PMMA/SWCNTs Nanocomposites for Prostate Brachytherapy MRI Contrast Agent Markers

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ABSTRACT

Interstitial brachytherapy became a standard treatment for prostate cancer in the last decade with outstanding long-term results. Magnetic Resonance Imaging (MRI) is the imaging modality of choice for the prostate, however, for prostate brachytherapy (PB) it is currently not utilized to its full potential because the radioactive titanium seeds generate MRI artifacts and appears as black holes (negative contrast) leading to unreliable localization within the prostate and periprostatic tissue by using MRI. To overcome this disadvantage, we developed a novel medical device referred to as Encapsulated Contrast Agent Markers (ECAMs), contained Co-based or Gd-based T_1 contrast agents that allows visualization of the precise location of radioactive titanium seeds by using MRI. We report here on fabrication of reinforce poly(methy1 methacrylate) (PMMA) with single-walled carbon nanotubes (SWCNTs) nanocomposites that can be potentially used as capsulation materials for MRI prostate brachytherapy markers and study of their MRI response. In vitro testing of fabricated markers using clinical MRI sequencing protocols have demonstrated positive T_1 signal enhancement. This study revealed that fabricated PMMA/SWCNTs composites show potential as capsule materials for PB MRI markers.

Keywords: MRI marker, prostate brachytherapy, polymeric implant, SWCNT/PMMA nanocomposite, MRI contrast agent

1. INTRODUCTION

Prostate brachytherapy (PB) is an alternative to traditional external beam radiation or surgery for men who have prostate cancer [1]. PB uses tiny radioactive titanium seeds (0.8 mm in diameter and 4.5 mm in length) implanted directly into the prostate gland and has increased in popularity over recent years due to its effectiveness, relative convenience and minimal invasiveness under imaging guidance. The radiation from the titanium seeds penetrates the surrounding prostate tissue for a distance of less than 15 mm and most of the radiation is concentrated within the prostate. A recent technological development involves placing the seeds inside a biocompatible strand in order to prevent seed migration during the delivery of therapy. A typical clinical case involves placement of 70-130 of the titanium seeds in 20 to 30 strands. These seeds are left implanted permanently, but the radioactivity in them decays fairly rapidly, depending on the type of seeds used.

2. IMAGING OF THE BRACHYTHERAPY RADIACTIVE SEEDS

Currently, the location of the titanium radioactive seeds used for prostate brachytherapy with respect to the tumor and normal critical organ structures remain ill defined with standard imaging modalities like ultrasound and computed tomography (CT). Positive contrast of the titanium seeds on CT permit accurate localization of the seeds for post-implant dosimetry but a lack of contrast in prostate anatomy and surrounding critical structures, as well as star/streak artifacts from the seed themselves, confound efforts to provide highly accurate treatment planning and verification (see Figure 1).

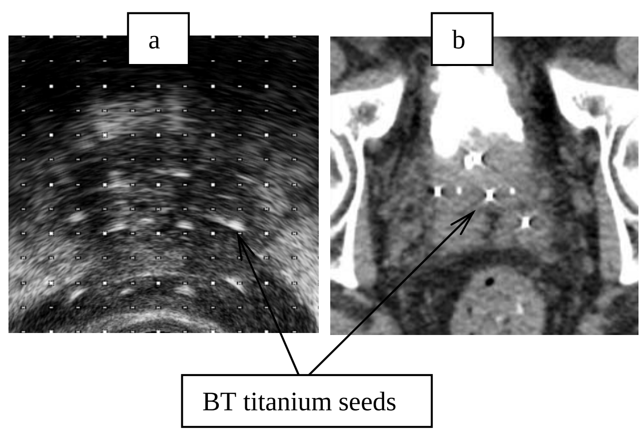

Figure 1: Post-implant axial images of the prostate (Base) with (a)-ultrasound, (b)-computer tomography.

These standard imaging modalities, which are used during treatment planning, treatment delivery, and post-implant treatment quality evaluation, provide inferior visualization of the prostate and surrounding critical organ structures, this leads to subjective determination of the quality of treatment. During the evaluation of the implant, if there is inadequate dosimetric coverage of the prostate, patients should be taken back to the operating room with additional seeds implanted to optimize dose to the prostate cancer. Since MRI was shown to be sensitive and specific for prostate imaging the radioactive titanium seeds generate MRI artifacts and appear as black holes (negative contrast) and cannot always be accurately localized within the prostate and periprostatic tissue (see Figure 2).

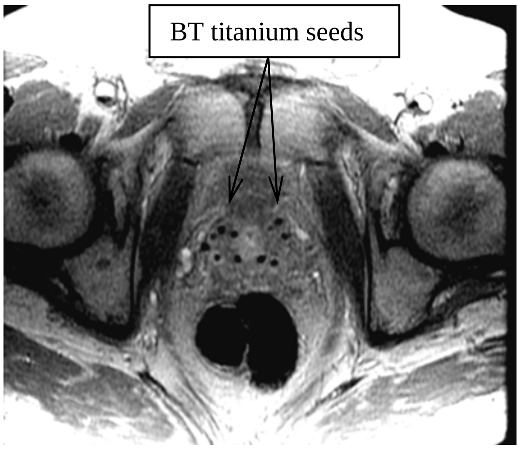

Figure 2: Post-implant axial T1-weighted images of the prostate (Base) with MRI (1.5 T).

3. RECENT DEVELOPMENTS

To overcome this disadvantage, we developed a novel "medical marker" referred to as Encapsulated Contrast Agent Markers (ECAMs), contained Co-based or Gd-based T_1 contrast agents, that allows visualization of the accurate location of radioactive titanium seeds by clinical MRI protocol [2,3]. These markers were fabricated by using poly(methy1 methacrylate) (PMMA), Polyetheretherketon (PEEK) and Polycarbonates as capsule materials. A very low electrical conductivity of these polymers makes the capsules transparent for high radio frequency signals, which are important for MRI application. Good mechanical properties and high melting temperature of these polymers make them a preferred choice as construction materials for implantable biomedical applications. Overall, polymeric biomaterials display several key advantages. These include ease of manufacturing into products with a wide variety of shapes, reasonable cost, wide availability, and wide variety of mechanical and physical properties.

4. PROBLEM DEFINITION

The most frequently implanted isotopes in brachytherapy are Iodine-125 and Palladium-103 with varied from 0.1 to 10 mCi seed activities. The half-life of I-125 is about 60 days, while the half-life of Pd-103 is 17 days. This means the I-125 and Pd-103 seeds lose 80% of their radioactivity within 135 and 35 days, respectively. While seeds lose 80% of their radioactivity I-125 and Pd-103 seeds are essentially biologically harmless after 275 and 102 days, respectively. I-125 seeds are used for low to high grade prostate cancer, while Pd-103 is used more for moderate to high-grade cancers with rapid growth rates. Thus, the ECAMs mechanical durability and radiation resistance are important characteristic for clinical performance and safety applications. Consequently, markers capsule should be fabricated by using high robust materials having a durable mechanical straight, radioactive resistance and MRI transparency. Recent advances in polymer development have shown that addition of SWCNT into PMMA can reinforce polymer properties and increase radiation resistance [4, 5].

One of the important goals in nanocomposites MRI marker fabrication is to enhance mechanical properties while at the same time prevent loss in MRI transparency. We report here on fabrication of composite material based on poly(methy1 methacrylate) (PMMA) with single-walled carbon nanotubes (SWCNTs) that can be potentially used as capsulation materials for MRI brachytherapy markers and study of their MRI response.

5. RESULTS AND DISCUSSION

5.1 PMMA/SWCNTs nanocomposites preparation

Carbon nanotubes have shown outstanding hardness and strength and significant thermal and electrical properties, which make them ideal candidates for the development of multifunctional composites material systems. Previous research has demonstrated the fabrication and characterization of carbon nanotube/polymer composites with enhanced elastic modulus and decomposition temperature [6, 7].

Uniform dispersion and well alignment of SWCNTs within the polymer matrix, as well as improved matrix/nanotube wetting and adhesion properties are critical factors in the processing of these materials. PMMA (molecular weight 10,000 g/mol) was chosen as matrix in this study for its good mechanical properties, high electrical resistivity, biocompatibility, high solubility in N,N-dimethylformamide (DMF) and MRI transparency. We used here coagulation method [8] to prepare PMMA/SWCNT composites for MRI contrast agent markers. This method allows a better dispersion of SWNTs in a polymer matrix and nanocomposites homogeneity that increases the mechanical properties and radiation resistivity of the material. SWNTs have been used in this work due to better mechanical properties than MWNTs.

To generate the carboxyl function groups on SWCNT surface and increase the dispersibility of SWCNTs in N,N-Dimethylforamide the carbon nanotubes were treated in a solution containing hydrogen peroxide and de-ionized water (1:1). The treated SWCNTs were immersed in the solution containing hydrochloric acid with de-ionized water in ratio (1:10) and sonicated during 2 h. Biocompatible PMMA (2 g) powder was dissolved in DMF (10 ml) and then 1-10 wt. % of SWCNTs was added to PMMA/DMF suspension and sonicated again for 2 h. To evaporate DMF solvent the mixture was dried in a vacuum till PMMA/SWCNT solidified into flakes.

The flakes were then extruded by using Laboratory Mixing Extruder (LME, Dynisco) for forming PMMA/SWCNT nanocomposite fiber with 0.8 mm. First, we extruded several nanocomposites using different conditions to explore the impact of the extrusion process parameters, in particular, force, rotor speed and rotor/head temperatures on the nanocomposite quality and geometry. Based on these first results, we continued by extruding at a fixed temperature and speed, and the corresponding force required was optimized for obtaining polymer flow steady-state regime. The extrusions performed at different conditions have shown that the temperature range of 180-210°C is appropriate. Experiment revealed that PMMA/SWCNT nanocomposite extrusion is limited by die swell at lower temperatures and by thermal degradation of polymer at higher temperatures.

Scanning electron microscopy (SEM, JEOL, JAX8600, Japan) was used to observe the dispersion and distribution of SWNTs within the extruded rod. All specimens are mounted such that the plane viewed under the microscope is a cross-sectional fracture perpendicular to the extrusion direction. Micrographs in Figure 3 show that the carbon nano tubes are well dispersed. High resolution SEM images confirmed the average size of carbon nanotubes ~12 nm in diameter and ~ 1-2 μm in length.

Mechanical properties of the MRI markers specimens were evaluated by measuring elastic modulus and tensile tests. Table 1 shows dependence of the elastic modulus and tensile strength of the extruded single filament on the SWCNT concentration in the polymer matrix. The extruded composites with up to 10 wt % of SWCNT exhibit larger elastic modulus and tensile strength compared with plain PMMA .

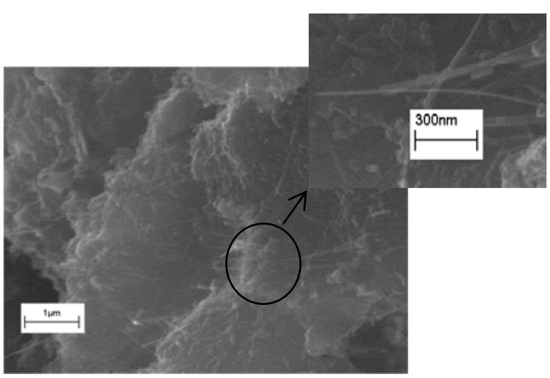

Figure 3: SEM images of PMMA/SWCNTs nanocomposite at 5 wt. % of SWCNTs.

Table 1: Mechanical properties of extruded PMMA and PMMA/SWCNT nanocomposite samples

Sample	Elastic modulus, (GPa)	Tensile strength, (GPa)
PMMA	2.5	0.53
PMMA/5wt.% SWCNT	2.9	0.68
PMMA/8wt.% SWCNT	3.5	0.72
PMMA/10wt.% SWCNT	3.7	0.83

5.2 Fabrication of the MRI Markers and BT Strands

The extruded fibers were used as a robust material for encapsulation of contrast agents. The microphotograph of the one side of the MRI marker is shown in Figure 4. The extruded fibers were processed to obtain hollow cylinders of 5.5 mm in length, 0.8 mm in OD, and 0.6 mm in ID. One polymer tap fastened to one of the tube ends. The tap was locally glued to secure the conjunction. The contrast agents (Co- or Gd-based) were injected into the polymer seed by using high pressure stainless steel syringe. The second tap was fastened to the tube and was also glued to prevent any leakage of the contrast agent.

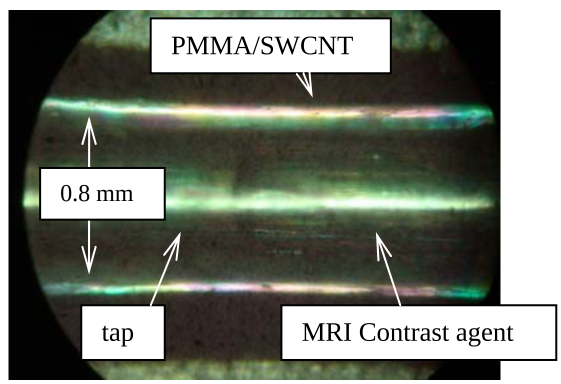

Figure 4: A microphotograph of the MRI brachytherapy marker fabricated by using PMMA/SWCNT (5 wt. %) nanocomposites and Co-based contrast agent.

5.3 Integration of the MRI Markers and BT Titanium Seeds

For integration of MRI markers next to the BT titanium seeds and to fabricate elastic brachytherapy strand we used flexible and biodegradable polyglycolic acid (PGA) (IsoStrand, CP Medical) tubing. This standard PGA tubes typically has an internal diameter of 0.9 mm. This size is suitable for passing the titanium seeds and fabricated markers into the PGA tube. By using a needle having an interior diameter 0.84 mm the markers and seeds were set.

Figure 6 shows the schematic diagram of an integrated MRI visible brachytherapy strand with titanium seeds and MRI markers. Similar to conventional radioactive brachytherapy seeds, the BT strands can be precisely implanted in many different target tissues without the need for invasive surgery.

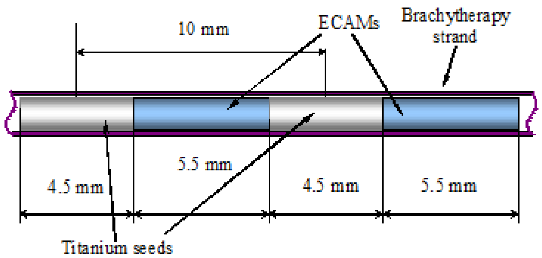

Figure 5: Schematic diagram of the integrated brachytherapy strand with the ECAMs.

Fig. 6 shows fabricated tube, MRI markers, dummy Ti-seeds, PB strand and fractured edges SEM microstructure of PMMA/SWCNT (5 wt. %) composite.

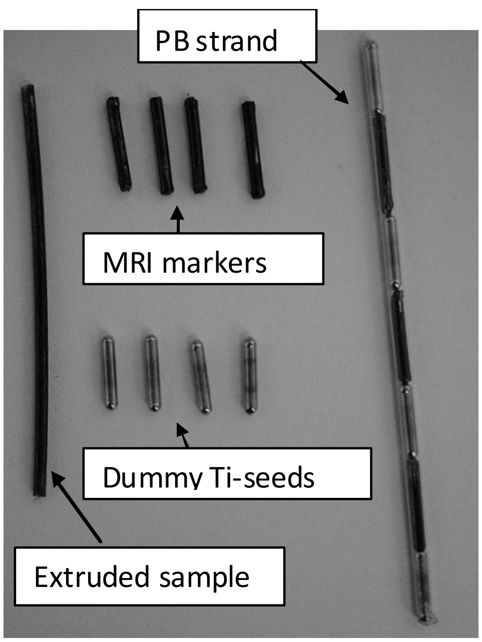

Figure 6: Fabricated PMMA/SWCNTs tubes, dummy Ti-seeds, MRI markers and MRI visible prostate brachytherapy strand.

In vitro testing of the integrated markers with BT seeds using clinical MRI sequencing protocols as well as a 3D T_1-W fast spoiled gradient echo protocol have displayed well T_1 positive signal (see Fig.7). The study revealed that fabricated PMMA/SWCNTs composites can be used as capsule materials for PB MRI markers.

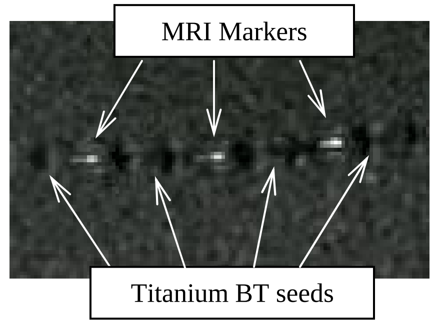

Figure 7: Magnetic resonance image (1.5 T) of brachytherapy strand with integrated MRI markers and BT titanium seeds. MRI markers displayed T_1 positive images.

6. CONCLUDING REMARKS

A coagulation method was implemented to obtain an enhanced dispersion of SWNTs within a PMMA matrix. These composites exhibited improvements in mechanical properties in comparison with pure PMMA composites and did not generate any MRI artifacts. Fabricated MRI markers by using extruding technology were well visualize by clinical MRI under 1.5 T. The detailed study to evaluate its biocompatibility and radiation resistance is underway.

MRI-based approach to prostate brachytherapy with MRI markers will permit immediate post-operative MRI dosimetric evaluation of the quality of the radioactive titanium implants and would facilitate intra-operative dosimetric evaluation to the prostate cancer and surrounding critical organ structures.

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