2015 International Nuclear Atlantic Conference - INAC 2015
São Paulo, SP, Brazil, October 4-9, 2015
ASSOCIAÇÃO BRASILEIRA DE ENERGIA NUCLEAR - ABEN
ISBN: **978-85-99141-06-9**

METHODOLOGY STUDY FOR FIXATION OF RADIOACTIVE IODINE IN POLYMERIC SUBSTRATE FOR BRACHYTHERAPY SOURCES

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ABSTRACT

Cancer is now the second leading cause of death by disease in several countries, including Brazil. Prostate cancer is the most common among men. Brachytherapy is a modality of radiotherapy in which radioactive seeds are placed inside or in contact with the organ to be treated. The most widely used radioisotope in prostate brachytherapy is Iodine-125 which is presented fixated on a silver substrate that is subsequently placed inside a titanium capsule. A large dose of radiation is released only in the targeted tumor protecting healthy surrounding tissues. The technique requires the application of 80 - 120 seeds per patient. The implants of seeds have low impact and non-surgical procedures. Most patients can return to normal life within three days with little or no pain. This work proposes an alternative to the seeds that have already been developed, in order to reduce the cost by obtaining a better efficiency on fixing the radioactive iodine onto the epoxy resin. Methods have been developed to perform the fixation of Iodine-125 onto polymeric substrates. The parameters analyzed were the immersion time, type of static or dynamic reaction, concentration of the adsorption solution, the specific activity of the radioactive source, the need for carrier and chemical form of the radioactive Iodine. These experiments defined the most effective method to fixate the Iodine onto the polymeric material (epoxy resin), the Iodine activity in the polymeric substrate, the activity of the distribution of variation in a plot of polymeric cores and the efficiency of the epoxy resin to seal the seed.

1. INTRODUCTION

According to global estimates project Globocan 2012, the International Agency for Research on Cancer (IARC), the World Health Organization (WHO), there were 14.1 million new cancer cases and a total of 8.2 million deaths cancer, worldwide, in 2012. Recent studies conducted show that in 2030 the global burden will be 21.4 million new cancer cases and 13.2 million cancer deaths. [1]

In Brazil, the estimate for the year 2014, which will be valid for the year 2015, points to the occurrence of about 576,000 new cases of cancer. [2]

1.1 Prostate Cancer and Forms of Treatment

It is estimated that 68,800 new cases of prostate cancer to Brazil in the year 2014.

The latest global estimate indicated prostate cancer as the second most common in men, about 1.1 million new cases in 2012. Approximately 70% of diagnosed cases in the world occur in developing countries.

In Brazil, the increase in life expectancy, the improvement and the development of diagnostic methods and the quality of the country's information systems, and the occurrence of diagnosis, due to the spread of screening for prostate cancer with PSA and touch rectal, may explain the increased incidence rates over the years. The only well-established risk factor for the development of prostate cancer is age. Approximately 62% of diagnosed cases in the world occur in men aged 65 years or more. With increasing expectation of global life, it is expected that the number of new cases of prostate cancer rise by 60% by the year 2015. [3]

The type of treatment for prostate cancer should consider various factors such as tumor size and extent, apparent aggressiveness (pathological features), age, health, and patient preferences. Treatment can be by surgical intervention, radiation among others. The first option, radical prostatectomy is a surgical procedure where the prostate and surrounding tissue are removed. The main side effects are urinary incontinence, which affects 35% of patients, and impotence, which reaches 65% to 90% of patients. The second option is radiation therapy, which can be of two types: brachytherapy and teletherapy. In teletherapy, which is the most used method, prostate and adjacent tissues are treated by a radiation beam from a linear accelerator of electrons, i.e., the radiation source is external to the patient. [4, 5]

The other type of treatment, called brachytherapy, which has been widely used in the early and intermediate stages of the disease, is the introduction of seeds with radioactive material inside the body near the tumor, affecting at least other organs nearby. The implant permanent iodine-125 seeds have a number of advantages over traditional methods, because the method is associated with low rates and sexual impotence and incontinence patients can resume normal activities, including work within one to three days with little or no pain. In the case of radical prostatectomy patients remain in the hospital for three to five days and, for retrieval, several weeks at home. Those who undergo external beam radiation must go to the treatment center daily for seven to eight weeks.

1.2. Iodine Seeds

Treatment of prostate cancer with permanent implant seeds iodine-125 increased significantly worldwide in recent years. In the international market, the minimum cost of seed is $ 45.00 and the amount of seed required for implantation is 80 to 120 units. In Brazil, the implants are made with imported seed. IPEN-CNEN / SP has established a project for development and production of iodine-125 seeds (Figure 1) in order to minimize costs and enable the distribution to public health entities, since Brazil's demand for this type of therapeutic product is great. [6, 7]

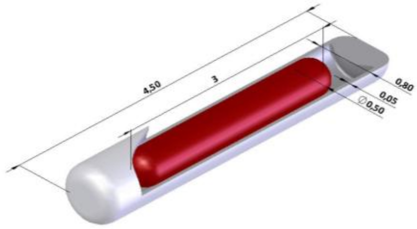


Figure 1 - Seed illustration with dimensions in millimeters.

These seeds are encapsulated sources basically composed of a material in which the radionuclides are incorporated, a casing, usually of titanium and a radiopaque marker inside. The difference between the seeds are the type of sealing titanium tube and inner structure, where there are several types of materials responsible for the opacity and loading of the radionuclide, as well as different options radionuclide. Some seeds models have been developed in order to improve the dose distribution, to facilitate production and reduce the overall cost of production. [8, 9, 10]

Among the materials available for making the core of iodine-125 seeds, we opted for the use of polymeric materials. The main advantages of polymeric materials are relatively low cost, feasible handling compared to other materials (metals), possibility of various chemical reactions for the immobilization of radioactive material, wide availability of distributors in the domestic market, among others. In this work, we evaluated two types of polymers: Polypropylene and epoxy matrix.

1.3. Polymers

1.3.1 Polypropylene

Polypropylene (PP) or polypropene is a polymer or plastic, derived from propylene or propylene and recyclable. Its molecular form is $(C_3H_6)_x$. Polypropylene is a type of plastic that can be molded using heat alone, namely, it is a thermoplastic. It has very similar properties to those of polyethylene (PE), but with higher softening point. At room temperature, the polypropylene (PP) has good physical, thermal and mechanical, such as relative hardness, high melting point, low density and impact resistance. The use of polypropylene in medicine is widely known as highlighting applications suture. [11]

1.3.2 Epoxy Resin

The epoxy resins also called polyepoxide is a thermosetting plastic that hardens when mixed with a catalyzing agent or "hardener". The most common epoxy resins are products of a reaction between e bisfenol-epichlorohydrin. There are also the resins based on bisphenol F and Novolac epoxy resins.

These resins have good adhesion to other materials, good chemical and environmental resistance, good mechanical properties and good electrical insulation properties. The epoxy resins or simply epoxy resins are polymers characterized by the presence of glycidyl groups in its molecule, besides other functional groups.

These epoxy resins deserve high interest to be employed in the manufacture of polymer matrix immobilization material radioactive, by presenting:

- high bond strength;
- easy application;
- the commercial epoxy resins, for the most part, does not contain significant amounts of radioactive impurities, leading to exhibit very low background, not committing, so the overall activity and calibration procedures of the sealed source;
- are of low toxicity, and hence, low possibility of chemical contamination during handling;
- do not release by-products;
- high chemical resistance, especially to weathering and moisture. [12]

A huge variety of curing agents is used in the processing of epoxy resins. The curing resin is a process defined as the change in chemical and physical properties of a given formulation resin / hardener The reagent type determines the type of reaction, the reaction speed and gelation. The most common curing agents are amine divided into aliphatic amines and aromatic amines. Aliphatic are very reactive, while exhibiting relatively low gel at room temperature. Aromatic have low reactivity and require high temperatures (150 to 180 ° C) cure. The anhydride type curing agents, including nadic methyl anhydride and phthalic anhydride, have lower reactivity than the aromatic amines, allowing longer usage time during the process. The epoxy / hardener ratio affects, after curing, the glass transition, the elastic modulus and mechanical strength. In principle, there should be no group or epoxy curing agent not reacted after the curing process, in order to obtain optimized properties.

2. METHODOLOGY

The methodologies were chosen taking into account the infrastructure found in the lab and the researchers group's experience in previous experiment. [7] After that was done study of compounds and parameters required for Iodine-125 fixation on the polymeric substrate, it was researched in patents, books and articles the methods already in use or are being studied and made a comparison between the different polymers selected for fixing. With the epoxy resin thermal analysis was performed which determined the physical and chemical properties of the material.

2.1. Preparation of the Radioactive Solution

The preparation begins with the NaI solution (sodium iodide) which is supplied by the company Nordion Advancing Health Science. Then this solution is diluted with NaOH (sodium hydroxide) in a concentration of 0.001 mol / L. This concentration was determined in previous studies, which evaluated the optimal concentration for fixing the Iodine-125 radionuclide.

2.2. Substrates Polypropylene

This substrate choice was made by observing other work carried out by the group. [7] During this work, it was noted that the radioactive iodine easily adhered to polypropylene bottles. For this reason, it was decided to test the theory with substrates already formed as wire and beads.

2.3. Spheres

The polypropylene beads, provided by Braskem Company, which were selected for tests are homogeneous and have a diameter of 5 mm, as illustrated in Figure 2.

Figure 2 - Image of Polypropylene beads used.

Assays with polypropylene beads were performed with the addition of carrier, since several studies in the literature argue that the use of a carrier facilitates the reaction solution.

This assertion is based on the theory that the more reagent will be greater tendency to the formation of product. [7] Therefore, the more Iodine (in the form of iodide ions), it being radioactive or not, are present the greater the deposition of iodide on the polymer surface. This solution is made from three dilutions from a starting solution with sodium hydroxide and non-radioactive sodium iodide. It is typically used to complete the final volume of the reaction. After earnings were compared to check which of the two alternatives was the best. [13]

2.4 Wires

The polypropylene sutures, provided by PolySuture Inc. having a diameter of 3 mm and cut into pieces 10 mm long (Figure 3).

Figure 3 - Image of polypropylene thread.

2.5 Static and Dynamic Process

In previous experiment, it was found that the movement of radioactive solution improves homogeneity of the mixture. [7] In this work, we chose to check whether these parameters also interfere with polymeric substrates.

Therefore, the assays were performed statically and dynamically. In static, samples were placed in a radioactive solution and allowed to stand. In dynamic experiments the samples were immersed in a radioactive solution and placed in motion (trademark roller SIRE).

2.6 Fixation of Radioactive Material Polypropylene

For the polypropylene took place two tests, in different shapes with materials (beads and wires). The experiments are described below:

Experiment 1

Took an aliquot of 100 µL of iodine-125 solution with primary activity 7.46 mCi and added to 1500 µL of NaOH, a total of 1600 µL solution (called here - secondary solution) was divided into four test tubes 400 µL each.

First tube: 400 µL the secondary solution + a 10 mm wire suture (2.5 mg) + NaOH 100 µL, 500 µL total. The wire was immersed in the solution for a week, with activity of 2.21 mCi (wire + solution).

Second tube: 400 µL the secondary solution + a 10 mm wire suture (2.5 mg) + NaOH 100 µL, 500 µL total. The wire was immersed in the solution for two weeks, with activity of 2.85 mCi (wire + solution).

Third tube: 400 µL secondary solution + a ball with 5 mm in diameter (26.7 mg) + 100 µL of carrier solution, totaling 500 µL. The ball was immersed in the solution for a week, with activity of 2.17 mCi (spheres + solution).

Fourth tube: 400 µL secondary solution + a ball with 5 mm in diameter (21.4 mg) + 100 µL of carrier solution, totaling 500 µL. The ball was immersed in the solution for two weeks, with activity of 1.95 mCi (spheres + solution).

Experiment 2

5 polymer spheres were placed in a jar with 100 µL of carrier solution + 70 µL of primary solution (radioactive) + 830 µL of NaOH, totaling 1000 µL. The measured activity was 12.54 mCi (spheres + solution).

In another flask were placed 5 sutures with the same certain proportions to the beads also totaling 1000 µL. In both cases, the glass bottles were in the drive roller for 24 hours.

2.7. Matrix Epoxy

2.7.1. Characteristics of Resin

The resin used for the immobilization of radioactive solution was SQ 2004 with its hardener SQ 3131. Table 1 shows the characteristics of the resin and hardener.

Table 1 - Characteristics of Resin [13]

	Resina SQ 2004	**Endurecedor SQ 3131**
Aparência	Liquido incolor viscoso	Liquido âmbar
Viscosidade, 20ºC, cPs	500 a 800	3.000 +/- 1000
Peso especifico, 20ºC, g/m^3	1,12 +/-0,01	1,10 +/- 0,05

2.7.2. Thermal Analysis

Thermal analysis is a term which encompasses a group of techniques in which a physical or chemical property of a substance or its reaction products, is monitored as a function of time or temperature.

Thermal analysis sample of resin chosen was performed, TGA (Thermal Gravimetric Analysis), a technique used in polymers in which it monitors the variation of the mass of the sample as a function of temperature or time. The equipment used was Model: SDT Q600 N2 and heating ramp of 10 ° C / 30 min.

2.7.3 Immobilization of Radioactive Material in Epoxy Resin

2.7.3.1 Experiment 3

A silicone mold with four cavities, which have the same format seed core was prepared.
In this assay, 10 ml (11.2 g) resin (reaction of epichlorohydrin and bisphenol A) was mixed with 20% hardener (modified polyamine of diethylenetriamine - DETA used in all experiments) 2.04 ml (2, 24 g), with a total mass of 13.4 g solution. They were added 100 of

iodine-125, the primary solution + 1 ml of NaOH with activity of 11.38 mCi. The mixture was homogenized manually placed in the mold for curing.

After the resin curing process the four *pellet* (nuclei) were removed and brought to an ionization chamber Capintec CRC-15R (Figure 3), so that the activities were measured.

Figure 3 - Ionization chamber (Capintec CRC-15R).

The four *pellets* were measured in the balance Mettler Toledo - AB304-S with precision of milligram. Then, the activity per gram (µCi/g) was determined.

2.7.3.2 Experiment 4

In this assay, 10 ml (11.2 g) resin was mixed with 20% hardener, 2.04 ml (2.24 g) with a total mass of 13.4 g of solution. They were added 300 µL of Iodine-125 with 1410 µCi/g activity. In 3% of the total weight of titanium dioxide (TiO 2) approximately 0.402 g. The mixture was homogenized manually placed in the mold for curing.

After filling in all the spaces in the mold, the beaker with remaining resin over the pipette and pipette tips were taken to the ionization chamber, where were measured and showed an activity of 842 µCi. The initial test tube after transfer to the resin was also measured and showed an activity of 135 µCi. So with all the measurements was calculated Iodine-125 activity used in the experiment that showed the value of 433 µCi.

2.7.3.3 Experiment 5

In experiment 5 was carried out the same procedure as the experiment 4, but without the use of the titanium dioxide. Then using the same mold, there have been new *pellets*, which have the same format seed core.

It was added 5 ml (5.6 g) resin was mixed with 20% hardener 1.02 ml (1.12 g) with a total mass of 6.7 g of solution. They were added 300 µL of Iodine-125 with 1410 µCi/g activity. The mixture was homogenized manually placed in the mold for curing. Within these spaces was placed in each seed a silver only as reference radiopaque material, as shown in the following figure (Figure 5).

Figure 5 - Template image and silver seeds (radiopaque material).

After filling in all the spaces in the mold, the beaker with remaining resin over the pipette and pipette tips were taken to the ionization chamber, where were measured and showed an activity of 0,842 mCi. The initial test tube after transfer to the resin was also measured and showed an activity of 0,135 mCi. So with all the measurements was calculated iodine-125 activity used in the experiment that showed the value of 0,433 mCi.

2.8 Studies of the Properties of the Material

2.8.1 Test of Immersion in Distilled Water at Room Temperature

For the leak test, the unit was left in a Petri dish with distilled water. This test is performed soaking the source liquid that does not attack the foreign material of the source and considered to be effective in removing any external radioactive material. The source was left under these conditions at room temperature for 24 hours and then removed to measure the activity of the liquid. For activity measurements source also used a detector of sodium iodide, NaI (Tl).

2.8.2 Smear Test

For the rub test used a NaI (Tl) detector. With a piece of filter paper, the surface of the cured resin was wiped. It was also evaluated at the source the possibility of iodine-125 to vaporize and escape the epoxy matrix. For this test, we made multiple measures of activity and compared with the theoretical activity that the source should present at the time the measure given the decay of iodine-125.

3. RESULTS

3.1. Substrate Polypropylene

3.1.1. Experiments 1 and 2

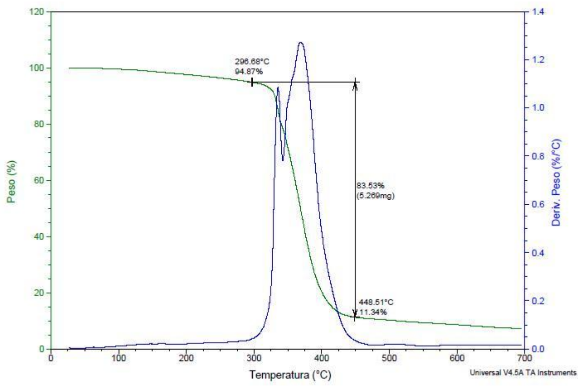
After the time of the experiments, the activity of tubes and balls was measured in order to assess the establishment in each assay. However, in all cases it was noted that there was no clamping on polypropylene substrates. Some points that can justify the experiment of failure are:

- Insufficient duration of the experiments;
- Low concentration of carrier solution;
- bottle used in the experiment may have competed with the substrate for fixing iodine;
- External factors such as temperature and pressure can have more influence than expected;
- Changes in the quality of the solution of iodine-125 provided;
- Possibility of iodide simply not fix the substrate but only stay adhered to the surface being easily removed;
- The possibility that these materials chosen have some pre surface treatment. For example, in the suture as the best low friction surface of its utility in surgical cases.

3.2. Matriz epóxi

3.2.1 Thermal Analysis

In Graph 1, the thermal analysis of resin values are displayed. Heated to 700 ° C.



Graph 1 - Thermal Analysis of epoxy resin, using the TGA technique.

It can be seen that the initial degradation temperature is 296.68 ° C and the end is 448.51 ° C. This shows that the application of the epoxy matrix for the preparation of iodine-125 seeds is entirely feasible. The Iodine-125 seeds must be sterilized before use in implants, in general, the most used method is sterilization by temperature (an autoclave), with values of up to 140 ° C.

3.2.2. Experiment 3

The curing process of the resin was 40 minutes. The four *pellet* (nuclei) are shown in Figure

6.

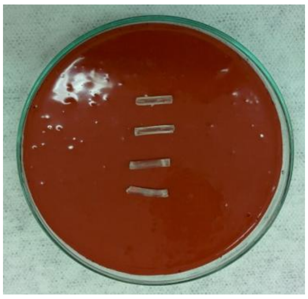


Figure 6 - ***Pellets*** **removed after the resin curing process.**

All *pellets* were properly weighed as shown in Table 1.

Table 1 - Mass measurement of each core

Cores	Masse (mg)
1	70
2	63
3	64
4	46

Table 2 shows the activity per gram of cores measures.

Table 2 - Shows the activity per gram of cores measures

Cores	Specific activity (µCi/g)
1	707,6
2	640,7
3	620,3
4	736,2

With the measurement value of the initial activity of the iodine solution per mass (774.2 µCi/g) was achieved for each core the immobilization efficiency as shown in Table 3.

Table 3 - Efficiencies obtained from each core

Cores	Percentage efficiency (%)
1	91,4
2	82,7
3	80,1
4	95,1

And all the results showed a high percentage of effectiveness. The evaluation of the immobilization reaction yield was calculated as follows (Equation 1):

$$E_{\%} = \frac{\sum A_N}{A_T} \cdot 100 \qquad (1)$$

$E_{\%}$ = Process efficiency in percent;

$\sum A_N$ = Sum of the activities of the nuclei;

A_T = Total activity of the solution corrected for radioactive decay.

The differences in efficiency between nuclei must be static fluctuations in the detection and balance system, but the average efficiency of the cores is 87.3 ± 7.1%, considered satisfactory for the purposes of work. The results achieved in the experiment 3 are consistent with the values obtained in previous works, for making seeds with silver cores.

Experiment 4

In this experiment, after all procedures carried out, it was noted that with the use of titanium dioxide was not possible to measure the activities of the cores. Titanium dioxide has a high atomic number, which made the whole energy of the radiation emitted inside the core was absorbed by the material. What prevented the radiation reached the detector for measuring the activity.

Experiment 5

In experiment 5 all pellets were properly weighed three times so that an average was made of their masses (Table 4) and then measures its activities by using the average mass of each core, as shown in Table 6.

Table 4 - Measure the mass of each core and its mean

Cores	Average 1 (g)	Average 2 (g)	Average 3 (g)	Average masses (g)
1	0,39	0,40	0,41	0,40
2	0,43	0,39	0,41	0,41
3	0,42	0,42	0,42	0,42
4	0,44	0,43	0,45	0,44
5	0,38	0,41	0,41	0,40
6	0,44	0,42	0,46	0,44
7	0,41	0,43	0,42	0,42
8	0,38	0,40	0,42	0,40
9	0,40	0,39	0,41	0,40
10	0,39	0,42	0,39	0,40

After 24 hours curing the resin, the new pellets were removed and measured three times each, and an average conducted as shown in Table 5.

Table 5 - Average activities of the cured pellets

Cores	Activity average (µCi)
1	22
2	21
3	22
4	24
5	22
6	24
7	21
8	22
9	21
10	20

After curing of the pellets were measured the same ionization chamber. 10 pellets were measured in the balance. Then, by mass activity (µCi/g) was determined.
Table 6 shows the mass by activity measurements of cores.

Table 6 - Activity by mass of each core

Cores	Specific activity (µCi/g)
1	55,0
2	51,2
3	52,4
4	54,5
5	55,0
6	54,5
7	50,0
8	55,0
9	52,5
10	50,0

With the measurement value of the initial activity of the iodine solution per mass (64.6 µCi/g) was achieved for each core the immobilization efficiency as shown in Table 7.

Table 7 - Efficiencies obtained from each core

Cores	Percentage efficiency (%)
1	85,1
2	79,3
3	81,1
4	84,4
5	85,1
6	84,4
7	77,4
8	85,1
9	81,3
10	77,4

All results showed a high percentage of effectiveness. The evaluation of the immobilization reaction yield was calculated using the equation of efficiency (equation 1).

The difference in efficiency between the cores must be static fluctuations of the detection system and scale, but the average efficiency of the cores is 82.1 ± 3.2%.

3.2.3 Sealing of Cores

They were taken multiple measures of activity and compared with the theoretical activity that the source should present at the time of measurement. For both tests used the same detector, iodide, NaI (Tl). After his accomplishments the source was deemed to be watertight and show no activity on the filter paper to the smear test. And for the immersion test in distilled water at room temperature did not exceed the limit allowed by the ISO 9978 standard that is 5 nCi (185 Bq). [14] It can be concluded that there was no leakage of radioactive material through the resin, even before the power was encapsulated with titanium capsule. What allowed the epoxy matrix for making the cores.

4. CONCLUSIONS

The results showed that the polypropylene substrates tested showed no measurable fixing Iodine-125. The methodology developed in the epoxy resin was satisfactory when used with silver, unlike titanium dioxide, which prevented measurement of the activities of pellets. It is believed that self-absorption prevented the activity measured in the detector, however, it is necessary that there be further studies, since the material can be a great ally powder because of its availability. However, by using the silver wire as a marker, made possible the manufacture of radioactive nuclei with iodine-125, the methodology allows the use of a polymeric material in radioactive seed nuclei for the treatment of cancer.

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