(54) Title: PROCESS FOR MAKING CERAMIC MICROSPHERES

This invention is directed to a novel process for the preparation of microspheres comprising a ceramic material. The process comprises first forming droplets comprising (a) water, and (b) a ceramic precursor which may be thermally decomposed to form the ceramic material. The droplets are then heated to vaporize and remove the water from the droplets and thermally decompose the ceramic precursor, thereby forming the microspheres. The rate of heating is such that at least about 90% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 10% of the substantially continuous spherical outer surface.
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PROCESS FOR MAKING CERAMIC MICROSPHERES

BACKGROUND OF THE INVENTION

The present invention relates generally to a process for the preparation of ceramic microspheres, and more particularly to the preparation of ceramic microspheres useful in the treatment of cancerous and tumor bearing tissue.

In the treatment of patients with certain kinds of cancer, methods are known in which radioactive particles are introduced intravascularly to trap the radioactive particles at particular sites for their radiation effect. According to this technique, a small quantity of the radioactive particles are injected into the patient and a diffuse, homogeneous field of radiation within a selected region of the body is achieved by permanent lodgement of the particles in the capillary bed of the affected area, typically the location of a tumor.

In early applications of this technique, yttrium oxide powder was suspended in a viscous medium before administration. Yttrium was selected for the technique because of its suitable characteristics, e.g., it emits nearly 100 percent beta radiation. See, e.g., Nolan, et al., "Intravascular Particulate Radioisotope Therapy," Am. Surgeon 35: 181-188 (1969) and Grady, et. al., Intra-Arterial Radioisotopes to Treat Cancer," Am. Surgeon 26: 678-684 (1960). This method, however, is not totally satisfactory. Two disadvantages of yttrium oxide powder are its high density (5.01 gm/cm³) and irregular particle shape. The high density of the powder makes it difficult to keep the particles in suspension in the liquids used to inject them into the body, and accelerates their tendency to settle in the blood stream before they reach the desired area of the tumor. The sharp corners and edges of yttrium oxide particles also irritate surrounding tissue in localized areas, and interfere with the uniform distribution of the radioactive particles in the tumor to be treated.

In later applications, the particles employed have been microspheres composed of an ion exchange resin, or crystalline ceramic core, coated with a radioactive isotope such as P-32 or Y-90. Both ion exchange resin and crystalline ceramic microspheres offer the advantage of having a density much less than that of yttrium oxide particles, and the ion exchange resin offers the additional advantage of being particularly easy to label. See, e.g., Zielinski and Kasprzyk, "Synthesis and Quality Control Testing of 32 P labeled Ion Exchange Resin Microspheres for Radiation Therapy of Hepatic
Neoplasms," *Int. J. Appl. Radiat. Isot.* 34: 1343-1350 (1983). However, whenever a microsphere comprises a core material having an external surface coating which contains the radioactive isotope, there is a risk that the radioactive coating may separate from the underlying microsphere core. Any mechanical breakage of the coating can release unwanted radioactivity to other parts of the human body which is highly undesirable. Further disadvantages are presented by the special handling and precautions that are necessary to coat a radioactive isotope onto a crystalline ceramic core, or to label ion exchange resin.

In still another application, microspheres have been prepared which comprise a ceramic material and have a radioactive isotope incorporated into the ceramic material. While the release of radioactive isotopes from a radioactive coating into other parts of the human body may be eliminated by incorporating the radioisotopes into ceramic spheres, the latter product form is nevertheless not without its disadvantages. Processing of these ceramic microspheres is complicated because potentially volatile radioactivity must be added to ceramic melts and the microspheres must be produced and sized while radioactive, with concomitant hazards of exposure to personnel and danger of radioactive contamination of facilities.

In U.S. Patent Nos. 4,789,501, 5,011,677, and 5,302,369, Day et al. disclose glass microspheres containing an isotope distributed substantially uniformly throughout the glass. The isotope can be activated to a beta or gamma radiation emitting isotope by neutron irradiation. These microspheres offer several advantages. One such advantage is that they do not release a radioactive coating or isotope into remote parts of the body of the patient after administration. Such microspheres also do not require any technicians to handle any radioactive materials during the formation of the microspheres because they initially may be produced in a non-radioactive form and stored until needed, at which time they may be made radioactive by neutron radiation.

One method for manufacturing the glass microspheres is flame spheroidization. Under this method, the raw materials for the microspheres are heated to a high temperature to form a high-temperature melt and then cooled to form a glass ingot. The glass ingot is then crushed into small particles and fed into a flame sprayer. The particles melt as they fall through the flame, spheridize due to surface tension, and cool rapidly to as they emerge from the flame to form microspheres. The microspheres are then collected in, for example, a stainless steel drum. Because this method requires that the raw
materials first be converted into a homogenous, high-temperature melt, it often produces microspheres that lack satisfactory homogeneity, particularly if the microspheres are based on materials having high melting points or materials that are immiscible in the liquid state. In addition, because this method tends to produce a non-uniform size distribution of microspheres, it generally requires an additional time-consuming step such as sieving, sedimentation, or air elutriation to obtain the desired size distribution. See G. J. Ehrhardt & D. E. Day, "Therapeutic Use of $^{90}$Y Microspheres," Int'l J. Radiation Appl. Instrum., Part B, Nucl. Med. Biol. 14(3): 233-45 (1987). Poor homogeneity or size uniformity of the microspheres can detrimentally affect the activity of the microspheres, and eventually the dose delivered to the patient.

Erbe discusses preparing $Y_2O_3$ containing microspheres using an aerosol synthesis technique employing sol-gel technology. See E. M. Erbe, Structure and Properties of $Y_2O_3-Al_2O_3-SiO_2$ Glasses (1991) (Ph.D. dissertation, University of Missouri-Rolla). Erbe's technique is similar to other aerosol synthesis techniques that have been widely used in other fields, such as to prepare ceramic powder and to form glass from organo-metallic precursors for optical fibers. See E. Matijeciv, "Production of Monodispersed Colloidal Particles," Ann. Rev. Mater. Sci. 15: 483-92 (1985); S. E. Pratsinis & S. V. R. Mastrangelo, "Materials Synthesis in Aerosol Reactors," Chem. Eng'g Prog., May: 62-65 (1989); L. C. Klein, "Sol-Gel Processing of Silicates," Ann. Rev. Mater. Sci. 15: 227-48 (1985). Erbe describes feeding a sol consisting of water, ethanol, Si($OC_2H_5$)$_4$ (also referred to as "TEOS"), Al($NO_3$)$_3$, 9$H_2$O, and Y($NO_3$)$_3$, 6$H_2$O through an ultrasonic nozzle to generate a spray of droplets that subsequently solidify as they fall vertically through a heated tube containing an ammonia atmosphere. This technique, however, tends to produce microspheres that are cracked and wrinkled.

**SUMMARY OF THE INVENTION**

Among the objects of this invention, therefore, is the provision of a process for making high-purity, ceramic microspheres useful in the treatment of cancerous and tumor bearing tissue. More particularly, an object of this invention is the provision of an improved process for making homogeneous, uniformly sized ceramic microspheres. Another object of this invention is the provision of a process to prepare ceramic microspheres having few, if any, detrimental deformations (i.e., recesses, bulges, and holes) at their surfaces.
Briefly, therefore, the present invention is directed to a novel process for making microspheres comprising a ceramic material. In this embodiment, the process comprises first forming droplets comprising (a) water, and (b) a ceramic precursor which may be thermally decomposed to form the ceramic material. These droplets are then heated to vaporize and remove the water from the droplets and thermally decompose the ceramic precursor, thereby forming the microspheres. The rate of heating is controlled so that at least about 90% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 10% of the substantially continuous spherical outer surface.

In another embodiment directed to the preparation of microspheres comprising a ceramic material, the process comprises forming a droplet comprising a ceramic precursor which may be thermally decomposed to form the ceramic material. The droplet is then heated to thermally decompose the ceramic precursor. The rate of heating is such that the ceramic precursor throughout the droplet thermally decomposes at substantially the same time.

In another embodiment directed to the preparation of microspheres comprising a ceramic material, the process comprises forming a droplet comprising a ceramic precursor which may be thermally decomposed to form the ceramic material. The droplet is then heated to thermally decompose the ceramic precursor. The rate of heating is such that a substantially uniform temperature exists throughout the droplet when the ceramic precursor begins to thermally decompose.

In another embodiment directed to the preparation of microspheres comprising a ceramic material, the process comprises forming droplets comprising a ceramic precursor which has a thermal decomposition temperature at which the ceramic precursor thermally decomposes to form the ceramic material. The droplets are pre-heated with a first heat source to a temperature which is from about 5 to about 100°C less than the thermal decomposition temperature of the ceramic precursor, and then heated with a second heat source to a temperature which is no less than the thermal decomposition temperature of the ceramic precursor.

In another embodiment directed to the preparation of microspheres comprising a ceramic material, the microspheres also comprise a therapeutic dopant material. The therapeutic dopant material comprises a therapeutic dopant which, upon being subjected to neutron irradiation, emits a therapeutic intensity and amount of beta or
gamma radiation. The process comprises forming droplets comprising (a) a ceramic precursor having a thermal decomposition temperature at which the ceramic precursor thermally decomposes to form the ceramic material, and (b) a therapeutic dopant precursor having a thermal decomposition temperature at which the therapeutic dopant precursor thermally decomposes to form the therapeutic dopant material. The droplets are pre-heated with a first heat source to a temperature which is from about 5 to about 100°C less than the least of (a) the thermal decomposition temperature of the ceramic precursor, and (b) the thermal decomposition temperature of the therapeutic dopant precursor. Afterwards, the pre-heated droplets are heated with a second heat source to a temperature which is greater than the thermal decomposition temperatures of the ceramic precursor and the therapeutic dopant precursor.

Another embodiment of this invention is directed to the preparation of microspheres for radiation therapy of a mammal. The process comprises first forming droplets from a precursor solution which is prepared by a process comprising combining Si(OCH₃)₄ and Y(NO₃)₃·6H₂O. These droplets are pre-heated with a first heat source to a temperature which is from about 200 to about 295°C; and then heated with a second heat source to a temperature which is greater than about 450°C.

In another embodiment directed to a process for the preparation of microspheres for radiation therapy of a mammal, the process comprises first forming droplets from a precursor solution which is prepared by a process comprising combining Al(NO₃)₃·9H₂O and Y(NO₃)₃·6H₂O. These droplets are pre-heated with a first heat source to a temperature which is from about 140 to about 235°C; and then heated with a second heat source to a temperature which is greater than about 450°C.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 is a schematic diagram showing one embodiment of an apparatus that may be used for ceramic microsphere production in accordance with this invention.

Figure 2 is a top view of a microsphere having a substantially continuous spherical outer surface. A portion of the surface has been displaced by a recess.

Figure 3 is a cross-sectional view of the microsphere and the recess in Figure 2.
Figure 4 is a second cross-sectional view of the microsphere and recess in Figure 2. Figure 4 shows the portion of the substantially continuous spherical outer surface that has been displaced by the recess.

5 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a novel method for making high-purity, ceramic microspheres which are useful, for example, in the treatment of cancerous and tumor bearing tissue. This method may be used to prepare homogeneous ceramic microspheres having few, if any, detrimental deformations at their surfaces. It also may be used to produce uniformly sized microspheres without requiring a time-consuming sorting step. Microspheres prepared in accordance with this invention generally may range in size from about 0.1 to about 100 μm, more typically from about 1 to about 100 μm, and most typically from about 1 to about 10 μm.

Figure 1 is a schematic diagram showing one embodiment of an apparatus that may be used to prepare ceramic microspheres in accordance with this invention. A precursor solution is fed into an ultrasonic nozzle 1, which in turn generates a spray of droplets from the precursor solution. An example of a suitable ultrasonic nozzle is the Sono-Tek Model No. 8700-60MS (Sono-Tek, Highland, New York). This ultrasonic nozzle contains a pair of disc-shaped ceramic piezoelectric transducers sandwiched between two titanium cylinders. The transducers receive an electrical input in the form of a high frequency signal from a power supply 2 (e.g., Sono-Tek Model No PS-88) that acts as a combination oscillator/amplifier. The transducers convert the electrical input into mechanical energy, which is transferred to an atomizing surface causing the surface to vibrate at high frequencies. Droplets are formed when the precursor solution comes into contact with the vibrating atomizing surface.

The composition of the precursor solution may vary widely. Typically, the precursor solution comprises water and a ceramic precursor which may be thermally decomposed to form a ceramic material. The ceramic material may be a glass material or any other ceramic material, and preferably is biologically compatible with the animal in which the microspheres are to be administered (i.e., the material preferably does not produce any significant undesirable effects when the microspheres are administered into the animal). Examples of often suitable ceramic materials include silicon-based ceramics (e.g., SiO₂), aluminum-based ceramics (e.g., Al₂O₃), zinc-based ceramics (e.g., ZnO), and
lead-based ceramics (e.g., PbO). A wide range of suitable compounds are available which may be thermally decomposed to form the ceramic material. Often, these include hydroxide compounds, nitrates (i.e., metal salts of nitric acid), sulfates (i.e., metal salts of sulfuric acid), acetates (i.e., metal salts of acetic acid), carbonates (i.e., metal salts of carbonic acid), and chloride salts. By way of illustration, SiO₂ may be formed by thermally decomposing, for example, Si(OC₃H₇)₄, Si(OH)₄, or Si(C₂H₅O₂)₄; Al₂O₃ may be formed by thermally decomposing, for example, Al(NO₃)₃·9H₂O, Al(C₂H₅O₂)₃, or Al(C₆H₅O₂)₃; ZnO may be formed by thermally decomposing, for example, Zn(NO₃)₂·6H₂O or Zn(C₂H₅O₂)₂·2H₂O; and PbO may be formed by thermally decomposing, for example, Pb(NO₃)₂ or Pb(C₂H₅O₂)₂·3H₂O.

Using droplets formed from a precursor solution prepared by a process comprising combining water and Si(OC₃H₇)₄ is particularly preferred due to the low-viscosity, low-surface tension, and low cost of Si(OC₃H₇)₄. Because Si(OC₃H₇)₄ and water are immiscible, a solvent (e.g., ethanol) preferably also is added to form a single solution. Without being bound by any particular theory, it is believed that the Si(OC₃H₇)₄ in such a solution hydrolyzes to Si(OH)₄, which, in turn, may be thermally decomposed to form SiO₂.

The precursor solution preferably also contains at least one therapeutic dopant. In a particularly preferred embodiment of this invention, the therapeutic dopant emits a therapeutic intensity and amount of short-range (i.e., a penetration of the target cancer tissue on the order of about several millimeters or less) beta or gamma radiation upon being subjected to neutron irradiation. Depending on the therapeutic application, such therapeutic dopants may include various elements such as yttrium, samarium, dysprosium, holmium, rhenium, phosphorus, or combinations thereof.

Typically, the therapeutic dopant is a constituent of a compound present in the precursor solution. In a particularly preferred embodiment of this invention, the therapeutic dopant containing compound is a compound (sometimes referred to as the “therapeutic dopant precursor”) which thermally decomposes to form another therapeutic dopant containing compound (preferably an oxide of the therapeutic dopant) when subjected to high temperatures. Suitable therapeutic dopant precursors often include hydroxide compounds, nitrates, sulfates, acetates, carbonates, and chloride salts which contain the therapeutic dopant. To illustrate, Y(NO₃)₃·6H₂O, Y(C₂H₅O₂)₃, and Y(OH)₃ are examples of compounds which may be thermally decomposed to form Y₂O₃; and
Sm(NO₃)₃·6H₂O, Sm(OH)₃, and Sm₂(C₂O₄)₃ are examples of compounds which may be thermally decomposed to form Sm₂O₃.

The precursor solution may contain various other materials in addition to the ceramic precursors and the therapeutic dopant containing compounds. For purposes of this invention, the radiation effects of each element in the precursor solution generally depend on its cross-section, number density, and the half-life of the product after neutron irradiation. Trace species having cross-sections of less than about 1 barn typically have negligible adverse effects. The precursor solution, however, preferably does not contain a significant amount of elements (other than the one or more therapeutic dopants) which have a large cross-section for neutrons. Such elements tend to emit unwanted beta and gamma radiation following neutron irradiation. An example of one such element that has a large cross-section for neutrons is boron, which has a cross-section of 3837 barns. In a particularly preferred embodiment of this invention, the precursor solution does not contain a significant amount of elements (except for the therapeutic dopant(s)) which have a cross-section for neutrons greater than about 200 barns. The purity of each material in the precursor solution preferably is greater than about 99.9 weight%.

The precursor solution may be fed into the ultrasonic nozzle 1 by, for example, a syringe pump 3 (e.g., Compact Infusion Pump Model No. 975, Harvard Apparatus, Millis, MA) or a rotary tube pump (e.g., Model No. 7520-25, Barnant Co., Barrington, IL) that is capable of dispensing liquid at the desired flow rate. The feed rate of the precursor solution generally will vary depending on the desired droplet size, the viscosity of the solution, the vibrational frequency of the nozzle 1, and the energy input to the nozzle 1. Many commercially available ultrasonic nozzles (e.g., Sono-Tek Model No. 8700-60MS) come with instructions which enable one skilled in the art to adjust the feed rate, vibrational frequency, and energy input to obtain the desired droplet size for a given solution. Typically, a wide range of droplet sizes may be obtained using an ultrasonic nozzle. This versatility is particularly advantageous for preparing microspheres for therapeutic applications, which typically require microsphere diameters ranging from about 5 to about 75 μm, depending on the application.

Upon being generated, the droplets preferably are introduced into a carrier gas to form an aerosol. The carrier gas preferably does not interfere with the formation of the ceramic material from the ceramic precursor, and more preferably is a noble gas (e.g., Ar, He, or Ne) or N₂. Preferably, the carrier gas is passed through an in-line gas drier 4
(e.g., Drierite gas drier, Fisher Scientific, Pittsburgh, PA) and an in-line filter 5 having a pore size preferably no larger than about 0.2 μm (e.g., a polytetrafluoroethylene filter, Gelman Scientific, Ann Arbor, MI).

When the aerosol has been formed, it preferably is heated to vaporize and remove water in the droplets and thermally decompose the ceramic precursor. In a particularly preferred embodiment of this invention, this heating takes place in one or more horizontal reactor tubes. In this embodiment, the carrier gas preferably has a flow rate which is sufficient to maintain the droplets at a constant speed to minimize the amount of coagulation between the droplets. Such a system is advantageous over a system employing a vertical reactor tube because droplets of different sizes in a vertical reactor tube tend to settle at different rates and therefore have a greater tendency to coagulate with each other, which, in turn, ultimately causes less homogeneity and a less uniform size distribution of microspheres.

It has been found in accordance with this invention that the tendency for the formation of detrimental deformations at the surfaces of the microspheres may be minimized by controlling the rate of heating of the precursor droplets. Preferably, the rate of heating is controlled so that at least about 90% (more preferably at least about 95%, and most preferably at least about 99%) of the microspheres produced each have a substantially continuous spherical outer surface with no single deformation displacing more than about 10% (more preferably, with no single deformation displacing more than about 5%; even more preferably, with no single deformation displacing more than about 1%; and most preferably, with no single deformation displacing more than about 0.1%) of the substantially continuous spherical outer surface.

Figures 2, 3, and 4 show a deformation displacing a portion of a substantially continuous spherical outer surface of a microsphere. Figure 2 is a top view of a microsphere 99 having a radius R and a substantially continuous spherical outer surface 100. The microsphere 99 has a recess 101 which has a perfectly circular edge 102 defined by the diameter w. Figure 3 is a cross-sectional view of the same microsphere 99 and recess 101. Figure 4 is a second cross-sectional view of the microsphere 99 showing the portion 103 of the substantially continuous surface 100 which has been displaced by the recess 101. As shown in Figure 4, the portion 103 displaced by the recess 101 is the outer surface area of the volume defined by the height h. This area equals 2πhR. Thus, the percentage of the substantially continuous spherical outer surface 100 which has been
displaced by the recess 101 equals (h/2R) x 100% (i.e., (2πhR + 4πR^2) x 100%). It should be recognized that the recess 101 having a perfectly circular edge 102 was chosen for simplicity purposes to illustrate the portion 103 of the substantially continuous spherical outer surface 100 that such a recess 101 displaces. Deformations, however, are not limited to recesses. Nor are they limited to deformations having perfectly circular edges. Instead, any shape of deformation may be possible. Deformations may include, for example, various sizes and shapes of recesses, elevations (e.g., bulges), and openings (e.g., cracks and bores) at the surface. The amount of area displaced by a deformation will, of course, depend on the particular shape and size of the deformation.

Without being bound by any particular theory, it is presently believed that a detrimental deformation at the surface of a microsphere may be caused, at least in part, by water in the precursor droplets vaporizing non-uniformly and too quickly when the droplets are heated. For example, if a droplet is heated too quickly, it is believed that the water near the surface of the droplet vaporizes, thereby creating a skin layer on the surface of the droplet which is impermeable to water vapor. When the water on the interior of the droplet subsequently vaporizes, it creates pressure on the interior of the skin which causes the skin to deform and rupture. This deformation and rupturing is presently believed to be a source of detrimental deformations at the surface of the microsphere produced. To avoid this problem, the droplet preferably is heated at a slower rate so that the vaporization and removal of water from the droplet results in few, if any, detrimental deformations at the surface of the resulting microsphere. Likewise, if the droplet also contains an alcohol which vaporizes and exits the droplet during the heating step, the droplet preferably is heated at a rate such that the vaporization and removal of the alcohol from the droplet also does not create a detrimental deformation at the surface of the resulting microsphere.

It is also believed that a detrimental deformation may be caused, at least in part, by non-uniform thermal decomposition of the ceramic precursor or the therapeutic dopant precursor. If thermal decomposition of a precursor in one region of the droplet occurs at a different time than the thermal decomposition in another region, stresses may form between the two regions, ultimately causing detrimental deformations in the microsphere. Heating a droplet too quickly can cause such a non-uniform thermal decomposition. For example, when the droplet is heated, a temperature gradient typically forms in the droplet (the coolest temperature being at the center and the hottest temperature being at the surface) because heat is not transferred instantaneously from the
surface to the center. As the heating rate increases, the temperature at the surface of the droplet will increase significantly faster than the temperature at the center of the droplet because the rate of heat transfer in the droplet does not increase proportionately with the heating rate. This causes thermal decomposition of the components on the surface of the droplet to occur sooner than the components at the center of the droplet, thereby causing internal stresses in the droplet which ultimately lead to detrimental deformations at the microsphere surface. To avoid this, the droplet preferably is heated at a rate which is slow enough so that a substantially uniform temperature exists throughout the droplet when the ceramic precursor begins to thermally decompose. If the droplet also contains a therapeutic dopant precursor which is to be thermally decomposed during the heating process, the droplet preferably also is heated at a rate which is slow enough so that a substantially uniform temperature also exists throughout the droplet when the therapeutic dopant precursor begins to thermally decompose. In a particularly preferred embodiment, the droplet is heated at a rate such that the ceramic precursor throughout the droplet thermally decomposes at substantially the same time. In addition, if the droplet also contains a therapeutic dopant precursor, it is preferred that the therapeutic dopant precursor throughout the droplet thermally decomposes at substantially the same time.

In one embodiment of this invention, the droplets are transformed into microspheres using two heating zones in series: (a) a first heating zone (also referred to as the “pre-heater”) having a first heat source, and (b) a second heating zone (also referred to as the “reactor”) having a second heat source. In Figure 1, the aerosol is pre-heated in the pre-heater 6 before the aerosol enters the reactor 7 (which operates at greater temperatures than the pre-heater 6). This pre-heating step avoids fast surface evaporation of the water (and any alcohol) present in the droplets. This, in turn, leads to microspheres which ultimately exhibit fewer detrimental deformations at their surfaces than those prepared without pre-heating the aerosol.

While in the pre-heater 6, the droplets preferably are heated to a temperature which is less than the thermal decomposition temperature of the ceramic precursor (i.e., the temperature at which the ceramic precursor begins to thermally decompose). If the droplets also contain a therapeutic dopant precursor, the temperature to which the droplets are pre-heated also preferably is less than the thermal decomposition temperature of the therapeutic dopant precursor. If the precursor solution contains more than one ceramic precursor or more than one therapeutic dopant precursor, the droplets
preferably are pre-heated to a temperature which is less than the thermal decomposition temperatures of each ceramic precursor and therapeutic dopant precursor. Pre-heating to a temperature which is less than the thermal decomposition temperature of the ceramic precursor(s) (and therapeutic dopant precursor(s), if present) tends to prevent the development of encrusted droplets. Such pre-heating also tends to drive off water (and alcohol, if present) that might vaporize and fracture a droplet particle when it is later heated in the reactor 7. In a particularly preferred embodiment, substantially all the water (and alcohol, if present) in the droplets is vaporized and removed from the droplets while they are in the pre-heater 6.

In a particularly preferred embodiment of this invention, the pre-heater 6 heats the droplets to a temperature of from about 5 to about 100°C (more preferably from about 5 to about 20°C, and most preferably from about 5 to about 10°C) less than the thermal decomposition temperature of the ceramic precursor. If the droplets also contain a therapeutic dopant precursor, the pre-heater 6 preferably heats the droplets to a temperature of from about 5 to about 100°C (more preferably from about 5 to about 20°C, and most preferably from about 5 to about 10°C) less than the thermal decomposition temperature of the ceramic precursor or the therapeutic dopant precursor, whichever is less. If the droplets contain more than one ceramic precursor or more than one therapeutic dopant precursor, the pre-heater 6 preferably heats the droplets to a temperature of from about 5 to about 100°C (more preferably from about 5 to about 20°C, and most preferably from about 5 to about 10°C) less than the thermal decomposition temperature of the ceramic precursor or the therapeutic dopant precursor which has the lesser decomposition temperature out of all the ceramic precursors and therapeutic dopant precursors present in the droplets.

Various commercially available devices are suitable for pre-heating the droplets. The pre-heater 6 may, for example, comprise a horizontal Pyrex® glass tube (suitable glass tubes may be obtained, for example, from Schott Processes, Trenton, NJ) having heater tape (suitable heater tape may be obtained, for example, from Fisher Scientific, Pittsburgh, PA) wrapped around the outer surface of the tube. In a particularly preferred embodiment of this invention, the droplets are heated by contacting the aerosol containing the droplets with a heated surface which has a temperature that is less than the thermal decomposition temperature of the ceramic precursor(s) (and the therapeutic dopant precursor(s), if present).
The residence time required to pre-heat the droplets to the desired temperature depends on what carrier gas is used, the configuration of the pre-heater 6, the temperature profile of the carrier gas, and the velocity profile of the carrier gas. The Example below illustrates the use of an example of a suitable configuration for the first heating zone. Using these teachings, those of ordinary skill in the art can determine without undue experimentation the necessary residence time for this to be achieved using other configurations.

After exiting the pre-heater 6, the aerosol preferably is fed into the reactor 7 to thermally decompose the ceramic precursor(s) (and, if present, the therapeutic dopant precursor(s)), thereby converting the droplets into ceramic microspheres. While in the reactor 7, the droplets preferably are heated to a temperature which is greater than the decomposition temperature of the ceramic precursor. In a particularly preferred embodiment of this invention, the droplets are heated to a temperature which is from about 0 to about 100°C (more preferably from about 0 to about 20°C, and most preferably from about 0 to about 5°C) greater than the decomposition temperature of the ceramic precursor. If the droplets also contain a therapeutic dopant precursor, the droplets preferably are heated to a temperature which is greater than the decomposition temperatures of the ceramic precursor and the therapeutic dopant precursor. In a particularly preferred embodiment, the droplets are heated to a temperature which is from about 0 to about 100°C (more preferably from about 0 to about 20°C, and most preferably from about 0 to about 5°C) greater than the decomposition temperature of the ceramic precursor or therapeutic dopant precursor, whichever is greater. If the droplets contain more than one ceramic precursor or more than one therapeutic dopant precursor, the droplets preferably are heated to a temperature which is greater than the decomposition temperatures of the ceramic precursor(s) and the therapeutic dopant precursor(s). In a particularly preferred embodiment, the droplets preferably are heated to a temperature which is from about 0 to about 100°C (more preferably from about 0 to about 20°C, and most preferably from about 0 to about 5°C) greater than the decomposition temperature of the ceramic precursor or therapeutic dopant precursor which has the greatest decomposition temperature of all the ceramic precursors and therapeutic dopant precursors in the droplets.

Various suitable reactors are commercially available. In a particularly preferred embodiment, the aerosol containing the droplets is contacted with a heated
surface which has a temperature that is greater than the decomposition temperature of the ceramic precursor(s) (and therapeutic dopant precursor(s), if present). In one embodiment of this invention, the reactor 7 comprises a horizontal reactor tube heated by a single zone furnace (e.g., Model No. F21125, Thermolyne, Dubuque, IA). The reactor tube may be made from a wide variety of materials, such as ceramic materials (preferably quartz).

The droplets preferably are heated in the reactor 7 until substantially all the ceramic precursor(s) (and, if present, the therapeutic dopant precursor(s)) has thermally decomposed, thereby causing the droplets to solidify to form ceramic microspheres. Heating beyond this point generally will not affect the microspheres thus produced. The Example below illustrates a suitable embodiment of this invention for heating the aerosol in a reactor to form microspheres. Using these teachings, those of ordinary skill in the art can determine without undue experimentation the necessary residence time for the desired heating to be achieved.

After the microspheres exit the reactor 7, they preferably are collected.

Various mechanisms (many of which are commercially available) may be used to collect the microspheres. In one embodiment of this invention, the microspheres are collected by an etched membrane filter 8 having a pore size slightly less than the size of the microspheres being produced. In another embodiment, the microspheres are collected by bubbling the carrier gas through a liquid which wets and collects the microspheres as a suspension.

It should be noted that the smoothness of the microsphere surface is dependent on many factors. In addition to being dependent on how the microspheres are prepared, the smoothness of the microsphere surfaces is also dependent on the composition of the droplets being transformed into the microspheres. For example, it has been observed in accordance with this invention that microspheres prepared using a nitrate (particularly a nitrate of zinc or lead) as the sole ceramic precursor have a greater tendency to have holes (typically in the form of cracks) at their surfaces than microspheres prepared using an acetate as the ceramic precursor. It has also, for example, been observed that when the predominant ceramic precursor is Si(OCH₃)₄, the presence of Al(NO₃)₃·9H₂O in the droplets can lead to recesses (i.e., dimples) being formed in the crusts of the resulting microspheres.
EXAMPLES

A. Preparation of Precursor Solution

Approximately 15.45 g of Al(NO$_3$)$_3$·9H$_2$O (98+%), Cat. No. 23,797-3, Aldrich Chemicals Co., Milwaukee, WI) and 15.78 g of Y(NO$_3$)$_3$·6H$_2$O (99+%, Aldrich Chemicals Co., Milwaukee, WI) was dissolved in 72 ml of water at room temperature. Next, 117 ml of ethanol was added to the solution. After stirring the solution, 223 ml of Si(OC$_2$H$_5$)$_4$ (99+%, Cat. No. 23,620-9, Aldrich Chemicals Co., Milwaukee, WI) was added, and the solution was stirred for 10-15 minutes.

B. Preparation of Microspheres from Precursor Solution

Approximately 100 ml of the precursor solution was placed into a 100 ml glass syringe (Cat. No. 79-4110-03, PGC Scientific, Gaithersburg, MD) and then pumped at 10 ml/min by a syringe pump (Model 975, Harvard Apparatus Compact Infusion Pump, Millis, MA) into an ultrasonic nozzle (Model 8700-60MS, Sono-Tek, Highland, NY). The ultrasonic nozzle was powered by a Sono-Tek PS-88 power supply (Highland, NY). The electrical input into the ultrasonic nozzle was set at 6-8 watts, the nominal atomizing frequency of the nozzle was set at 60 KHz, and the orifice size was 0.23 mm. The mean diameter of the droplets thus formed was 28 µm.

The ultrasonic nozzle was housed in a horizontal tubular quartz chamber (95 mm diameter x 569 mm length). The tubular quartz chamber had two 12 mm diameter inlet ports into which argon gas was fed at 3.5 L/min., after first being filtered through a 0.2 µm in-line filter (Gelman Scientific, Ann Arbor, MI) and then dried by passage though a Drierite gas drier (Fisher Scientific, Pittsburgh, PA). As the droplets existed the ultrasonic nozzle, they entered the argon gas stream to form an aerosol.

Upon formation, the aerosol was directed out of the ultrasonic nozzle's tubular quartz chamber through a 12 mm diameter outlet port and into a pre-heater. The pre-heater was a Pyrex® glass tube having a 22 mm diameter and a 460 mm length. The heating length of the pre-heater was 216 mm. Heat was supplied by a standard 192-watt heater tape wrapped around the glass tube. The heat input from the tape was adjusted with a 155 V variable transformer. The aerosol was heated to approximately 150°C while in the pre-heater. This temperature was chosen based on the thermal decomposition temperatures of the Al(NO$_3$)$_3$·9H$_2$O, Y(NO$_3$)$_3$·6H$_2$O, and Si(OC$_2$H$_5$)$_4$. Using thermogravimetric analysis (explained in more detail below), it was determined that the
onset temperatures for the thermal decomposition of Al(NO$_3$)$_3$·9H$_2$O to Al$_2$O$_3$ and Y(NO$_3$)$_3$·6H$_2$O to Y$_2$O$_3$ are about 240°C and about 450°C, respectively. The onset thermal decomposition temperature of Si(OC$_2$H$_5$)$_4$ was roughly estimated to be between about 300 and about 450°C. Use of the 150°C temperature allowed heating of the aerosol without thermal decomposition of the Al(NO$_3$)$_3$·9H$_2$O, Y(NO$_3$)$_3$·6H$_2$O, and Si(OC$_2$H$_5$)$_4$, thereby avoiding solidification of the droplets. The residence time of the aerosol in the pre-heater (i.e., pre-heater tube volume in the heating zone divided by the volumetric aerosol feed rate) was approximately 1.4 seconds.

Upon exiting the pre-heater, the aerosol was directed through 6.5 mm diameter Teflon® tubing to a high-temperature reactor. The reactor consisted of a quartz reactor tube (ZSI, Inc., Columbus, OH) having a 51 mm diameter and a 620 mm length. The tube was inside a furnace (Model No. F21125, Thermolyne, Dubuque, IA) having a single 305 mm heating zone. The reactor was used to heat the aerosol to a temperature of about 500°C. That temperature, like the temperature used for pre-heating the aerosol, was chosen based on the onset thermal decomposition temperatures of Al(NO$_3$)$_3$·9H$_2$O, Y(NO$_3$)$_3$·6H$_2$O, and Si(OC$_2$H$_5$)$_4$. Because 500°C is greater than the thermal decomposition temperatures of Al(NO$_3$)$_3$·9H$_2$O, Y(NO$_3$)$_3$·6H$_2$O, and Si(OC$_2$H$_5$)$_4$, it was sufficient to cause the droplets in the aerosol to solidify into microspheres. The residence time (i.e., reactor tube volume in the heating zone divided by the volumetric aerosol feed rate) was approximately 11 seconds.

Upon exiting the reactor, the microspheres were collected by a 25 mm diameter track etched membrane filter with 0.1 μm pores (Millipore Corp., Bedford, MA).

C. **Microsphere Characterization**

The size and shape of the microspheres were analyzed using scanning electron microscopy (also referred to as "SEM"). The Millipore filter (upon which the microspheres were collected) was mounted on aluminum stubs with double-sided tape. The samples then were coated with a 20 nm thick layer of gold in a Conductavac III Sputter Coater (Seevac Inc., Pittsburgh, PA). SEM observations were made on an Amray Model No. 1600 SEM (Amray, Inc., Bedford, MA) operating in the SE mode with electron beam voltages of 10-30 kV.
An SEM image of the microspheres showed that the microspheres were spherical in shape, and had no detrimental deformations (i.e., recesses, bulges, or holes) at their surfaces.

D. Thermogravimetric Analysis of the Metal Salts in the Precursor Solution

As noted above, the decomposition characteristics of the precursor (i.e., Al(NO₃)₃·9H₂O and Y(NO₃)₃·6H₂O) were studied using thermal gravimetric analysis (TGA). The measurements were carried out with a Mettler Thermoanalyzer (TA-3000, Mettler Instrument Corp., Hightstown, NJ). A heating rate of 10°C/min. and a N₂ gas flow rate of 100 ml/min. at atmospheric pressure was used in each test. The mass of each sample tested was 1 g.

* * * * * * *

The above description of the preferred embodiment is intended only to acquaint others skilled in the art with the invention, its principles, and its practical application, so that others skilled in the art may adapt and apply the invention in its numerous forms, as may be best suited to the requirements of a particular use. The present invention, therefore, is not limited to the above embodiments, and may be variously modified.
WE CLAIM:

1. A process for the preparation of microspheres comprising a ceramic material, the process comprising:
   forming droplets comprising (a) water, and (b) a ceramic precursor which may be thermally decomposed to form the ceramic material; and
   heating the droplets to vaporize and remove water from the droplets and thermally decompose the ceramic precursor, thereby forming the microspheres,
   wherein the droplets are heated at a rate such that at least about 90% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 10% of the substantially continuous spherical outer surface.

2. The process of claim 1 wherein the droplets are heated at a rate such that at least about 90% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 5% of the substantially continuous spherical outer surface.

3. The process of claim 1 wherein the droplets are heated at a rate such that at least about 90% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 1% of the substantially continuous spherical outer surface.

4. The process of claim 1 wherein the droplets are heated at a rate such that at least about 90% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 0.1% of the substantially continuous spherical outer surface.

5. The process of claim 1 wherein the droplets are heated at a rate such that at least about 95% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 10% of the substantially continuous spherical outer surface.
6. The process of claim 1 wherein the droplets are heated at a rate such that at least about 95% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 5% of the substantially continuous spherical outer surface.

7. The process of claim 1 wherein the droplets are heated at a rate such that at least about 95% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 1% of the substantially continuous spherical outer surface.

8. The process of claim 1 wherein the droplets are heated at a rate such that at least about 95% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 0.1% of the substantially continuous spherical outer surface.

9. The process of claim 1 wherein the droplets are heated at a rate such that at least about 99% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 10% of the substantially continuous spherical outer surface.

10. The process of claim 1 wherein the droplets are heated at a rate such that at least about 99% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 5% of the substantially continuous spherical outer surface.

11. The process of claim 1 wherein the droplets are heated at a rate such that at least about 99% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 1% of the substantially continuous spherical outer surface.
12. The process of claim 1 wherein the droplets are heated at a rate such that at least about 99% of the microspheres each have a substantially continuous spherical outer surface with no single deformation displacing more than about 0.1% of the substantially continuous spherical outer surface.

13. The process of claim 1 wherein the ceramic material is a glass.

14. The process of claim 1 wherein the ceramic material comprises an element selected from the group consisting of silicon, aluminum, zinc, and lead.

15. The process of claim 1 wherein the ceramic material is a compound selected from the group consisting of $\text{Al}_2\text{O}_3$, $\text{SiO}_2$, $\text{ZnO}$, and $\text{PbO}$.

16. The process of claim 1 wherein the ceramic precursor comprises silicon.

17. The process of claim 16 wherein the droplets are formed from a precursor solution which is prepared by a process comprising combining water and a compound selected from the group consisting of $\text{Si(OC}_2\text{H}_5)_4$, $\text{Si(OH)}_4$, and $\text{Si(C}_2\text{H}_3\text{O}_2)_4$.

18. The process of claim 1 wherein the ceramic precursor comprises aluminum.

19. The process of claim 18 wherein the droplets are formed from a precursor solution which is prepared by a process comprising combining water and a compound selected from the group consisting of $\text{Al(NO}_3)_3 \cdot 9\text{H}_2\text{O}$, $\text{Al(C}_2\text{H}_3\text{O}_2)_3$, and $\text{Al(C}_2\text{H}_6\text{O}_3)_3$.

20. The process of claim 1 wherein the ceramic precursor comprises zinc.

21. The process of claim 20 wherein the droplets are formed from a precursor solution which is prepared by a process comprising combining water and a compound selected from the group consisting of $\text{Zn(NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and $\text{Zn(C}_2\text{H}_3\text{O}_2)_2 \cdot 2\text{H}_2\text{O}$.
22. The process of claim 1 wherein the ceramic precursor comprises lead.

23. The process of claim 22 wherein the droplets are formed from a precursor solution which is prepared by a process comprising combining water and a compound selected from the group consisting of Pb(NO₃)₂ and Pb(C₂H₅O₂)₂·3H₂O.

24. The process of claim 1 wherein the droplets further comprise a therapeutic dopant which, upon being subjected to neutron irradiation, emits a therapeutic intensity and amount of beta or gamma radiation.

25. The process of claim 24 wherein the therapeutic dopant comprises an element selected from the group consisting of yttrium, samarium, dysprosium, holmium, rhenium, and phosphorus.

26. The process of claim 24 wherein the therapeutic dopant is a constituent of a compound selected from the group consisting of a hydroxide, a chloride salt, a nitrate, an acetate, a carbonate, and a sulfate.

27. The process of claim 24 wherein the therapeutic dopant comprises yttrium.

28. The process of claim 27 wherein the droplets are formed from a precursor solution which is prepared by a process comprising combining water and a compound selected from the group consisting of Y(NO₃)₃·6H₂O, Y(C₂H₅O₂)₃, and Y(OH)₃.

29. The process of claim 24 wherein the therapeutic dopant comprises samarium.

30. The process of claim 29 wherein the droplets are formed from a precursor solution which is prepared by a process comprising combining water and a compound selected from the group consisting of Sm(NO₃)₃·6H₂O, Sm(OH)₃, and Sm₃(C₂O₄)₃.
31. The process of claim 24 wherein the droplets consist essentially of (a) the therapeutic dopant, and (b) elements having cross sections of no greater than about 200 barns.

32. The process of claim 24 wherein the droplets comprise two therapeutic dopants.

33. The process of claim 32 wherein the droplets consist essentially of (a) therapeutic dopants, and (b) elements having cross sections of no greater than about 200 barns.

34. The process of claim 1 further comprising introducing the droplets into a carrier gas to form an aerosol before the droplets are heated.

35. The process of claim 34 wherein the carrier gas comprises a gas selected from the group consisting of a noble gas and nitrogen.

36. A process for the preparation of a microsphere comprising a ceramic material, the process comprising:
   forming a droplet comprising a ceramic precursor which may be thermally decomposed to form the ceramic material; and
   heating the droplet to thermally decompose the ceramic precursor, wherein the droplet is heated at a rate such that the ceramic precursor throughout the droplet thermally decomposes at substantially the same time.

37. The process of claim 36 wherein the droplet further comprises a therapeutic dopant precursor which may be thermally decomposed to form a therapeutic dopant material which comprises a therapeutic dopant which, upon being subjected to neutron irradiation, emits a therapeutic intensity and amount of beta or gamma radiation.

38. The process of claim 37 wherein the droplet is heated at a rate such that the therapeutic dopant precursor throughout the droplet thermally decomposes at substantially the same time.
39. A process for the preparation of a microsphere comprising a ceramic material, the process comprising:

forming a droplet comprising a ceramic precursor which may be thermally decomposed to form the ceramic material; and

heating the droplet to thermally decompose the ceramic precursor, wherein the droplet is heated at a rate such that a substantially uniform temperature exists throughout the droplet when the ceramic precursor begins to thermally decompose.

40. The process of claim 39 wherein the ceramic precursor comprises silicon.

41. The process of claim 40 wherein the droplet is formed from a precursor solution which is prepared by a process comprising combining water and a compound selected from the group consisting of Si(OC₆H₅)₄, Si(OH)₄, and Si(C₂H₅O₂)₄.

42. The process of claim 39 wherein the ceramic precursor comprises aluminum.

43. The process of claim 42 wherein the droplet is formed from a precursor solution which is prepared by a process comprising combining water and a compound selected from the group consisting of Al(NO₃)₃·9H₂O, Al(C₂H₅O₂)₃, and Al(C₄H₉O)₃.

44. The process of claim 39 wherein the ceramic precursor comprises zinc.

45. The process of claim 44 wherein the droplet is formed from a precursor solution which is prepared by a process comprising combining water and a compound selected from the group consisting of Zn(NO₃)₂·6H₂O and Zn(C₂H₅O₂)₂·2H₂O.

46. The process of claim 39 wherein the ceramic precursor comprises lead.
47. The process of claim 46 wherein the droplet is formed from a precursor solution which is prepared by a process comprising combining water and a compound selected from the group consisting of Pb(NO₃)₂ and Pb(C₂H₅O₂)₃·3H₂O.

48. The process of claim 39 wherein the droplet further comprises a therapeutic dopant precursor which may be thermally decomposed to form a therapeutic dopant material which comprises a therapeutic dopant which, upon being subjected to neutron irradiation, emits a therapeutic intensity and amount of beta or gamma radiation.

49. The process of claim 48 wherein the droplet is heated at a rate such that a substantially uniform temperature exists throughout the droplet when the therapeutic dopant precursor begins to thermally decompose.

50. The process of claim 49 wherein the therapeutic dopant is selected from the group consisting of yttrium, samarium, dysprosium, holmium, rhenium, and phosphorus.

51. The process of claim 49 wherein the therapeutic dopant is yttrium.

52. The process of claim 51 wherein the droplet is formed from a precursor solution which is prepared by a process comprising combining water and a compound selected from the group consisting of Y(NO₃)₃·6H₂O, Y(C₂H₅O₂)₃, and Y(OH)₃.

53. The process of claim 49 wherein the therapeutic dopant is samarium.

54. The process of claim 53 wherein the droplet is formed from a precursor solution which is prepared by a process comprising combining water and a compound selected from the group consisting of Sm(NO₃)₃·6H₂O, Sm(OH)₃, and Sm₃(C₂O₄)₃.

55. A process for the preparation of microspheres comprising a ceramic material, the process comprising:

forming droplets comprising a ceramic precursor having a thermal decomposition temperature at which the ceramic precursor begins to thermally decompose to form the
ceramic material,
    pre-heating the droplets with a first heat source to a temperature which is from
about 5 to about 100°C less than the thermal decomposition temperature of the ceramic
precursor, and
    heating the pre-heated droplets with a second heat source to a temperature which is
no less than the thermal decomposition temperature of the ceramic precursor.

56. The process of claim 55 wherein the first heat source comprises a
heated surface having a temperature which is less than the thermal decomposition
temperature of the ceramic precursor.

57. The process of claim 55 wherein the droplets further comprise water,
and substantially all the water is vaporized and removed from the droplets during the pre-
heating step.

58. The process of claim 55 wherein the droplets further comprise water
and alcohol, and substantially all the water and alcohol is vaporized and removed from the
droplets during the pre-heating step.

59. The process of claim 55 wherein the first heat source pre-heats the
droplets to a temperature which is from about 5 to about 20°C less than the thermal
decomposition temperature of the ceramic precursor.

60. The process of claim 55 wherein the first heat source pre-heats the
droplets to a temperature which is from about 5 to about 10°C less than the thermal
decomposition temperature of the ceramic precursor.

61. The process of claim 55 wherein the second heat source heats the pre-
heated droplets to a temperature which is from about 0 to about 100°C greater than the
thermal decomposition temperature of the ceramic precursor.
62. The process of claim 55 wherein the second heat source heats the pre-heated droplets to a temperature which is from about 0 to about 20°C greater than the thermal decomposition temperature of the ceramic precursor.

63. The process of claim 55 wherein the second heat source heats the pre-heated the droplets to a temperature which is from about 0 to about 5°C greater than the thermal decomposition temperature of the ceramic precursor.

64. A process for the preparation of microspheres comprising a ceramic material and a therapeutic dopant material, the process comprising:
   forming droplets comprising (a) a ceramic precursor having a thermal decomposition temperature at which the ceramic precursor begins to thermally decompose to form the ceramic material, and (b) a therapeutic dopant precursor having a thermal decomposition temperature at which the therapeutic dopant precursor begins to thermally decompose to form the therapeutic dopant material;
   pre-heating the droplets with a first heat source to a temperature which is from about 5 to about 100°C less than the least of (a) the thermal decomposition temperature of the ceramic precursor, and (b) the thermal decomposition temperature of the therapeutic dopant precursor; and
   heating the pre-heated droplets with a second heat source to a temperature which is greater than the thermal decomposition temperatures of the ceramic precursor and the therapeutic dopant precursor,
   wherein
   the therapeutic dopant material comprises a therapeutic dopant which, upon being subjected to neutron irradiation, emits a therapeutic intensity and amount of beta or gamma radiation.

65. The process of claim 64 wherein the first heat source comprises a heated surface having a temperature which is less than the thermal decomposition temperatures of the ceramic precursor and the therapeutic dopant precursor.
66. The process of claim 64 wherein the droplets further comprise water, and substantially all the water is vaporized and removed from the droplets during the pre-heating step.

67. The process of claim 64 wherein the droplets further comprise water and alcohol, and substantially all the water and alcohol is vaporized and removed from the droplets during the pre-heating step.

68. The process of claim 64 wherein the first heat source pre-heats the droplets to a temperature which is from about 5 to about 20°C less than the least of (a) the thermal decomposition temperature of the ceramic precursor, and (b) the thermal decomposition temperature of the therapeutic dopant precursor.

69. The process of claim 64 wherein the first heat source pre-heats the droplets to a temperature which is from about 5 to about 10°C less than the least of (a) the thermal decomposition temperature of the ceramic precursor, and (b) the thermal decomposition temperature of the therapeutic dopant precursor.

70. The process of claim 64 wherein the second heat source heats the pre-heated droplets to a temperature which is from about 0 to about 100°C greater than the greatest of (a) the thermal decomposition temperature of the ceramic precursor, and (b) the thermal decomposition temperature of the therapeutic dopant precursor.

71. The process of claim 64 wherein the second heat source heats the pre-heated droplets to a temperature which is from about 0 to about 20°C greater than the greatest of (a) the thermal decomposition temperature of the ceramic precursor, and (b) the thermal decomposition temperature of the therapeutic dopant precursor.

72. The process of claim 64 wherein the second heat source heats the pre-heated droplets to a temperature which is from about 0 to about 5°C greater than the greatest of (a) the thermal decomposition temperature of the ceramic precursor, and (b) the thermal decomposition temperature of the therapeutic dopant precursor.
73. A process for the preparation of microspheres for radiation therapy of a mammal, the process comprising:

forming droplets from a precursor solution prepared by a process comprising combining Si(OC$_2$H$_5$)$_4$ and Y(NO$_3$)$_3$·6H$_2$O;

pre-heating the droplets with a first heat source to a temperature which is from about 200 to about 295°C; and

heating the pre-heated droplets with a second heat source to a temperature which is greater than about 450°C.

74. The process of claim 73 wherein the first heat source has a temperature which is from about 200 to about 295°C.

75. A process for the preparation of microspheres for radiation therapy of a mammal, the process comprising:

forming droplets from a precursor solution prepared by a process comprising combining Al(NO$_3$)$_3$·9H$_2$O and Y(NO$_3$)$_3$·6H$_2$O;

pre-heating the droplets with a first heat source to a temperature which is from about 140 to about 235°C; and

heating the pre-heated droplets with a second heat source to a temperature which is greater than about 450°C.

76. The process of claim 75 wherein the first heat source has a temperature which is from about 145 to about 235°C.

77. The process of claim 75 wherein the droplets are formed from a precursor solution prepared by a process comprising combining Al(NO$_3$)$_3$·9H$_2$O, Y(NO$_3$)$_3$·6H$_2$O, and Si(OC$_2$H$_5$)$_4$. 
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**X** Further documents are listed in the continuation of box C.  
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Borst, M
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