

EVALUATION OF DIFFERENT REACTION METHODS RESULTING IN THE FORMATION OF AgI125 FOR USE IN BRACHYTHERAPY SOURCES

C. D. SOUZA, F. S. PELEIAS JR., M.E.C.M. ROSTELATO, C.A. ZEITUNI, M.A.G. BENEGA, R. TIEZZI, F.R. MATTOS, B.T. RODRIGUES, T.B. OLIVEIRA, A. FEHER, J.A. MOURA, O.L. COSTA

*Instituto de Pesquisas Energéticas e Nucleares (IPEN / CNEN - SP)
Av. Professor Lineu Prestes 2242 05508-000 São Paulo, SP - BRAZIL*

ABSTRACT

Prostate cancer represents about 10% of all cases of cancer in the world. Brachytherapy has been extensively used in the early and intermediate stages of the illness. The radiotherapy method reduces the damage probability to surrounding healthy tissues. The present study compares several deposition methods of iodine-125 on silver substrate (seed core), in order to choose the most suitable one to be implemented at IPEN. Four methods were selected: method 1 (assay based on electrodeposition) which presented efficiency of 65.16%; method 2 (assay based on chemical reactions, developed by David Kubiawicz) which presented efficiency of 70.80%; method 3 (chemical reaction based on the methodology developed by Dr. Maria Elisa Rostelato) which presented efficiency of 55.80%; new method developed by IPEN with 90.5% efficiency. Based on the results, the new method is the suggested one to be implemented.

1. INTRODUCTION

1.1 Cancer in Brazil and Worldwide

According to World Health Organization (WHO) cancer 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 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, the National Cancer Institute (INCA) estimates 518.510 new cases of cancer for 2013. 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 cancer. 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 [1,7,8].

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, reducing unnecessary damage to surrounding healthy

tissues. Currently, the radioactive isotope Iodine-125 is one of the most used in prostate brachytherapy. 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 within one to three days with little or no pain [6,7].

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 main goal of this paper is the comparison of Iodine-125 fixation, in a silver wire substrate, using 3 different methods. Working with iodine presents serious difficulties. The reagent is manufactured as NaI¹²⁵ in NaOH medium form. Iodine is known to be volatile, to permeable plastic, glass and even platinum containers. Those rules are not set as ultimate true. The parameters change as one change the experiment.

2. METHODOLOGY

2.1 Presentation

- 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 was 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.

$$E_{\%} = \frac{\sum A_n}{A_T} \cdot 100 \quad (1)$$

$E_{\%}$ = Efficiency of the process (percentage)

$\sum A_n$ = Sum of each core activity

A_T = Total solution activity considering radioactive decay

2.2 Description of the Tests

All assays were performed in two steps. At the pre-fixation step, a treatment on the silver substrate was performed. At the fixation step, treated silver substrates reacted with the radioactive solution. The detailed methodology used is described below.

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

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 0.3 mA, 0.5 mA and 1 mA for 4-8 hours.

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 μCi 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 mol/L, 0.01 mol/L and 0.001 mol/L). Afterwards, the yields were compared to check which one shown the best results.

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 1 and are based on values used in the academic literature consulted.

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

Tab 1: Parameters kept constant in method 1

2.2.2 Method 2: Treatment with chemical reagents

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.

Fixation

- The concentration of radioactive iodine solution was 100 μCi 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.

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

Tab 2: Parameters kept constant in method 2

2.2.3 Method 3: Treatment with chemical reagents (IPEN)

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).

Fixation

- The silver wires were put into a sodium sulfide (Na_2S) solution. The values of concentration ranged from 0.3 mol/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 (100 μCi 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.

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

Tab 3: Parameters kept constant in method 3

3. RESULTS AND DISCUSSION

3.1 Preliminary Test

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

3.2. 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: 6.5 h; Without the presence of light; With the presence of a carrier; Reaction time: 20 h.

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.

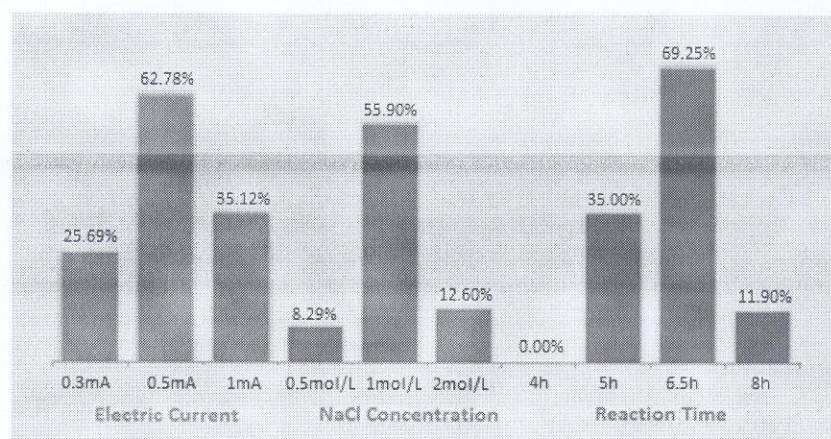


Figure 1: First part of results obtained using method 1

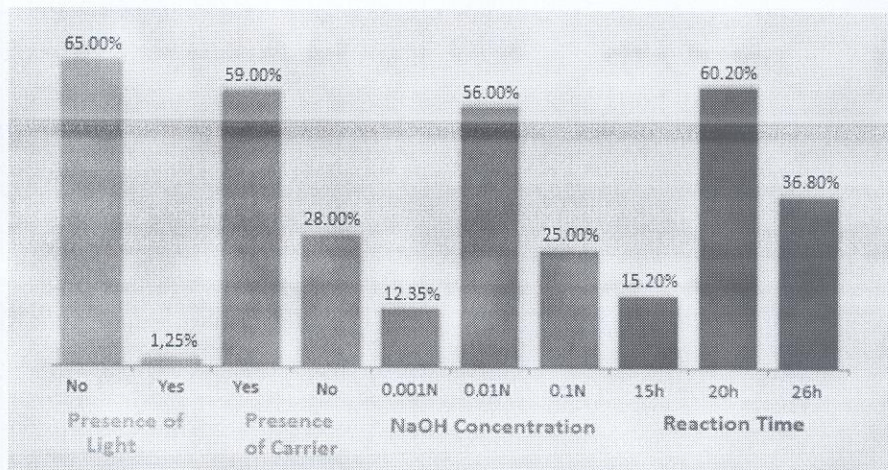


Figure 2: Second part of results obtained using method 1

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

Silver Core	Exp 1 Activity (μCi)	Exp 2 Activity (μCi)	Exp 3 Activity (μCi)
$\sum A_n$	681	634	640
A_T	1 mCi	1 mCi	1 mCi
$E_{\%}$	68,1	63,4	64,0
Average %	65,16		

Tab 4: Activity measurements for the three final tests and global efficiency using method 1

* $\sum A_n$: 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. The cost of each seed manufactured by method 1 was R\$ 7.39.

3.3. 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.

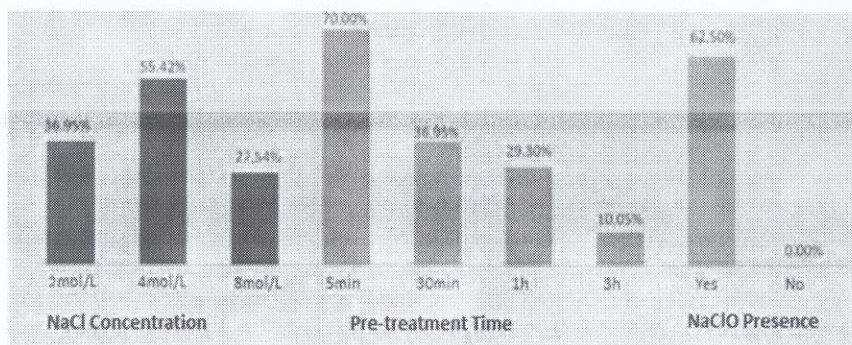


Figure 3: First part of results obtained using method 2

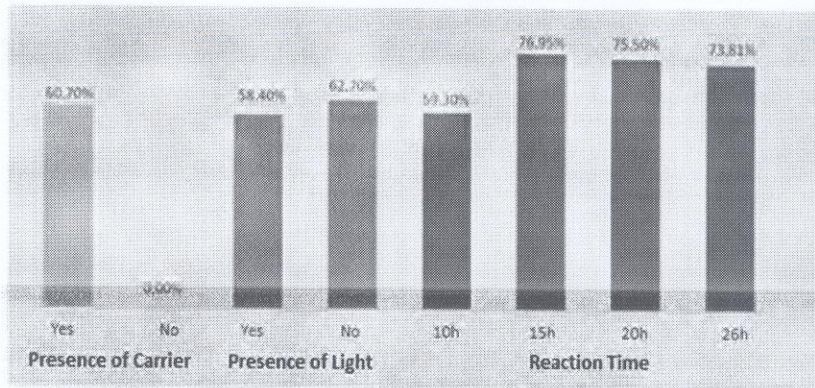


Figure 4: Second part of results obtained using method 2

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

Silver Core	Exp 1 Activity (μCi)	Exp 2 Activity (μCi)	Exp 3 Activity (μCi)
$\sum A_n$	767,35	721	699,37
A_T	1,03	1,03	1,03
E_{eff}	74,50%	70%	67,90%
Average %	70,80%		

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

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

Observations and Recommendations:

- This method is easy to implement at IPEN since it does not require absence of light.
- Good results concerning global fixation.
- Time required to perform the test: two days. Reaction time considered "fast".
- The price of each seed was R\$ 6.93.

3.4. 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: 20 h; Light had no influence in the fixation; NaOH concentration: 0.001 mol/L; Reaction time: 25 h.

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:

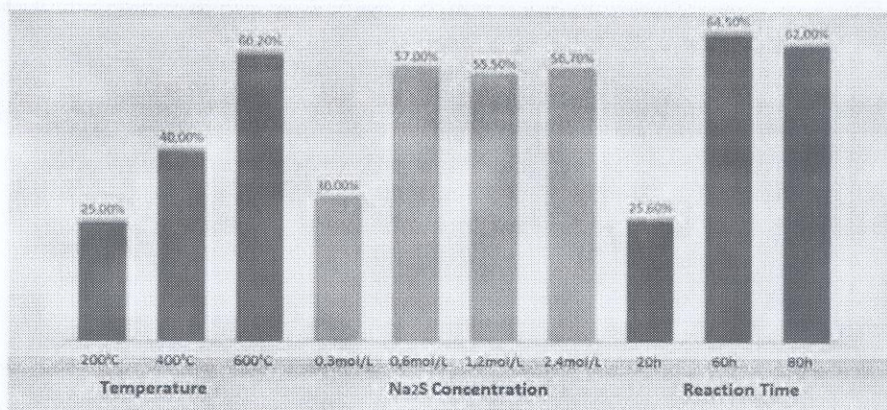


Fig 5: First part of results obtained using method 3

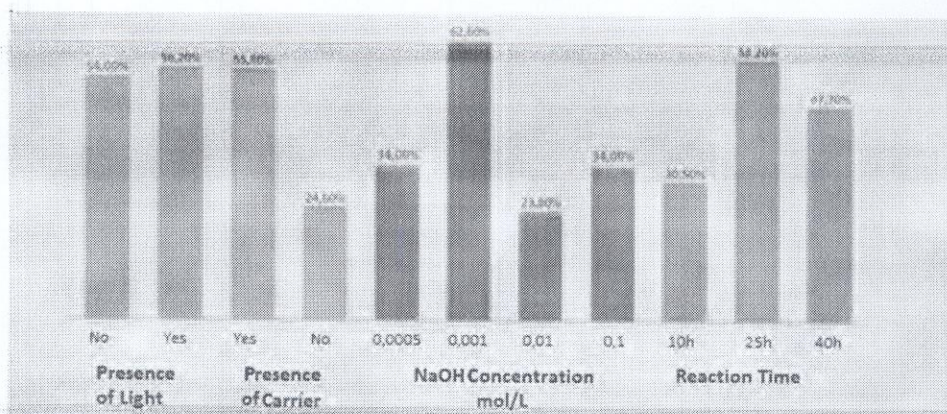


Figure 6: Second part of results obtained using method 3

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

Silver Core	Exp 1 Activity (μCi)	Exp 2 Activity (μCi)	Exp 3 Activity (μCi)
$\sum A_n$	561,35	618	544,87
A_T	1,03	1,03	1,03
$E_{\%}$	54,50%	60%	52,90%
Average %	55,80%		

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

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

Observations and Recommendations:

- This procedure is not as easy as those described in methods 1 and 2.
- Long reaction times – it takes 5 days to cover all steps.
- Good results concerning global fixation.
- The price of each seed was R\$ 8.59.

3.5 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. We have already developed four new methods, and one in particular is being refined for industrial application.

4. 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. Kubiawicz) 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 20 h. This method

is relatively fast (2 days), but it must be done in the absence of light. 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. Kubiawicz - 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 parameters were used: temperature of 600 °C, 0.6 mol/L concentration of sodium sulfide, Na₂S 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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