2013 International Nuclear Atlantic Conference - INAC 2013
Recife, PE, Brazil, November 24-29, 2013
ASSOCIAÇÃO BRASILEIRA DE ENERGIA NUCLEAR - ABEN
ISBN: **978-85-99141-05-2**

COMPARISON BETWEEN METHODS FOR FIXING RADIOACTIVE IODINE IN SILVER SUBSTRATE FOR MANUFACTURING BRACHYTHERAPY SOURCES

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ABSTRACT

Cancer is a term used generically to represent a group of more than 100 illnesses, including malignant tumors from different locations. According to World Health Organization (WHO), is a leading cause of death worldwide, accounted for 7.6 million deaths. Prostate cancer is the sixth most common type in the world, representing about 10% of all cases of cancer and its treatment may be by surgery, radiotherapy or even vigilant observation. A method of radiotherapy which has been extensively used in the early and intermediate stages of the illness is brachytherapy, where radioactive seeds are placed inside or next to the area requiring treatment, which reduces the probability of unnecessary damage to surrounding healthy tissues. Currently, the radioactive isotope Iodine-125, adsorbed on silver substrate, is one of the most used in prostate brachytherapy. The present study compares several deposition methods of radioactive Iodine on silver substrate, in order to choose the most suitable one to be implemented at the laboratory of radioactive sources production of IPEN. The methodology used was chosen based on the available infrastructure and experience of the researchers of the institute. Therefore, Iodine-131 was used for testing (same chemical behavior of Iodine -125). Three methods were selected: method 1 (test based on electrodeposition method, developed by David Kubiatowicz) which presented efficiency of 65.16% ; method 2 (chemical reaction based on the method developed by David Kubiatowicz - HCl) which presented efficiency of 70.80%; method 3 (chemical reaction based on the method developed by Dr. Maria Elisa Rostelato) which presented efficiency of 55.80% . Based on the results, the second method is the suggested one to be implemented at the laboratory of radioactive sources production of IPEN.

1. INTRODUCTION

1.1 Cancer in Brazil and Worldwide

Cancer is a term used generically to represent a group of more than 100 illnesses, including malignant tumors from different locations. According to World Health Organization (WHO), it is a leading cause of death worldwide. Only in 2007, 12 million new cases of cancer were diagnosed and a total of 7.9 million deaths were accounted, about 13% of worldwide deaths. The continued ageing and population growth will affect significantly the impact of cancer in the world. This impact will fall most heavily on countries of medium and low development1. Recent studies carried out by the International Agency for Research on Cancer (IARC) estimates that in 2030 will be 26.4 million new cases diagnosed, with 17 million deaths accounted worldwide [1,2].

In Brazil, estimates made in 2012 are valid for 2013, and according to National Cancer Institute (INCA) 518.510 new cases of cancer will be diagnosed. The most incidents, excluding non-melanoma skin cancer are prostate and lung cancer in males and breast and cervical cancer in females [3,4].

1.2 Prostate Cancer

Prostate cancer is the sixth most common type in the world, and the second most common cancer in men, with an estimated 1.5 million diagnoses in recent years representing about 10% of all cases of cancer1. It is also considered cancer of the elderly, since about three-quarters of the cases occur among patients *65 years* old or over [1,4,5,6].For Brazil, the number of new cases of prostate cancer in 2012 was 60,180 [1]. Treatment of prostate cancer may be by surgery, radiation or even vigilant observation. In cases of locally advanced disease, radiotherapy or surgeries in combination with hormonal treatment have been used. Choosing the most appropriate treatment must be individualized and defined after discussing the risks and benefits of treatment with the doctor [7,8].

1.3 Brachytherapy and Iodine-125 Seeds

A method of radiotherapy which has been extensively used in the early and intermediate stages of the illness is brachytherapy, where radioactive seeds are placed inside or next to the area requiring treatment, which reduces the probability of unnecessary damage to surrounding healthy tissues. Currently, the radioactive isotope Iodine-125 is one of the most used in prostate brachytherapy.

The minimum cost of the seed, in international market, is US$ 40.00 and the amount of seeds required for the implantation is 80 to 120 units 9. In Brazil, the implants are performed with imported seeds. The IPEN-CNEN/SP established a project for development and production of iodine-125 seeds in order to minimize costs and allow the distribution to public health, since there is a considerable demand for this type of therapeutic product [6,8].

The seeds have quite small dimensions and all are composed of a titanium capsule with 0.8 mm of outer diameter, 0.05 mm of wall thickness and 4.5 mm long [8]. The internal structure varies from model to model. Seeds used in Brazil, uses a silver wire as a substrate. All seeds are encapsulated in titanium, since this element is an inert material classified as biocompatible, that is, does not cause rejection when in direct contact with human tissue. The typical activity of seeds of iodine-125 is 0.5 mCi (18.50 MBq) [6,8].

Iodine-125 seed permanent implantation features a number of advantages over traditional methods because it is related with low rates of sexual impotence and urinary incontinence, and patients can return to normal activity, including work, within one to three days with little or no pain [6,7]f. The main goal of this paper is the comparison of Iodine-125 fixation, in a silver wire substrate, using 3 different methods.

2. METHODOLOGY

2.1 Patents and Important Papers

The first Iodine-125 seeds were developed in 1965 by Donald C.Lawrence, and it was published in his patent called "*Therapeutic metal seed containing within a radioactive isotope disposed on a carrier and method of manufacture*" [9]. The shape and dimensions of the seeds were the same of the current used ones. The author recommended the use of plastic materials, as nylon, silicone rubber and teflon for the core of the seeds. Palladium-103, Cesium-131 and Iodine-125 may be used as radiation sources. Stainless steel and titanium are recommended for the coating.

The second patent called "*Radioactive iodine seed*" was published in 1982 by David Kubiatowic [10]. The author proposes the use of silver chloride or silver bromide for the ion exchange, resulting in silver iodide (AgI^{125}). It is recommended to avoid blue and ultraviolet light exposure. Four examples of iodine-125 deposition, onto silver substrates are described.

In the first example, five silver wires, with length of 70 mm and diameter of 0.25 mm are put in a 1mol/L sodium chloride solution. A platinum wire is also positioned in the solution. The silver wire is connected to the positive electrode and the platinum wire to the negative electrode and then, electric current is applied. This process, known as electroplating, creates a layer of silver chloride on the substrate. The silver wires are cut into pieces, 3 mm long, and placed in a 0.2 mol/L sodium iodide (NaI^{125}) + 0.01 mol/L sodium hydroxide solution . Non-radioactive iodine in the form of sodium iodide combined with sodium hydroxide solution are added and then, the solution is stirred for 17 hours. In the end, the cores are sealed in titanium capsule. The author claims 97% efficiency in this process.

In the second example, silver wires are cut into 3mm long pieces, with a diameter of 0.5 mm, and put in a 0.1 mol/L sodium chloride solution. The vessel is conected to the positive electrode and a basket, cointaning the seeds, is conected to the negative electrode. The electric current is applied for 6,5 hours. A layer of silver chloride is created on the silver wires surface.

In the third example, the wires are also cut into 3mm long pieces with a diameter of 0.5 mm and are put into beaker containing a 6 mol/L hydrochloric acid and a 1 mol/L sodium hypochlorite solution. After stirring for 1 hour at room temperature, a layer of silver chloride is formed on the wires. The seed cores are placed in a solution with iodine-125 (NaI^{125}) and 4.10 mol/L sodium hydroxide and non-radioactive sodium Iodine (carrier solution), in order to standardize the distribution of iodine. After that, the solution is stirred for 19 hours in the absence of light. Then, the cores are plasma sealed in a titanium capsule.

In the fourth example, 18 silver cores, 3 mm long and with a diameter of 0.5mm are placed into a container containing a platinum sheet, connected to the negative pole, and a platinum wire connected on the positive pole. The NaI^{125} solution is diluted with 1.5 ml of a NaOH solution (pH 10) An electric current of 25 µA is applied for two hours. The container must be constantly stirred. The fixation efficiency is 97%.

2.2 Considerations for the methodology

- For each step of methods 1, 2 and 3, the experiments were repeated changing only one parameter and keeping the others constant. The remaining parameters were kept constant as described in the literature;
- The range of parameters chosen for the experiments (concentration, reaction time, etc.) was applied in order to study the behavior of fixation. The amount and type of changing varies. The ones chosen for this work were those considered relevant, safe, practical and economical for the infrastructure available. If necessary, additional variations of parameters were performed during the execution of experiments.
- All the three methods were repeated three times and the global efficiency were calculated from the fixation mean of these three experiments.
- Each lot contained 10 cores. Each step were performed with 2 lots.
- The activity, per core, of the radioactive solution used was 100 µCi. It was measured by a Carpintec CRC 15W ionization chamber.
- The evaluation of fixation reaction efficiency was calculated by equation 1.

$$E_{\%} = \frac{\sum A_n}{A_T} \, . \, 100 \qquad (1)$$

$E_{\%}$ = Efficiency of the process (percentage)
$\sum A_n$ = Sum of each core activity
A_T = Total solution activity considering radioactive decay.

2.3 Description of the Tests

The methodologies were chosen based on the infrastructure of the laboratory and the experience of the researchers involved . All assays were performed in two steps. At the pre-fixation part, a treatment on the silver substrate was performed. At the fixation part, treated silver substrates reacted with the radioactive solution. The detailed methodoly used is described below.

2.3.1 Method 1: Treatment with the use of chemical reagents / electric current

1. Pre-fixation

- The device for electroplating was filled with a solution of sodium chloride (NaCl). The optimal concentrations obtained experimentally were 0.5 mol/L, 1 mol/L and 2 mol/L. It was used about 1 liter of the solution.
- A stainless steel plate was attached at the negative electrode and the device, at the positive electrode.
- The parameters of electric current used were 0.3mA, 0.5mA and 1mA for 4-8 hours.

2. Fixation

- After pre-treatment, the wires were rinsed and placed inside a radioactive solution of sodium iodide (NaI^{125});
- The concentration of radioactive iodine used was 100 mCi per seed core;
- The reaction was carried for 17 hours and 26 hours;
- The influence of light and the carrier was tested. The carrier solution used was a non-radioactive iodine with a concentration equivalent to half of the concentration of radioactive iodine. The purpose of adding Iodine is that by increasing the concentration of it, the equilibrium of the reaction will shift to the formation of AgI. When the carrier was not used, the volume was completed with sodium hydroxide solution with different concentrations (0.1, 0.01 and 0.001 mol / L). Afterwards, the yields were compared to check which one shown the best results.

As previously explained, the experiments were repeated changing only one parameter and keeping the other constant in order to make comparisons step by step. For this test, the first comparison to be performed is the test with different concentrations of NaCl solution. To check which of the three achieves the highest efficiency, the silver wire was prepared and the fixation efficiency measured. For this purpose, other parameters such as electric current, time, etc. were kept constant. The values used for these parameters are shown in the Table 1and are based on values used in the academic literature consulted.

Table 1: Parameters kept constant in method 1

Parameter	Value
Electric current	0,5mA
Time Using Electric Current	7 h
NaOH Concentration	0,01 mol/L
Reaction Time	20 h
Carrier	Present
Light presence	Not Present

2.3.2 Method 2: Treatment with chemical reagents

1. Pre-fixation

- The silver wires are placed into a beaker containing 20mL of hydrochloric acid (HCl) with different concentrations – 2mol/L, 4mol/L and 8mol / L. Then, 2ml of sodium hypochlorite (NaClO), 1 mol / L were added to the solution.
- The stirring times selected were: 30 minutes, 2 hours and 4 hours, at room temperature.

2. Fixation

- The concentration of radioactive iodine solution was 100 mCi per seed core;
- The reaction was carried for 17 hours and 26 hours;
- The influence of light and presence of a carrier was tested in the same way as described in method 1, but the concentration of NaOH used was fixed at 10^{-4} mol/L, for the test has not shown fixation of the material for higher concentrations.

The table 2 shows the parameters kept constant in each step of the assays.

Table 2: Parameters kept constant in method 2

Parameter	Value
Stirring Time	1 hour
NaClO	Present
Reaction Time	19 h
Light	Present
Carrier	Not Present

2.3.3 Method 3: Treatment with chemical reagents (IPEN)

1. Pre-fixation

- The silver wires were put into a oven (equipment manufactured by Giron, designed by IPEN researchers with digital temperature control, and able to reach temperatures up to 700 ° C) with temperatures of 300°C, 500°C and 600 ° C, for 150 minutes and with an atmosphere of oxygen (3 L/min).

2. Fixation

- The silver wires were put into a sodium sulfide (Na_2S) solution. The values of concentration ranged from 0.3mol/L to 2.4 mol/L and reaction time varying from 50 to 70 hours. The wires were then, removed from the sodium sulfide solution and placed into a solution of radioactive iodine (100mCi per seed core). Afterwards, it was stirred for 10h and 40h.
- The influence of light and presence of a carrier was tested in the same way as described in method 1. The table 3 shows the parameters kept constant in each step of the tests.

Table 3: Parameters kept constant in method 3

Parameter	Values
Temperature	600°C
Sodium Sulfide Concentration	0.6 mol/L
Reaction Time with Sodium Sulfide	64h
Sodium Hydroxide Concentration	0.1 mol/L
Reaction Time	26 h
Light	Present
Carrier	Present

4. RESULTS AND DISCUSSION

4.1 Preliminary Test

In order to justify the pre-fixation step, a test was performed using only silver cores with 100μCi, per core, activity, without further treatment. Radioactive Iodine-125 was not fixed on the substrate, confirming the need of a pre-fixation treatment.

4.2. Method 1: Treatment with Electric Current

The parameters with the most effective fixation were:

- Electric current: 5 mA electric current;
- NaCl concentration: 1 mol / L;
- Electric current application time: 6,5h
- Without the presence of light;
- With the presence of a carrier;
- Reaction time: 20h.

As higher values of fixation were obtained with the use of carrier solution, it was not necessary to use the NaOH solution. The values for each test are presented in Fig. 1 and 2.

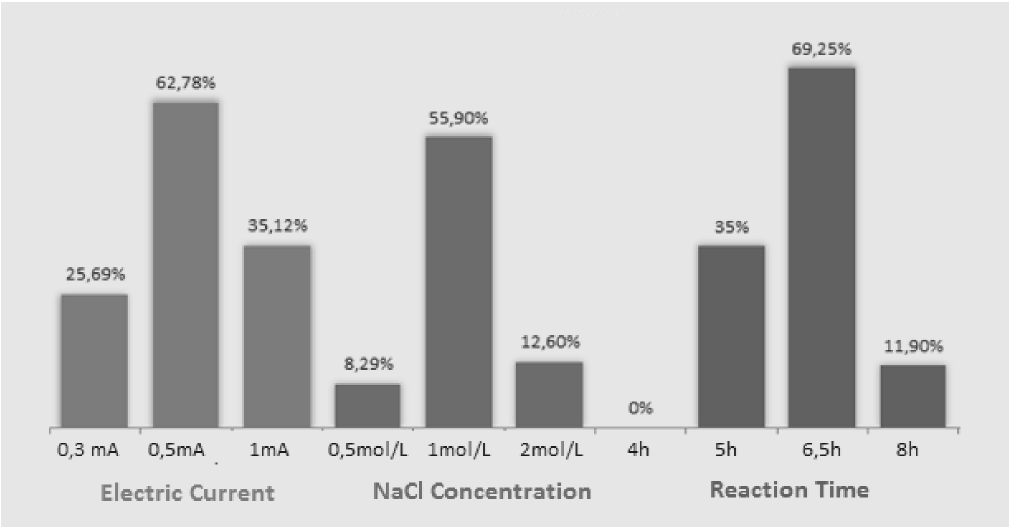

Figure 1: First part of results obtained using method 1

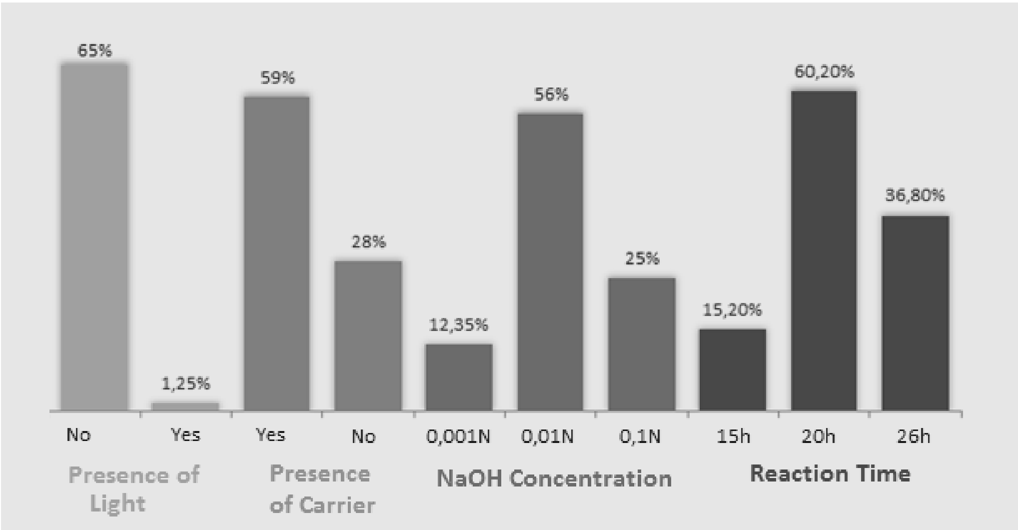

Figure 2: Second part of results obtained using method 1

After the selection of the best efficiency result for method 1, a final test were performed again. The data gathered are reported in table 4.

Table 4: Activity measures results for the three final tests and global efficiency using method 1

Silver Core	Exp 1 Activity (µCi) Exp 1	Exp 2 Activity (µCi) Exp 2	Exp 3 Activity (µCi) Exp 3
1	68,9	66,3	65,2
2	70,5	59,7	68,9
3	64,2	60,2	67
4	85,4	68,7	58,4
5	***<u>87,3</u>***	55,4	63,5
6	62,9	73,2	58,9
7	59,9	65	67,4
8	58,9	58,9	69,4
9	70,2	64,7	60,2
10	***<u>52,8</u>***	61,9	61,1
$\sum A_n$	681	634	640
A_T	1 mCi	1 mCi	1 mCi
$E_{\%}$	68,1	63,4	64,0
Average %		65,16	

* $\sum A_n$: Total fixed - A_T : Total activity considering radioactive decay - $E_{\%}$: Efficiency

Observations and Recommendations:

1. This method is easy to implement but performing the experiment in the absence of light is extremely complicated due to the size of the substrate. If this is the method chosen for the production, it will be necessary to install a darkroom.
2. Good results concerning global fixation
3. Time required to perform the test: two days. Reaction time considered "fast".

4.3. Method 2: Treatment with Chemical Reagents (HCl)

The parameters with the most effective fixation were:

- HCl concentration: 4 mol/L;
- Pre-treatment time: 5 min. This parameter was added due to its inversely proportional relation to fixation efficiency;
- With the presence of NaClO;
- With the presence of a carrier
- Light had no influence in the fixation
- Reaction time: 15 hours. This parameter was added because the fixation was similar using 20 and 26 hours. The result was the same using 15 hours.

The values for each test are presented in Fig.3 and 4.

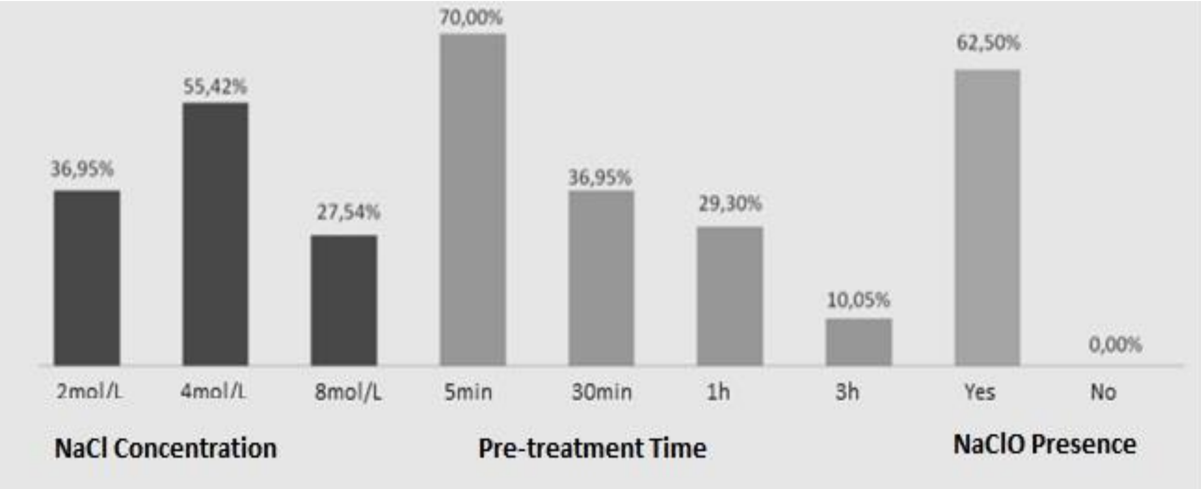

Figure 3: First part of results obtained using method 2

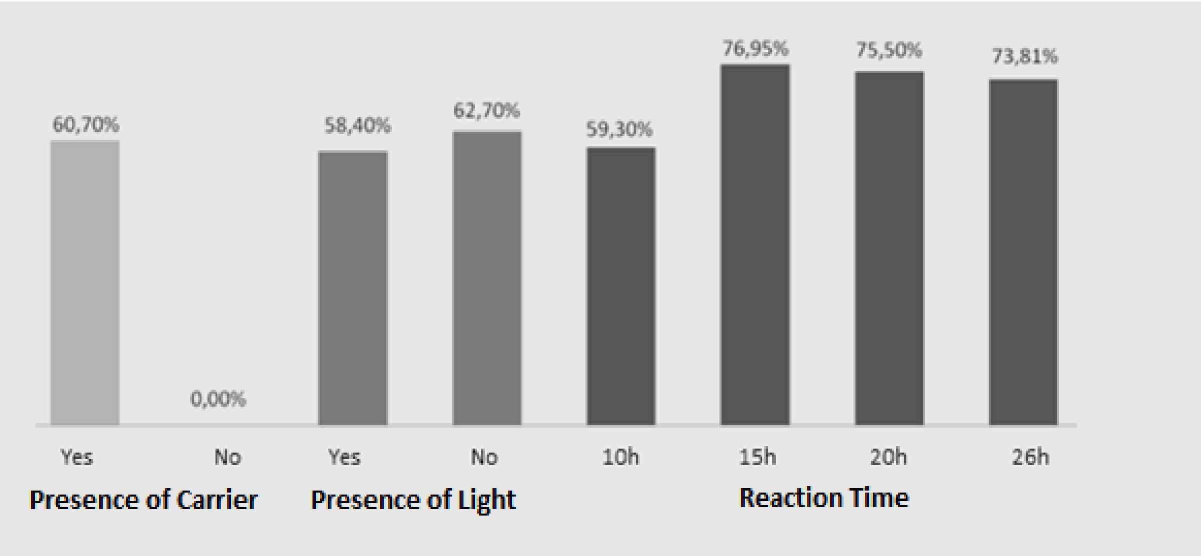

Figure 4: Second part of results obtained using method 2

After the selection of the best efficiency result for method 2, a final test were performed again. The data gathered are reported in table 5.

Table 5: Activity measures results for the three final tests and global efficiency using method 1

Silver Core	Exp 1 Activity (µCi) Exp 1	Exp 2 Activity (µCi) Exp 2	Exp 3 Activity (µCi) Exp 3
1	74,5	67	78,5
2	67,8	58,9	56,7
3	69	67	84,7
4	87,4	59,4	58,9
5	86	89,5	67,8
6	***56***	***92,1***	65,8
7	88,3	76	73,4
8	75,3	75,4	64,3
9	80	67	76
10	83,05	68,7	73,27
$\sum A_n$	767,35	721	699,37
A_T	1,03	1,03	1,03
$E_{\%}$	74,50%	70%	67,90%
Average %		70,80%	

* $\sum A_n$: Total fixed - A_T : Total activity considering radioactive decay - $E_{\%}$: Efficiency

Observations and Recommendations:

1. This method is easy to implement at IPEN since it does not require absence of light
2. Good results concerning global fixation
3. Time required to perform the test: two days. Reaction time considered "fast".

4.4. Method 3: Treatment with Chemical Reagents (IPEN: Heating/Sodium Sulfide)

The parameters with the most effective fixation were:

- Temperature: 600°C (highest temperature possible considering the available equipment);
- Na_2S concentration: 0,6 mol/L.
- Na_2S reaction time: 20h;
- Light had no influence in the fixation
- NaOH concentration: 0,001 mol/L;
- Reaction time: 25h.

As the highest fixation values were obtained with a 0,001mol/L NaOH solution, the use of a carrier solution was not necessary. The values for each test are presented in Fig. 5 and 6:

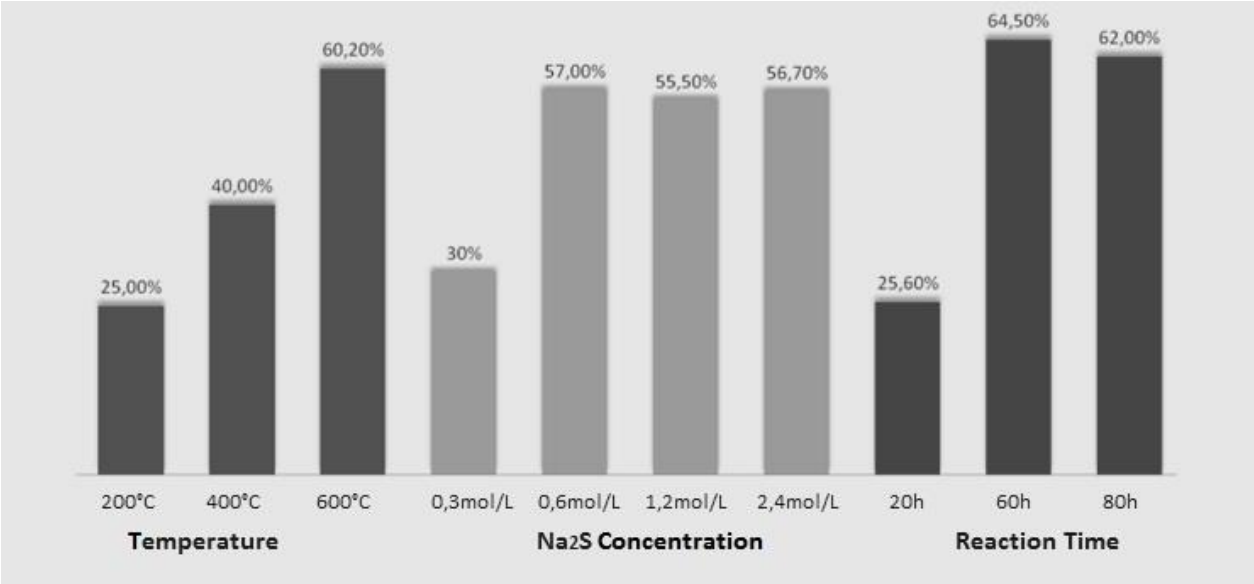

Figure 5: First part of results obtained using method 3

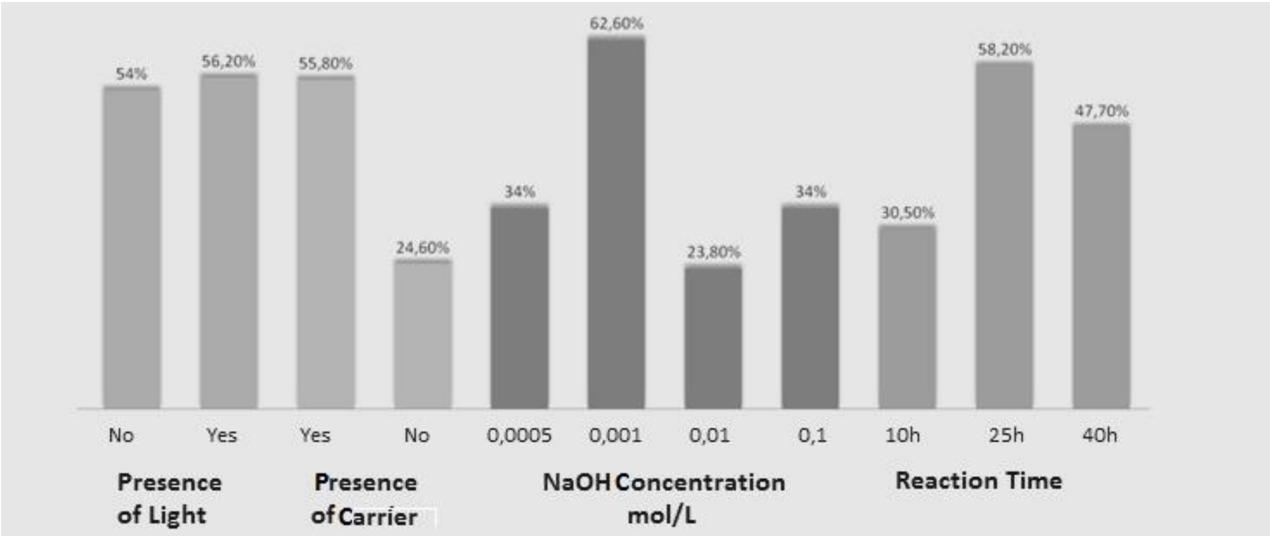

Figure 6: Second part of results obtained using method 3

After the selection of the best efficiency result for method 3, a final test were performed again. The data gathered are reported in table 6.

Table 6: Activity measures results for the three final tests and global efficiency using method 3.

Silver Core	Exp 1 Activity (μCi) Exp 1	Exp 2 Activity (μCi) Exp 2	Exp 3 Activity (μCi) Exp 3
1	78,4	***95,3***	60,6
2	80	49,6	42,3
3	***19,9***	48	51,2
4	45,6	63,8	56,4
5	42	59	55
6	59,5	65	39,5
7	63,4	***95,3***	25,6
8	31,2	53,2	69,4
9	71,4	47	70
10	69,95	41,8	74,87
$\sum A_n$	561,35	618	544,87
A_T	1,03	1,03	1,03
$E_{\%}$	54,50%	60%	52,90%
Average %		55,80%	

* $\sum A_n$: Total fixed - A_T : Total activity considering radioactive decay - $E_{\%}$: Efficiency

Observations and Recommendations:

1. This procedure is not as easy as those described in methods 1 and 2.
2. Long reaction times – it takes 5 days to cover all steps;
3. Good results concerning global fixation

4.5 Indication of the best method

The results presented above show that the method 2 had the best results. The time required to manufacture the seeds are two days which is considered good for implementation at IPEN.A parameter that was not fully controlled was the distribution of the activity among the cores. In order to make the distribution the best possible, the cores should be pre-selected, considering its size, quality of the cut and surface condition. This pre-selection proved to be unfeasible for this work and for production routine, therefore it was not performed. The results highlighted the need to research a new method with better efficiency results. Such method is under development by the Ph.D. student Carla Daruich de Souza.

6. CONCLUSIONS

In this paper, several methods of Iodine-125 deposition on a silver substrate were compared in order to choose the most suitable alternative for the production of iodine-125 seeds.Based on the available literature, three methods were selected.

Using method 1 (test based on electrodeposition developed by D. Kubiatowicz) the best result (65.16% efficiency), was obtained using the following parameters: electrical current of 0.5

mA, 1 mol / L NaCl concentration, 6 hours of electric current application, without the presence of light, with the presence of a carrier, and total reaction time of 20h. This method is relatively fast (2 days), but it must be done in the absence of light dark. The cost of each seed manufactured by method 1 was R$ 7.39.

For Method 2 (chemical reaction based on the method developed by D. Kubiatowicz - HCl) to obtain the best result (70.80% efficiency), the parameters should be: 4 mol/L HCl concentration, 5 minutes of pre-treatment, reaction time of 15h, presence of sodium hypochlorite, does not require absence of light and requires a carrier. Method 2 is relatively fast (2 days) and simple. The price of each seed was R$ 6.93.

Using Method 3 (chemical reaction based on the method developed by Dr. M. Rostelato) the best result obtained was 55.80% efficiency. The following paramers were used: temperature of 600 °C, 0.6 mol/ L concentration of sodium sulfide, Na_2S reaction time of 20 hours, with the presence of light; 0.001 mol/L NaOH concentration and reaction time of 25h. This method is not as easy to perform as the others two previously explained and requires 5 days to be completed. The price of each seed was R$ 8.59.

As the method 2 has shown better fixation of the radioactive material (which represents the major cost of the seed), it was the most efficient one. New methods are still being developed.

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