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Studies on the development of ^{169}Yb-brachytherapy seeds: New generation brachytherapy sources for the management of cancer

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ABSTRACT

This paper describes development of ^{169}Yb-seeds by encapsulating 0.6–0.65 mm (ϕ) sized $^{169}Yb_2O_3$ microspheres in titanium capsules. Microspheres synthesized by a sol–gel route were characterized by XRD, SEM/EDS and ICP-AES. Optimization of neutron irradiation was accomplished and ^{169}Yb-seeds up to 74 MBq of ^{169}Yb could be produced from natural Yb_2O_3 microspheres, which have the potential for use in prostate brachytherapy. A protocol to prepare ^{169}Yb-brachytherapy sources (2.96–3.7 TBq of ^{169}Yb) with the use of enriched targets was also formulated.

1. Introduction

Sealed sources incorporating various radionuclides find extensive use in the treatment of cancer by delivering radiation dose to the tumor cells. Large and deep-seated tumors can be treated by external beam therapy using linear accelerators or by teletherapy using high intensity radiation sources such as those of ^{60}Co by keeping the source away from the body. On the other hand, in brachytherapy, radiation sources incorporated with various radioisotopes such as ^{137}Cs, ^{192}Ir, ^{125}I, ^{103}Pd, etc., are kept in the close proximity of the effected lesion to irradiate the tumor site. In most common types of brachytherapy treatments, sealed radioactive sources are used as temporary implants and sources are removed from the body after delivering the required radiation dose to the lesion. In other type of treatment, e.g., in the case of prostate cancer, the sources are left within the organ permanently to impart the radiation dose and this technique is known as Permanent Implantation Technique. Radioactive seeds incorporating low energy emitting radionuclides such as ^{125}I, ^{103}Pd, etc. are in demand for the treatment of eye, prostate and brain cancers (Perez et al., 1997; Finger, 1997). Ytterbium-169 (half-life 32.02 days; mean gamma emission 93 keV, after excluding photons of energy less than 10 keV) is a radionuclide with interesting potential for brachytherapy applications and is known to be superior to some currently available brachytherapy nuclides (Loft et al., 1992). Natural ytterbium contains 0.13% of ^{168}Yb that on account of fairly large thermal neutron capture cross-section of 2300 barns can be conveniently converted to ^{169}Yb in a nuclear reactor. ^{169}Yb decays by electron capture to ^{169}Tm, emitting photons of energies between 49.8 keV and 307.7 keV with a mean energy of 93 keV. There is a renewed interest in considering ^{169}Yb seeds as a substitute for higher-energy HDR ^{192}Ir-seeds in temporary interstitial brachytherapy applications (Das et al., 1995). Several groups have investigated the use of encapsulated sources of radioactive ^{169}Yb as a brachytherapy source (Mason et al., 1992; Piermattei et al., 1992; Perera et al., 1994). The characteristics of ^{169}Yb are highly interesting for its use as high dose-rate brachytherapy sources. Introduction of brachytherapy equipment containing ^{169}Yb sources

Abbreviations: BDL, below detection limit; BET theory, Brunauer, Emmette and Teller theory; BJH method, Barrett–Joyner–Halenda method; EDS, energy dispersive spectroscopy; EOB, end of bombardment; EDX, energy dispersive X-ray; HDR, high dose rate; HPGe, high purity germanium; ICP-AES, inductively coupled plasma-atomic emission spectroscopy; IGP, internal gelation process; LDR, low dose rate; MCA, multi-channel analyzer; ND :YAG, neodymium doped yttrium aluminium garnet; OD, optical density/outer diameter; SEM, scanning electron microscopy; XRD, X-ray diffraction

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will lead to smaller required thicknesses of the materials used in radiation protection barriers compared with the use of conventional sources such as ^{192}Ir and ^{137}Cs sources (Granero et al., 2006). This radionuclide possesses high specific activity with the emission of relatively low-energy photons, i.e. mostly < 100 keV, and a half-life suitable for regular source exchanges in the afterloader. Hence, ^{169}Yb is a possible substitute for ^{125}I or ^{103}Pd permanent implants as well as ^{137}Cs or ^{192}Ir temporary implants in brachytherapy applications (Papagiannis et al., 2007). Over the last few years, high dose rate ^{169}Yb sources have been produced, which are thought to be an attractive alternative to ^{192}Ir in MammoSite® RTS applications. These sources provide significant advantages in terms of radiation protection and shielding requirements and comparable dose distributions for a breast, multi-planar interstitial treatment plan (Granero et al., 2006; Lymperopoulou et al., 2006a, 2006b, 2005). ^{169}Yb (0.5–2 mCi seed) is also an alternate to conventially used ^{125}I or ^{103}Pd seeds in permanent implantation as ^{169}Yb provides a higher initial dose rate for permanent implants compared to ^{125}I or ^{103}Pd. In recent years, brachytherapy has become a viable treatment option. Low dose rate implants using permanently implanted radioactive seeds and high dose rate treatments using afterloading machines are two methods regularly used in brachytherapy practices. Both techniques require close integration between imaging and the placement of the radioactive sources (Bownes and Flynn, 2004). Different techniques like electrodeposition, impregnation of radioactivity into ceramics/resins, ion implantation etc., are adapted by different manufacturers for fabrication of these sources (Bret et al., 2001). In the present communication, we describe the studies that have been carried out at our end to develop a new design of ^{169}Yb-seed, consisting of six microspheres ~0.6–0.65 mm (ϕ) arranged within a titanium capsule. Our work includes the optimization of conditions for preparing a stable source core, their characterization, laser encapsulation in tiny titanium capsules of size 0.8 mm (OD) × 4.75 mm (l), thermal neutron irradiation planning and quality assurance. This paper describes the feasibility study for making uniformly distributed microspheres of ^{169}Yb to generate adequate levels of radiation and yet exhibit very low rates of leaching for their potential application in brachytherapy.

2. Materials and methods

Natural high purity Yb $(NO_3)_3$ was procured from M/s T.A. Corporation, Mumbai. Specific suface area and pore size determination was done with the help of a 'SORPTOMATIC-1990 Analyzer', procured from M/s C.E. Instruments, Italy. Density measurement was carried out with the help of Pycnomatic ATS-Helium Pycnometer procured from M/s Thermo Electron, Italy. X-ray diffraction (XRD) analysis of microspheres was carried out with STOE powder diffraction system. Scanning electron microscope; Model-Vega MV-2300T/40, supplied by M/s TESCAN, former Czechoslovakia was used for scanning electron microscopy (SEM) analysis. The elemental distribution on microspheres was analyzed by energy dispersive x-ray (EDX) analysis (Oxford, Model INCA E350). Determination of trace level of metals was done in Analytical Chemistry Division of our Institute using inductively coupled plasma-atomic emission spectroscopy (ICP-AES JY-238, Emission Horiba Group, France). A HPGe multichannel coaxial photon detector system (Canberra Eurisys, France) with a 0.5 keV resolution having a range from 1.8 keV to 2 MeV and a ^{152}Eu standard source for energy and efficiency calibration was used for quantitative estimation of ^{169}Yb and ^{175}Yb during the tracer experiments. A well type ion chamber was used for radioactivity measurement of radioactive microspheres and encapsulated seeds. Titanium capsules of 0.8 mm (OD) × 4.75 mm (l) were fabricated by M/s Titan Company Limited, Bangalore. A 50 W neodymium doped yttrium aluminum garnet (Nd: YAG) laser welding system was procured from M/s Quanta Systems, Italy. Neutron irradiation of targets was carried out in DHRUVA research reactor of our Institute. Well-type NaI (Tl) scintillation counter was available in our Division. All other chemicals used in our work were of GR/AR grade procured from reputed manufacturers.

3. Experimental

3.1. Preparation of microspheres

Yb_2O_3 microspheres were prepared by internal gelation process (IGP) of Sol–Gel technique. Briefly, 1.0 mol of Yb $(NO_3)_3$ solution with natural abundance of ^{168}Yb was pre-treated with 0.13 mol of hexamethylene tetramine (HMTA). The IGP process involved mixing of pre-cooled HMTA–Urea solution with cooled pretreated salt solution. Droplets of the feed solution were allowed to pass through a column containing hot silicon oil. Gel spheres could be prepared from the solution having [Yb]=0.85 and [HMTA, Urea]= 2.5. The gel particles were degreased with CCl_4 and washed free off unwanted chemicals from gel particles with NH_4OH solution for 3 h. The spheres so formed were dried at 100 °C and then were heated to 1000 °C for 2 h. After sieving through sieves of proper size, microspheres in the size range of 0.6–0.65 mm (ϕ) were segregated for further experiments and characterization.

3.2. Characterization of microspheres

3.2.1. Physical properties

Surface area and porosity of microspheres was carried out by N_2 gas with the help of the 'SORPTOMATIC 1990' analyzer by studying adsorption–desorption isotherms. The lower part of the adsorption or desorption isotherm (i.e. $0.05 \leq P/P_o \leq 0.35$) was used for the measurement of specific surface area by the multipoint BET method; Brunauer, Emmett and Teller method (Brunauer et al., 1938). The entire adsorption/desorption isotherm was used for pore size analysis. The pore volume and pore radius were calculated by considering the adsorbed film at the pore walls as cylindrical pores model (Barratte et al., 1951). Density of microspheres heated at 950–1000 °C for 2 h was determined by standard gas displacement method with the help of helium pycnometer.

3.2.2. Surface characterization

Uniformly sized Yb_2O_3 microspheres ranging between 0.6 and 0.65 mm (ϕ) were used for these studies. Prior to analysis a thin gold coating was provided on microspheres samples to ensure adequate conductivity during analysis. SEM analysis of microspheres was carried out for studying the morphology of microspheres and EDS analysis was carried out to examine the distribution of elements present in the samples.

3.2.3. X-ray diffraction

In order to examine the crystallinity of ytterbium oxide, XRD pattern of Yb_2O_3-microspheres was obtained by standard powder diffraction method and spectra obtained were analyzed for the presence of Yb_2O_3 peaks.

3.2.4. Leachability

The leachability of non radioactive Yb_2O_3 microspheres was determined in double distilled water at ambient temperature. A weighed amount of the microspheres (50 mg) was placed in 100 ml of water and kept for 48 h at ambient temperature. At the end, concentration of Yb^{3+} and Si^{4+} metal ions in the filtrate was