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Comparing different methods for radioactive iodine fixation intended for brachytherapy sources manufacture

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A B S T R A C T

Brachytherapy, a method of radiotherapy, is being extensively used in the early and intermediate stages of the illness. In this treatment, 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, fixated 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. 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

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. The number of new cases of prostate cancer in 2012 in Brazil was 60,180 (World Health Organization, 2012).

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 resulting in low rates of sexual impotence and urinary incontinence. 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, including work, within one to three days with little or no pain (Souza, 2009; Srougi, 2002). The main goal of this paper is the comparison of Iodine-125 fixation, in a silver wire substrate, using 3 different methods.

The amount of seeds required for the implantation is 80–120 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 (Souza, 2009; Rostelato, 2006).

The seeds-type sources are composed of a titanium capsule, classified as biocompatible, with 0.8 mm of outer diameter, 0.05 mm of wall thickness and 4.5 mm long. The internal structure varies from model to model. Seeds used in Brazil, uses a silver wire as a substrate. The iodine-125 is deposited in the silver substrate that also works as a radioactive marker. The typical activity of seeds

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of iodine-125 is 0.5 mCi (18.50 MBq) (Souza, 2009; Rostelato, 2006; Lawrence, 1967).

The goal of this work is to compare 3 well-known methods: 1: Electrodeposition method based in Kubiatowicz (Kubiatowicz, 1982); 2: Chemical deposition method also based in Kubiatowicz (Kubiatowicz, 1982); new method developed in IPEN-CNEN/SP in Brazil (Rostelato, 2006).

This comparison is extremely important because the iodine-125 represents almost 95% of the seed cost. Thus, the more efficient this method is, the cheaper the seeds will be. Working with iodine, radioactive or not, is related to several issues. The material is volatile, which is a major concern when working with radioactive material. The reaction must occur in an alkaline media but one must be careful, because a high concentration of OH^- could result in silver hydroxide surface instead of the desirable silver iodide surface. A strict impurities control must be performed since 1 mCi(37 MBq) of iodine-125 corresponds to 10^{-8} g.

The three methods used in this work consider the laboratory infrastructure of IPEN, as well as the desirable configuration of the seed core: silver wire with deposited iodine-125.

The first iodine-125 seeds were developed in 1965 by Donald C. Lawrence (Lawrence, 1967). 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 was published in 1982 by David Kubiatowicz (Kubiatowicz, 1982). 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.

2. Methodology

All assays were performed in two steps: pretreatment of the silver surface and fixation of iodine-125 on it. The detailed methodology used is described below.

2.1. Method 1: ion exchange of chlorides on iodides based in Kubiatowicz (Kubiatowicz, 1982)

Kubiatowicz published this method in 1982. The silver cores are placed in a 0.1 mol/L sodium chloride solution. The vessel is connected to the positive electrode and a basket, containing the seeds, is connected to the negative electrode. The electric current is applied for 6.5 h. The silver wires are placed in a 0.2 mol/L sodium iodide (NaI^{125}) with 0.01 mol/L sodium hydroxide solution. Nonradioactive iodine in the form of sodium iodide combined with sodium hydroxide solution is added and then, the solution is stirred for 17 h. The author claims 97% efficiency in this process. This methodology was reproduced using the following conditions.

2.1.1. Pretreatment: electrochemical deposition of chlorides on silver wire

In this step, electric current is applied in a sodium chloride solution resulting in the formation of a silver chloride layer. The electroplating device was filled with a solution of sodium chloride (NaCl). The optimal concentrations were stipulated between 0.5 mol/L, 1 mol/L and 2 mol/L. It was used about 1 L of electrolyte 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 h.

2.1.2. Fixation process

- After pre-treatment, the wires were placed inside a radioactive solution of sodium iodide (NaI^{125}). An ion–exchange reaction must occurs between chloride and iodine;
- The activity of radioactive iodine used was 100 mCi per seed core;
- The fixation reaction was carried for 17 h and 26 h;
- The influence of light and the carrier was tested. The carrier solution used was 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).

The values used for these parameters are shown in Table 1 and are based on values used in the academic literature consulted.

2.2. Method 2: treatment with chemical reagents also based in Kubiatowicz (Kubiatowicz, 1982)

Kubiatowicz published this method in the same patent as the one mentioned before. The wires are placed in a solution containing a 6 mol/L hydrochloric acid and a 1 mol/L sodium hypochlorite solution. After stirring for 1 h 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 10^{-4} 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 h in the absence of light. The author claims about 90% efficiency in this process. This methodology was reproduced using the following conditions.

2.2.1. Pretreatment

The silver wires are placed into a beaker containing 20 mL of hydrochloric acid (HCl) with different concentrations—2 mol/L, 4 mol/L and 8 mol/L. Then, 2 mL of sodium hypochlorite (NaClO-oxidant agent), 1 mol/L were added to the solution. The stirring times selected were: 30 min, 2 h and 4 h, at room temperature. After stirring, a layer of silver chloride is formed on the wires.

2.2.2. Fixation process

- The activity of radioactive iodine solution was 100 mCi per seed core;
- The process was carried for 17 h and 26 h;
- The influence of light and presence of a carrier was tested in the same way as described in method 1. The concentration of NaOH was fixed at 10^{-4} mol/L.

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

Table 1
Parameters kept constant in method 1.

Parameter	Value
Electric current	0.5 mA
Time Using Electric Current	7 h
NaOH Concentration	0.01 mol/L
Reaction Time	20 h
Carrier	Present
Light presence	Not Present

2.3. Method 3: treatment with chemical reagents (IPEN)

This method was developed by our research group IPEN brachytherapy sources production researchers. It involves heating the silver cores and them placing them in Na_2S solution resulting in an Ag_2S layer. The treated cores are put in contact with a NaI^{125} solution and ion-exchange reaction should occur. The method is under patent process. Table 3 presents the parameters used by the researchers.

2.3.1. Pretreatment

The silver wires were put into an oven with temperatures of 300 °C, 500 °C and 600 °C, for 150 min and with an atmosphere of oxygen (3 L/min). After this process, 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 h.

2.3.2. Fixation process

The wires were then, removed from the sodium sulfide solution and placed into a solution of radioactive iodine (100 mCi per seed core). Afterwards, it was stirred for 10 h and 40 h.

The influence of light and presence of a carrier was tested in the same way as described in method 1. Table 3 shows the parameters kept constant in each step of the tests.

2.4. 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 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 Capintec 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.

Table 2
Parameters kept constant in method 2.

Parameter	Value
Stirring Time	1 h
NaClO	Present
Reaction Time	19 h
Light	Non-Present
Carrier	Present

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	64 h
Sodium Hydroxide Concentration	0.1 mol/L
Reaction Time	26 h
Light	Present
Carrier	Non-present

3. Results and discussion

3.1. Preliminary test

In order to justify the pre-fixation step, the iodine-125 solution with 100 μCi activity per core was place in contact with the silver cores without any pretreatment. Iodine-125 was not fixed on silver, confirming the need of a pre-fixation treatment.

3.2. Method 1

The parameters with the most effective fixation were:

- Electric current: 0.5 mA electric current;
- NaCl concentration: 1 mol/L;
- Electric current application time (Reaction time): 6.5 h;
- Without the presence of light;
- With the presence of a carrier;
- NaOH concentration: 0.01 mol/L;
- 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 Figs. 1 and 2.

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

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. A good result concerning global fixation was achieved in only two days. Some parameters were not presented by Kubiatowicz in the patent such as, the electrical current used and NaCl concentration. A broad parameter experiment was made and the variation values were determined. The optimal electric current was 0.5 mA during 6.5 h with a NaCl concentration of 1 mol/L. Increasing or decreasing this parameter shows worse results, perhaps because the surface reached its threshold. The absence of light is understandable because the silver halides reacts producing metallic silver. The carrier is necessary to increase the iodine mass favoring the formation of silver iodide. The average efficiency was 65.16%, not 97% as was claimed. Sure, there are more steps not presented by the author. The cost of each seed manufactured by method 1 was BR$ 7.39.

3.3. Method 2

The parameters with the most effective fixation were:

- HCl concentration: 4 mol/L;
- Pre-treatment time: 5 min;
- With the presence of NaClO;
- With the presence of a carrier;

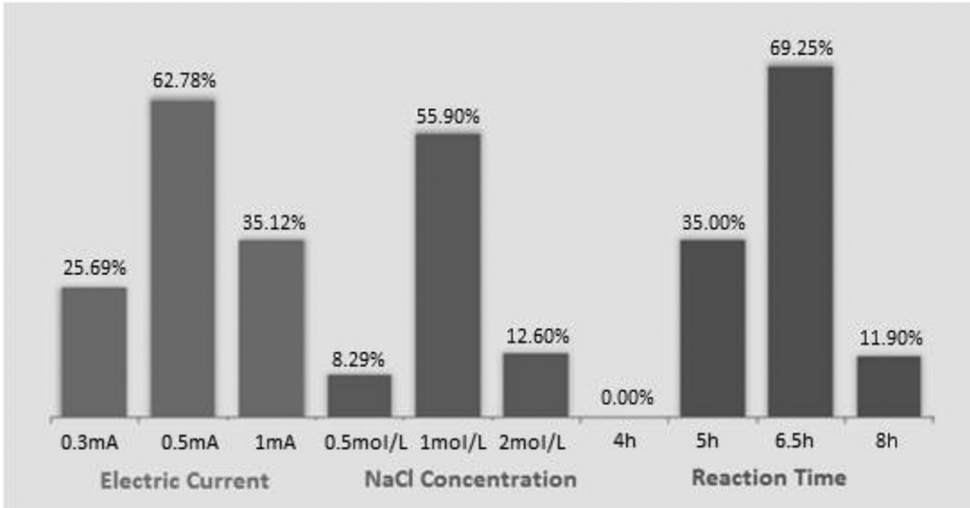

Fig. 1. First part of results obtained using method 1.

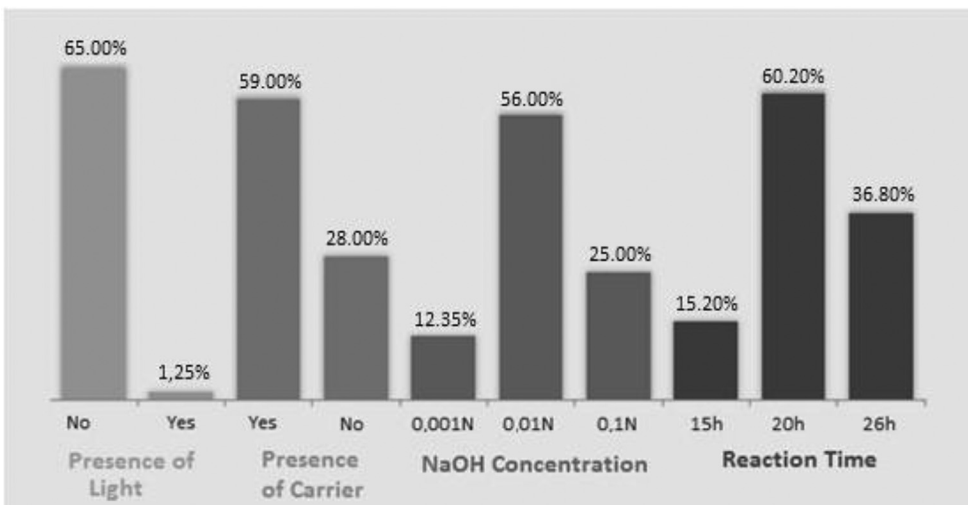

Fig. 2. Second part of results obtained using method 1.

- Light had no influence in the fixation;

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

Silver Core	Exp 1 Activity (μCi)	Exp 2 Activity (μCi)	Exp 3 Activity (μCi)
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	*87.3*	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	*52.8*	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		

Italics and underline indicates highest and lowest value.
*$\sum A_n$ Total fixed A_T Total activity considering radioactive decay $E_{\%}$ Efficiency.

- Reaction time: 15 h.

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

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

This method is easy to implement at IPEN since it does not require absence of light (inexplicably, because light should have the same influence as in method 1) and it achieved great results in global fixation in only two days. The pre-treatment is necessary to remove the silver oxide layer formed in silver surface. The author doesn't give the pretreatment time. Other differences were find such as: 4 mol/L HCl concentration instead of 6 mol/L, 15 h reaction time instead of 19 h and 70.80% efficiency instead 90%. The price of each seed was BR$ 6.93.

3.4. Method 3: treatment with chemical reagents (IPEN: heating/sodium sulfide)

The parameters with the most effective fixation were:

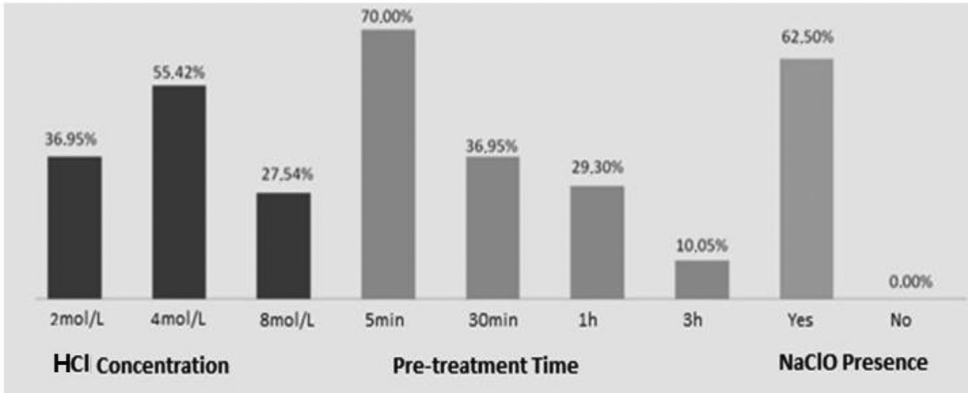

Fig. 3. First part of results obtained using method 2.

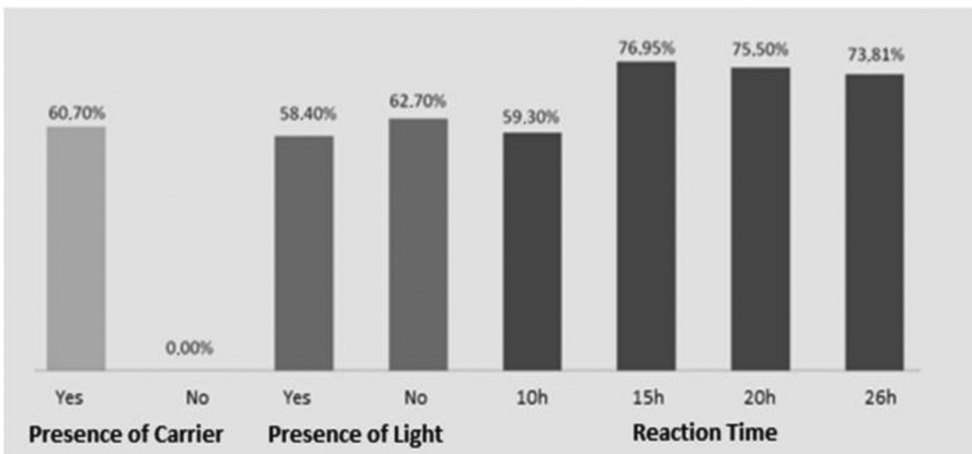

Fig. 4. Second part of results obtained using method 2.

- Temperature: 600 °C (highest temperature possible considering the available equipment);
- Na_2S concentration: 0.6 mol/L;
- Na_2S reaction time: 60 h;
- Light had no influence in the fixation;
- Presence of carrier;
- NaOH concentration: 0.001 mol/L;
- Reaction time: 25 h.

As the highest fixation values were obtained with a 0.001 mol/L NaOH solution, the use of a carrier solution was not necessary. The values for each test are presented in Figs. 5 and 6:

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

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

Silver core	Exp 1 Activity (μCi)	Exp 2 Activity (μCi)	Exp 3 Activity (μCi)
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%		

Italics and underline indicates highest and lowest value.
*$\sum A_n$ Total fixed A_T Total activity considering radioactive decay $E_{\%}$ Efficiency.

3.4.1. Observations and recommendations

This procedure is not as easy as those described in methods 1 and 2. It has several steps that take 5 days to be completed; however, it showed good results in global fixation. The high temperature applied should remove the water that is inside the silver crystals. The Na_2S reacts with silver producing Ag_2S. Then, a salt metathesis reaction occur generating AgI. Some differences were found: 60 h Na_2S reaction time instead 64 h and 0.001 mol/L NaOH concentration instead 0.1 mol/L. The chemical reactions that occur in this method require further studies (ongoing). The price for manufacturing each seed was BR$ 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. In order

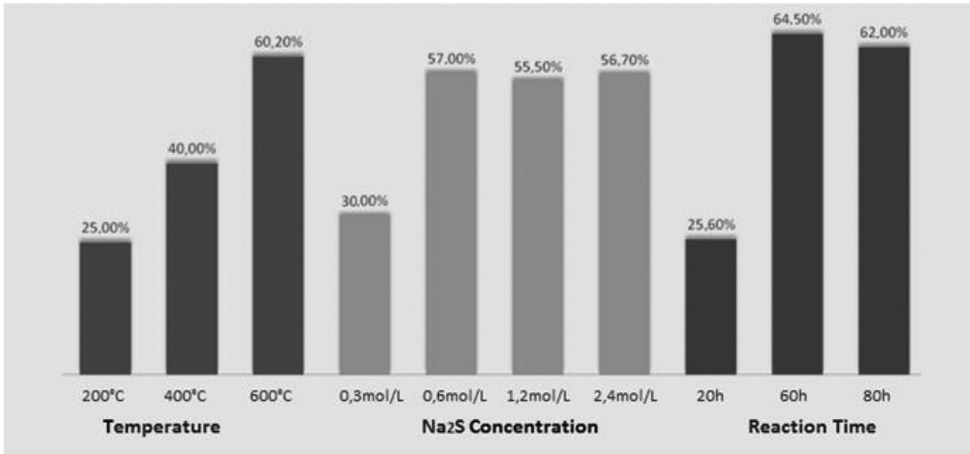

Fig. 5. First part of results obtained using method 3.

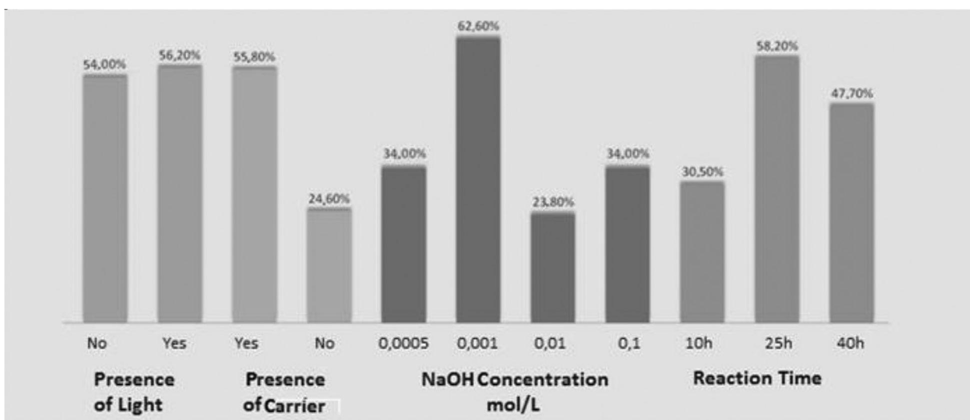

Fig. 6. Second part of results obtained using method 3.

to make the distribution the best possible, the cores should be preselected, 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 new method with better efficiency results. Such method is under development.

Several aspects were not considered in this study such as:

- Activity distribution among the cores: this happen because of core uniformity, sparse deposition, surface imperfections, among other factors;
- The influence of the parameters in one-another: a test like these will be too long and impractical for all the methods mentioned in this work. The IPEN's brachytherapy group will perform these tests only for the chosen method.

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

Silver core	Exp 1 Activity (μCi)	Exp 2 Activity (μCi)	Exp 3 Activity (μCi)
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%		

Italics and underline indicates highest and lowest value.
*$\sum A_n$ Total fixed A_T Total activity considering radioactive decay $E_{\%}$ Efficiency.

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 citation, three methods were selected.

Using method 1 the best result (65.16% efficiency − not 97% as presented by the developer author), was obtained using the following parameters: electrical current of 0.5 mA, 1 mol/L NaCl concentration, 6 h 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 dark. The cost of each seed manufactured by method 1 was BR$ 7.39.

For Method 2 to obtain the best result (70.80% efficiency - not 90% as presented by the developer author), the parameters should be: 4 mol/L HCl concentration, 5 min of pre-treatment, reaction time of 15 h, 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 BR$ 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, Na_2S reaction time of 20 h, with the presence of light; 0.001 mol/L NaOH concentration and reaction time of 25 h. 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 BR$ 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. This calculations were performed without any technology transfer costs. As our knowledge of the subjects increase, we hope to develop a better and new methods. We also plan to master the iodine-125 production in order to diminish the cost even more. Our ultimate goal is to have a national (without paying royalties), comparable and less costly product to provide to the Brazilian population.

Note: The experiences provided by executing these experiments, have provided knowledge for the group to develop a new method that has 95% efficiency and require 6 h to be completed. This method is under patent process and will be presented in future work.

References

Minnesota Mining and Manufacturing Company, Kubiatowicz, D.O., 6 Apr. 1982. Radioactive Iodine Seed. US Pat. n. 4.323.055.

Hazleton-Nuclear Science Corporation, Lawrence, D.C., Nov. 1967. Therapeutic Metal Seed Containing within a Radioactive Isotope Disposed on a Carrier and Method of Manufacture. US Pat. n. 3.351.0497.

Rostelato, M.E.C.M., 2006. Estudo e Desenvolvimento de uma nova Metodologia para Confecção de Sementes de Iodo-125 para Aplicação em Braquiterapia. Instituto de Pesquisas Energéticas e Nucleares, São Paulo. Thesis (Ph.D.).

Souza, C.D., 2009. Braquiterapia com sementes de Iodo-125: manufatura e tratamento, Monograph (Bachelor's degree). Universidade Estadual Paulista, Instituto de Biociências, Botucatu, São Paulo.

Srougi, M., 2002. A próstata como ela é. Folha De São Paulo, Caderno Cotidiano, São Paulo.

World Health Organization (WHO), Cancer, Fact Sheet n° 297—Fev-2012, http://www.who.int/mediacentre/factsheets/fs297/en/, 12 jul. 2012.