HIGH-TEMPERATURE AND MASS-SEPARATOR METHODS FOR SELECTIVE PRODUCTION OF MEDICAL RADIONUCLIDES AT PROTON AND NEUTRON BEAMS

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1. Introduction

Special pharmaceuticals, prepared on the basis of radionuclides, are very efficient tools for diagnostic and therapy of many kinds of different diseases. Presently, reactors on thermal neutrons and high current cyclotrons are utilized to this end. Regardless of the production method, the desired radionuclides should be separated from the irradiated target material and other undesired radionuclides. Generally, the so called “wet” radiochemical methods are used for extraction and purification of targeted medical radionuclides. However, these methods are accompanied by a large amount of liquid radioactive waste. Nevertheless, the problem of the isotope purification was successfully solved more than sixty years ago by building of special installations for nuclear physics studies – isotope separator on-line (ISOL) facilities working at beams of different projectile particles.

2. Mass-separator method

Shortly, the mass-separator method may be described as follows. At an ISOL installation, radioactive atoms are produced in an irradiated mass-separator target kept at a high temperature in a high vacuum. Then the atoms diffuse out of the target material and effuse as neutral atoms from the target container into the cavity of an ion source, where they are ionized. Finally, they form radioactive ion beams [1] after passing through a system of electrostatic lenses and a magnet analyser.

This method is usually applied for short-lived isotope production in nuclear physics experiments for study of exotic nuclei. The mass-separator method gives the possibility to produce very pure beams of radioisotopes. Another advantage of the mass-separator method is that several radioisotopes separated according to their mass numbers can be obtained and investigated simultaneously.

The mass separator can be applied for production of radionuclides in various modes:

- On-line mode (radionuclides are accumulated in the process of the target irradiation);
- Semi on-line mode (radionuclides are accumulated after the switching off the irradiating beam);
- Off-line mode (the target is irradiated separately and after that it is installed at the mass-separator).

In any case, certain requirements on the target material should be fulfilled. It should be a high-temperature resistant (to avoid destruction at a temperature of the targeted radionuclide evaporation) and should have a low vapor pressure ($< 10^{-4}$ mbar) at the working temperature to ensure a proper work of a high voltage system of the mass-separator. Provided these requirements are fulfilled, long-term operation of the mass-separator can be ensured with the efficiency of some radionuclide production up to 80%.

First experiments on the production of mass-separated medical radioisotopes were successfully carried out at the on-line mass-separator facility ISOLDE at CERN [2, 3]. These experiments have shown very promising prospects of the method, provided that it would be possible to increase significantly the activities of the obtained radionuclide samples. This can be achieved by using high current cyclotrons or high neutron-flux reactors.

3. High-temperature method of separation of the target material and the produced radionuclide

In case of non-compliance the above mentioned conditions for collection of long-lived radioisotopes with the half-lives of several tens of hours or more, a method of thermal preseparation in vacuum of the target material and the selected radionuclides was proposed [4].

For this purpose, the difference in volatility of atoms of the desired radionuclide, the target material, and other produced radionuclides at a certain target temperature was used. In other words, the separation can be done if the target material and the atoms of targeted radionuclides have a considerable difference in the saturated vapour pressure in vacuum at a certain temperature. In general, this difference correlates with

the difference in enthalpy of adsorption on the surface of refractory metals from which the target containers are usually manufactured [5].

If the target material is much more volatile (has much higher vapour pressure) than the resulting radionuclide, it can be easily evaporated at a certain temperature from the target container into some cold ballast volume without loss of the resulting radionuclide. As it was demonstrated in our previous work, the radionuclide ^{82}Sr used for positron emission tomography (PET) diagnostics can be isolated from the binary compound of the RbCl target material with the efficiency better than 99% by heating it in a high vacuum for one hour [4, 6]. It was also shown that this principle works for separation of ^{82}Sr from metallic rubidium and a therapeutic radionuclide ^{67}Cu from a target made of metallic zinc [7].

These results show that the effect of thermal separation is universal regardless of whether the target substance is a molecular compound or it is in the natural metallic state. It is very important that the carrier-free radionuclide samples prepared by this method can be further utilized for isotopic separation using a mass-separator. This is necessary, when other radioisotopes of the selected element are present in the resulting sample.

Our previous work is related in general to the development of a thermal method for the separation of radionuclides obtained by irradiation of a target by protons of different energy [1, 4, 7, 8]. The main objective of the present work is to test experimentally whether this method could also be used to isolate the radionuclides produced in reactions with neutrons. For this purpose, ^{177}Lu which is the most promising radionuclide for the treatment of prostate tumors and ^{99m}Tc, widely used for diagnostics, were selected. In the experiments, a metallic ytterbium target was used in order to obtain ^{177}Lu. For ^{99m}Tc production, the molybdenum oxide MoO_3 target was used.

4. Radioisotope complex ISOTOPE project

A detailed description of the ISOTOPE project which is constructed at the beam of high current cyclotron C-80 [9] can be found in Ref. [10]. Below its main features are presented.

The cyclotron C-80 with the proton beam energy 40–80 MeV and the intensity of 100 μA is designed to produce a wide spectrum of medical radionuclides for diagnostics and therapy. The use of three target stations will allow one to investigate and introduce different new methods of radionuclide production. They are the high-temperature separation method [1] and the mass-separator method, in which a specially constructed target is used [4]. A mass-separator with its target station will allow one for the production of isotopically separated medical radionuclides of a high purity, which will be implanted into corresponding collectors from which they can be easily extracted. Radionuclides which are planned for production at ISOTOPE are listed in Table 1. Additionally new methods are being developed for the following radionuclide production: ^{64}Cu, ^{67}Cu, ^{149}Tb, ^{177}Lu, ^{188}Re, ^{212}Pb, ^{212}Bi.

Table 1

Radionuclides planned for production at ISOTOPE

Radionuclide	Decay half-life, $T_{1/2}$
^{68}Ge	270.8 d
^{82}Sr*	25.55 d
^{99}Tc	6 h
^{111}In*	2.8 d
^{123}I*	13.27 h
^{124}I*	4.17 d
^{223}Ra*	11.4 d
^{224}Ra*	3.66 d
^{225}Ac*	10 d

* Radioisotopes, which can be produced by means of a mass-separator.

5. High-temperature separation of lutetium radionuclides from an ytterbium target irradiated by protons and neutrons

^{177}Lu is considered to be a very efficient radionuclide for the prostate cancer therapy [11]. It can be produced by thermal neutrons in the ^{176}Yb(n, γ)^{177}Yb → ^{177}Lu reaction. Usually, to extract ^{177}Lu from an irradiated ytterbium target, a complex radiochemical procedure, called "wet radiochemistry" is used. According to Ref. [5], ytterbium and lutetium are elements with very different enthalpy of adsorption on refractory metal surfaces – ~ 3.6 and ~ 6.6 eV, respectively. As is pointed out above, enthalpies of adsorption in general are in good correlation with the boiling points of the corresponding elements. In particular, this is confirmed for the couple ytterbium–lutetium with their boiling points of 1 194 and 3 393°C, respectively.

The first tests of a high-temperature method for separation of $^{171, 172}$Lu from an ytterbium metal target were described in Ref. [12]. In that work, an ytterbium metal target was irradiated by a proton beam of the PNPI synchrocyclotron SC-1000 with a proton energy of 100 MeV. Such a beam was achieved by using a calibrated copper degrader [13] with remote change of its thickness.

For the neutron irradiation experiment for ^{177}Lu production, a neutron lead converter was used. The ytterbium target material was placed in a water tank, staying close to the neutron converter. The water tank with a metal ytterbium target is shown in Fig. 1. The target mass of metallic ytterbium for the experiment with neutron irradiation was about 100 mg. After three days of radiation cooling, the target was placed into a quartz vessel, which was inserted into a tungsten oven, heated by resistant heating at the vacuum test bench. The target material processing procedure was completely identical to that described in Ref. [12].

Fig. 1. The water tank used for slowing down of scattered neutrons. A metal ytterbium target is placed in a cylindrical channel inside the tank

During all the time of the target heating, the evaporated target material (metallic ytterbium) was collected in a special cooled volume. In the process of the target material evaporation, the oven temperature was kept in the interval of 800–900°C for the period of one hour in a high vacuum about 10^{-5} mbar.

In Figure 2*a*, the spectra with γ-lines of proton-irradiated ytterbium before (*black points*) and after (*red points*) the target heating in the quartz vessel are shown. The γ-line with the energy of 396 keV follows the ^{175}Yb ($T_{1/2}$ = 4.2 d) β$^-$-decay. This line was used for calculation of the target material evaporation efficiency x, which can be expressed by the formula

$$x = (S_1^{\mathrm{Yb}} - S_2^{\mathrm{Yb}})/S_1^{\mathrm{Yb}}, \quad (1)$$

where S_1^{Yb} – the γ-line intensity of ^{175}Yb before the irradiated sample heating; S_2^{Yb} – the intensity of the same γ-line after the sample heating.

The γ-line with the energy of 740 keV belongs to the ^{171}Lu ($T_{1/2}$ = 8.24 d) β^+-decay. A comparison of its intensity before and after heating shows what part of lutetium atoms remains in the vessel after heating. One can calculate the efficiency of lutetium isotope production ε using the following expression:

$$\varepsilon = S_2^{\mathrm{Lu}}/S_1^{\mathrm{Lu}},$$

where S_1^{Lu} – the γ-line intensity of ^{171}Yb before the irradiated sample heating; S_2^{Lu} – the intensity of the same γ-line after the sample heating.

In Figure 2*b*, the spectra with γ-lines of neutron irradiated ytterbium before (*black points*) and after (*red points*) target heating in a quartz vessel are shown. The γ-lines with the energies of 177 and 198 keV follow the ^{169}Yb ($T_{1/2}$ = 32 d) β^+-decay. These lines were used for monitoring of the target material evaporation. The γ-line with the energy of 208 keV belongs to the ^{177}Lu ($T_{1/2}$ = 6.73 d) β^--decay and shows what part of lutetium atoms remains in the vessel after heating.

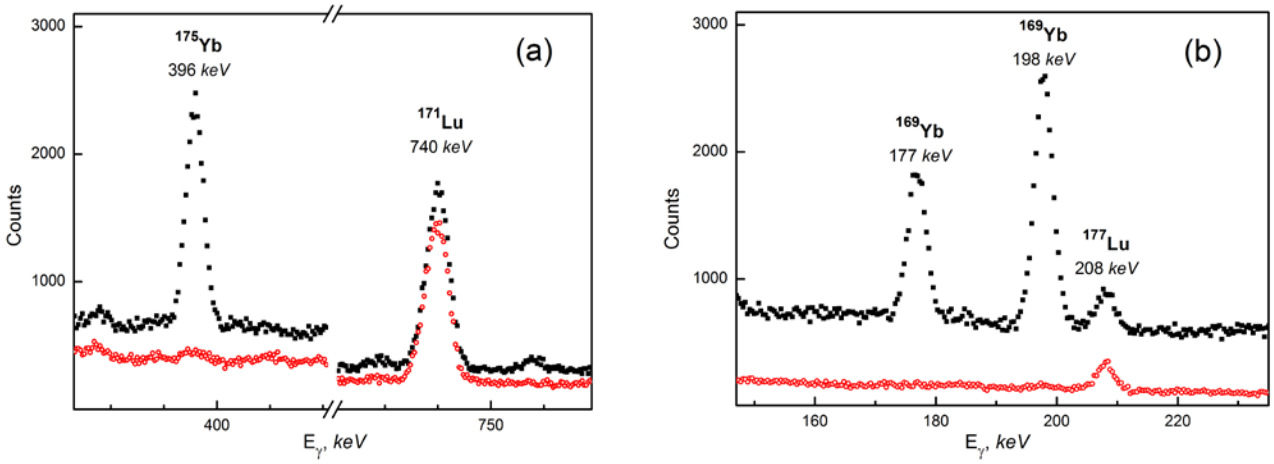

Fig. 2. Gamma spectra of the ytterbium target before (*black squares*) and after (*red open circles*) heating of the sample irradiated: *a* – by protons; *b* – by neutrons

The γ-lines intensities of the ytterbium and lutetium isotopes mentioned above are shown in Table 2. A comparison of the results of two experiments presented in Fig. 2 and Table 2 demonstrates that the method of thermal separation of lutetium isotopes does not depend on whether the required radionuclide are produced in the target material by protons or by neutrons.

Table 2

Gamma-lines intensities of the ytterbium and lutetium isotopes

Irradiation method	Protons (100 MeV)		Thermal neutrons	
Radionuclide	^{175}Yb	^{171}Lu	^{169}Yb	^{177}Lu
E_γ, keV	396	740	198	208
S_γ before heating	19 500	20 500	20 000	2 680
S_γ after heating*	870	19 940	300	2 060

* Corrections for S_γ after heating were introduced in accordance with decay half-lives.

The evaporation efficiency *x* for the Yb target material irradiated by protons and the production efficiency ε were determined as 0.96(1) and 0.97(2), respectively. For identical Yb target material irradiated by thermal neutrons these values were 0.99(1) and 0.77(7).

Despite the pronounced effect of efficient separation of lutetium isotopes produced by protons or neutrons from the metallic ytterbium target and relatively small statistical errors, the difference between the values of the production efficiency for different projectiles (protons or neutrons) is about 20%. This

discrepancy can be explained by a possible systematic error resulting from not precisely controlled procedure of the temperature rise while reaching the optimal temperature of the target material evaporation. In that case, if the temperature increases too rapidly, the desired radionuclides can be entrained by the flow of atoms of the target substance.

6. High-temperature separation of ^{99m}Tc from a molybdenum trioxide ^{99}Mo / ^{99m}Tc target irradiated by protons and neutrons

The ^{99}Mo / ^{99m}Tc radionuclide generator is the most widely used in diagnostic medicine. In the diagnostic procedures ^{99m}Tc ($T_{1/2}$ = 6.01 h) is used. It is extracted from the generator containing the parent isotope ^{99}Mo ($T_{1/2}$ = 2.75 d). The most common method for obtaining ^{99}Mo is the fission reaction of highly enriched ^{235}U with thermal neutrons. An alternative way is the method based on the application of a proton cyclotron. The mass of the target material MoO_3 for experiments with proton and neutron irradiation was about 200 mg. The molybdenum trioxide was irradiated by a proton beam of the PNPI synchrocyclotron SC-1000 with a proton energy of 100 MeV.

For the neutron irradiation of the molybdenum trioxide, a neutron lead converter was used. Similar to the experiment with Yb/Lu, the target material was placed into a water tank, staying close to the neutron converter (see Fig. 1). In each experiment, the irradiation time was about 24 h. The majority of isotopes produced by protons in a MoO_3 target have a fairly short life-time. Therefore, the cooling time of the irradiated target was only three hours. After that it was placed into a quartz vessel, which was inserted into a tungsten oven heated by resistant heating at the vacuum test bench. During all the time of the target heating, the evaporated target material MoO_3 was collected in a special cooled volume. During the target material evaporation, the oven temperature was kept in the interval of 600–800°C for the period of one hour in a high vacuum about 10^{-5} mbar.

The time interval between measurements of the spectra before and after target material heating was two hours. Corrections for isotope decay half-life were introduced when comparing the γ-lines intensities. In Figure 3*a*, the γ spectra of the proton irradiated molybdenum trioxide target before (*black points*) and after (*red points*) target heating in the quartz vessel are shown.

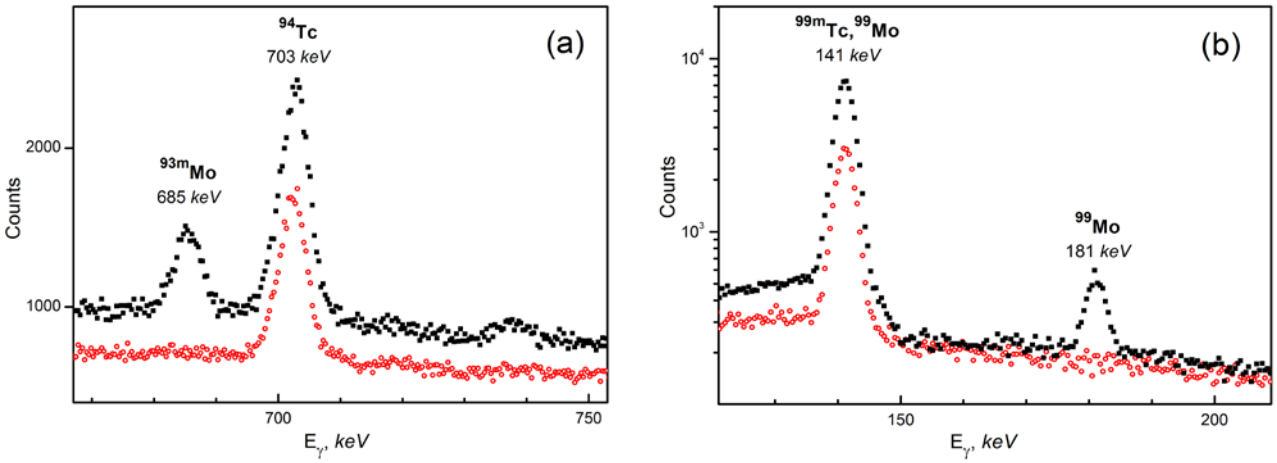

Fig. 3. Gamma spectra of the molybdenum trioxide target before (*black squares*) and after (*red open circles*) heating of the sample irradiated: *a* – by protons; *b* – by neutrons

In Figure 3*a*, the γ-line with the energy of 685 keV follows the ^{93m}Mo ($T_{1/2}$ = 6.85 h) β^--decay. This line was used for monitoring the target material evaporation. The part of the evaporated MoO_3 target material was calculated by the following formula:

$$x = (S_1^{\mathrm{Mo}} - S_2^{\mathrm{Mo}})/S_1^{\mathrm{Mo}}, \tag{3}$$

where S_1^{Mo} – the γ-line intensity of ^{93m}Mo before the target material heating; S_2^{Mo} – the intensity of the same γ-line after the sample heating.

The γ-line with the energy of 703 keV belongs to the ^{94}Tc ($T_{1/2}$ = 4.88 h) β^--decay, and a comparison of its intensity before and after heating shows what part of technetium atoms remains in the vessel after heating. One can calculate the efficiency of technetium isotope production using the following expression:

$$\varepsilon = S_2^{\mathrm{Tc}}/S_1^{\mathrm{Tc}},$$

where S_1^{Tc} – the γ-line intensity of ^{94}Tc before the target material heating; S_2^{Tc} – the intensity of the same γ-line after the sample heating.

In Figure 3*b*, the spectra of neutron irradiated molybdenum oxide before (*black points*) and after (*red points*) target heating are shown. The γ-line with the energy of 181 keV follows the ^{99}Mo ($T_{1/2}$ = 2.75 d) β^--decay. This line was used for monitoring the target material evaporation. The γ-line with the energy of 141 keV belongs to the ^{99m}Tc ($T_{1/2}$ = 6.01 h) isomeric transition and shows what part of technetium atoms remains in the vessel after heating. The γ-lines intensities of the molybdenum and technetium isotopes mentioned above are presented in Table 3. A comparison of the results of two experiments presented in Fig. 3 and Table 3 demonstrates that the method of thermal separation of technetium isotopes does not depend on whether the required radionuclide are produced in the target material by protons or by neutrons.

Table 3

Gamma-lines intensities of the molybdenum and technetium isotopes

Irradiation method	Protons (100 MeV)		Thermal neutrons	
Radionuclide	^{93m}Mo	^{94}Tc	^{99}Mo	^{99m}Tc
E_γ, keV	685	703	181	141
S_γ before heating	7 450	24 600	2 800	64 300
S_γ after heating*	0	22 500	0	35 800

* Corrections for S_γ after heating were introduced in accordance with decay half-lives.

The evaporation efficiency *x* for the MoO_3 target irradiated by protons and the production efficiency ε were determined as 0.96(3) and 0.92(3), respectively. For the identical MoO_3 target material irradiated by thermal neutrons these values were 0.99(3) and 0.56(1).

Apparently, the difference between the production efficiency values for different projectiles (protons or neutrons) can be ascribed as in the case of Lu to the not precisely controlled procedure of temperature rise while reaching the optimal temperature of the target material evaporation. Another possibility of uncontrolled escape of technetium during the thermal injection from MoO_3 target is discussed in the next section.

7. Discussion

The goal of this work was to check the applicability of the method of thermal separation in vacuum of the desired isotopes from targets irradiated not only by protons but also by neutrons. For this purpose, the target materials were selected that ensure the production of radionuclides of lutetium and technetium both with proton and neutron beams. They were: metallic ytterbium for lutetium production and a binary molecular compound molybdenum oxide MoO_3 for technetium production.

It is natural to assume that in the case of a metal target the process of separation of the target substance and the produced radionuclides should not depend on how radionuclides are produced – using protons or neutrons, since both the target substance and the produced radionuclides are in the form of atoms. Therefore, it should be expected that at a significantly higher degree of volatility of the atoms of the target substance (ytterbium) with respect to the atoms of the generated lutetium (boiling points, respectively, 1 194°C and 3 393°C) a possibility arises to evaporate selectively the atoms of the target substance, while keeping the atoms of lutetium in the heated capsule. As it can be seen in Figures 2*a* and 2*b*, the thermal separation process is quite efficient, regardless of the method of obtaining lutetium from a metal ytterbium target.

A similar process occurs when a molecular compound is used as a target substance in the case of irradiation by protons. In this case, the molecular bonds are destroyed due to the bombardment of the target by protons with the energy of several tens of MeV and the produced nuclides are presented in the target as atoms rather than retain their molecular form. Therefore, the process of separation of the target substance (in this case MoO_3 with the boiling point 1 255°C) and the produced radionuclide technetium (with the boiling point 4 265°C) will proceed as efficiently, as in the case of the above-discussed lutetium.

A somewhat different situation may arise when a molecular compound is irradiated by neutrons. In this case, the destruction of the molecular bonds may not occur, as the recoil energies are commensurate with the binding energy of the molecule. This can lead to the formation of a new molecular compound, containing the produced radionuclide, with a high volatility, which will not allow the thermal separation of the target substance and the desired radionuclide. In the case of the target substance MoO_3, such a compound may be TcO_2, which has the boiling point about 1 100°C. Therefore, for each target substance in the form of a molecular compound (oxide, chloride, fluoride) preliminary experiments should be carried out to study the efficiency of production of the target material and the desired radionuclide, if they are produced by neutrons.

8. Conclusion

The present work shows that the method of thermal separation in vacuum can be used to isolate the produced radionuclides from the target substances irradiated not only with proton but also with neutron beams. The value of the efficiency of extraction of ^{177}Lu from the target of metallic ytterbium irradiated with neutrons is 77% with the efficiency of evaporation of the target substance being close to 100%. This value is somewhat different from the value of the efficiency of ^{171}Lu extraction, obtained by its isolation from exactly the same target material irradiated by a proton beam. The reason for this can be insufficiently precisely controlled rate in the process of reaching the operating temperature of evaporation of the target substance.

The value obtained for the production efficiency of ^{99m}Tc from the MoO_3 target material irradiated with neutrons is about 56%. This value differs significantly from the value of the production efficiency ε = 92% of ^{94}Tc from the same target material irradiated by protons.

Another possible reason for this discrepancy, beside the mentioned above for the lutetium case, is the formation of the molecular compound TcO_2, which has a boiling point of about 1 100°C very close to that of the target material. In this case, some of technetium atoms included in the formed TcO_2 molecules will evaporate at the same rate as the molecules of the target substance. But it should be pointed out here that at this stage of the research this assumption requires additional experimental verification.

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