



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

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ABSTRACT

Since 2001, Nuclear and Energy Research Institute IPEN-CNEN has produced weekly ultrapure iodine-123, using a manual irradiation system, fully developed in IPEN. Iodine-123 radiopharmaceuticals have been produced and distributed to hospitals and clinics of nuclear medicine, where several diagnostic imaging procedures for thyroid, brain and cardiovascular functions are performed. Due to the short half-life and emission of low-energy photons, this radioisotope becomes suitable for diagnosis in children. In the present work, 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 is presented. This new system consists of a target, a water and helium cooling system, a cryogenic system, an electric power system, and a control and process monitoring unit, composed of supervisory software, connected to a programmable logic controller via personal computer. In this new concept, there is no need for human intervention during radioisotope production, reducing the possibility of eventual failures or incidents involving radioactive material. By using this new system, a specific yield of 2.70 mCi/ μAh per irradiation was achieved in validation runs, and after three years of routine production of iodine-123, the system showed reliability and resilience.

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 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 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., 1987, 1992; 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 intervention in many phases of the process, increasing the chances of failures and incidents with radioactive material.

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

2. Materials and methods

2.1. System description

The new system design consists of: a target, a closed pressurized

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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 in MS Visual Basic 6® specifically developed for that purpose (Microsoft Corporation, 1998). Fig. 1 shows a block diagram of the developed system.

2.1.1. Target

The new target consists of a frontal collimator, a set for mounting the molybdenum windows, separating the irradiation chamber from the cyclotron beam line, a cone-shaped irradiation chamber with a volume of 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 scheme of the target.

2.1.2. Water cooling system

The water and helium cooling system must dissipate the beam power, which reaches 70 μA of beam current and 30 MeV of beam energy, resulting in 2100 W of maximum beam power. Fig. 3 shows a schematic view of the ^{124}Xe target cooling system. Cooling is independently performed in three parts of the irradiation system: collimator, target body and beam dump. The same system also chills the heat exchanger and helium compressor, of the molybdenum windows cooling system. The target has an independent water purge system, used only for preventive and/or corrective maintenance purposes.

2.1.3. Helium cooling system

Fig. 4 shows a scheme of helium cooling system, employed to chill the target molybdenum windows. Initially, the system is purged with helium gas flow during about 15 s. After purging in this way, the system works in loop. After passing through the molybdenum windows, the helium gas temperature is monitored by a thermocouple installed in the gas outlet pipe.

2.1.4. Cryogenic system

For ^{124}Xe transfers, 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 around each of these

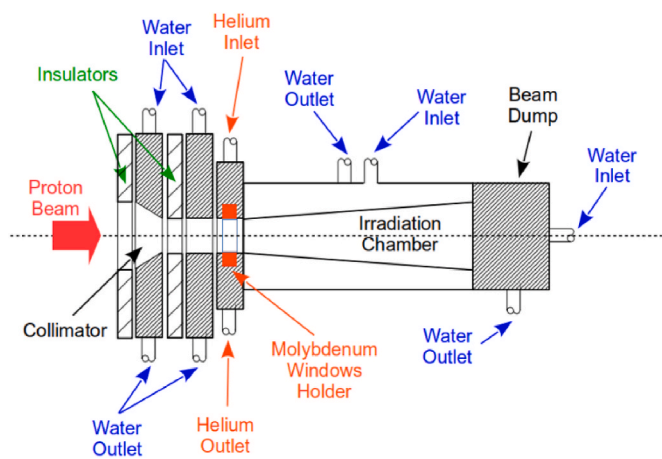


Fig. 2. Scheme of the target for ^{123}I production.

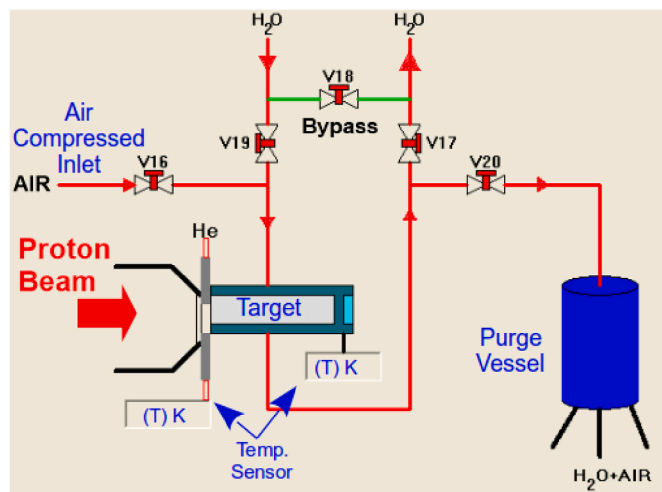


Fig. 3. Water cooling system.

cylinders, there is a set of power resistors in belt-shape, 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 dissolution of ^{123}I , 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 subsequently recovered 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.

2.1.5. Power and Control Cabinet

During xenon-124 irradiation, the radiation levels inside the irradiation room are very high, mainly due to the high energy neutrons emitted during the target bombardment. The maximum radiation levels, close to the wall, outside the irradiation room, reaches $33.4 \mu\text{Sv h}^{-1}$ for gamma radiation and $12.5 \mu\text{Sv h}^{-1}$ for neutron (Silva, 2012) (Fig. 6). Abolaban et al. (2021) measured the maximum dose rate as 2.46 Sv h^{-1} , inside a cyclotron vault (PETtrace 880, General Electric), for gamma and neutron radiation. For this reason, in electrical system design, it is necessary to consider the effects of the radiation, on the electric circuits and their components, since it may cause degradation and irreversible damages, compromising the durability and reliability of the system (Da

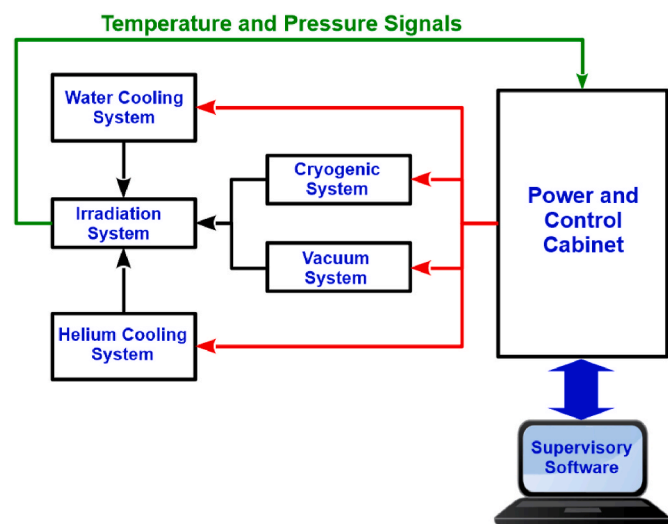


Fig. 1. Block diagram of the irradiation system.

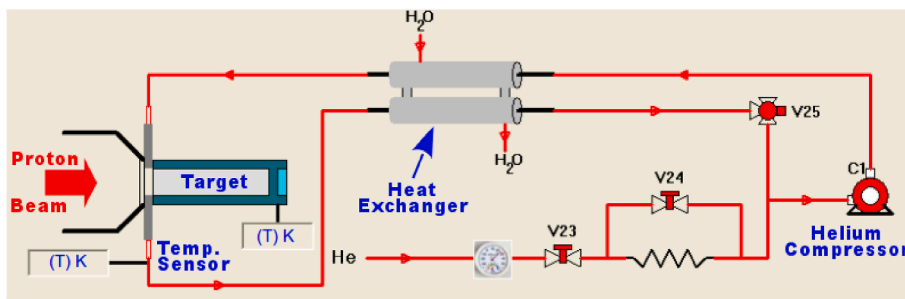


Fig. 4. Helium cooling system.

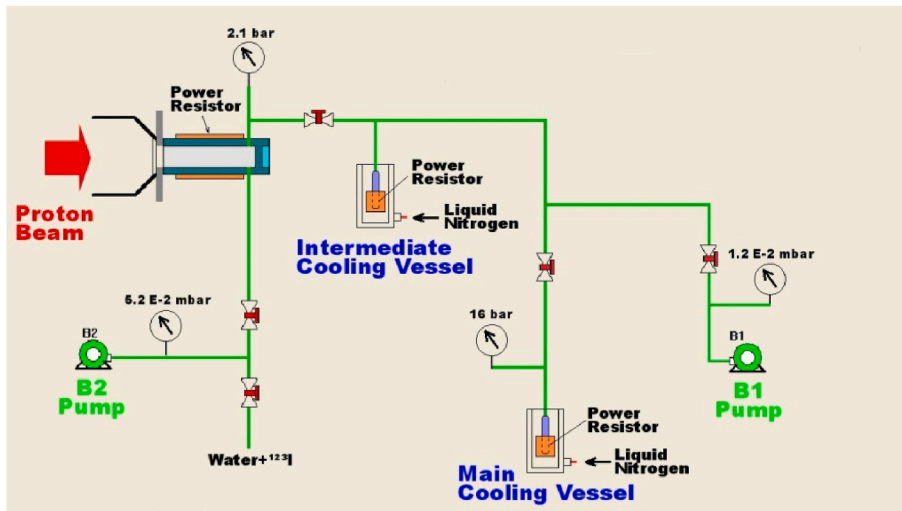


Fig. 5. Cryogenic system.

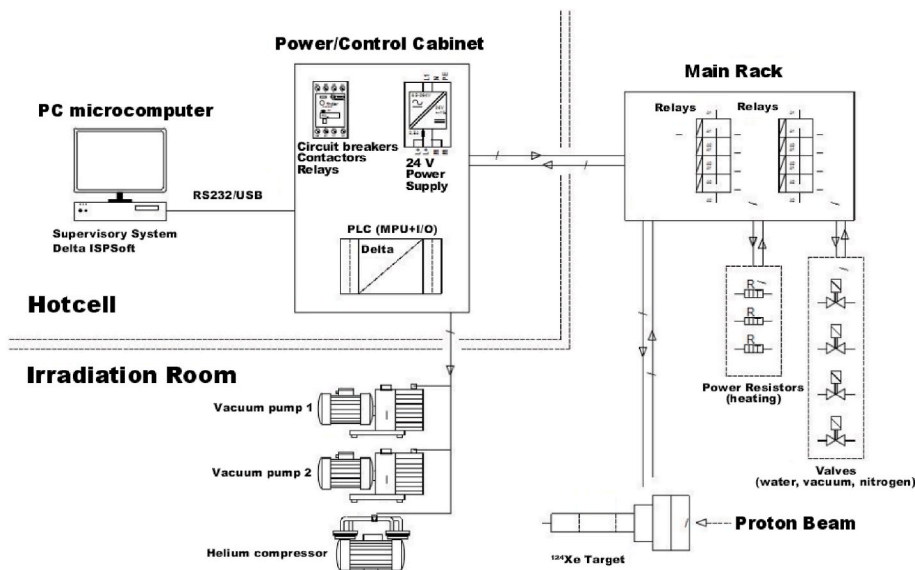


Fig. 6. Power system for ¹²³I production.

Costa, 2014). For this reason, the electrical system (distribution, control and monitoring) was divided or subdivided into units, considering the need of protection of the components, either installing in remote locations or protecting some sensors with shields. Furthermore, when possible, using electromechanical components, thermocouples, etc., which are more resistant to radiation.

The Electrical Power System consists of a Main Rack located at the irradiation room, and a Control Cabinet interconnected to a micro-computer 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. The

vacuum pumps and the helium compressor are also connected to this rack. The Control Cabinet 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. Besides, 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.

2.1.6. Process control software

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

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

2.2. Procedures for ¹²⁴Xe irradiation and ¹²³I production

2.2.1. Target load

When starting the target loading, the water cooling system valves must be opened. The helium cooling system should be purged for approximately 15 s, 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, by turning on the vacuum pumps B1 and B2 (Fig. 7). After 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 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

Table 1

Safe access levels of ¹²⁴Xe irradiation system.

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

intermediate cylinder is started up to 323 K (50 °C), the valve that communicates 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 the irradiation. The Target Control Cabinet sends a signal to the Cyclotron Control Cabinet, communicating that the target is ready to irradiation.

2.2.2. Target irradiation

During ¹²⁴Xe irradiation (¹²⁴Xe (p,2 n)¹²³Cs, Equation (2)), the flow and temperatures of the water and helium cooling systems must be monitored at all time, and 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 of the 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, there is a 2 min wait, 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 h, waiting for the decay chain ¹²³Cs → ¹²³Xe → ¹²³I, as seen in Equations (2) and (3).

2.2.4. ¹²⁴Xe recovery and ¹²³I removal

After the decay time, the ¹²³I remains adhered to the inner walls of the irradiation chamber as powder form, and the ¹²⁴Xe 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 ¹²⁴Xe gas and the

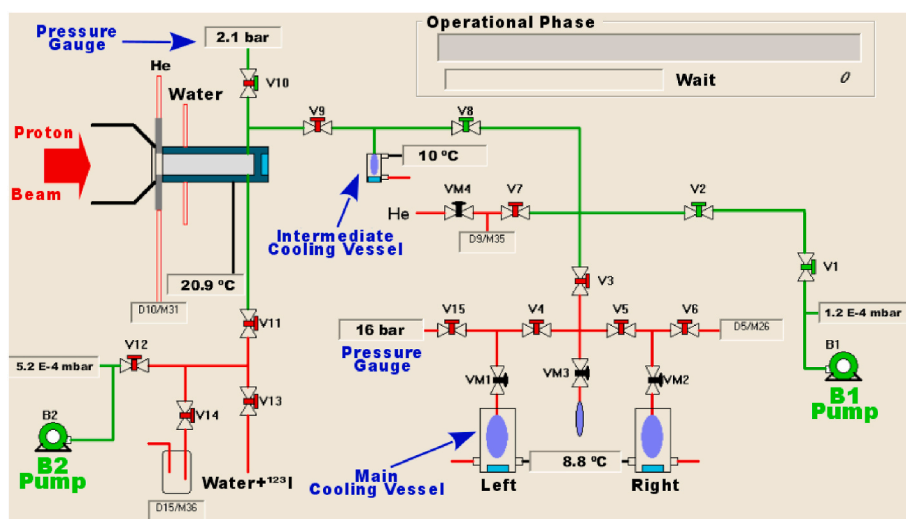


Fig. 7. Supervisory software window used for ¹²⁴Xe transfer and recovery.

^{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 ($-196\text{ }^\circ\text{C}$), 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 the extraction of the ^{123}I , which adheres to the inner walls of the irradiation chamber. The chamber is completely filled with sterile water ($\sim 130\text{ mL}$), heated to 343 K ($70\text{ }^\circ\text{C}$) and held at this temperature for 20 min, this allows the ^{123}I adhering to the walls to be absorbed by the water. After this time, the cooling water system is turned on to cool the chamber and its contents until the temperature reaches 298 K ($25\text{ }^\circ\text{C}$). 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 $70\text{ }^\circ\text{C}$ 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 2 min a continuous flow of helium gas circulates through the irradiation chamber, whose function is to remove the 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 is 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 runs

It was executed five runs to validate the ^{123}I Production System, employing the materials and methods described before. In the first run, 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 run, 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 measured with a high purity germanium detector (Mirion Canberra, Extended Range Coaxial Ge Detector-XtRa, GX1518, software Genie 2000 (Canberra Industries, 2006), 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 runs. 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 Run 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 runs is enough to attend the Brazilian demand for this radiopharmaceutical. The Activity 6 h after EOB is used as standard to calculate the Specific Activity (Yield). The maximum yield was obtained in Run 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 runs.

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

Fig. 8 shows the behavior of monitored parameters during the Run 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 $^\circ\text{C}$ over the irradiation.

Fig. 9 shows the profile of monitored parameters during Run 4. The target was pressurized to 1.0 bar with xenon-124, and irradiated until 300 μAh of integrated current, with 30 MeV protons. Target pressure has the same profile of target current, oscillating between 1.0 and 2.4 bar, while target current oscillates between 0 and 65 μA . The helium cooling temperature increased 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 $^\circ\text{C}$.

Two radiopharmaceuticals based in iodine-123 are manufactured in

Table 2

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

	Run 1	Run 2	Run 3	Run 4	Run 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 ^a (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

^a Calculated.

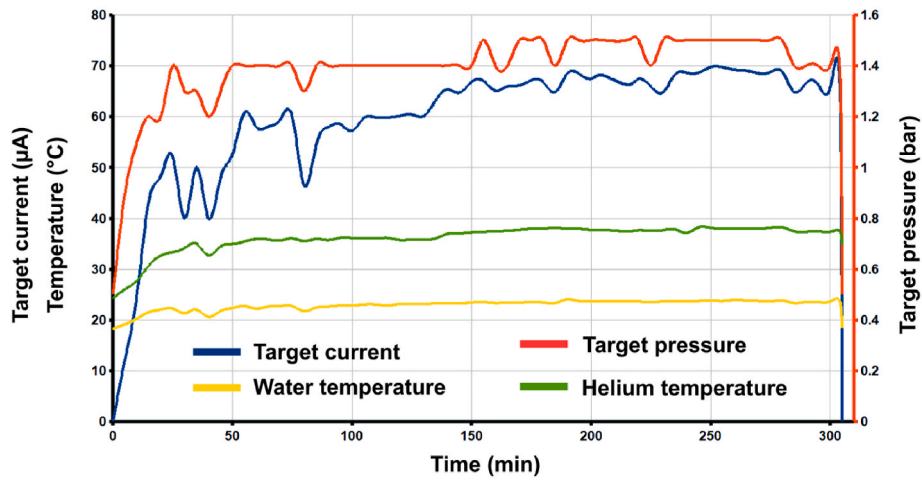


Fig. 8. Monitored parameters, during the irradiation with 30 MeV protons, of a xenon-124 target pressurized to 0.5 bar (Run 2).

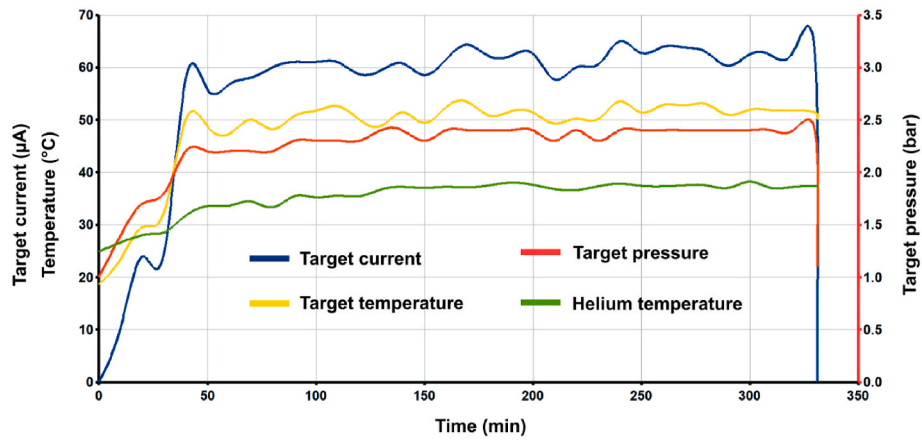


Fig. 9. Monitored parameters, during the irradiation with 30 MeV protons, of a xenon-124 target pressurized to 1.0 bar (Run 4).

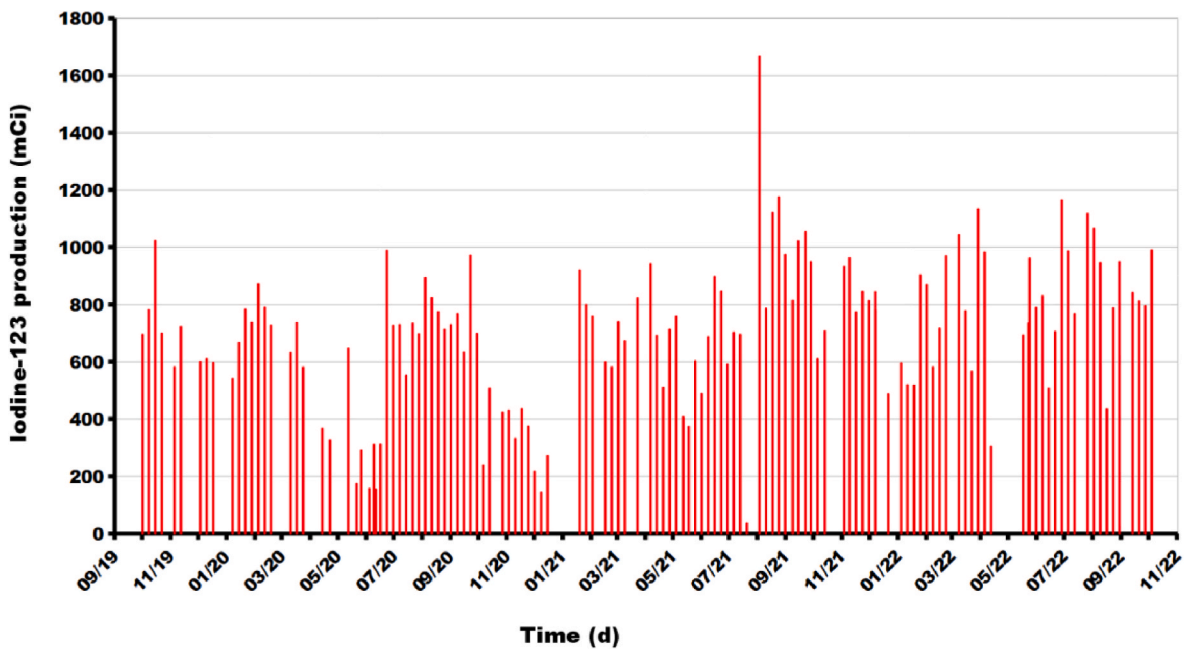


Fig. 10. Iodine-123 activities produced during three years, using the new ^{124}Xe irradiation system.

IPEN: Sodium iodide I-123 in oral form {sodium; iodine-123 (1-)}, and MIBG I-123 {2-[(3-(¹²³I)iodanylphenyl)methyl]guanidine}. These products are evaluated by quality control tests before releasing to Nuclear Medicine clinics and hospitals to be used as diagnostics agent: pH, radiochemical purity identity, radionuclide purity, sterility test, and bacterial endotoxin test for the injectable form.

Fig. 10 shows the iodine-123 activities weekly produced to supply the demand of Brazilian radiopharmaceutical market of this radionuclide over three years. The highest activity was 1667 mCi (61.679 GBq) while the lowest production was 35 mCi (1.295 GBq), and the average was 703 mCi (26.011 GBq). The target pressure oscillated between 0.2 and 2.5 bar. The minimum integrated dose was 50 μ Ah and the maximum integrated dose was 500 μ Ah. This gas irradiation system has to run with beam power parameters sufficient to produce the require activity of radionuclide up to the limit, which would not cause the rupture of molybdenum target window. The new xenon-124 irradiation system for iodine-123 production showed reliability and resilience over three years. Furthermore, the xenon-124 gas recovery system save money of a high cost supply, and the automation of the systems decreases the radiation dose of employees.

4. Conclusions

A new ¹²⁴Xe irradiation system was designed, manufactured, evaluated and used in routine for ¹²³I production.

The validation runs of the system presented a maximum production yield (specific activity 6 h 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 ¹²³I production.

The system proposed was supervised during three years successfully, supplying iodine-123 for Sodium iodide I-123 and MIBG I-123 radiopharmaceutical productions.

CRedit authorship contribution statement

Oswaldo L. da Costa: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Conceptualization. **Henrique Barcellos:** Methodology, Investigation, Conceptualization, Resources, Writing – original draft, Writing – review & editing. **Hylton Matsuda:** Conceptualization, Investigation, Methodology, Resources. **Luiz C. do A. Sumiya:** Conceptualization, Investigation, Methodology, Resources. **Fernando de C. Junqueira:** Visualization, Methodology. **Margareth M. N. Matsuda:** Visualization, Methodology, Data curation. **André L. Lapolli:** Writing – original draft, Software, Resources, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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