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DEVELOPMENT OF AN ENCAPSULATION METHOD USING PLASMA ARC WELDING TO PRODUCE IODINE-125 SEEDS FOR BRACHYTHERAPY

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ABSTRACT

The prostate cancer, which is the second cause of death by cancer in men, overcome only by lung cancer is a public health problem in Brazil. Brachytherapy is among the possible available treatments for prostate cancer, in which small seeds containing Iodine-125 radioisotope are implanted into the prostate gland. The seed consists of a titanium sealed capsule with 0.8 mm external diameter and 4.5 mm length, containing a central silver wire with adsorbed Iodine-125. The Plasma Arc Welding (PAW) is one of the viable techniques for sealing process. The equipment used in this technique is less costly than in other processes, such as, Laser Beam Welding (LBW). The main purpose of this work was the development of an encapsulation method using PAW. The development of this work has presented the following phases: cutting and cleaning titanium tube, determination of the welding parameters, development of a titanium tube holding device for PAW, sealed sources validation according to ISO 2919 - Sealed Radioactive Sources - General Requirements and Classification, and metallographic assays. The developed procedure to seal Iodine-125 seeds using PAW has shown high efficiency, satisfying all the established requirements of ISO 2919. The results obtained in this work will give the possibility to establish a routine production process according to the orientations presented in resolution RDC 17 - Good Manufacturing Practices to Medical Products defined by the ANVISA - National Agency of Sanitary Surveillance.

1. INTRODUCTION

The use of permanent implants of Iodine-125 seeds as a prostate cancer treatment has increased with the introduction of new products and technological advances. The seed implants provide a less aggressive type of radiotherapy than surgical procedures. A certain amount of seed is implanted in the patient using a fine needle through the skin into the prostate. A large dose of radiation is released only in the prostate where the tumor is, not affecting healthy organs nearby. The technique of brachytherapy requires an application that varies between 80 and 120 seeds per patient [1].

The advantages of radioactive seeds implants are the preservation of healthy tissues and organs near the prostate, the low rate of impotence and incontinence compared to conventional treatments, such as radical prostatectomy and external beam radiotherapy (teletherapy) [2,3].

The seeds are implanted during a non-surgical procedure. Small seeds are injected directly into the prostate, between the rectum and scrotum, using a fine needle through the skin [4,5]. A large dose of radiation is released only in the tumor, as Iodine-125 has a half-life of 59.6 days and its radiation, a low average energy (29 keV) that is slightly penetrating, thus preserving the surrounding tissue [6,7].

The seed consists of a titanium sealed tube (biocompatible material for the human body) measuring 0.8 mm external diameter, 0.05 mm wall thickness and 4.5 mm in length, containing a silver wire with Iodine-125 adsorbed. The silver wire measures 0.5mm in diameter and 3 mm in length, as illustrated in Fig.1. The sealing of the titanium tube is made, at both ends, by welding process using electric arc (in this case PAW) or laser beam [8]. The typical seed activity is 0.5 mCi, assuming a maximum variation of ± 5% in the same batch.

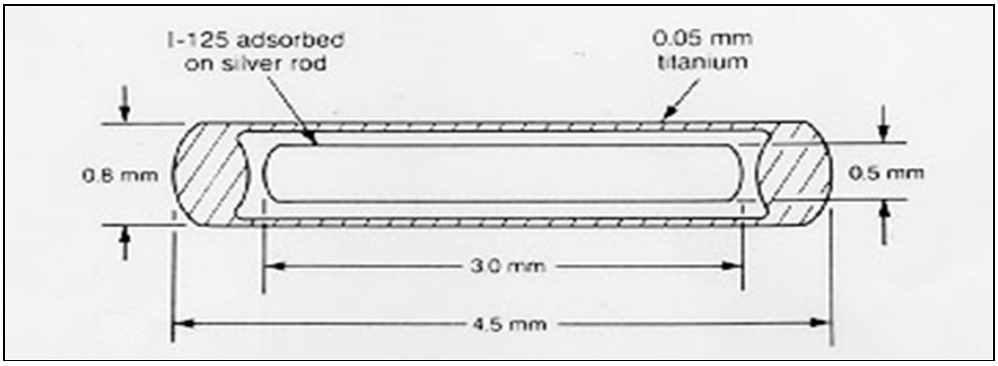

Figure 1. Schematic drawing of the Iodine-125 seed.

One of the Iodine-125 seed production stages is the titanium tube sealing by welding to be held at both ends, so as to allow classification of the seeds as sealed sources, attending to the stringent tests set out in relevant standardization, according to the international standard ISO 2919 – Radiation protection - Sealed Radioactive Sources – General Requirements and Classification [9].

This sealing should be watertight, free from cracks, avoiding the Iodine-125 adsorbed onto silver wire to escape and spread through the human body.

The seed applicators require the completion of the sealing is as spherical as possible, to avoid lock when loading of seeds.

The laser beam and plasma arc welding are viable techniques for sealing Iodine-125 seeds. The plasma arc technique has a lower cost than the process using the laser beam technique for Iodine-125 seeds routine production.

The term plasma arc is used to describe a family of processes using a constricted arc. Plasma arc processes are used for welding, cutting and coatings (with metallic or ceramic powder) [10].

2. METHODOLOGY

2.1. Materials

The material used in the experiments of welding the sealed sources was titanium, commercially pure grade 2 (CP GR2 Titanium), manufactured by Accellent Endoscopy; presented in the form of a tube with outer diameter ranging from 0.790 to 0.808 mm and thickness of wall ranging from 0.043 to 0.058 mm at 1 meter in length.

2.2. Methods

2.2.1. Material cutting and cleaning

The titanium tubes were cut with the aid of a cutting machine Buehler LTD, model Isomet 11-1180 Low Speed Saw, using an aluminum oxide disk, Struers 357CA. After cutting, the tubes faces were sanded with sandpaper 400 and degreased, for a period of one hour, in a mixture of 8 mL of distilled water and 2 mL of neutral detergent Merck Extran MA 02, in ultrasonic cleaning equipment UNIQUE USC1450. After this procedure, the tubes were washed in 10 mL of distilled water and placed for drying.

2.2.2. Welding equipment

It was used in the experiments for sealing the titanium tubes ends a plasma welding machine Secheron Soudure SA, model Plasmafix 50E, maximum current 50 A, pilot arc maximum current 5 A. The welds were made in direct current (DC), plasma arc with a 90° angle in relation to the tube face.

2.2.3. Motorized linear stages

It was used for positioning the titanium tubes in the sealing experiments a XY translation stage Syncro, with travel 500 mm x 500 mm, 2 stepper motors, 25 µm positioning accuracy, 2 controllers for stepper motors and a motion control software.

2.2.4. Titanium tube sealing devices

2.2.4.1. Device No. 1

A first device was developed for sealing small titanium tubes ends. It was set on the XY translation stage.

The device consisted of a copper bar measuring 250 mm x 19 mm x 5.5 mm. This device had 42 holes with 0.9 mm in diameter and 10 mm equidistant, 21 holes with 5.5 mm depth, for sealing the first side of the tube and 21 holes with 4.5 mm depth for the second seal. The device base was made of structural aluminum measuring 250 mm x 19 mm x 5.5 mm. Device No. 1 is showed in Fig. 2 and 3.

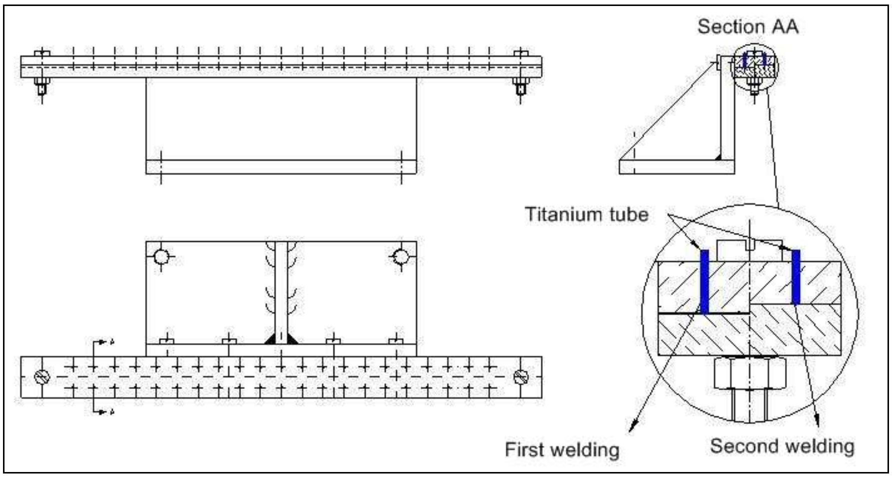

Figure 2. Device No. 1 schematic drawing.

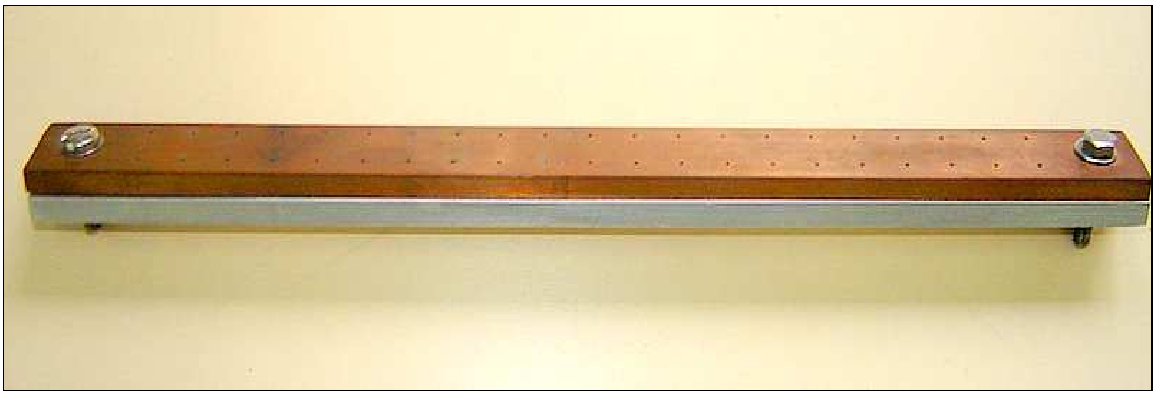

Figure 3. Sealing device No. 1.

2.2.4.2. Device No. 2

A second device was developed for sealing small titanium tubes ends. It was set on the device No. 1.

This device consists of a brass plate split in two, measuring 18 mm x 18 mm x 9.5 mm and a micrometer accurate to 0.01 mm.

The titanium tube was positioned on the device No. 2 between two brass plates. Micrometer was used to adjust extra titanium tube length, which was necessary for sealing. Titanium tube was used itself as extra material to eliminate the need of using filler metal (cap) for sealing the seed. The brass plates were fixed mechanical regulator and screws.

Fig. 4 and 5 illustrate device No. 2 for sealing the titanium tube.

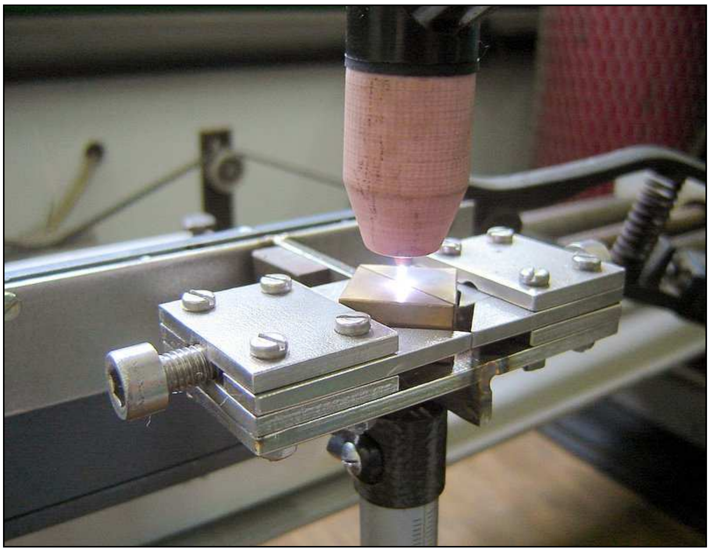

Figure 4. Sealing device No. 2.

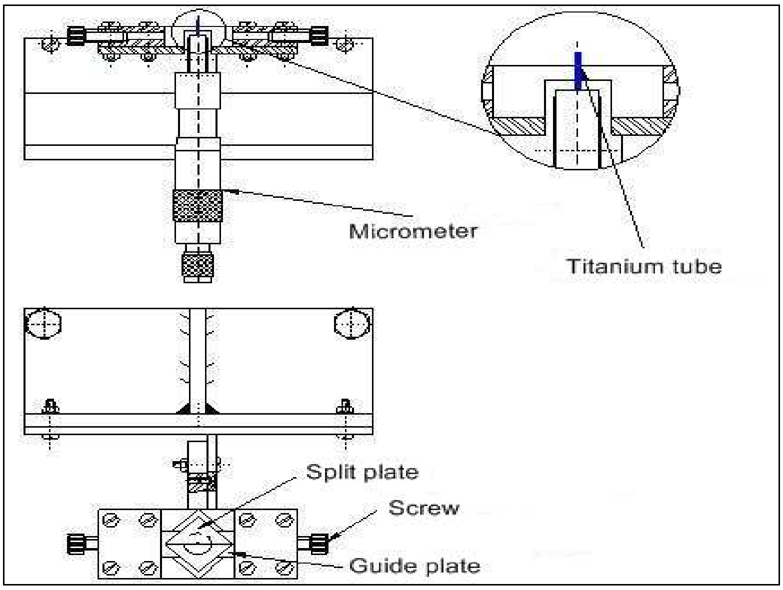

Figure 5. Device No. 2 schematic drawing.

2.2.5. Welding parameters determination

Sealing experiments of titanium tubes were conducted with the two devices described in items 2.2.4.1 and 2.2.4.2 to determine the welding parameters for Iodine-125 seeds preparation.

The following parameters were evaluated on these experiments:

- Plasma arc current;
- Pilot arc current;
- Arc time;
- Constriction nozzle diameter;
- Standoff - Distance from outer face of the constricting nozzle and the workpiece [11];
- Plasma arc gas flow rate (ultra pure argon gas);
- Protection gas flow rate (commercial argon gas); and
- Extra titanium tube length for sealing.

2.2.6. Sealing experiments

2.2.6.1. Experiments with device No. 1

The titanium tube was put in the device No. 1 hole. The tube was positioned under the nozzle constriction of the plasma torch with pilot arc turned off by the XY translation stage. It was set the welding parameters as mentioned in item 2.2.5.

With the pilot arc turned on, it was switched on the automatic welding of the PAW machine.

After sealing one side, the tube placed in the device No. 1 was inverted, so that the other side of the tube was positioned as in the beginning of the experiment.
A silver wire was put inside the titanium tube and it was fired again the automatic welding switch.

2.2.6.2. Experiments with device No. 2

A titanium tube was put in the split brass plate center. Using a micrometer it was adjusted the extra titanium tube height. The tube was fixed by the plates through screws.

With the pilot arc turned off, using the XY translations stage, the tube was centralized with the nozzle constriction axis of the plasma torch. They were set the welding parameters as mentioned in item 2.2.5.

With the pilot arc turned on, it was switched on the automatic welding of the PAW machine.

After sealing one side, the tube placed in the device No. 2 was inverted, so that the other side of the tube was positioned as in the beginning of the experiment.

Using a micrometer it was adjusted the different extra titanium tube height.

A silver wire was put inside the titanium tube and it was fired again the automatic welding switch.

Tab. 1 presents the parameters used in the experiments with the sealing devices No. 1 and 2.

Table 1. Plasma Arc Welding (PAW) parameters.

Parameters	Device No. 1	Device No. 2
Plasma arc current (A)	1 - 4.5	0.5 - 2
Pilot arc current (A)	2	2
Arc time (s)	0.5 - 0.7	0.2 - 0.6
Constriction nozzle diameter (mm)	0.8 - 1.2	1 - 1.2
Standoff (mm)	5.1	4.6
Plasma arc gas flow rate (L/min)	0.1 - 0.3	0.1 - 0.3
Protection gas flow rate (L/min)	8 - 10	8 - 10
Extra titanium tube length for sealing No. 1 (mm)	2 - 2.7	1 - 2
Extra titanium tube length for sealing No. 2 (mm)	0.5 - 0.7	1 - 2

2.2.7. Classification and identification of the Iodine-125 seeds according to ISO 2919

The classification of sealed sources according to ISO 2919 - Radiation protection - Sealed Radioactive Sources - General Requirements and Classification is oriented towards the application of the product, requiring performance or features that prevent the radioactive material leak. The sealed sources must be submitted to groups of thermal and mechanical tests with different levels of severity, depending on the performance required for your application.

2.2.8. Metallographic testing

The metallographic tests, although not required in ISO 2919, was conducted in order to check the metal welding from the point of view of its structure, trying to relate it to the manufacturing process, in order to explain or predict their behavior to final application. The test was performed using an optical microscope (micrograph test or micrography). These tests were done on material sections, polished and etched with appropriate reagents.

It was analyzed the whole aspect of the workpiece material, such as, homogeneity, distribution, nature, amounts of certain impurities and the manufacturing process, in order to ensure that after sealing there would not be cracks or porosity in the weld region. The tests were conducted on seeds with silver wire, without radioactive material adsorbed (dummy).

It was used a cold mounting kit with acrylic resin Metalotest, in preparing the samples. This mounting kit allows the samples preparation for metallographic tests, because it facilitates handling of small parts, prevents the samples with edges tear the sandpaper or polishing cloth, which influences the sample surface finish.

The seed was positioned to be embedded in the mold center, leaving a space of, at least, 5 mm between the seed and mold wall, so that it could fill this space with the resin.

In a Pyrex Becker were placed two measures of acrylic resin powder and mixed with a measure of catalyst.

Carefully, acrylic resin was poured into the embedded mold to fill it. It waited for a period longer than 25 minutes at room temperature for the resin polymerization occurred. After this time the piece embedded in acrylic resin was extracted from the mold.

Sandpaper 320, 600 and 800 were used until about the middle of the samples in a polisher Fortel PLF, 250 rpm.

Mechanical polishing was performed using a felt impregnated with diamond paste grain of 6 µm size. The lubricant used was a mixture of glycerin with alcohol (10% glycerin and 90% alcohol). Mechanical polishing was performed for approximately 15 minutes in a polishing machine Panambra SD-10, 300 rpm.

The chemical attack was carried out by shaking the polished surface submerged in reactive solution in a small bowl for 10 s, approximately. After the attack, the attacked surface was immediately washed with soap and water and then a drying was performed, first by passing a small cotton swab moistened with alcohol and then a jet of hot air at the surface.

The reactive solution used was composed by:

- 10 mL of 40% hydrofluoric acid;
- 10 mL of 65% nitric acid; and
- 30 mL of lactic acid.

3. RESULTS

3.1. Material Cutting and Cleaning

After cutting operation of the titanium tube it was noted excess burrs caused by cutting disk, illustrated in Fig. 6.

It was necessary to finish the titanium tube ends with 400 sandpaper to eliminate the burrs produced by the cutting disk.

In Fig. 7 it can be observed the absence of burrs and the desired finish on the titanium tube end for the Iodine-125 seeds manufacture.

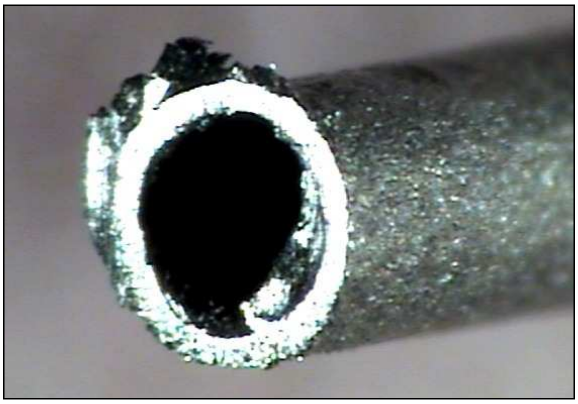

Figure 6. Titanium tube with burrs after cutting operation.

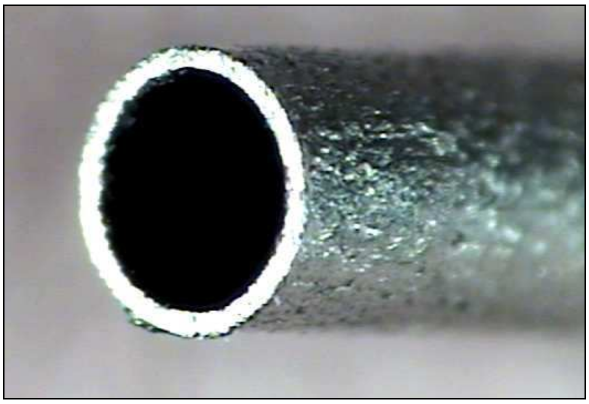

Figure 7. Titanium tube end after sanding process.

The seeds have millimetric dimensions, which complicate significantly the samples handling and settings during the tests. Due to that, it took about 900 trials to optimize the sealing welding parameters and determine the design of the tube fixation device for seeds manufacturing.

3.2. Titanium Tube Sealing Devices

3.2.1. Selling device No. 1

The selling device No. 1 has been developed for welding 21 seeds per production cycle. However, some difficulties were found during the trials with this device. The failure occurred trying to open the plasma arc, due to bad electric contact between the titanium tube and the sealing device, promoting color changes on titanium tube by a longer exposition of the pilot arc, as shown in Fig. 8.

In Fig. 9 can be observed a failure on the titanium tube sealing by PAW, with partial melting, due to the variation of tube length.

The selling device No. 1 had two different thicknesses. One with 5.5 mm designed to seal the first titanium tube side and the other with 4.5 mm for sealing the second tube end. Variation on the titanium tube lengths for these both situations was responsible for the failure showed in Fig. 9.

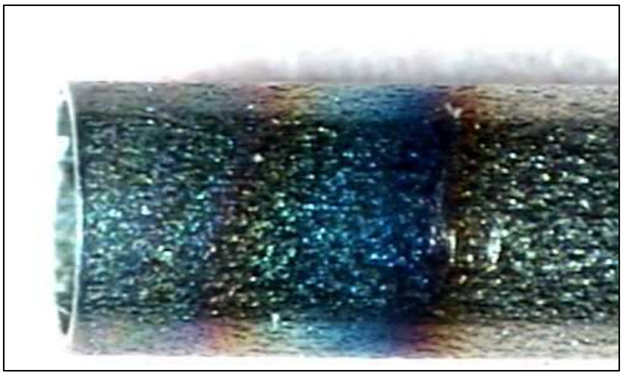

Figure 8. Plasma arc opening failure on titanium tube.

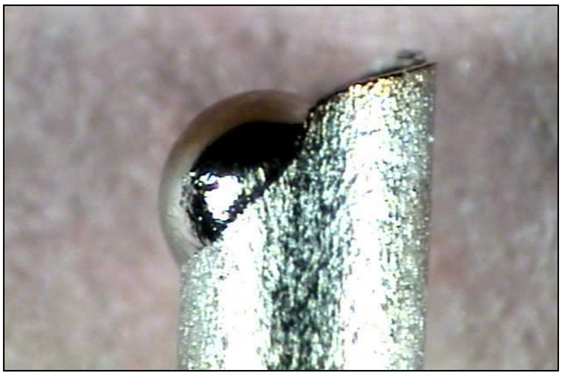

Figure 9. Seal failure on titanium tube by PAW.

In Fig. 10 it can be observed an excess of metallic material on the titanium tube side due to a high current (4 A) used to try to solve the problems of bad electric contact between the titanium tube and the sealing device. This excess material is solidified in the region where the melt came into contact with the copper of the welding device.

Although described in literature about a bigger arc stability it can be seen in Fig. 11 an asymmetry in the titanium tube welding due to oscillation of the plasma arc at the time of sealing [11,12].

Approximately, 250 tests were performed with the sealing device No. 1. As this device had several problems for sealing the titanium tube, it was decided to develop a new device to try to eliminate the problems described in item 3.2.1.

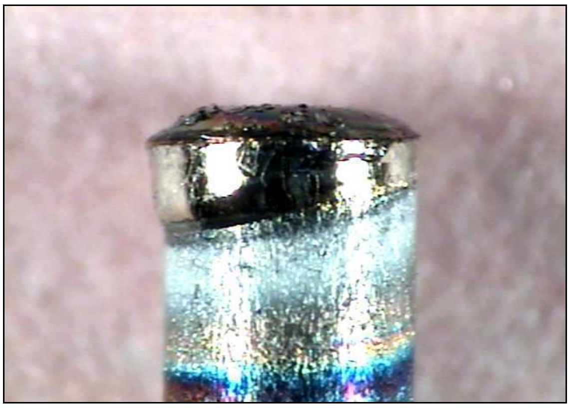

Figure 10. Over-current plasma arc on titanium tube side.

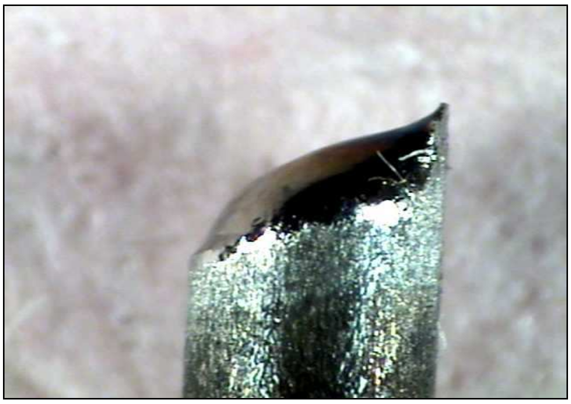

Figure 11. Asymmetric weld on titanium tube end.

3.2.2. Device No. 2

The device No. 2 has been developed with the purpose of weld one seed at a time, fixed by split plates and presenting the ability of adjusting extra titanium tube length.

Using a fixation system by split plates, the difficulty of opening the plasma arc was eliminated, since the tube is trapped between the two plates, with four electric contact points. It is a different conception of the selling device No. 1, in which the titanium tube stayed loose in the copper bar hole. Another difficulty was solved with a micrometer adjustment on the selling device No. 2, allowing the extra titanium tube length fine-tuning used for sealing the tube ends.

The ultra pure argon gas flow from the plasma arc torch can cause turbulence in the liquid weld pool. The gas flow rate recommended in the literature varies from 0.25 to 5 L/min, but the flow rate indicated in the welding machine manual varies from 0.1 to 0.3 L/min [13,14]. Fig. 12 illustrates a sealed tube using a gas flow of 0.3 L/min, producing an internal pressure and causing an increase in diameter on the weld region. To correct this problem the gas flow was reduced to the minimum value (0.1 L/min), as indicated on the machine manual.

Improving the fixation system, providing a good electric contact between the titanium tube and the plasma arc machine, and also using a suitable gas flow rate, it was possible to improve the weld region finish. It can be seen in Fig. 13 a sealed titanium tube with a better finish and little variation on the weld symmetry.

To eliminate the variation on the weld symmetry, due to the plasma arc oscillation, it was used a nozzle constriction with larger diameter (1.2 mm) than the titanium tube diameter (0.8 mm).

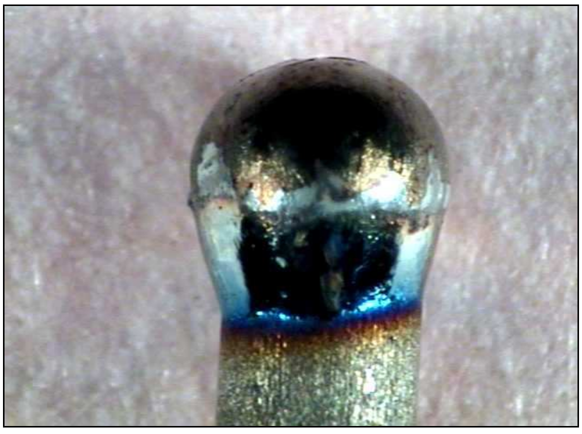

Figure 12. Titanium tube sealing with incorrect gas flow rate.

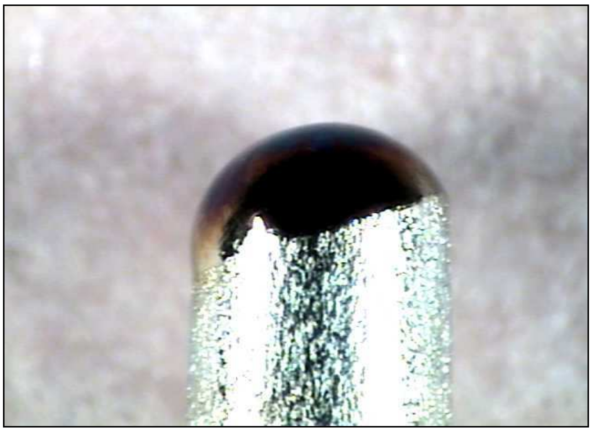

Figure 13. Titanium tube sealing with an asymmetric weld region.

In Fig. 14 and 15 are shown the titanium tubes sealing, using a plasma arc nozzle constriction with 1.2 mm in diameter. They also illustrate Iodine-125 seeds that were sealed using the final plasma arc welding parameters, which were considered optimized on the welding tests, presented in Tab. 2.

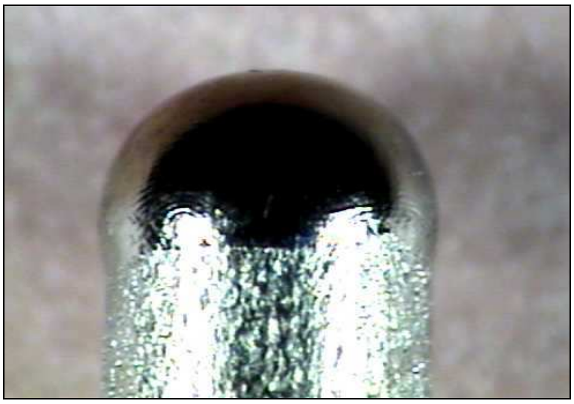

Figure 14. Titanium tube sealing with adjusted welding parameters (first end).

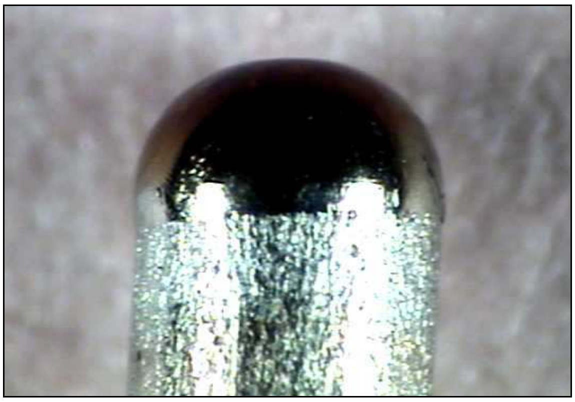

Figure 15. Titanium tube sealing with adjusted welding parameters (second end).

It can be seen in Tab. 2 a variation of length in parameters "Extra titanium tube length for sealing No. 1" and "Extra titanium tube length for sealing No. 2", which occurred due to the pressure formed inside the titanium tube on the second PAW, with the need to reduce the amount of metallic material to be melted.

Table 2. Final Plasma Arc Welding (PAW) parameters.

Parameters	Value/Range
Titanium tube length (mm)	6.90 - 6.97
Plasma arc current (A)	0.85
Pilot arc constant current (A)	2
Arc time (s)	0.3
Constriction nozzle diameter (mm)	1.2
Standoff (mm)	4.6
Plasma arc gas flow rate (L/min)	0.1
Protection gas flow rate (L/min)	10
Extra titanium tube length for sealing No. 1 (mm)	1.9
Extra titanium tube length for sealing No. 2 (mm)	1.3

3.3. Final length of the Iodine-125 Seeds

In Fig. 16 it can be verified that the variations which occurred in the final length of the Iodine-125 seeds are within the acceptable range (4.5 to 5 mm), as indicated on the literature [15,16].

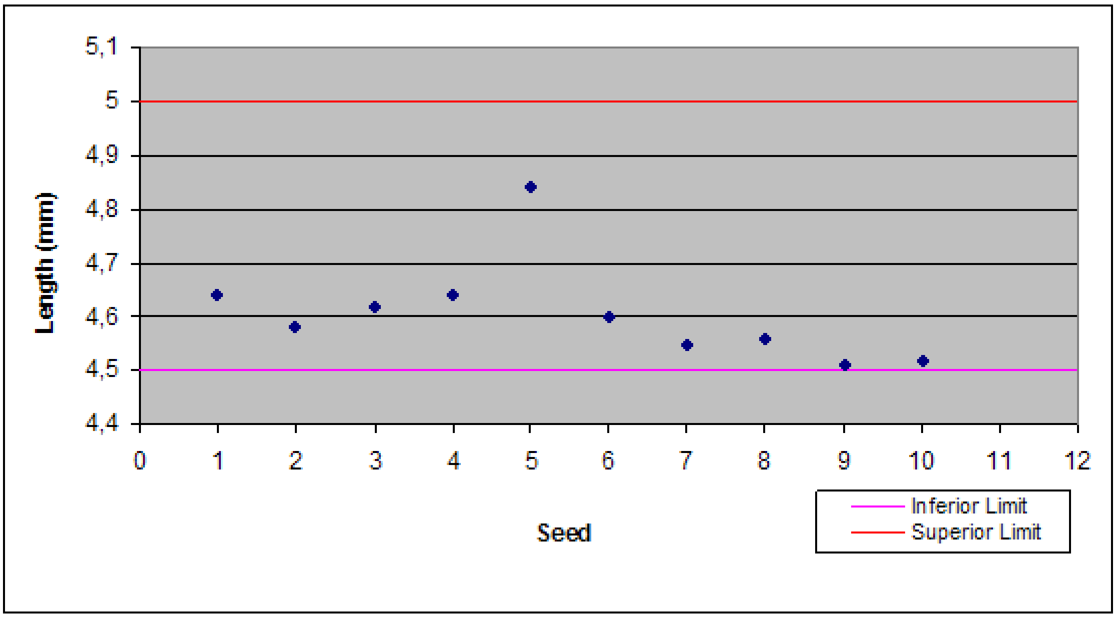

Figure 16. Length variation of the Iodine-125 seeds after reproducibility test.

3.4. Classification and Identification of the Iodine-125 Seeds According to ISO 2919

According to ISO 2919 the Iodine-125 seeds are considered radioactive sources for medical application in brachytherapy and were classified with the code ISO/99/C53211, where the two numbers after the code ISO/ indicate the year of the standard approval used following a solid bar (/), followed by a letter C or E that indicates whether the activity of the sealed source exceeds the specified limits according to the group of radionuclide listed in the standard.

The following five digits set in ascending order, the degree of severity that the sources must support for the testing of temperature, external pressure, impact, vibration and puncture.

As identified above, the brachytherapy sources must be approved in the tests:

- Temperature - Class 5 [- 40°C (20 min), 600°C (1 h) and thermal shock at 20°C];
- External pressure - Class 3 (25 kPa absolute to 2 MPa absolute);
- Impact - Class 2 (50 g of 1 m or equivalent energy);
- Vibration - Class 1 (not applicable); and
- Puncture - Class 1 (not applicable).

3.5. Metallographic Assays

Fig. 17 and 18 illustrate the titanium tube welding region. It can be observed the absence of failure in the sealing. It can also see the quality of the weld along the wall tube, that is free of cracks and that the solidification of the drop occurred without porosity.

The drop region was solidified spherical, following the tangency of the tube, which eliminates potential interference with mechanical locking during the charging of the seeds into brachytherapy needles.

Figure 17. Titanium tube weld detail (125x).

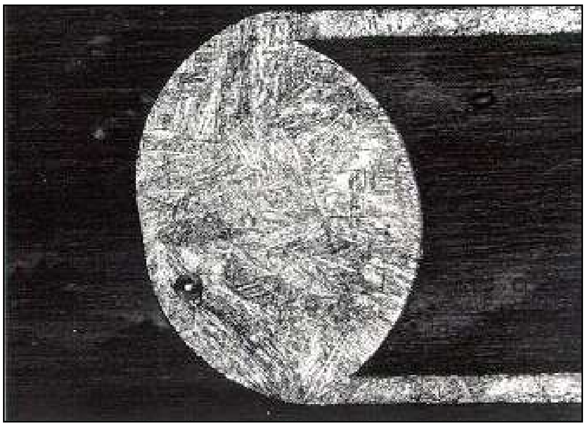

Figure 18. Titanium tube weld detail (100x).

4. CONCLUSIONS

Since it is a welding arc process, there is a need for good electrical contact between the part to be welded and the grounding system of the plasma welding machine, so the selling device No. 2 was more efficient to keep titanium tube always in contact with the ground's plasma welding.

Having the need to vary the extra titanium tube length of the first and second sealing ends, device No. 1 proved to be unviable, since its design does not allow this variation, unlike the device No. 2, which has a micrometer system to adjust extra metallic material, necessary for the drop region to solidify spherically, free of cracks and without porosity.

The metallographic tests results showed that the welding parameters, determined and optimized, using the welding device No. 2 have been effective. Thus, both the device No. 2 and the welding parameters can be used in automation design of Iodine-125 seeds production.

Further tests will be prepared as recommended by ISO 2919 to medical sources for brachytherapy, according to the specific severity degree to each test.

The results presented on this R&D work will allow for the development of methods and controls to be used in sealing of Iodine-125 seeds attending the Good Manufacturing Practices.

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