

A new ^{124}Xe irradiation system for ^{123}I production

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ABSTRACT

Since 2001, the Nuclear and Energy Research Institute IPEN-CNEN has produced iodine-123, weekly, using a manual irradiation system, fully developed in IPEN. Ultrapure ^{123}I has been produced and distributed to hospitals and clinics, where several diagnostic imaging procedures are done for thyroid, brain and cardiovascular functions. Due to the short half-life and emission of low-energy photons, this radioisotope becomes suitable for diagnosis in children. In the present work, will be presented all the technical and constructive aspects of a new fully automated irradiation system, dedicated to ^{123}I routine production, employing enriched xenon-124 gas as the target material. This new system consists of a target, a water and a helium cooling system, a cryogenic system, an electric power system, and a control and process monitoring unit, composed of a supervisory software, connected to a programmable logic controller via personal computer. In this new concept, there is no need for human interference during radioisotope production, reducing the possibility of eventual failures or incidents involving radioactive material. In this way, with this new system, a specific yield, of 2.70 mCi/ μAh per irradiation was achieved, in validation essays of the system and, after three years of routine production of iodine-123, the system showed reliability and resilience.

Keywords: cyclotron, iodine-123 production, targetry, proton beam, radioisotope production.

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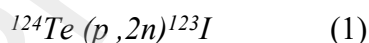
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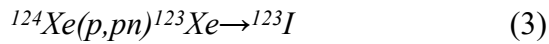
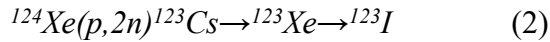
1. Introduction

Iodine-123 is a radionuclide that has been widely used worldwide for imaging diagnosis of thyroid, brain and cardiovascular system disorders (International Atomic Energy Agency, 2006; Lebowitz et al., 1971; Legoux et al., 1985). Due to its short half-life (13.2230(19) h) and emission of low-energy photons (159 keV, 83.6 %; 528.97 keV, 1.27 %), it is well suited for diagnoses in children (International Atomic Energy Agency Nuclear Data Section, 2020; Stöcklin et al., 1995).

Until the late 1990's, Nuclear and Energy Research Institute (IPEN) had a cyclotron accelerator (CV-28 - The Cyclotron Corporation), and started the experimental production of ^{123}I , employing the route shown in Equation (1) by irradiating a solid target of enriched tellurium oxide (Guillaume et al., 1975; Hupf et al., 1968).



In 1998, with the acquisition of a new cyclotron (Cyclone 30 - Ion Beam Applications), the ^{123}I routine production was started at IPEN, using an irradiation system fully developed by its own researchers, employing the route shown in Equations (2) and (3) (Firouzbakht et al., 1992, 1987; Konjachin et al., 1989; Kurenkov et al., 1989; Sumiya and Sciani, 2008; Tárkányi et al., 1991).



Until 2009 all ^{123}I routine productions were performed using this irradiation system, however, because it was a manual system, there was a need for human interference in many phases of the process, increasing the chances of failure and incidents with radioactive material.

For this reason, in order to make the ^{123}I production more safely, minimizing human interference and the risks of incidents with radioactive material, a new fully automated ^{123}I production system has been developed, that allows the ^{124}Xe transfer to the target, gas recovery after irradiation, removal of ^{123}I produced, and cleaning and drying of the irradiation system.

2. Materials and methods

2.1 System description

The new system design consists of: the target, a closed pressurized helium-cooled circuit for molybdenum windows, a cryogenic system for ^{124}Xe transfers before and after irradiation, a vacuum system to maintain the irradiation system at low pressure, temperature and pressure gauges, an electric power system for the vacuum pumps, valves and heating resistors activation. All such systems are remotely controlled and monitored by a programmable logic controller (PLC), via RS232/USB interface, with a personal computer employing a supervisory software developed in MS Visual Basic 6[®] specifically for that purpose (Microsoft Corporation, 1998). Fig. 1 shows a block diagram of the developed system.

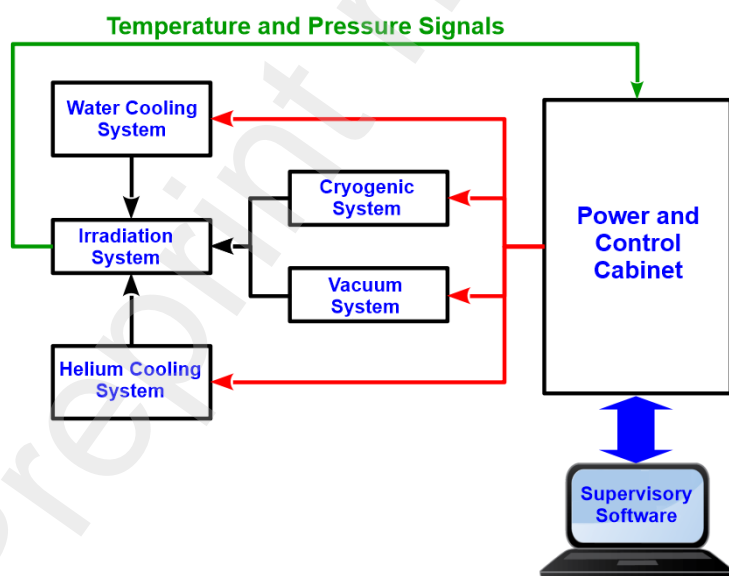


Fig. 1. Irradiation system block diagram.

2.1.1 Target

The new target consists of a front collimator, a set for mounting the molybdenum windows, separating the irradiation chamber from the cyclotron beam line, a cone-shaped irradiation chamber with 140 mL, an external cooling jacket and a beam dump at the bottom of the target (Bechtold et al., 1989; Robertson and Stuart, 1986). Fig. 2 shows a sketch of the target.

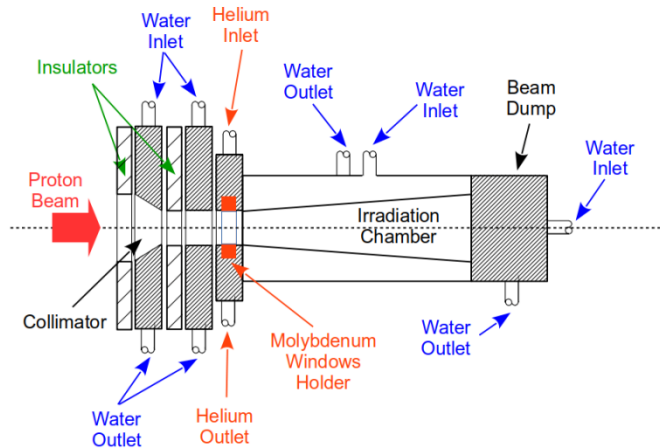


Fig. 2. Sketch of the target for ^{123}I production.

2.1.2 Water cooling system

Fig. 3 shows a schematic view of the ^{124}Xe target cooling system. Cooling is performed independently in three parts of the irradiation system: collimator, target body and beam dump. The same system also chills the heat exchanger and the helium compressor, of the molybdenum window cooling system. The target has an independent water purge system, used only for preventive and/or corrective maintenance purposes.

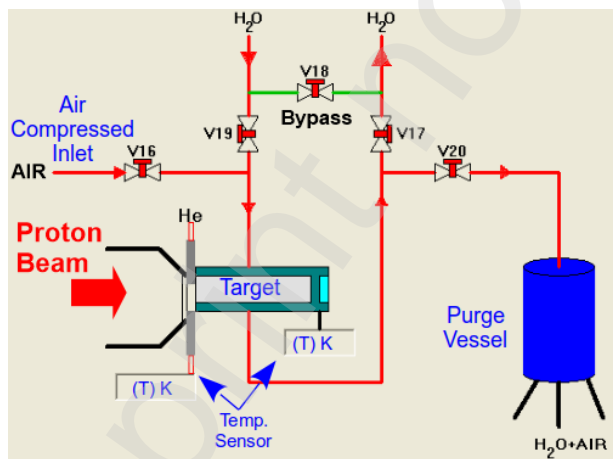


Fig. 3. Water cooling system.

2.1.3. Helium cooling system

Fig. 4 shows a schematic of the helium cooling system, employed to chill the target molybdenum windows. Initially, the system is purged with gas helium flow about 15 seconds.

After purging in this way, the system works in loop. After passing through the molybdenum windows, the helium gas temperature is monitored, by means of a thermocouple installed in the gas outlet pipe.

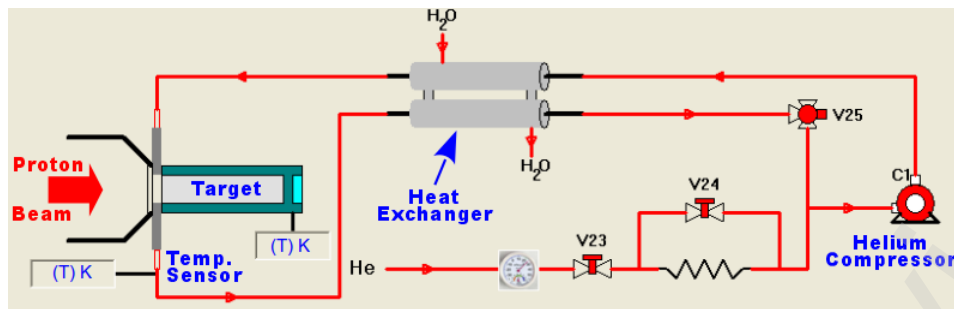


Fig. 4. Helium cooling system.

2.1.4 Cryogenic system

For the ^{124}Xe transfer, both into the target and its future recovery, after ^{123}I production, a cryogenic system was developed as shown in Fig. 5. Liquid nitrogen can be transferred to either the main cooling vessel or the intermediate cooling vessel, near the target. Inside these cooling vessels are housed the storage ^{124}Xe cylinders, and connected to each of these cylinders, there is a set of power resistors used for the liquid nitrogen evaporation, and also to facilitate the transfer of the gas by thermal gradient. Likewise, around the target body, there is another set of power resistors, used to heat the water, which facilitates the ^{123}I adsorption, which is adhered to the inner walls of the irradiation chamber. For gas transfer to be efficient, in addition to the temperature gradient, the piping must be under vacuum (around 10^{-3} mbar). In this case, the gas is transferred into the target and the subsequent recovery after irradiation. Vacuum pump B1 (Fig. 5) maintains the loading and unloading gas tubing under vacuum prior to and after irradiation, and vacuum pump B2 (Fig. 5) is responsible for drying and maintaining under vacuum the tubing through which water with ^{123}I is withdrawn.

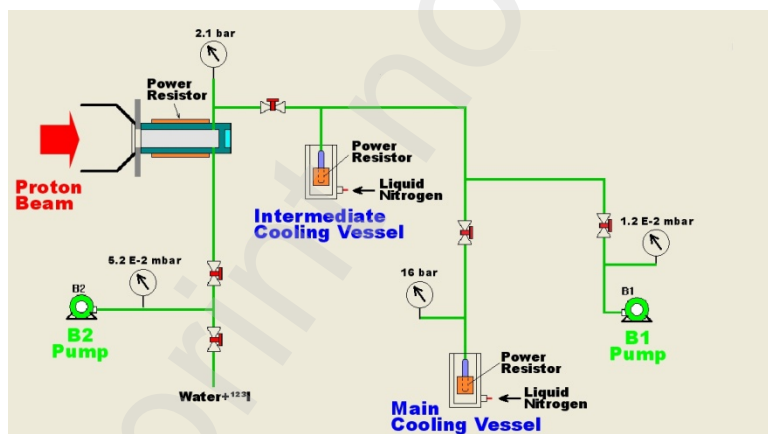


Fig. 5. Cryogenic system.

2.1.5 Power and Control Cabinet

During xenon irradiation, the radiation levels inside the irradiation room are very high, mainly due to the high energy neutrons emitted during the target bombardment. For this reason, in the electrical system design, it is necessary to consider the effects of this radiation,

on the electric circuits and their components, since the radiation may cause degradation and irreversible damages in its structures, compromising the system durability and reliability (Da Costa, 2014). In this way, the electrical system (distribution, command and monitoring) was divided or subdivided into units, considering the protection of its components, either through its installation in remote locations, and even the use of shields, such as used in some sensors. Also, when possible, electromechanical components, thermocouples, etc., which are more resistant to radiation were used.

The Electrical Power System consists of a Main Rack located at the irradiation room, and a Control Cabinet interconnected to a microcomputer located in an external room. The Main Rack, via remote control signals (from the Control Cabinet), energizes directly or indirectly (through electromechanical relays) the respective solenoid valves (pneumatic, water, nitrogen, etc.), as well as heating resistors. Also, in this rack are connected the vacuum pumps and the helium compressor. As for the Control Cabinet, responsible for sending the respective control signal to the Main Rack, it consists of circuit breakers, contactors, thermal relays and the control unit itself, i.e. a programmable logic controller (PLC) (Delta, DVP-SX2), composed of a main module and six I/O extension modules (digital inputs and outputs and analog inputs for sensor connection), which perform the acquisition of system process status (positions, temperatures, pressures, etc.), as well as the control of various actuators (electric, pneumatic) of the Main Rack. Also, a PC microcomputer, running supervisory software developed in MS Visual Basic®, connected to the PLC via RS-232/USB interface, monitors the process. Fig. 6 shows a summary of the Electrical System developed for this application.

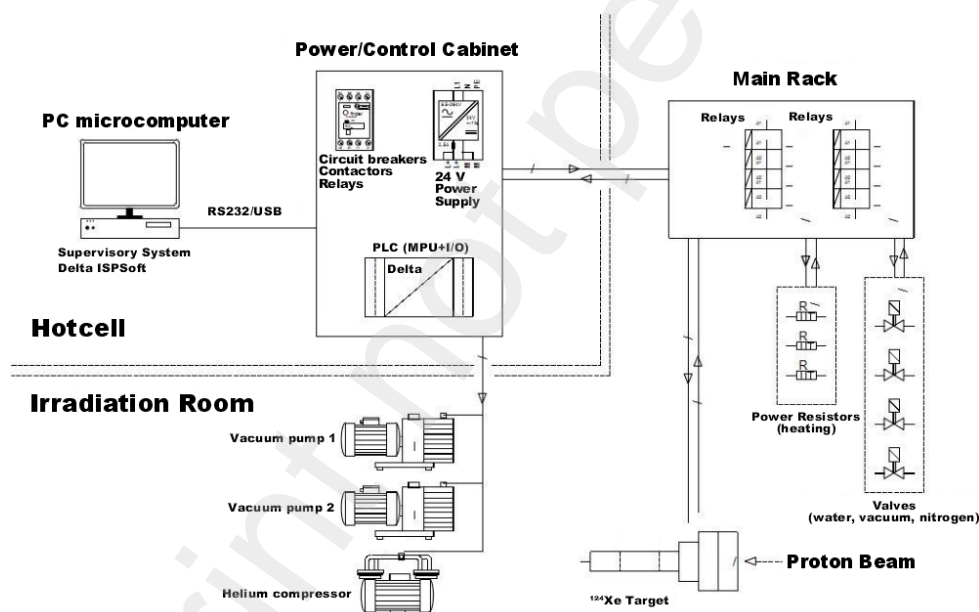


Fig. 6. Power system for ^{123}I production.

2.1.6. Process control software

The entire ^{123}I production process is remotely controlled by a software supervisory developed in MS-Visual Basic 6®. Fig. 7 shows to the system operator the supervisory software main screen, where the process control windows appear. According to the access level, the system allows the execution of tasks according to two security modes, described in Table 1.

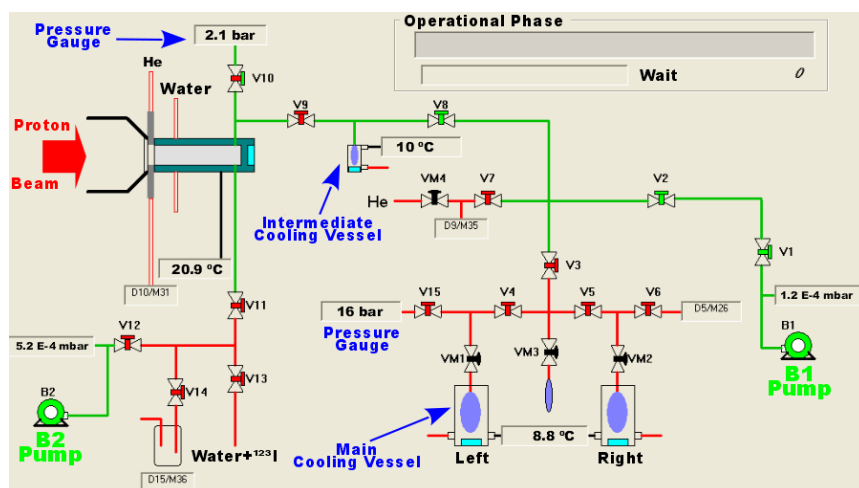


Fig. 7. Supervisory software window used for ^{124}Xe transfer and recovery.

Table 1

Safe access levels of ^{124}Xe irradiation system.

Safety Mode	Description
Maintenance	All devices unlimited access mode. Used in maintenance activities. Access allowed for qualified personnel only.
Operational	Limited access only to the ^{123}I production process. The operator can access all command buttons related to the process step and monitor the relevant parameters of each step (temperature, pressure, etc).

In ^{123}I routine productions, the Operational Safety Mode must be used allowing the operator to control the process steps. The next item will be described in more detail the steps involved in the production of ^{123}I using the Automatic System developed at IPEN.

2.2 Procedures for ^{124}Xe irradiation and ^{123}I production

2.2.1. Target load

When starting the target loading, the water cooling system valves must be opened. The helium cooling system should then be purged for approximately 15 seconds, to clean transfer line, compressor and valve tests. The system is commissioned for the next step.

The helium gas inside the irradiation chamber must be removed prior to the xenon gas loading, this is done by turn on the vacuum pumps B1 and B2 (Fig. 7). After this cleaning, the system is ready to receive the gas load.

The intermediate storage cylinder should be chilled to 77 K (-196 °C), by the cryogenic system, at the same time that the main storage cylinder is heated to 323 K (50 °C), to facilitate the gas transfer from the main cylinder to the intermediate cylinder, due to the thermal gradient. When the two temperatures reach their nominal values, the valves that communicate the cylinders are opened, and the gas flows naturally from the main cylinder to the intermediate one.

Due to the cryogenic effect, the gas is trapped in the intermediate cylinder and all valves are closed. At this point, the heating of the intermediate cylinder is started up to 323 K (50 °C), the valve communicating this cylinder with irradiation chamber is opened, even as the valve of the target pressure sensor. The gas is naturally transferred by temperature difference and the pressure is monitored by the supervisory software. The remaining gas in the intermediate cylinder is removed by cryogenic pumping to the main cylinder. At this point the system is ready to initiate irradiation. The Target Control Cabinet sends a signal to the Cyclotron Control Cabinet, communicating which the target is ready to irradiation.

2.2.2. Target irradiation

During ^{124}Xe irradiation ($^{124}\text{Xe}(p, 2n)^{123}\text{Cs}$, Equation (2)), the flow and temperatures of the water and helium cooling systems must be monitored at all time, if any of the parameters are outside of the defined operating limits, the system issues an alert to the cyclotron operator and the irradiation is immediately suspended. Another parameter that must be constantly monitored is the irradiation chamber internal pressure, which should increase gradually over time with increasing beam current. If a drop in target pressure is observed, the irradiation must be interrupted because a leak must be present.

2.2.3. End of bombardment (EOB)

At the end of irradiation, it is waited for 2 minutes, until the whole system has returned to room temperature. After this time, all cooling systems can be switched off and the system will be in standby mode for a period of 15 hours, waiting for the decay chain $^{123}\text{Cs} \rightarrow ^{123}\text{Xe} \rightarrow ^{123}\text{I}$, as seen in Equation (2) and (3).

2.2.4 ^{124}Xe recovery and ^{123}I removal

After the formation time, the ^{123}I remains adhered in powder form to the inner walls of the irradiation chamber, and the ^{124}Xe remaining in the irradiation chamber must be recovered for future irradiation.

This process step is essential for a good outcome of the whole production process. In this step, the vacuum pumps B1 and B2 are turned on again, cleaning the transfer lines through which the ^{124}Xe gas and the ^{123}I solution will circulate.

The first step to be implemented must be the xenon gas recovery for future use, as it is a very expensive material. To do this, the main storage cylinder must be cooled to 77 K (-196 °C), then the valves connecting the irradiation chamber to the main cylinder are opened, and the gas is naturally transferred due to the thermal gradient between these two points. After the transfer is completed, the valves are closed and the enriched xenon remains trapped inside the main cylinder.

The next step is to extract the ^{123}I , which is adhered to the inner walls of the irradiation chamber. For this, the chamber is completely filled with sterile water (~130 mL), heated to 343 K (70 °C) and held at this temperature for 20 minutes, this allows that ^{123}I adhered to the walls to migrate to the water remaining adsorbed thereon. After this time, the cooling water system is turned on to cool the chamber and its contents until the temperature reaches 298 K (25 °C). At this point, the ^{123}I solution must be transferred to a hot cell specially prepared for

this purpose. The transfer is done by pressurizing the chamber with helium gas. At the end of this process, the step of cleaning and drying can be started.

The decay time of 15 h and the target temperature of 70 °C to ^{123}I removal were implementations from the research of Sumiya and Sciani (2008), about the irradiation parameters for ^{123}I production.

2.2.5 Target cleaning and standby mode

This step requires a long period of time, because it is necessary that the moisture left in the system, due to the target washing, be removed. For about two minutes a continuous flow of helium gas circulates through the irradiation chamber, whose function is to remove humidity present after the ^{123}I solution transfer. Vacuum pump B2 cleans the irradiation chamber and the pipe through which the water with iodine is removed. Likewise, the vacuum pump B1 cleans the xenon transfer tubing. When the B2 vacuum sensor reaches 5.0×10^{-2} mbar, this part of the system will already be clean. The entire process is complete when the B1 vacuum sensor reaches 1.0×10^{-3} mbar. Since the iodine production is not daily, the system is put into standby mode by filling the irradiation chamber with helium gas up to 2 bar of pressure. This operation has a dual function: to inhibit the entrance of air and humidity in the irradiation chamber, and to verify possible leaks in the target before the next irradiation.

2.3 Validation essays

It was executed five essays to validate the ^{123}I Production System, employing the materials and methods described before. In the first essay, the target was pressurized to 0.2 bar (20 kPa), with enriched ^{124}Xe (Center of Molecular Research, > 99.9 %), and irradiated with 30 MeV protons up to 120 μAh of integrated current (Ion Beam Applications, Cyclone 30). From second to fifth essay, the integrated current was modified to 300 μAh , and the target was pressurized to 0.5, 0.9, 1.0 and 1.1 bar (50, 90, 100 and 110 kPa), keeping other parameters unchanged. During irradiation, several parameters were monitored, as target current, target pressure, water cooling temperature, helium cooling temperature and target temperature. Temperatures were measured using K-type thermocouples and the pressure was monitored by means of strain gage sensor (Jumo, dTRANS p30). In the next day after irradiation, approximately 15 h after EOB, the ^{124}Xe recovery and the ^{123}I removal were executed, and the ^{123}I solution was sent to IPEN Radiopharmacy Center, to verify the activity and the radionuclide purity. Activity measurements were made employing an ionization chamber (CRC-15 Dual PET, Capintec, Inc.), and the radionuclide purity was accomplished with a high purity germanium detector (Mirion Canberra, Extended Range Coaxial Ge Detector-XtRa, GX1518, software Genie 2000, Gamma Analysis S501 and module Basic Spectroscopy S500). The system efficiency was calibrated with a multinuclide reference radioactive source (^{210}Pb , ^{241}Am , ^{133}Ba , ^{134}Cs , ^{137}Cs , ^{22}Na , ^{60}Co , ^{57}Co , ^{109}Cd), from Instituto de Radioproteção e Dosimetria (IRD), mass of 1.039267 g, uncertainty of 0.1 %, on October 1, 2010 (12 h GMT).

2.4 Iodine-123 production

The system was supervised during three years of iodine-123 routine production to verify the reliability and resilience.

3. Results and discussion

In Table 2 are presented the results of five essays. In the three initial lines are the irradiation parameters (target pressure, irradiation time and integrated current), thereafter the results are shown. The higher the target pressure the greater the ^{124}Xe into the target, and therefore, the ^{123}I production yield trends to be higher. The Integrated current determines the quantity of proton beam bombarded the target. The Irradiation time is directly proportional to the Integrated current and inversely proportional to the mean proton beam current. The Activity measured followed the proportion of Target pressure, with Essay 2 as exception. In the gaseous target irradiation, the shape of proton beam may affect the production yield, because a concentrated beam trends to be less effective than a scattered beam, which fulfills the whole target entrance, however, it is not possible to confirm this assertive because was not recorded the proton beam profile. The production activity of ^{123}I reached in the essays is enough to attend the Brazilian demand for this radiopharmaceutical. The Activity 6 hours after EOB is used as standard to calculate the Specific Activity (Yield). The maximum yield was obtained in Essay 5 (2.70 mCi/ μAh), Bechtold et al (1989) obtained 10 mCi/ μAh , with similar parameters (30 MeV protons, 50 μA of current, 6 h after EOB) and target pressure of 14 bar, Tárkányi et al. (1991) cite in high current productions runs at Karlsruhe was obtained a yield ≥ 7.3 mCi/ μAh , and at Eindhoven the high current production yield amounts to 6 mCi/ μAh . The Radionuclide purity presented results greater than 99.9 % in the five essays.

Table 2

Validation essays results from iodine-123 production system, irradiating xenon-124 targets with 30 MeV protons.

	Essay 1	Essay 2	Essay 3	Essay 4	Essay 5
Target pressure (bar)	0.2	0.5	0.9	1.0	1.1
Integrated current (μAh)	120	300	300	300	300
Irradiation time (min)	182	305	339	330	354
Activity measured (mCi)	121.3	386.7	370.0	429.0	441.0
Activity 6h after EOB* (mCi)	223.2	698.1	672.67	761.72	812.3
Specific Activity 6h (mCi/ μAh)	1.86	2.32	2.24	2.54	2.70
Radionuclide purity (%)	>99.9	>99.9	>99.9	>99.9	>99.9

*calculated

The temperatures values of the cooling systems (water and helium) and pressure at the target were recorded and the results are shown in Fig. 8 and 9.

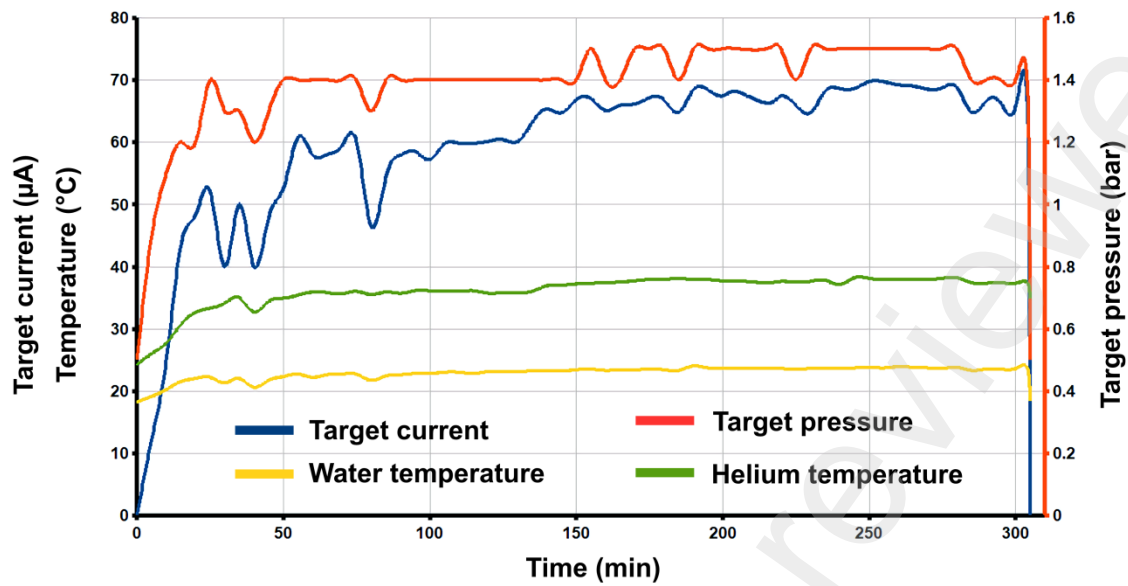


Fig. 8. Monitored parameters, during the irradiation with 30 MeV protons, from a xenon-124 target pressurized to 0.5 bar (Essay 2).

Fig. 8 shows the behavior of monitored parameters during the Essay 2. The target was pressurized to 0.5 bar with xenon-124, and irradiated until 300 μAh of integrated current, with 30 MeV protons. Fig. 8 shows the target pressure follows the behavior of target current, oscillating between 0.5 and 1.5 bar, while target current oscillates between 0 and 70 μA . The helium cooling temperature increases from 24 to 38 $^{\circ}\text{C}$, while water cooling temperature increases from 18 to 24 $^{\circ}\text{C}$ along the irradiation.

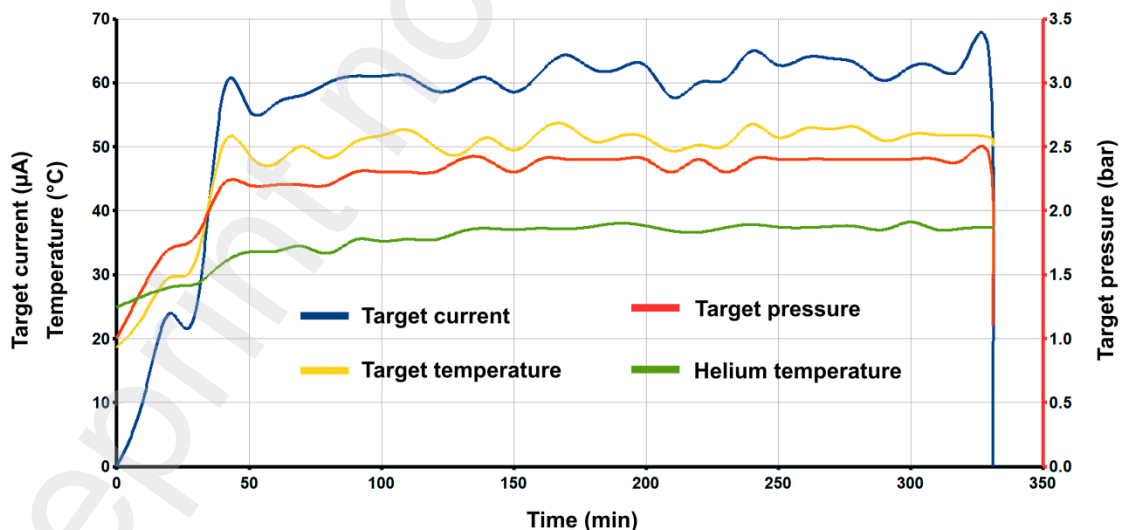


Fig. 9. Monitored parameters, during the irradiation with 30 MeV protons, from a xenon-124 target pressurized to 1.0 bar (Essay 4).

Fig. 9 shows the behavior of monitored parameters during Essay 4. The target was pressurized to 1.0 bar with xenon-124, and irradiated until 300 μAh of integrated current, with 30 MeV protons. As in Fig. 8, target pressure follows the behavior of target current, oscillating between 1.0 and 2.4 bar, while target current oscillates between 0 and 65 μA . The helium cooling temperature increases from 25 to 38 $^{\circ}\text{C}$. While in Fig. 8 the water cooling temperature was measured from water outlet beam dump, in Fig. 9 the target temperature was measured directly from the side of beam dump (Fig. 2), in this way, the target temperature follows the behavior of target current, oscillating between 19 and 54 $^{\circ}\text{C}$.

Three products iodine-123 based are manufactured in IPEN: Sodium iodide I-123 {sodium;iodine-123(1-)}, MIBG I-123 {2-[(3-(^{123}I)iodanylphenyl)methyl]guanidine} and Sodium iodohippurate I-123 {sodium;2-[(2-(^{123}I)iodanylbenzoyl)amino]acetate}. These products are submitted to the following quality control tests before being used in diagnostics or treatments: sterility control, bacterial endotoxin test, pH, radiochemical control and radionuclide purity.

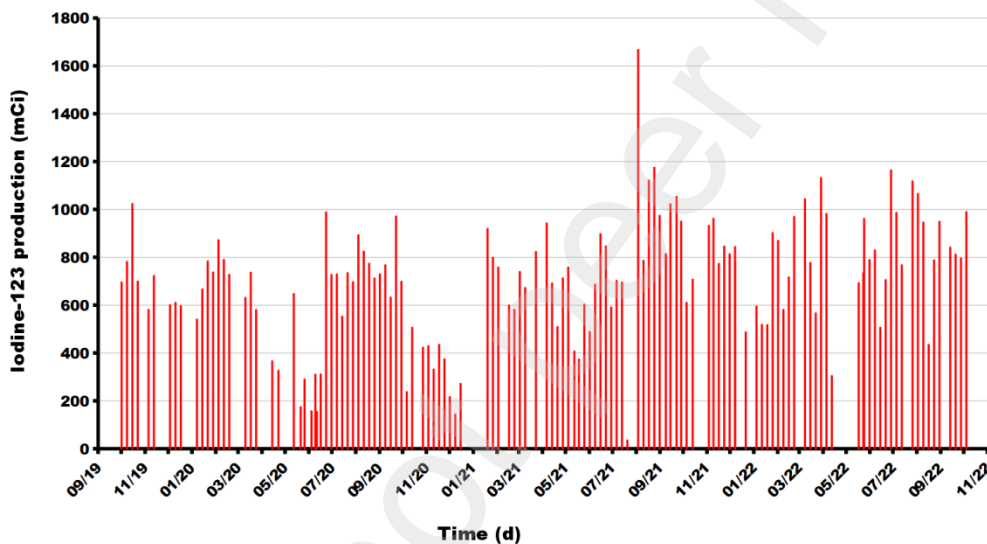


Fig. 10. Iodine-123 production, using the new ^{124}Xe irradiation system, during three years.

Fig. 10 shows the weekly production of iodine-123 along three years to supply the demand of Brazilian market. The greater production was 1667 mCi while the lesser production was 35 mCi, and the average of 703 mCi. The target pressure oscillated between 0.2 and 2.5 bar. The minimum integrated dose was 50 μAh and the maximum integrated dose was 500 μAh . The new xenon-124 irradiation system for iodine-123 production showed along three years reliability and resilience, because this gas irradiation system has to run with beam power parameters sufficient to produce the quantity of radionuclide need, however, always lower the limit which would cause the rupture of molybdenum target window. Furthermore, the xenon-124 recovery system guarantees the economy of a high cost supply, and the automation of systems decreases the radiation dose of employees.

4. Conclusions

It was designed, manufactured, tested and put in routine production a new ^{124}Xe irradiation system for ^{123}I production.

The validation essays of the system presented a maximum production yield (specific activity 6 hour after EOB) of 2.70 mCi/ μ Ah, with 1.1 bar of target pressure and 300 μ Ah of integrated current.

The monitoring of parameters as target pressure, target temperature, helium temperature and water temperature assure reliability to the system, avoiding molybdenum window broken and fail in production.

The system was supervised during three years of iodine-123 production, achieving success in supply Sodium iodide I-123, MIBG I-123 and Sodium iodohippurate I-123.

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