovative and immediate solution. ^{165}Ho has a high cross section for neutron capture and can be transmuted to ^{166}Ho in nuclear reactors where the neutron flux is relatively low. Besides the β^- particles, gamma rays are also emitted during the decay of ^{166}Ho to ^{166}Er. This radiation can be used to obtain images. In addition, holmium is highly paramagnetic and it is possible to be used in NMR imaging [10-11]. The decay of ^{166}Ho could be also used to check the lung shunt because γ-ray is emitted and the use of albumin macroaggregate is unnecessary. The choice of phosphate glass is based on its relatively low melting point, and the ^{31}P can be transmuted to ^{32}P which decays emitting β^- particles. Therefore the association of ^{166}Ho and ^{32}P can increase the dose deposited in the lesioned tissue. The phosphate glasses containing holmium were prepared by the traditional melting/cooling method and the glass particles were spheroidized by two previously reported methods [3]: the gravitational falling method, and the flame method. The density, chemical composition, crystalline phases, thermal proprieties and morphology of these materials were determined aiming the application in the selective internal radiotherapy.

2. EXPERIMENTAL PROCEDURE

Phosphate glasses containing holmium were prepared by melting mixtures of $(NH_4)_2HPO_4$, Ho_2O_3 , Al_2O_3, and Li_2CO_3 with stoichiometric compositions based on previously reported data [12, 13]. Table 1 shows the nominal composition evaluated in the present work.

Table 1: Nominal composition (%mol)

Glass code	P_2O_5	Ho_2O_5	Al_2O_5	Li_2O
HoP_1	75	25	-	-
HoP_2	70	10	15	5
HoP_3	70	10	10	10

The mixture was carried out by using a porcelain mortar and pestle during 20 minutes and it was melted in an bottom loading electric furnace (Lindberg model Blue M) at 1500ºC using an alumina crucible. The liquid was kept at this temperature during 2 hours, stirred each 30 minutes by using a silica rod for homogenization and fining. The liquid was cast in a stainless steel mold at room temperature and milled in a planetary mill with a tungsten sphere (Pulverizette). Steel sieves were used to separate particles in the range size of 45μm<ϕ<63μm. Glass particles were spherodized by using two different processes. In the first process glass microspheres were obtained by feeding a flame with irregular particles. The temperature of the torch was controlled by varying a mixture of oxygen and Petrol Liquefied Gas. The microspheres were collected in a metal cylinder. This process is known as "spheronization by flame". The second process consists of introducing glass particles with irregular shapes on the top of a vertical tubular furnace, and let them falling down. This process is named "spheronization by gravitational falling in a tubular furnace". Glasses and microspheres were characterized by X-rays diffraction (XRD), Energy Dispersive X-rays Fluorescence Spectroscopy (Shimadzu model 720), Scanning Electron Microscopy (Philips model – XL30), thermal analyzes (DSC - Netzsch model 404S). The density was determined by the helium pycnometry method.

3. RESULTS AND DISCUSSION

3.1 Thermal analyzes

Samples were analyzed by using DSC . The DSC curves are shown in the figure 1.

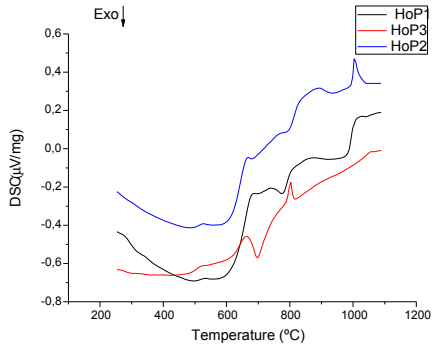

Figure 1: DSC curves of glass microspheres.

The HoP_1 composition has a glass transition temperature (Tg) equals to (500±1)ºC. The Tg for the HoP_2 is (490±1)ºC, which is similar for the HoP3 composition. The maximum crystallization temperatures could not be precisely determined due to the complexity of the DSC curves. Apparently Tc= 700ºC for the HoP_3, 792 ºC for the HoP_2, and 774 for the HoP_1 compositions, respectively. Therefore, further investigation is necessary, although crystallization has been detected by XRD (see next section).

3.2 X-ray Diffraction

The XRD patterns of glass powder before the spheroidization process and of microspheres are shown in the figure 2, 3, and 4.

a) irregular powder b) glass microspheres

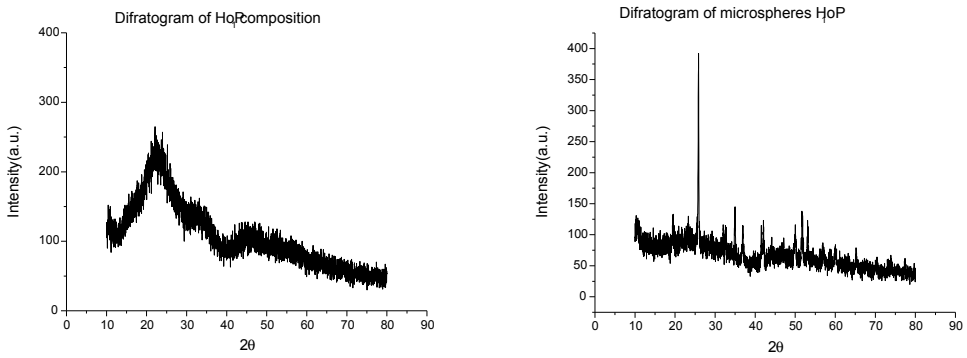

Figure 2: XRD patterns of HoP_1 composition a) irregular powder before spheroidization process. b) glass microspheres.

a) b)

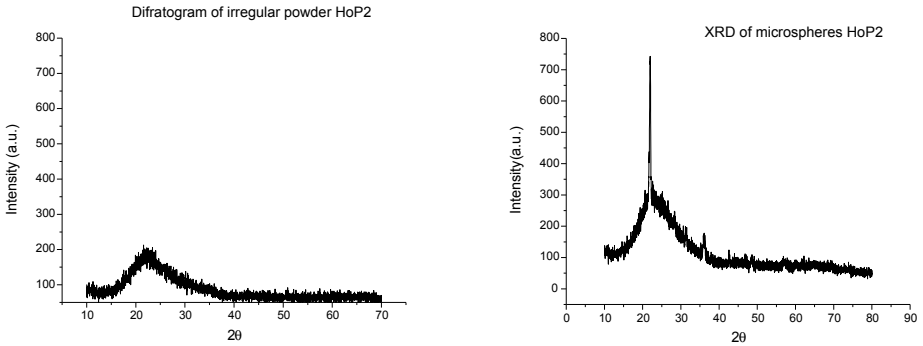

Figure 3: XRD patterns HoP_2 composition a) irregular powder before spheroidization process. b) glass microspheres after spheroidization process.

a) b)

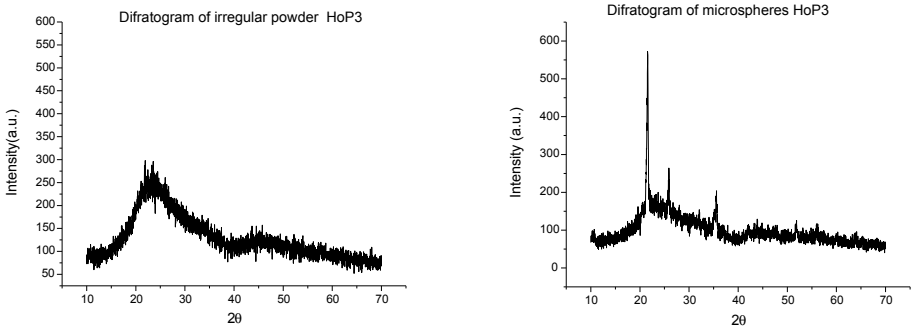

Figure 4: XRD patterns of HoP_3 composition a) irregular powder before spheroidization process. b) glass microspheres.

The gravitational falling method was performed at 1400ºC. During the cooling process, there is partially crystallization because the microspheres go through pass the crystallization

temperature. In the X-ray diffraction patterns of irregular powder shown in Figs. 2a, 3a, and 4a, halos are observed in the 2θ range of 15º - 40º indicating the presence of an amorphous phase. There are no evidences of crystalline phases. However, after the spheroidization process, peaks related to crystalline phases can be noticed (Figs. 2b, 3b, and 4b) . The presence of crystalline phases do not jeopardize the use of microspheres in the internal selective radiotherapy, but could decrease the chemical durability of the glasses.

3.3 Energy Dispersive X-ray fluorescence spectroscopy

The chemical composition was determined by EDX and the values are shown in Table 2.

Table 2: Chemical composition determined by EDX (mol %)

sample	component	P_2O_5	Ho_2O_3	Al_2O_3	SiO_2	Li_2O	Na_2O	Lu_2O_3
HoP_1		53.2 (3)	17.9(5)	3.37(22)	7.2(3)	-	17.21(16)	1.2(6)
HoP_2		50.7(4)	7.5(5)	21.8(6)	7.8(4)	8.8(4)	3.4(3)	0.2(1)
HoP_3		51.61(21)	7.7(4)	16.7(5)	5.5(2)	13(6)	6.1(8)	0.3(2)

The glasses contain sodium and lutetium which are impurities of the original chemical compounds. These contaminations do not make the therapy application impracticable since neither they have a long half life nor they have a high cross section for neutron capture.

3.4 Density

The density was determined by helium pycnometry. The values are shown in the table 3.

Table 3: Density determined by helium pycnometry

Samples	Density (g/cm^3)
HoP_1	2.95(4)
HoP_2	2.99(6)
HoP_3	2.92(4)

Comparing the density values of aluminosilicate glass microspheres containing yttrium (density ~3.2g/cm^3), the values of the phosphate glasses containing holmium are lower, even though the atomic weight of holmium is larger then the one of yttrium. Therefore, different glass structures should be responsible for this effect.

3.5 Scanning Electron Microscopy

The microspheres were observed in a scanning electron microscope. The images are shown in figure 5.

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

Fig. 5b shows that on the surface of the microspheres there is dark regions which could be related to surface crystallization. This assumption is in agreement with the data provided by XRD (Fig. 4), which indicates the presence of a crystalline phase after the

spheroidization process.

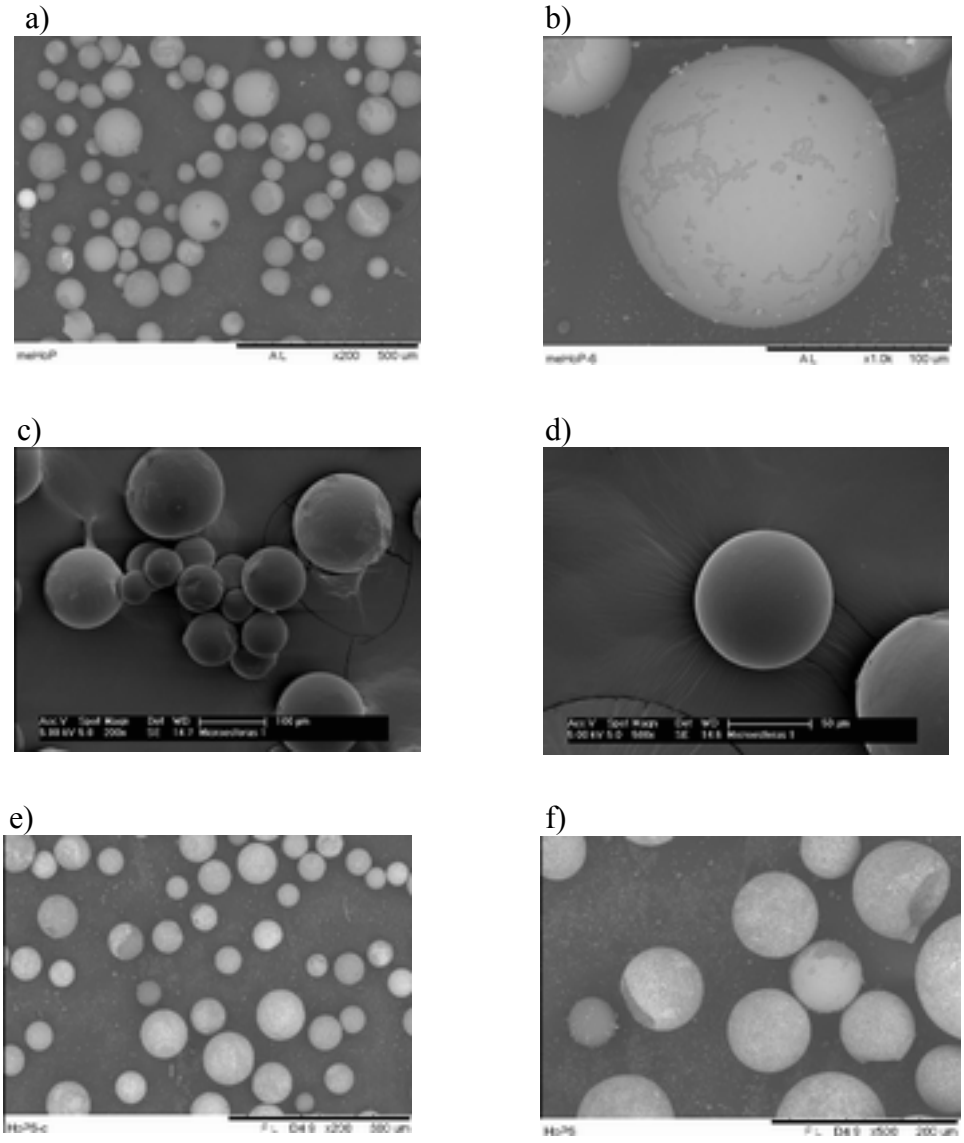

Figura 5: Micrograph of microspheres produced by the gravitational falling method. a) and b): HoP_1; c) and d) HoP_2; e) and f) HoP_3.

4. CONCLUSIONS

Phosphate glass microspheres containing holmium were obtained by the melting/cooling/ spheroidization process with suitable shape and size for selective internal radiotherapy. The density, chemical composition and thermal properties are also appropriate for this application. A partial crystallization occurs during the spheroidization process but the crystalline phases do not jeopardize the use of microspheres in the selective internal radiotherapy. Further investigation is necessary to determine the chemical durability of these glasses in Simulate Body Fluid, irradiation tests in a nuclear reactor, and cytotoxicity tests to

verify the potential useful of this material in selective internal radiotherapy.

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