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# Highly efficient method for production of radioactive silver seed cores for brachytherapy

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ABSTRACT

A simple and highly efficient (shorter reaction time and almost no rework) method for production of iodine based radioactive silver seed cores for brachytherapy is described. The method allows almost quantitative deposition of iodine-131 on dozens of silver substrates at once, with even distribution of activity per core and insignificant amounts of liquid and solid radioactive wastes, allowing the fabrication of cheaper radioactive iodine seeds for brachytherapy.

## 1. Introduction

Cancer is the second leading cause of deaths in Brazil and the third worldwide (INCA, 2015). Currently, radiotherapy is among the most effective and used treatments, in parallel with chemotherapy and surgery, but the access to such technology is limited by the associated high costs. In this context, developing more efficient and cheap technologies for radioactive seed fabrication is strategic to improve public health, especially in developing countries, where the public healthcare system cannot afford for the costs of such treatment. Accordingly, the Brazilian government and IPEN are concentrating efforts to develop a proprietary technology for fabrication of iodine-125 based radioactive seeds for treatment of tumors, for example men prostate cancer, a disease that is the second cause of deaths among men in Brazil.

Radiation sources for brachytherapy may come in all shapes and sizes, but one of the most stringent requirements is the possibility to load them at precisely defined positions inside the tumor with a proper needle or afterloading catheter. Pellets, seeds, wires, and malleable polymers are examples of the different forms in which they can be found and used. On the other hand, the choice of radioisotope depends on its energy and half-life in order to deliver the correct radiation dose to the tumor without harming the surrounding healthy tissues. Among the various high and low energy radionuclides, iridium-192, itrium-90, iodine-125, palladium-103, phosporous-32, gold-192, strontium-90 and ruthenium-106 satisfy those requirements and are been clinically used (Venselaar et al., 2013). Iodine-125 is a low energy photon emitter suitable for fabrication of seeds for permanent implantation since the radiation is less penetrating and decays very rapidly as a function of the distance from the source (Saxena et al., 2009).

A silver core of 3 mm of diameter and homogeneously covered with a thin [125I]AgI layer is positioned inside a titanium tube with suitable diameter, and the ends are laser welded to assure complete sealing of the seeds (Fig. 1). In this arrangement, silver acts as X-ray contrast whereas the titanium shell guarantees biocompatibility and avoid the leakage of harmful radioactive iodine. Each seed core should carry about 1.0 mCi of activity, high enough dose for application as permanent implants in brachytherapy (Saxena et al., 2009).

The first prostate implants were reported by Pasteau and Degrais (Venselaar et al., 2013) in 1913 starting the so called brachytherapy, but the clinical use of radiation was started (Venselaar et al., 2013) as early as 1901 by Marie Curie. It is characterized by the high proximity of the radiation source and target, thus maximizing the dose on the tumor while minimizing the exposition of normal tissues (Marwaha et al., 2013). Furthermore, the procedure is performed with local anesthesia only once and the patient is discharged at the same day. However, its usefulness and effectiveness were recognized only around the nineteen eighties when new radioisotopes and techniques for more precise diagnostic and imaging (ultrasound and tomography for 3D imaging) become available, allowing the exact positioning and monitoring of radioactive seeds (Venselaar et al., 2013). Nowadays it is used to treat intraocular (Marwaha et al., 2013), prostate (Heysek, 2007; Langley and Laing, 2004), lung (Bernard et al., 2015; Li et al., 2015), and brain (Schwarz et al., 2012) cancer tumors. In fact, becomes the

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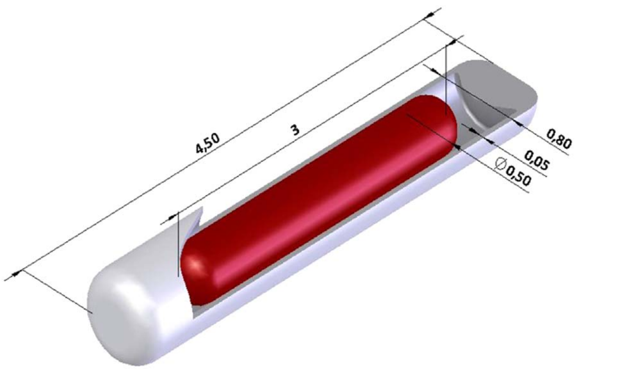


**Fig. 1.** Scheme showing the dimensions (in mm) of the prototype of a brachytherapy seed based on radioactive iodine being developed at IPEN, Brazil.

surface can be tricky because an homogeneous coverage of the entire surface of each substrate and nearly quantitative deposition must be achieved, even considering the very low amounts and concentrations of that radionuclide, associated with the challenge of scaling-up to larger production without losing efficiency. Of course, the hazards associated with radiation and radiochemistry is a constant treat that require stringent security protocols during the entire fabrication process, particularly considering the possibility of formation of volatile species such as iodine vapor that can be easily inhaled.

Efficiencies as high as 80–85% were reported for electrochemical deposition of 200–3200 μCi[2] of [125I]AgI per silver wire. However, they should be cut carefully, generally by an automated system, to avoid activity loss. Many publications described the deposition of iodine by adsorption on silver nuclei after treatment with hydrochloric acid and palladium (II) chloride (Mathew et al., 2002; Saxena et al.,

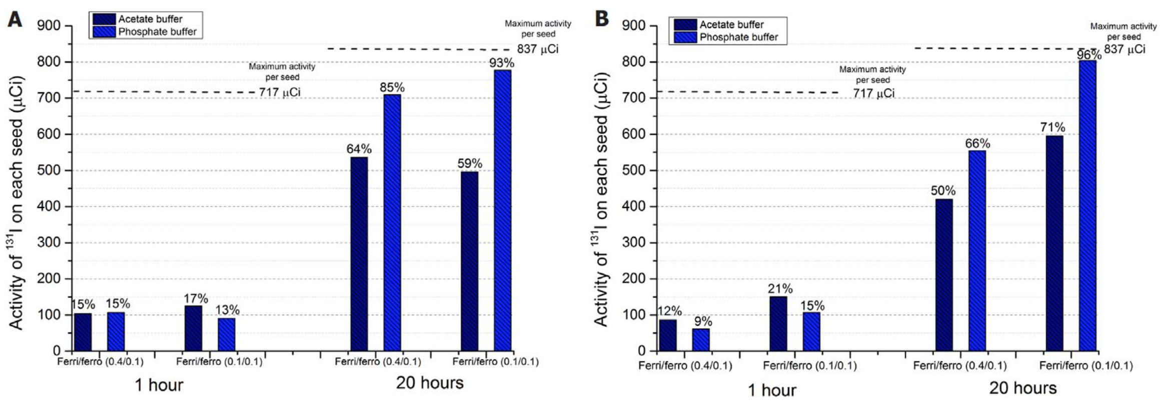


**Fig. 2.** Yield of silver iodide deposition process as a function of ferricyanide/ferrocyanide ratio, pH (phosphate or acetate buffer) and reaction time (1 or 20 h), using one silver substrate treated with (A) piranha solution and (B) nitric acid solution per batch. The horizontal dashed lines indicate the expected activity per seed.

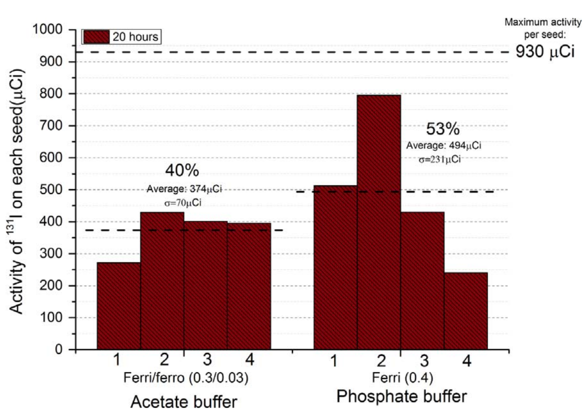


**Fig. 3.** Activity of each silver seed core prepared in acetate and phosphate buffer using ferricyanide/ferrocyanide method, and a reaction time of 20 h. The reactions were carried out using 4 silver substrates per batch. The horizontal dashed line on the top indicates the expected activity per seed core, whereas the dashed lines in the middle refer to the average activity per batch.

treatment of choice especially for prostate and breast cancer, the two most prevalent non-melanoma type of tumor in modern society (American Cancer Society, 2016).

There are several publications and patents describing the production of iodine-125 based seeds for brachytherapy, for example by adsorption (Han et al., 2007; Mathew et al., 2002; Park et al., 2008; Saxena et al., 2009) in silver wires and hybrid materials, by electrochemical deposition (Cieszykowska et al., 2005; Kubiatowicz, 1984; Manolkar et al., 2003) of $Ag^{125}I$, and by anion exchange (He et al., 2009; Kubiatowicz, 1984, 1982; Kumar et al., 2011; Yan, 2014; Ziegler and Mueller, 2000) by radioactive iodide in silver seeds covered with another silver halide. Nevertheless, binding iodine to silver metal

2006), with efficiency up to 60%, using 4 mCi or higher activity per source. In these processes, KI can be used as carrier and sodium sulfide as reductant to convert all iodine species to iodide thus improving the adsorption of radioactive iodine. Another related strategy is based on the oxidation and deposition of silver chloride on silver nuclei followed by the exchange of that halide by iodide (He et al., 2009; Kumar et al., 2011). Temperatures around 60 °C are reported to be ideal for those adsorption reactions (Kumar et al., 2011; Mathew et al., 2002; Saxena et al., 2009, 2006). However, those methods were not shown to be as effective as expected requiring higher concentrations of iodine-125 than that should be deposited, or several reprocessing steps, to achieve high enough activity per seed needed for application in brachytherapy.

The radionuclide and handling are responsible for more than 90% of the radioactive source cost, and are the bottlenecks of any production process. Accordingly, here on described is a protocol allowing virtually quantitative deposition of radioactive iodine on silver substrates. The method is simple, and versatile for production of dozens of radioactive nuclei per batch in a reproducible way, being suitable for production of cheaper high quality seeds for brachytherapy. A locally produced, shorter lived and easier to handle, iodine-131 alkaline solution was used in the development.

## 2. Experimental

All reagents were analytical grade and used as received. Hydrogen peroxide 35%, sulfuric acid 95%, nitric acid 70%, potassium ferrocyanide, and potassium ferricyanide were purchased from Aldrich. Silver wire (99.9%) was acquired from Aldrich.

[2] The radioactive activity is defined as the amount of nuclear disintegrations per unit of time. The SI unit is Bequerel (Bq) that means decays per seconds although most researchers continue to use Curie (Ci), that represents $3.7 \times 10^{10}$Bq, as unit.