

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



Roberta Mansini Cardoso^{a,1}, Carla Daruich de Souza^{b,1}, Maria Elisa Chery Martins Rostelato^b, Koiti Araki^{a,*}

^a Department of Fundamental Chemistry, Institute of Chemistry, University of Sao Paulo, Av. Prof. Lineu Prestes 748, Butanta, Sao Paulo, SP 05508-000, Brazil

^b Nuclear and Energy Research Institute, Avenida Lineu Prestes 2242, Butanta, Sao Paulo, SP 05508-000, Brazil

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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, iridium-90, iodine-125, palladium-103, phosphorus-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

* Corresponding author.

E-mail address: koiaraki@iq.usp.br (K. Araki).

¹ equal contributor in this work

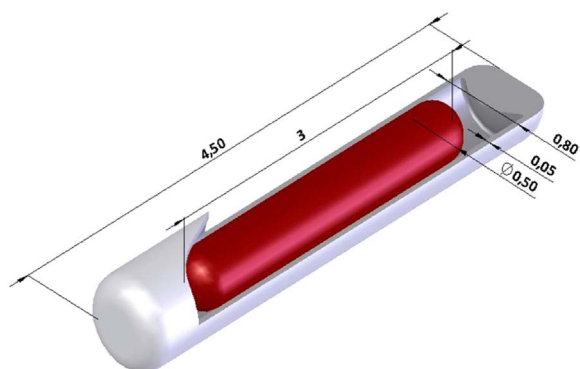


Fig. 1. Scheme showing the dimensions (in mm) of the prototype of a brachytherapy seed based on radioactive iodine being developed at IPEN, Brazil.

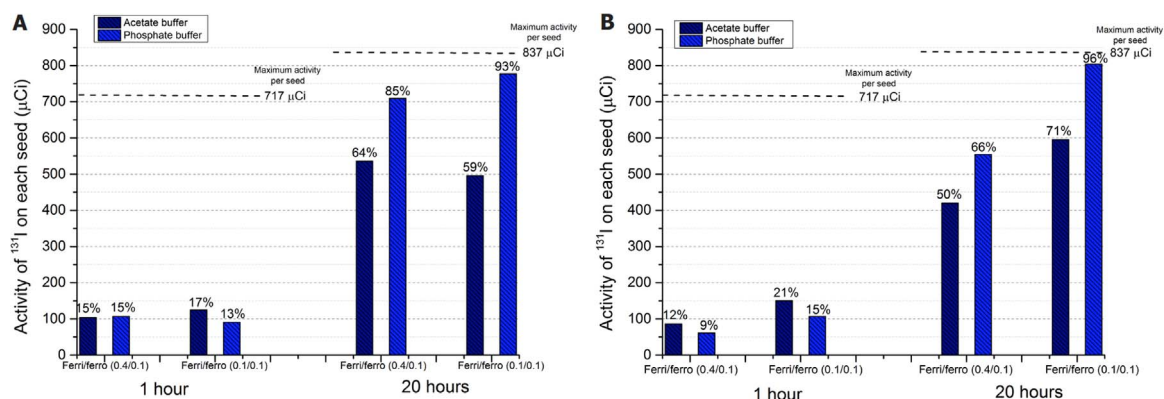


Fig. 2. Yield of silver iodide deposition process as a function of ferricyanide/ferrocyanide ratio, pH (phosphate or acetate buffer) and reaction time (1 or 20 h), using one silver substrate treated with (A) piranha solution and (B) nitric acid solution per batch. The horizontal dashed lines indicate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

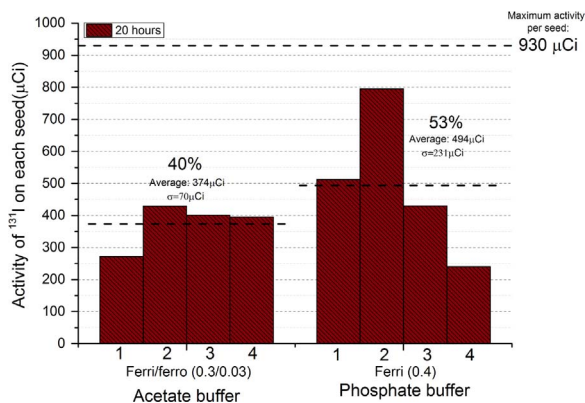


Fig. 3. Activity of each silver seed core prepared in acetate and phosphate buffer using ferricyanide/ferrocyanide method, and a reaction time of 20 h. The reactions were carried out using 4 silver substrates per batch. The horizontal dashed line on the top indicates the expected activity per seed core, 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; Kubiawicz, 1984; Manolkar et al., 2003) of Ag^{125}I , and by anion exchange (He et al., 2009; Kubiawicz, 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

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 $[\text{I}^{125}]\text{AgI}$ 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.,

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 Becquerel (Bq) that means decays per seconds although most researchers continue to use Curie (Ci), that represents $3.7 \times 10^{10}\text{Bq}$, as unit.

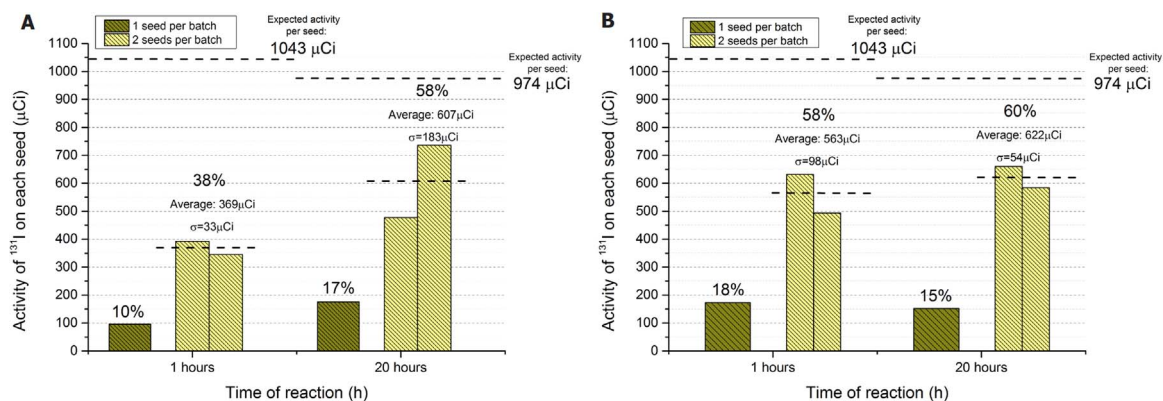


Fig. 4. Activity of each seed after deposition of [131I]AgI by method 2 using silver substrates pretreated with (A) piranha solution and (B) concentrated nitric acid. The reactions were performed with 1 and 2 substrates per batch. The horizontal dashed lines on the top indicate the expected activity per seed core, whereas the dashed lines in the middle refer to the average activity per batch.

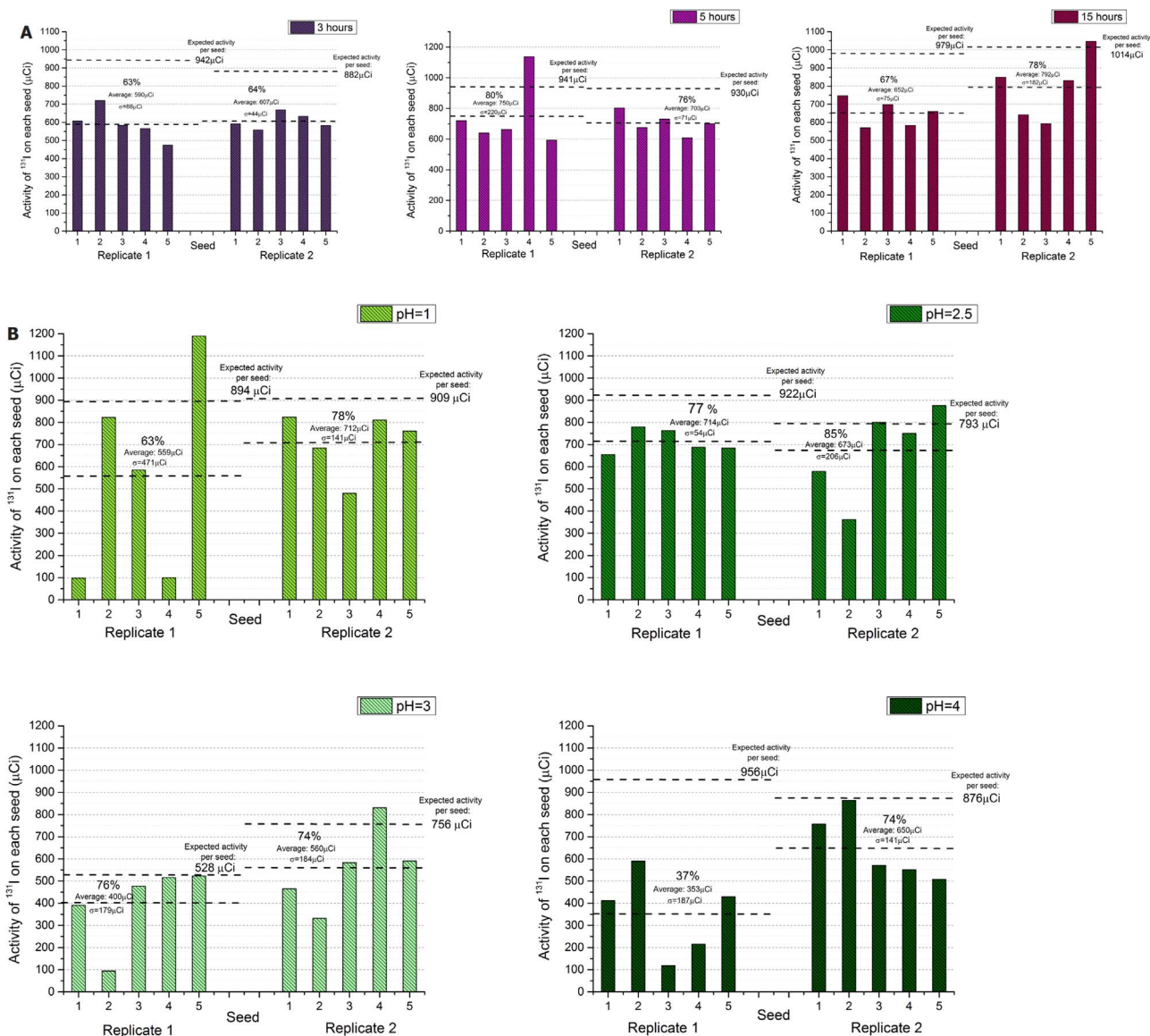


Fig. 5. Activity of radioactive seed cores after deposition of silver iodide by method 2 as a function of (A) reaction time and (B) pH. Reactions were carried out in duplicates using 5 substrates per batch. The horizontal dashed lines on the top indicate the expected activity per seed core, whereas the dashed lines in the middle refer to the average activity per batch.

Iodine-131 gas was produced in IPEN IEA-01 reactor by bombardment of xenon atoms, transported by nitrogen gas and collected in 0.1 M sodium hydroxide solution. A solution with total dose of 100 mCi

(3.7 GBq), measured with a Capintec 15 R ionization chamber, was used throughout.

Silver wire (0.5 mm diameter) was cut generating 3.0 mm long

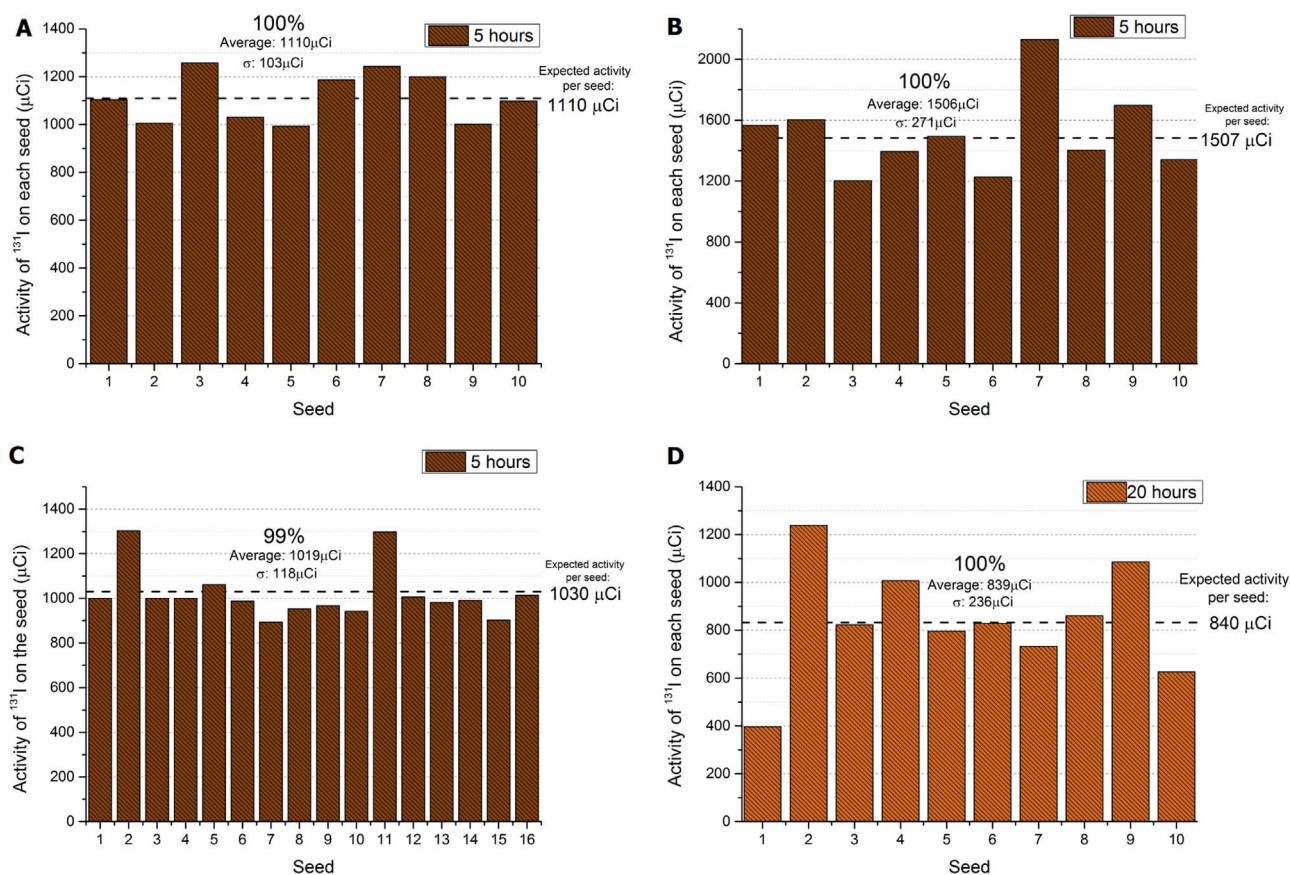


Fig. 6. Distribution of activity per substrate achieved using the optimized method 2, i.e. pH 2.5, deposition time of 5 hs, using 10 (A, B) and 16 (C) silver substrates per batch. The result for a batch prepared setting the reaction time to 20 hs is shown for comparison (D).

substrates. They were carefully washed with acetone and ethanol to remove organic contaminants, and etched with piranha solution, a 3:1 v/v mixture of hydrogen peroxide (Aldrich, 35%) and sulfuric acid (Aldrich, 95%), or with concentrated nitric acid before use. The initially shiny substrates become opaque and acquired a matte gray color upon pre-treatment.

2.1. Deposition procedures

2.1.1. Method 1: Ferricyanide

Solutions of potassium ferricyanide and mixtures of potassium ferricyanide and potassium ferrocyanide in different concentrations and molar ratios were prepared in 1.0 mol L⁻¹ phosphate buffer (pH 7.0) or acetate buffer (pH 4.6).

Typically, 100 μL of ferricyanide solution and 1 mCi (± 100 μCi) of iodine-131 were transferred to a cylindrical flask per silver substrate inside. The flask was tightly capped and rolled at 30 rpm for 1 up to 20 h to assure the formation of homogeneous thin AgI films on the surface. The effect of pH (4.6 or 7.0), concentration of ferricyanide and reaction time on the deposition process was studied using 1–4 silver substrates per batch.

2.1.2. Method 2: Borohydride

One third of iodine-131 solution was treated with 0.05 mol L⁻¹ sodium borohydride and 1 mol L⁻¹ acetic acid solution, mixed with the remaining 2/3 of the iodine-131 solution, and added on silver seeds inside a flask. This was tightly capped and rolled at 30 rpm from 1 up to 20 h, at room temperature. The effect of pH (4.6 or 7.0), temperature and reaction time on the deposition process was evaluated using 1–16 substrates per batch.

2.2. Measurement procedure

The radioactivity of flasks containing the deposition mixture and silver substrates was measured soon after mixing and capping (M1) and after the deposition time, just before opening the flask (M2). The supernatant was drained with a pipette and the radioactive seed cores placed in a filter paper to drain the liquid (about a minute), and the activity of each one was measured using a calibrated Capintec 15 R ionization chamber. The percentage yield was calculated according to equation 1 and 2.

$$\%Yield = \frac{\sum \text{Cores Activity} * 100}{(M1 - \%decay*)} \quad (1)$$

$$\%Yield = \frac{\sum \text{Cores Activity} * 100}{M2} \quad (2)$$

* Considering the maximum reaction time of 48 h, the contribution of decay on yield determination only will be relevant for a radionuclide with short half-life such as iodine-131 (8 days). For longer-lived radionuclides such as iodine-125 (59 days) that contribution is negligible.

3. Results and discussion

Iodine-125 is a gamma radiation emitter with half-life of 59 days, which decays to the toxic tellurium-125 isotope. Iodine-131 is a beta and gamma emitter with half-life of only eight days that decays to the harmless Xenon-131 isotope. Both already have been used for medical application, especially for thyroid imaging. However, iodine-125 emits lower energy gamma radiation more suitable for production of silver seeds for brachytherapy than iodine-131, whose short half-life is more

convenient for development of radioactive seed cores, and was used throughout.

Each radioactive seed used in prostate cancer treatment should carry an activity corresponding to ~ 1.0 mCi, equivalent to the deposition of 450 pmols of iodine-131 per seed. Such small quantity is difficult to monitor by conventional chemical analyses techniques, and the efficiency of iodine deposition process must be monitored based on more sensitive radiation counting methods such as scintigraphy.

The easiest way to attach iodine on silver metal is by formation of a thin silver iodide layer. However, the deposition process tends to be very sensitive to impurities present on silver metal surface, such that a careful cleaning procedure is fundamental. In our case, this step was carried out by washing the substrates with acetone, ethanol and water, followed by a piranha solution that etch and oxidize organic contaminants eventually present, cleaning and increasing the surface area enabling the homogeneous deposition of silver iodide.

However, silver metal does not but silver(I) ion reacts promptly with iodide ion generating sparingly soluble AgI that precipitates on the surface. Accordingly, considering that iodine is present as iodide, it ought to react as soon as silver metal is oxidized to silver(I) ion to avoid its diffusion and assure deposition just on the surface. Otherwise silver iodide will precipitate and separate out as undesirable radioactive slurry that would be responsible for major efficiency loss.

Accordingly, electrodeposition methods have already been used for direct deposition of silver iodide on metallic silver segments (Agency, 2006). This is an interesting approach since it is possible to control the kinetics of metal oxidation as desired by tuning the applied potential. The thermodynamic redox potential of silver is 0.80 V but the actual concentration of Ag^+ ion in solution will be very low in the presence of iodide because of the low solubility product of AgI ($K_{sp} = 8.5 \times 10^{-17}$), thus reducing the actual potential required to oxidize it. This indicates that mild oxidizing agents can be used to polarize silver substrates and promote that reaction. Another strategy is generating iodine derivatives with appropriate redox potentials in solution. Both approaches were used in this work because thin homogenous films covering completely the silver substrates, more suitable for application in brachytherapy, can be generated. Furthermore, such chemical processes are easier to scale-up for production of larger quantities of radioactive cores.

Two routes are possible for chemical deposition of AgI: a) a mild oxidant can be used to slowly convert metallic silver in Ag^+ ions in the presence of iodide ions, promoting the precipitation of silver iodide on the surface; and b) oxidizing iodine species capable to react directly with silver can be generated in solution leading to the formation of AgI on the surface. Both strategies were exploited as detailed below.

When a mixture of ferricyanide/ferrocyanide and iodine-131 solution is added onto a silver substrate, the metal is slowly oxidized and silver iodide precipitates on covering up completely the silver substrates. In this case, the reaction rate is controlled by the ferricyanide/ferrocyanide ratio, and the results for the optimized process are displayed in Figs. 2 and 3. Longer reaction times were found to be beneficial increasing the overall efficiency of $[^{131}\text{I}]\text{AgI}$ deposition process, and phosphate buffer increased the average yield from 50% to 60% to 80–90% as compared with acetate buffer solution. The 1:1 ferricyanide/ferrocyanide mixture delivered better results.

Unfortunately, the average deposition yield decreased to about 40% in acetate buffer and 50% in phosphate buffer when the number of substrates was increased to four and the total initial activity to 4.0 mCi, even increasing the reaction time to 20 h (Fig. 3). In addition, the radioactivity was more evenly distributed when the cores were prepared in acetate buffer as shown on Fig. 3.

In order to improve the deposition process, the method 2 was devised and parameters optimized for deposition of AgI from radioactive iodine-131 solution. The preliminary studies were carried out with 1 substrate per batch, and 2 substrates per flask, in order to verify the effectiveness of the borohydride as compared with ferricyanide/ferrocyanide method. In short, sodium borohydride solution (5 μL of

0.05 mol L^{-1}) was added on 34 μL of iodine-131 solution and then 5 μL of 1 mol L^{-1} acetic acid solution added to annihilate the excess of that reductant. Then, 68 μL of iodine-131 solution was added into the cylindrical flask to generate the deposition mixture. Similar procedure was used in the reaction with 2 substrates per batch simply doubling the volume of reagents, starting with 1 mCi of iodine-131 per substrate. The results of deposition reactions carried out at room temperature setting the time to 1 or 20 h are shown in Fig. 4.

In this case, increasing the number of substrates per batch was found to be advantageous and deposition efficiencies up to 60% were achieved after 20 h. Interestingly, the nitric acid pre-treatment of the silver substrates showed to be more effective than the one with piranha solution. This result was not assigned to the kinetics of oxidation and precipitation reaction but rather to the more effective wetting and contact of the substrates with the deposition solution because of the larger volume as compared with in the previous method (twice the initial volume).

Because of the good results achieved for short deposition times (Fig. 4B), experiments were carried out to evaluate the effect of time (3, 5 and 15 h) and pH (1, 2.5, 3, and 4) on deposition process, adjusting the volume of solution to 100 μL /substrate. This was found to be suitable to ensure more homogeneous and effective deposition reactions. The pH was adjusted with acetic acid. The results in Fig. 5A suggest that the reaction can be quite fast and is complete in 5 h, using pH 2.5 solution (Fig. 5B). In this condition, almost quantitative deposition was achieved in a shorter time, motivating us to test it for batches with larger number of substrates.

The number of seeds was then increased to 10 and 16 and the process started with an initial activity of 1 mCi per substrate. The results shown in Fig. 6 confirmed the excellent efficiency of this deposition method, in addition to more or less even distribution of activity per radioactive seed core. In fact, only few of them exhibited a large discrepancy from the expected average activity (dashed horizontal line), characteristics that were not degraded when the number of substrates per batch was increased from 10 to 16. Consequently, the amount of rejected seed cores and of radioactive liquid and solid wastes can be minimized while increasing the productivity (significant reduction of deposition time) using method 2. Additional experiments with up to 50 substrates per batch gave similar results confirming the high potentiality of the method for commercial production of radioactive iodine seeds for brachytherapy.

4. Conclusions

A simple and robust method allowing almost quantitative deposition of iodine-131 on silver substrates in a reproducible way, allowing the preparation of radioactive silver cores with even distribution of activity per core and insignificant amounts of liquid and solid radioactive waste, scalable to higher number of cores without losing those favorable features, was realized. The higher deposition efficiency associated with excellent productivity (shorter reaction time and almost no rework) assures high competitiveness and possibility to lower the price of radioactive iodine seeds for brachytherapy in the market. Thus, the deposition method is now being adapted to use a commercial iodine-125 source and the results will be published soon.

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- Roberta Mansini Cardoso** received the B.Sc in Chemistry with Technological Emphasis from University of São Paulo, Brazil, in 2013. She is a Ph.D. student in Science since 2014 in University of Sao Paulo (USP), Brazil. Her main research interest is the development and characterization of nanomaterials and the study of their interaction with biological systems, and their application in Theranostics.
- Koiti Araki** got his PhD in Chemistry from University of Sao Paulo, Brazil, in 1994 and is full professor of Institute of Chemistry since 2006, principal researcher of the Supramolecular Chemistry and Nanotechnology Lab, and was member of national committees (CNPq, CAPES and CCNano/MCTi). His interests include the preparation and characterization of hybrid nanomaterials and nanobiomaterials with potential application in areas such as energy, nanomedicine and environment; as well as the supramolecular chemistry of porphyrins and ruthenium polypyridine complexes by the coordinative approach, and their application in PDT, solar cells and functional interfaces.
- Maria Elisa Chuery Martins Rostelato** received the B.Sc in physics from Pontifícia Universidade Católica de São Paulo (PUC), Brazil, in 1979. Got her master's degree 1997 and the Ph.D. degree in 2005 in Nuclear Technology from University of Sao Paulo (USP), Brazil. Elisa is the chief of The laboratory for radioactive sources production for in radiotherapy in IPEN – Instituto de Pesquisas Energéticas e Nucleares that belongs to the National Nuclear Energy Commission. Her interests include radioactive sources development, radiochemistry, dosimetry, nanobrachytherapy, radiation effects, and calibrations sources. Member of IOMP- International Organization on Medical Physics (Science Committee). Consultant of IAEA – International Atomic Energy Agency, and of several national organs such as CNPq, CAPES, FAPESP, FACEPE, and FINEP.
- Carla Daruich de Souza** received the B.Sc in medical physics from Universidade Estadual São Paulo (UNESP), Brazil, in 2009. Got her master's degree in 2012 and will finish her Ph.D. in 2016 in Nuclear Technology from University of Sao Paulo (USP), Brazil. Carla was a fellow in Polatom – Poland (one month, IAEA– International Atomic Energy Agency fellow) and in Washington State University (one year, CAPES scholarship). Her interests include radiochemistry, radiation protection, radioactive sources production, and nano-brachytherapy.