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Development and production of radioactive sources used for cancer treatment in Brazil

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Abstract. The number of cancer patients in Brazil is increasing and part of the patients are submitted to brachytherapy treatment using iridium-192 wire and iodine-125 radioactive seeds. The Nuclear Energy Research Institute established a programme to produce iridium-192 wire and iodine-125 radioactive seeds. With the purpose of settling a laboratory for iridium-192 sources production, a wire activation method was developed and a hot cell for the wire manipulation, quality assurance and packaging was built. The iodine-125 seeds consist of a welded titanium capsule containing iodine-125 adsorbed onto a silver rod. Concerning the setup of the local production, the following activities were carried out: superficial treatment of the silver rod, development of a process to absorb the iodine in the silver rod, welding methodology to seal the seeds, leakage and contamination test and source activity measurement.

Key words: radioactive sources production • iodine-125 seeds • iridium-192 wires • brachytherapy • cancer treatment

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Introduction

In Brazil, cancer has become one of the major public health problems, reflected in an important cause of mortality. The National Institute of Cancer (INCA) estimated that 466,730 people had the disease in the country in 2008 [12]. The number of cancer patients in the country is increasing and some of these patients are treated with brachytherapy, using iridium-192 wire sources and iodine-125 seeds.

Brachytherapy irradiation at a very close distance is a form of lesions treatment which is based on the insertion of sources, in this case activated iridium wires inside tumours. During this process, the ionizing radiation destroys the malignant cells very efficiently [8]. Some of the major brachytherapy advantages over the external radiation, i.e. capacity to give form to isodose distribution in irregular lesions, considerably diminishing dose outside the implant area (saving normal tissues) and the treatment quickness can be highlighted.

These radioactive sources are imported at high cost, what restricts their application. The local production of these radioactive sources became a priority in order to reduce the cancer management impact in end users.

Owing to these reasons, the Energy and Nuclear Research Institute (IPEN), which belongs to the Nuclear Energy National Commission (CNEN), established a programme for the development of technique and production of iridium-192 wire sources and iodine-125 seeds in Brazil.

The purpose of this programme is to develop a technique and to establish a laboratory for the production of iridium-192 sources and iodine-125 seeds. This project target is to enable the country with the production of these sources, making the products accessible to clinics and hospitals, at low costs for the Brazilian people reality.

With the purpose of settling a laboratory for iridium-192 sources production, a wire activation method was developed and a hot cell for the wire manipulation, quality assurance and packaging was built. The wire activation was carried out in our nuclear reactor, IEA-R1. These sources are shaped as flexible wires of 0.3 mm in diameter and 50.0 cm long. The activity per unit length, for a low dose rate (LDR) therapy, is between 1 mCi/cm and 4 mCi/cm (37–148 MBq) [13].

The iodine-125 seeds consist of a titanium capsule of 0.8 mm in external diameter, 0.05 mm wall thickness and 4.5 mm long. The inner capsule houses a silver wire, 3.0 mm long and 0.5 mm in diameter, containing the adsorbed iodine-125. The typical seed apparent activity is of 0.4 mCi (14.8 MBq), with a recommended variation of about 5% at most, in a same lot of seeds [2, 14].

During the project execution, the following methods were developed: seed core (silver) cutting, titanium tube cutting, iodine immobilization through its deposition in a silver substrate and sealing of the seeds through welding process, so that the classification of the seeds, as sealed sources, and the leakage tests could be done according to the international norms.

Iridium-192 wire

Iridium-192, in wires, has been used as a source in brachytherapy since 1960. The isotope is produced in a nuclear reactor by the (n,γ) reaction:

$$^{191}_{77}\mathrm{Ir}(n,\gamma)^{192}_{77}\mathrm{Ir} \tag{1}$$

It has a half-life of 74 days, high specific activity, it decays by beta and gamma emission to the stable isotope Pt-192. The beta rays emitted present energy ranging form 530 keV to 670 keV, and the main gamma rays emitted have an average energy of 370 keV. Iridium-191 also shows a high absorption section for (n,γ) reaction (910 barns) [4, 13].

The activity per unit length, for a low dose rate (LDR) therapy, is between 1 mCi/cm and 4 mCi/cm, requesting activity homogeneity along the wire, not presenting a variation larger than 5% in a 50 cm long wire [13].

These sources are usually shaped as flexible wires with 0.3 mm and 0.5 mm in diameter and can be easily cut in lengths appropriate for each application. These wires comprise a platinum-iridium alloy core (80/20), encapsulated in a platinum or stainless steel tube. The coating target is to filter the beta rays.

Methods and materials

The 0.3 mm in diameter iridium-platinum wire (20/80) was acquired in the international market and submitted to the following analyses:

- scanning electronic microscopy,
- X-rays fluorescence,
- neutronic activation analysis.

The wire was irradiated in the IEA-R1m reactor to define the activation parameters and several irradiation positions and experimental arrangements were tried out, ensuring the homogeneity of the activity all along the 50 cm of these wires, since the literature researched does not specify what activation method should be used. A special irradiation element was built, TEI-01, and the flux profile measurement of local neutrons was performed.

A hot cell was built for the sources manipulation, packaging and quality control. It was based on an iron and acrylic structure and covered with 5 cm thick lead bricks. An operation panel four remote control pliers and two lead glass viewers, are located in the frontal side.

In the lateral and back sides, two doors were installed, one for the material entrance and the other for maintenance. In the inner cell, the opening device for the irradiation recipient, the mean activity detectors and the wire packaging system were placed.

For the sources quality control, a system comprising a high-tension source, electrometer, ionizing chamber, a 1 cm wide collimator shield and a set of pulleys and straps was built, allowing the wire to pass, centimeter by centimeter, in the front of the collimator window.

Results and discussion

In Table 1, the neutrons flux profile of the IEA-R1m reactor, in the reactor core position number 48, is shown.

Through the X-rays fluorescence technique, besides the iridium and platinum, the presence of 0.35% of chrome, 0.73% of iron, 0.08% of manganese, 0.05% of cobalt, 0.51% of nickel, 0.21% of copper and 0.59% of zinc were determined in the coating.

The scanning electronic microscopy and the microanalysis showed this wire to be constituted of a well-centered iridium-platinum nucleus and a platinum coating. Using the neutronic activation analysis, the iridium and platinum elements were the only elements found.

The wire was irradiated in the IEA-R1m nuclear reactor for 40 h, reactor core position number 48, shelf 7 and a neutron flux of 1.96×10^{13} $n \cdot cm^{-2} \cdot s^{-1}$.

Main activation products were shown in Table 2.

The evaluation of homogeneity was performed along each centimetre during three times in the quality

Table 1. Neutron flux profile

Shelf	Thermal flux ($\times 10^{13}$ $n \cdot cm^{-2} \cdot s^{-1}$)	Relative error (%)	Absolute error (%)
1	0.116	3.0	5.0
2	0.387	3.0	5.0
3	0.641	3.0	5.0
4	1.240	3.0	5.0
5	1.670	3.0	5.0
6	1.920	3.0	5.0
7	1.960	3.0	5.0
8	1.880	3.0	5.0

Table 2. Activation products

Nuclide	Half-life	Cross section (barns)	Isotopic abundance	Reaction	Main energy photons (keV)
Ir-192	74 days	924	37.3%	Ir-191(n,γ)Ir-192	317; 468; 295 and 308
Pt-197	18.3 h	0.7	25.3%	Pt-196(n,γ)Pt-197	77.7 and 191.4
Pt-199	30.8 min	3.7	7.2%	Pt-198(n,γ)Pt-199	186; 246; 317; 493; 543 and 714

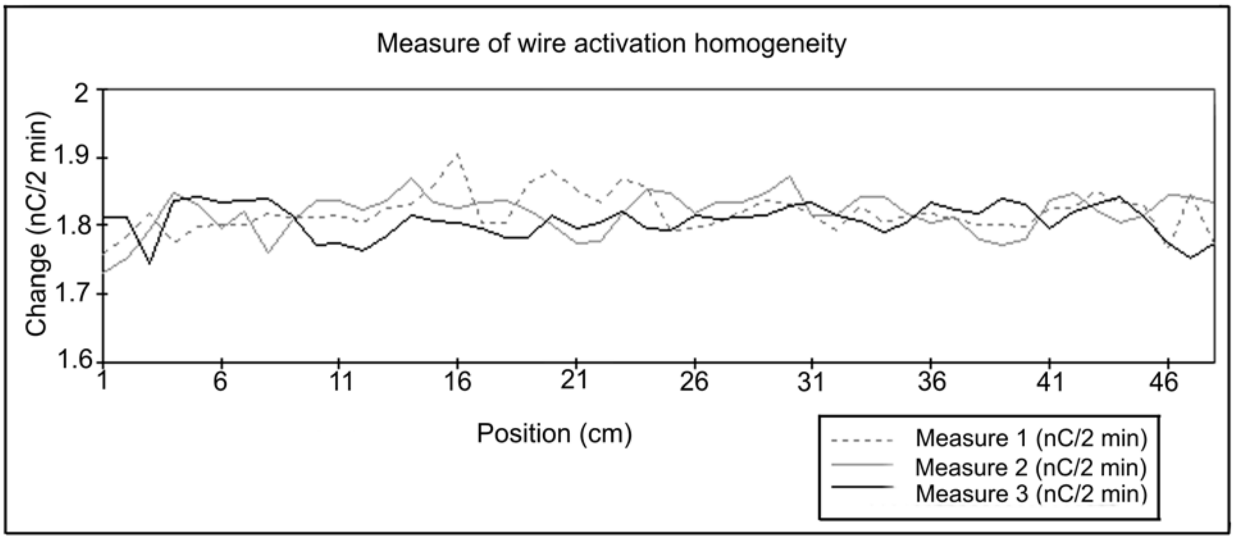

Fig. 1. Measurement of wire activation homogeneity.

control system installed inside the hot cell (Fig. 1). The percentage of the arithmetic average and deviation in relation to the mean, for each series of measurements, were as follows:

The wire:

– Measurement 1: $X = 2.2056$, $E = 1.74\%$;
– Measurement 2: $X = 2.0228$, $E = 2.83\%$;
– Measurement 3: $X = 1.9230$, $E = 0.67\%$.

The total activity measurement was carried out in a Capintec model CRC-12 ionizing chamber. The value achieved was $A = 79.67$ mCi = 2947.8 MBq for a 47 cm long wire. Activity per unit length was $Ae = 1.7$ mCi/cm = 62.90 MBq/cm.

Conclusion

The results showed that the Ir-192 wire is appropriated for brachytherapy application, since the dispersion value of the activity distribution related to the measured arithmetical mean did not surpass 5%.

A laboratory to produce iridium-192 wires was set up. Nowadays, the product is available in the country, at low cost.

Iodine-125 seeds

One of the options for prostate cancer treatment is brachytherapy. By this technique, small seeds with iodine-125, a radioactive material, are implanted in the prostate. These seeds have the advantage of preserving both healthy tissues and organs near the prostate, with low rate of impotency and urinary incontinence, compared to conventional treatments, such as the radical prostatectomy and the external radiation beam [1, 5].

^{125}I is produced in a nuclear reactor, from xenone-124. It decays by electron capture and internal conversion to tellurium-125. In this process, it emits photons of 27 keV, 31 keV and 35 keV, with an average energy of 29 keV. Its photons have a short penetration, due to low average energy of emission. The isotope has a half-life of 60 days.

The seeds have milimetric dimensions and consist of a titanium capsule (material inert to human tissue) with 0.8 mm in external diameter, 0.05 mm wall thickness and 4.5 mm long. The inner capsule houses a silver wire, 3 mm long and 0.5 mm in diameter, containing the adsorbed iodine-125. The typical seed apparent activity is of 0.4 mCi (14.8 MBq), with a recommended variation of about 5% at most, in a same lot of seeds [14].

So far the iodine-125 seed implants have been carried out in Brazil with imported seeds, demanding the production of 2500 to 3000 seeds/month.

Taking into account the seeds price and the difficulties to import, the IPEN, which belongs to the CNEN, established a programme for the development of technique and production of iodine-125 seeds. The estimate for the iodine-125 seeds future demand is 8000 seeds/month and the laboratory to be implemented will need this production capacity [14].

The project aims to enable the country with the iodine-125 seeds production, at a cost meeting the Brazilian reality to allow the access to this therapy for a larger number of patients.

The project was divided in two phases: technological development of a prototype seed and a pilot plant implementation for the production of the iodine-125 seeds, in accordance with medical requests. This paper covers the technological prototype seed development.

Some aspects of the iodine sources production are reported in the literature. Mathew *et al.* investigated a method for iodine-125 adsorption on palladium coated silver wires [10]. Manolkar *et al.* presented studies on two different types of source core preparation, one based on electro deposition of ^{125}I on a silver wire and the other by physical adsorption on alumina microspheres [9]. Cieszykowska *et al.* showed the deposition of ^{125}I on a silver support in a electrochemical process [3]. Mielcarski *et al.* examined a method for electro deposition of ^{125}I on a silver electrode [11]. Saxena *et al.* described a method for ^{125}I adsorption on palladium coated silver wires [15].

Method

The seed core (silver) cutting and the titanium tube cutting were done with a "cut-off" device Buehler LTD, model Isomet 11-1180 using an aluminum oxide disc, and then the debris were sandpapered. The visual inspection was done in an optical microscope.

During the project execution, the iodine immobilization in silver substrate was performed using iodine-131 since its chemical behavior is the same as that of iodine-125 and this radioisotope is produced at IPEN. This deposition was carried out through adsorption at room temperature. The radioisotope iodine-131 was used in sodium iodide (NaI) chemical form, carrier free in sodium hydroxide solution (NaOH) at pH 10 to 12. The iodine-131 half-life is 8 days and the main gamma energies are: 80.2, 284.3, 364.5 and 636.4 keV.

Activities measurements were done in an ionization chamber Capintec model CRC-12, precalibrated for ^{131}I.

The silver wire was acquired in national market with a chemical purity of 99.99% and 0.5 mm in diameter.

After several experiments in which we have changed conditions of activity, silver core quantities, volume and time shaking, we could determine the ideal adsorption parameters.

The sealing of the seeds was performed through the microplasma welding process in a Secheron Soudure welding machine, model plasmafix 50E.

For the classification of the seeds, as sealed sources, and the leakage tests we used the international norms ISO-2919 and ISO-9978 [6, 7].

Results and discussion

A model of the iodine-125 seed was developed, as shown in Fig. 2. The silver core wire must undergo a perfect cutting, perpendicular to its own axis, without debris. Imperfections in the cutting can cause the seed isodose lines deformation.

The titanium tube cutting should also be perfect, free of debris and without deformations for the seed core insertion without difficulty.

In the iodine-125 deposition on the silver substrate, a reaction yield up to 90% was obtained, with an average value of 80% over 500 experiments. Variations in the activity of the ^{125}I 30-seed batch were allowed to be up to 15%. Meeting these requirements, a consistent yield of the radioactive material and a batch of seeds with homogeneous activities were achieved. A typical deposition results are showed in Table 3 and in Fig. 3.

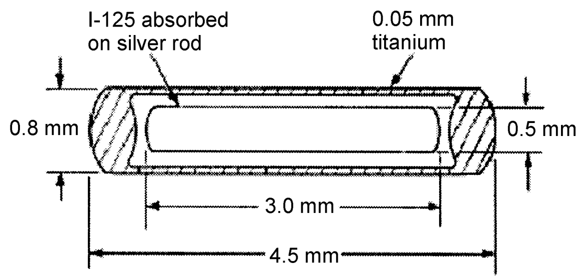

Fig. 2. Schematic diagram of the iodine-125 seed.

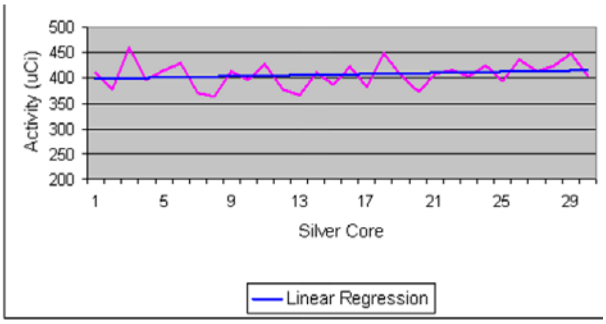

Fig. 3. Iodine-131 activity distribution in a silver core.

In this case, in Table 3 and in Fig. 3, it was shown that the total adsorption was 89.2% and the maximum variation was 13.2% for the average value ($A_{average}$ = 406.3 µCi).

The ideal parameters were 30 sample of 5 mm length and 7.6 mg weight per batch in 2 ml iodine solution with 15 mCi of activity and 26 h of shaking.

The seed sealing was accomplished by the microplasma welding process, resulting a homogeneous weld without inclusions, cracks or fissures, as seen in Fig. 4.

The seed sealing was performed in the following conditions:

- pilot arc current – 2.5 A (fixed);
- transferred arc current – 2.5 A (welding);
- opening welding arc delay – 2 s;

Table 3. Iodine-131 activity distribution in silver core

Silver core number	Activity (µCi)	Silver core number	Activity (µCi)
1	410	16	423
2	376	17	382
3	460	18	447
4	396	19	405
5	414	20	372
6	430	21	407
7	370	22	414
8	362	23	404
9	413	24	424
10	397	25	393
11	426	26	436
12	377	27	412
13	366	28	425
14	410	29	448
15	386	30	403

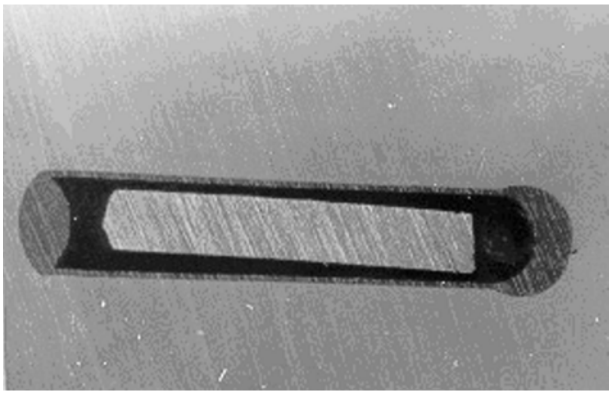

Fig. 4. The microplasma welding process can be watched in this longitudinal cut.

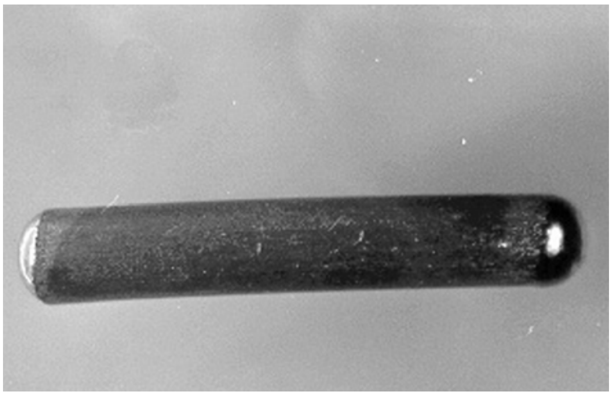

Fig. 5. Iodine-125 seed IPEN's prototype.

– argon pilot plasma gas flow – 0.2 l/min;
– argon shielding gas flow – 10 l/min.

The sealing should not present inclusions, cracks or fissures, which could cause radioactive material leakage. The weld should be as uniform as possible to diminish the anisotropy. The seed presented has a good weld quality and is compatible with other seeds in the market. After sealing, the weld integrity was evaluated with the use of an optical microscopy and leakage test, according to the norm ISO-9978 [6].

The iodine-125 seed prototype is shown in Fig. 5.

Conclusion

As targeted, a iodine-125 seed prototype was developed in Brazil. The seeds showed to be satisfactory as to the ^{125}I deposition, welding method and leakage tests carried out, according to the norm ISO-9978 [6]. This prototype is now being submitted to classification tests, according to the norm ISO-2919 [7].

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