Study of the spheronization process of glass particles for internal selective radiotherapy application.

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Abstract

The selective internal radiotherapy is an alternative to treat hepatocellular carcinoma. Glass microspheres containing a β^- emitter radionuclide are introduced in the liver, and they concentrate preferentially in the region where the cancer cells are located. The microspheres are trapped in the arterioles which feed the tumors, and the β^- particles annihilate the cancer cells. The glass particles must be spherical to avoid unnecessary bleeding, and the particle size must be restricted to a range which optimizes the blocking effect.

Glass microspheres can be produced by heating glass particles using a flame or in a hot zone of a furnace. The particle size distribution is not easily predicted since it depends on the variation of the aspect ratio and the presence of agglomerates. In the present work, the spheronization process to obtain microspheres with diameters appropriate for radiotherapy treatment is evaluated. Samples were characterized by X-rays diffraction and Energy Dispersive X-rays Fluorescence Spectroscopy. The glass dissolution rate was determined in water at 90ºC, and in Simulated Body Fluid (SBF) at 37ºC. Glasses with dissolution rates close to 10^{-8} g/(cm^2.d) were obtained, which make them suitable for the present application. Scanning Electron Microscopy was used to evaluate the surface of the microspheres before and after the dissolution tests.

Introduction

The Hepatocellular Carcinoma (HCC) is one of most common kind of cancer worldwide; due to the late diagnosis, only 10 to 15 % of patients are candidates for surgical resection or transplantation [1, 2]. One possible therapy for this kind of disease is the internal selective radiotherapy [3-9]. This therapy uses glass microspheres containing β^- emitter radionuclides, introduced into the liver through a catheter inserted in the hepatic artery. When microspheres are delivered in the liver, they migrate preferentially to hypervascular regions where cancerous tissues are concentrated [10]. The microspheres are trapped in the arterioles which feed the tumors, and the β^- particles annihilate the cancer cells [11].

Therefore the shape of glass particles should be preferentially spherical to avoid unnecessary bleeding and damage of health tissues, the particle size must be restricted to a range which optimize the blocking effect and avoid the migration to other parts of the human body. Good chemical durability is very important to the success of this therapy [12].

In the process used to obtain glass microspheres from vitreous particles the shape of irregular glass particles changes by reducing the viscosity of the glass as the temperature is raised. The glass particles pass through a hot zone and the spheronization of the particles occurs. The production of glass microspheres from irregular shape particles requires the softening of the glass at appropriate time and temperatures to avoid the crystallization of the material [13].

In a previous work [14] it was reported that the primarily particle size distribution was changed after the spheronization process. It was not possible to predict the final microsphere size distribution just by knowing the particle size distribution of the irregular glass particles, because the final distribution depends on the aspect ratio, variation of process parameters, and agglomeration of particles. It is therefore necessary to establish a correlation between the size distribution of particles with irregular shape and the microsphere size distribution. In this work the spheronization process was evaluated to obtain microspheres with diameters suitable for internal selective radiotherapy.

Experimental Procedures

Magnesium aluminosilicate glasses containing holmium were prepared by melting mixtures of Al_2O_3, SiO_2, MgO, and Ho_2O_3 (5 $^{wt}/_{o}$ and 25 $^{wt}/_{o}$) with stoichiometric composition based on the phase diagram for $MgO - Al_2O_3 - SiO_2$ [15]. The mixture was carried out for 20 minutes in a silica pestle and mortar, and melted at 1550^{o}C in an alumina crucible inside an electric furnace (Lindberg model Blue M). 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 to obtain a 10x10x50 mm^3 glass rod. The rod was cut in 1x1x10mm^3 which was used to determine the chemical durability in distilled water at 90ºC, and in simulated body fluid (SBF) at 37ºC. Samples were immersed in distilled water and SBF during 14 days. The material was also milled using three different kinds of milling processes: 1) particles were put on a stainless steel base and crashed by a hammer; 2) a knife mill; and 3) Fritsch Pulverizette planetary ball mill. Steel sieves were used to separate particles in different size ranges ($0<\Phi<38\mu m$; $38\mu m<\Phi<63\mu m$; $45\mu m<\Phi<63\mu m$; $40\mu m<\Phi<53\mu m$; $45\mu m<\Phi<56\mu m$; $56\mu m<\Phi<63\mu m$ and $63\mu m<\Phi<106\mu m$).

Glass particles were shaped to microspheres by using two different processes. In the first process glass microspheres were obtained by reducing the viscosity of irregular particles in a hot flame produced by a torch burning 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 fall in a tubular furnace”.

Samples were characterized by X-rays diffraction (XRD), Energy Dispersive X-rays Fluorescence Spectroscopy (Shimadzu model 720). Scanning electron microscopy (Philips model – XL30) was used to observe the surface of glass microspheres before and after being immersed in Simulated Body Fluid (SBF). The glass microsphere size distribution was determined by laser diffraction (Cilas model 1064).

Results and discussion

The X-ray diffraction patterns for microspheres and irregular glass powder do not show peaks related to crystalline phases in the samples. In principle the nucleation of crystalline phases is undesirable because it can cause mechanical stresses and jeopardize the microspheres performance by creating cracks and other defects.

The chemical composition of the microspheres and the starting material were determined by energy dispersive X-ray fluorescence spectroscopy (Table 1).

Table 1 – Chemical composition of glass with 5 wt% of Ho_2O_3 determined by EDX.

Chemical composition (wt%)		
Compound	*Microspheres*	*Starting material*
SiO_2	53.167 ± 0.708	54.254 ± 0.826
Al_2O_3	19.627 ± 0.519	19.715 ± 0.341
MgO	16.491 ± 0.739	17.157 ± 0.561
Ho_2O_3	9.205 ± 0.506	7.464 ± 1.20
Lu_2O_3	0.816 ± 0.097	0.939 ± 0.188
CaO	0.401 ± 0.102	0.310 ± 0.076
Fe_2O_3	0.267 ± 0.121	0.162 ± 0.117

There are no considerable changes in the composition of both materials. Iron, calcium, and lutetium oxides are considered contamination which can be reduced by using high pure materials. Those materials were not used in the present work since we were only investigating the process parameters.

Table 2 shows the dissolution rates for glasses containing 5 wt% 25 wt% of Ho_2O_3 immersed in distilled water at 90ºC during 14 days.

Table 2 – Dissolution rate (Dr) as a function of immersing time in water at 90ºC.

	Dr(g/cm².d)	
t(day)	*AlSiHo-5%*	*AlSiHo-25%*
1	$6.2x10^{-7}$	$8.4x10^{-8}$
3	$3.0x10^{-6}$	$1.2x10^{-7}$
7	$2.9x10^{-6}$	$2.6x10^{-6}$
14	$2.1x10^{-6}$	$9.6x10^{-7}$

Both materials show a decreasing dissolution rate as a function of time which is related to the decrease of mass transfer from the glass surface to the medium. This fact might be related to the precipitation of secondary phases on the glass surface or to the saturation of the leaching solution containing leached elements. In any case, these glasses have a higher chemical durability than commercial window glasses (DR= 10^{-5} g/cm² .d). It is noticed that the corrosion resistance of AlSiHo-25% glass is better than the one for the AlSiHo-5% glass composition.

Table 3 shows the size distribution data for glass microspheres produced from particles in different particle size ranges. These particles were crashed by a hammer in a stainless steel base. Table 4 shows the size distribution data for glass microspheres produced from particles milled in different process and sieved in the range 45μm<Φ<63μm .

Table 3 – Size distribution data for glass microspheres produced from different particle size ranges.

Microspheres size distribuition (μm)				
Range of starting material(μm)	*D10*	*D50*	*D90*	*Mean diameter*
0<Φ<38	38.76	105.63	172.05	106.55
38<Φ<63	50.79	105.64	199.95	116.73
40<Φ<53	37.48	54.13	75.50	54.44
45<Φ<56	45.86	64.45	93.76	67.14
45<Φ<63	48.99	75.63	115.74	78.49
56<Φ<63	50.59	65.65	91.20	68.02
63<Φ<106	61.24	84.87	121.49	88.06

In the present case it was determined that the most appropriate particle size range of the starting material for the production of microspheres to radiotherapy treatment is 40μm<Φ<53μm. The microsphere mean diameter is <Φ>=54.44 μm.

Table 4 – Size distribution data for glass microspheres produced from particles milled in different milling processes.

Microspheres size distribution (μm)				
Milling process	*D10*	*D50*	*D90*	*Mean diameter*
Stainless steel mill	48.99	75.63	115.64	78.49
Knife mill	45.88	59.40	78.37	60.48
Planetary ball mill	47.71	62.12	82.69	62.56

The use of the knife mill and the planetary ball mill are advantageous because the resulting microspheres have the smaller mean diameter. The powder produce by knife milling and planetary ball milling flow easily and particle agglomeration is avoided during the spheronization processes.

Figure 1 shows the micrographs of the starting materials after milling in different conditions. Figure 2 shows the micrographs of the resulting microspheres which are more appropriate to radiotherapy application.

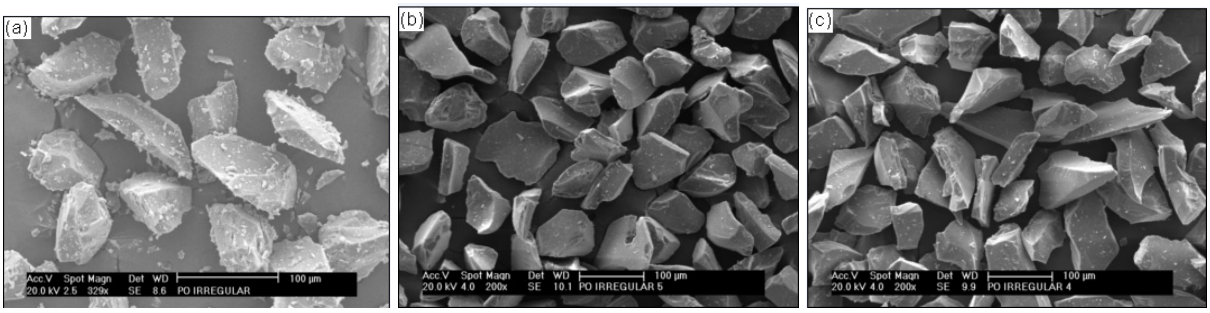

Fig 1: Micrographs of the starting materials (45μm<Φ<63μm) after milling in different conditions: a) stainless steel mill b) knife mill c) planetary ball mill.

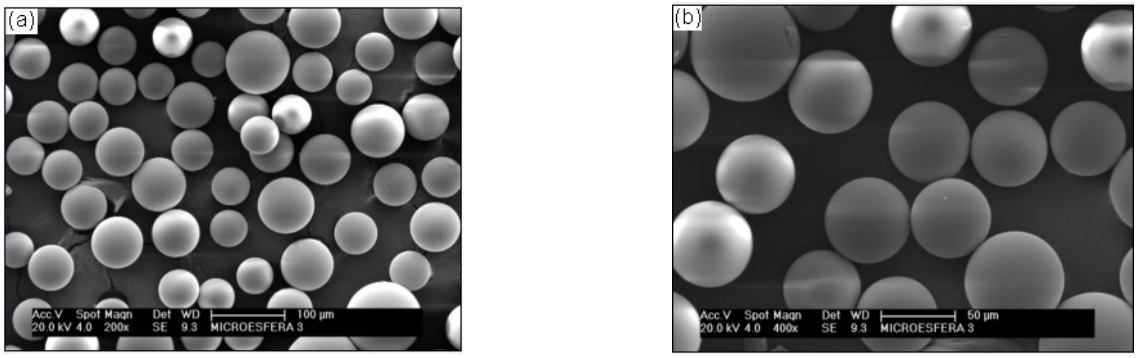

Fig 2: Microspheres more appropriate to radiotherapy treatment.

Figure 3 shows the micrographs of microspheres before, after 7 days, and after 14 days of the chemical durability tests in SBF, respectively.

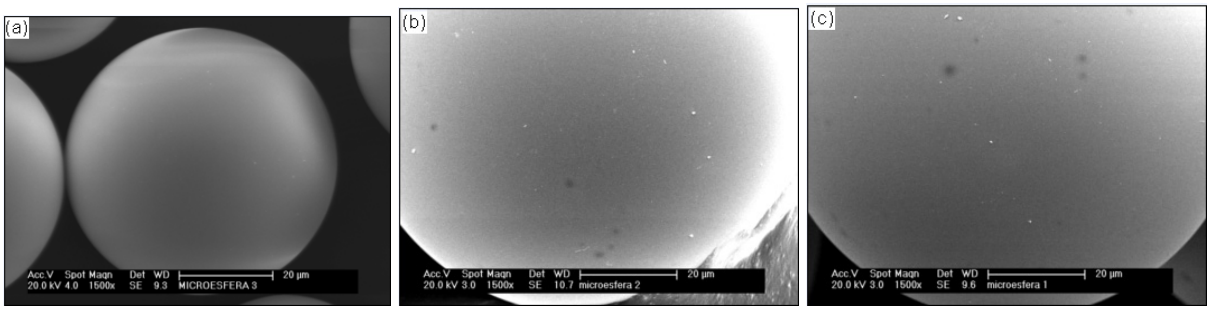

Fig 3: Microspheres after immersion in SBF a) before b) after 7 days c) after 14 days.

No corrosion and chemical attach at the surface of microspheres have been observed, even after 14 days immersed in simulated body fluids (SBF).This fact represents a good chemical durability of microspheres, hence these are promising materials to be used in selective internal radiotherapy.

Conclusion

Magnesium aluminosilicate glass microspheres containing holmium(5 $^{wt}/_{o}$ e 25 $^{wt}/_{o}$) with low dissolution rate in distilled water were produced. The chemical resistance increases as a function of Ho_2O_3 content. The particle size range of the starting material for the production of microspheres to radiotherapy treatment is 40μm<Φ<53μm. In this case the microsphere mean diameter is <Φ>=54.44 μm.

Knife mill and planetary ball mill are the most suitable milling process to produce easily flowing particles. No changes in shape and corrosion activity were observed on the surface of glass microspheres after immersion in simulated body fluid (SBF) during 14 days. These materials can be considered potentially useful for applications in radiotherapy treatment.

Citotoxicity tests are planned to evaluate the safety response of this material.

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