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DEVELOPMENT OF HIGH TEMPERATURE AND MASS-SEPARATION METHODS FOR SELECTIVE PRODUCTION OF MEDICAL RADIONUCLIDES

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Abstract. *At the National Research Center Kurchatov Institute – Petersburg Nuclear Physics Institute (Gatchina, Russia) a cyclotron C-80 designed to produce protons with the energy of 40–80 MeV and beam intensity of 100 μA (first stage) has been launched. One of the beams of the cyclotron will be used for the treatment of malignant eye tumors. At the same time the main goal of C-80 is the production of a wide range of medical radionuclides for diagnostics and therapy. For this purpose, the construction of the RIC-80 (Radioactive Isotopes on the C-80 cyclotron) complex intended to function on the C-80 beam has been planned. A brief description of the RIC-80 complex is given, and the results of the use of new methods and studies of target devices for the production of radionuclide generator ^{212}Pb/^{212}Bi and ^{223}Ra, ^{224}Ra, ^{225}Ac radioisotopes that undergo alpha-decay are discussed. The suggestions of the mass-separator use in the on-line and semi on-line mode to obtain high isotopic purity radionuclides, which is especially important for medical applications, are discussed. The results of a new high-temperature method use of lutetium radionuclide separation from the ytterbium target material in a high vacuum are presented.*

Keywords: *Radionuclides for medical applications, mass-separator, alpha-decay, high temperature method*

1. INTRODUCTION

The use of radionuclides decaying with the emission of different types of particles and gamma rays of different energies is a very effective tool for diagnostics and therapy of many kinds of malignant tumors and other diseases at an early stage of their appearance. Nowadays, high current cyclotrons are widely used for the production of radionuclides for medicine. One of the important characteristics of cyclotron produced radionuclides is the emission of positrons that allows using them for the PET (Positron Emission Tomography) diagnostics. At NRCKI-PNPI (National Research Center "Kurchatov Institute" – Petersburg Nuclear Physics Institute), a high current cyclotron C-80 has been started [1]. The planned beam parameters are: the proton energy up to 80 MeV and the beam intensity up to 100 μA (the first stage). The radioisotope complex RIC-80 (Radioactive Isotopes at cyclotron C-80) [2], which is planned to be constructed at the beam of C-80, will allow producing practically all radionuclides obtained for medicine with accelerators. An important feature of the RIC-80 facility is the installation of an on-line mass-separator connected to one of the target stations. One of the goals of RIC-80 is the production of alpha-particle emitters ^{223,224}Ra and ^{225}Ac. For the purpose of a high purity ^{223,224}Ra, ^{225}Ac obtaining the electromagnetic mass-separator will be utilized as well. The results of target and ion source tests for the production of radioisotopes ^{223,224}Ra and ^{225}Ac by different methods, including the one with the mass-separator use, have been described.

2. THE RIC-80 PROJECT SHORT DESCRIPTION

The detailed project description can be found in [2, 3]. The proton beam energy of C-80 can be varied in the interval of 40-80 MeV. At the first stage, the proton beam intensity of 100 μA is planned with the possibility to increase it up to 200 μA. The target stations will be constructed for the purpose of investigating and introducing new, different methods of radionuclide production. One of them is a high-temperature separation method of the target substance and the produced radionuclide [4]. The second one is the mass-separator method, in which a target constructed in a special way is utilized [5]. The mass-separator with its target station will allow for the production of isotopic separated medical radionuclides of a high purity, which will be implanted into the corresponding collectors where they can be easily extracted from. Radionuclides, planned for production at RIC-80 are presented in Table 1. Radioisotopes designated by the asterisks can be produced by means of the mass-separator.

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3. On-line or semi on-line mass-separator method implementation

The ISOL facility (Isotope Separator On-Line) use for the production of radioactive isotopes is the most efficient method for studies of the fundamental properties of the nuclei. Making use of beams of different bombarding particles – protons, neutrons, and heavy ions, the ISOL installations at present provide the production of considerably more than 2000 mass-separated isotopes of almost all elements of the periodic system. The on-line mass-separator facilities like ISOLDE (CERN, Switzerland) [6], ISAC (Isotope Separation and ACceleration, TRIUMF, Canada) [7], IRIS (Investigations of Radioactive Isotopes on Synchrocyclotron, PNPI, Gatchina) [8] and many others enabled the production of radioactive isotopes with half-lives from several milliseconds to several thousand years which are used for studying in nuclear physics, solid-state physics, and for some medical physics experiments.

Table 1. Radionuclides are planned for production at RIC-80. Asterisks radioisotopes designated, which can be produced by means of the mass-separator

Radionuclide	$T_{1/2}$ (half-life)
Cu-64	12.7 h
Cu-67	61.9 h
Ge-68	270.8 d
Sr-82*	25.55 d
Tc-99	6 h
In-111*	2.8 d
I-123*	13.27 h
I-124*	4.17 d
Ra-223*	11.4 d
Ra-224*	3.66 d
Ac-225*	10 d

The first experiments on receiving mass-separated medical radionuclides for tests on animals [9, 10] were made at the ISOLDE installation which is used in general for nuclear physics research. One of the general parts of any ISOL facility is its target-ion source unit which defines the set of produced radionuclides and the facility efficiency. The target-ion source unit of the mass-separator has to meet the following general conditions:

- A high value of production cross-section of the targeted radionuclide in the reaction of bombarding particle with used target material;
- A fast enough release (release time should be shorter than the half-life of the targeted radionuclide) of the produced radioisotope by the diffusion-effusion process from the target-ion source unit;
- The target material should have a very low pressure of saturated vapor at a high temperature when the release of produced radionuclides occurs. For normal conditions of a mass-separator function the vapor pressure of the target material should be lower than 10^{-3} mbar;
- A high value (several tens of percent) of the ionization efficiency of the ion source used, which allows providing the activity of the targeted separated radionuclide comparable with the one obtained by the ordinary methods.

If the target device fulfills the above-stated requirements, it can be used directly on the mass-separator in on-line (the beam is switched on) or off-line (after the beam is switched off) regime for the production of mass-separated medical radionuclides of high purity. Alpha-decaying radionuclides used for therapy: ^{223}Ra (T1/2=11.4 days), ^{224}Ra (T1/2=3.66 days), and ^{225}Ac (T1/2=10.0 days), can be produced by proton irradiation of uranium or thorium targets. A high-temperature method of extraction of ^{223,224}Ra produced by protons in ^{238}UC was described in detail in [11]. In our experiments, we used the UC target (uranium-238 mono carbide of a high density [8, 11]) for production and a high-temperature extraction of radium isotopes. It was demonstrated that investigated target materials can be used as well for the mass-separator target construction of the mass-separator station for production at RIC-80 radioisotope medical beams of very high purity. The uranium carbide target of a high density was also tested in experiments for the production of mass-separated ^{223,224}Ra and ^{225}Ac. A detailed description of the experiments is given in [12]. The radionuclides were produced at the ISOL facility IRIS (Investigation of Radioactive Isotopes at Synchrocyclotron) [8], working on-line with a 1-GeV proton beam of the synchrocyclotron of Petersburg Nuclear Physics Institute (Gatchina, Russia). ^{223,224}Ra and ^{225}Ac were produced in a UC target and ionized in a high-temperature surface ionization source. As a high-temperature surface ionization ion source, a specially manufactured tungsten tube with a high work function, 5 eV of the internal tube surface, was utilized [13]. The values of the efficiency of a similar surface ionization source with the use of the off-line mass-separator were determined for Sr and Rb in our previous experiments [3]. The values obtained in off-line and on-line experiments were in good agreement within the limits of experimental errors. In Table 2, the values of the production (ionization) efficiency for some radionuclides determined in on-line measurements are presented [13].

Table 2. On-line measured values of the production (ionization) efficiency for some radionuclides

Element	Ionization potential (eV)	Efficiency (%)
Cs	3.9	51(15)
Rb	4.2	47(10)
Ra	5.3	38(10)
In	5.8	33(8)
Tl	6.1	21(8)

As one can see from Table 2, the condition that the ion source efficiency should not be lower than several

tens of percent for efficient production of medical radionuclides by the mass-separator method is carried out for the investigated set of radioisotopes. This type of ion source also ensures the same ionization efficiency for isotopes of elements having ionization potentials approximately in the same interval (4-6 eV). Exclusions are isotopes of refractory elements, which do not escape from the target material at high temperature.

4. Thorium carbide target for radionuclides alpha-emitters

In our previous work [13], we pointed out that the high-density thorium carbide can be a very favorable target material for the production of ^{223,} ^{224}Ra and ^{225}Ac at high-energy proton cyclotrons. The ThC target has been used for production and a high-temperature method utilization of extraction ^{212}Pb and ^{224}Ra from the target material. It is similar to the method described in detail in [13] for uranium carbide targets. In the present work, the thorium carbide target of a density of about 6 g/cm^3 was irradiated during 24 h by the 1-GeV proton beam of the PNPI synchrocyclotron with an intensity of 0.1 μA. The target mass was about 1 g. After one month of radiation cooling, the target was placed into a graphite cavity which was inserted into a tungsten oven at the vacuum test bench and was heated by resistant heating. It was expected that lead and radium atoms should have considerably different enthalpies of adsorption [14], therefore ^{212}Pb and ^{224}Ra may be selectively extracted out of the target material at different temperatures. During the target heating, the radionuclides were collected on the copper collector cooled by the flowing water. In the experiments for ^{212}Pb separation from the target material, it was kept at a temperature of 1230 °C for one hour in a high vacuum of about 10^{-5} mbar. In Fig. 1 two spectra of α-decaying ^{212}Bi and ^{224}Ra are presented.

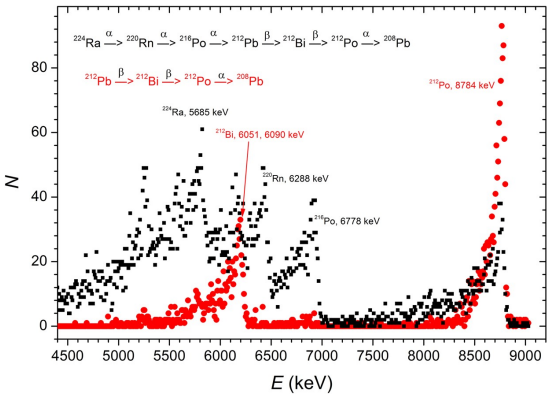

Figure 1. Alpha spectrum of the daughter isotopes of ^{212}Pb (^{212}Bi and ^{212}Po, red circles) and alpha spectrum of ^{224}Ra with α-lines of its daughter isotopes (black squares) measured on the copper collector.

In order to evaporate and collect ^{224}Ra after the process of ^{212}Pb extraction, the target was kept at a temperature of 1500 °C for a period of one hour in a high vacuum of about 10^{-5} mbar. The spectrum of α-decaying ^{224}Ra, containing all α-lines of the chain of its daughter isotopes, is presented. As one can see in Fig. 2, the alpha-line widths are rather large, which can be explained by a large dimension (about 20 mm in diameter) of the alpha activity spot at the collector. The comparison of measured ^{212}Pb and ^{212}Ra α-spectra shows, that in spite of a rather good effect of separation of lead and radium isotopes, there is a small admixture of ^{224}Ra in the extracted sample of ^{212}Pb. To decrease this undesirable contamination it is necessary to select the optimal heating temperature of the irradiated target material. This temperature evidently should be a little bit lower than the used processing temperature of 1230 °C. Respectively, the collection time should be increased as well. Additionally, the statistics of accumulated alpha spectra should be considerably higher to estimate reliably the purity of the ^{212}Pb sample.

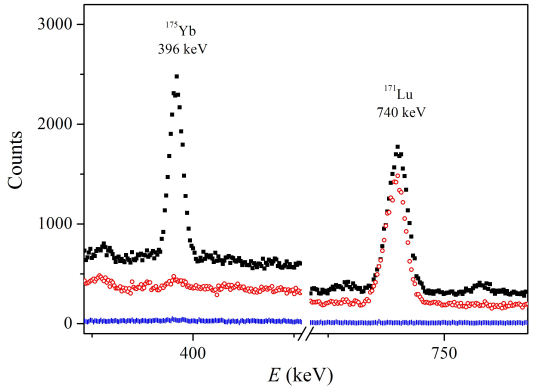

Figure 2. Gamma spectrum of irradiated ytterbium before (black squares) and after (red open circles) heating in the quartz vessel. The spectrum after washing the internal volume of the vessel by 10% solution of the hydrochloric acid is shown by blue bars.

The results obtained in the present work will be used in the target development for the RIC-80 isotope complex, whereas other radioisotopes are planned to be produced along with those mentioned above. The studies have demonstrated the efficiency of using high-density thorium carbide as a target substance.

On the basis of these studies, a new method has been suggested to utilize an irradiated thorium target as a very long-lived generator for permanent production of ^{224}Ra and ^{212}Pb (generator of ^{212}Bi). It should be stressed that in this case, it is necessary to use the thorium carbide target material which allows extraction of produced nuclides without the target destruction similar to targets from carbides of other metals, which are very temperature-resistant and can stay in intensive charged particle beams without any downfall for a long time. Another way to get a high purity ^{212}Pb is the use of mass-separated ^{224}Ra implanted into a refractory metal foil, which will be serving as a generator of ^{212}Pb. In that case, after the implantation of the mass-separated ^{224}Ra, the foils should be heated to the temperature for ^{212}Pb evaporation, while ^{224}Ra will remain in the foil.

The study carried out showed that the thorium carbide of a high density can be used as the target material for the mass-separator method that would enable the simultaneous production of three radioisotopes ^{223,} ^{224}Ra and ^{225}Ac that undergo alpha-decay.

Concluding this section, it is possible to say that on-line (when the targeted radionuclide is being produced and selected "on the beam"), or semi on-line (when the targeted radionuclide is selected after the beam was switched off) mass-separator method can be used for the production of radionuclide for medicine. Both methods mean that the mass-separator target-ion source unit is installed on the beam of bombarding particles and there is no additional step of the target transportation from the point of its irradiation to the place coupling with the mass-separator. The on-line and semi on-line method advantage is that they ensure the possibility of production and use radionuclides with considerably shorter lifetimes than were used so far.

5. First experiments on a high-temperature separation of lutetium radionuclides from irradiated ytterbium target

Radionuclide ^{177}Lu is a rather new, very efficient tool for prostate cancer therapy. It is produced in thermal neutron reactors by irradiation of metallic ytterbium in the ^{176}Yb (n,γ) →^{177}Yb(β$^-$) → ^{177}Lu reaction. For the process of ^{177}Lu extraction from irradiated ytterbium target a complex radiochemical procedure, called "wet radiochemistry" is utilized. According to [14], ytterbium and lutetium are just such elements with the enthalpies of adsorption values ~3.6 eV and ~6.6 eV correspondingly. As we pointed out above, enthalpies of adsorption of elements, in general, are in a good correlation with their boiling points. It is confirmed as well for the couple ytterbium – lutetium with their boiling points of 1194 °C and 3393 °C. In the first tests, a high-temperature method of separation of $^{171, 172}$Lu from the ytterbium metal target, similar to that described in [15] for copper metal target, has been utilized. In the present work, the ytterbium metal target was irradiated during 24 h by the proton beam of the PNPI synchrocyclotron with the proton energy of 100 MeV. The target mass was about 0.1 g. After five 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 ytterbium with a considerably lower boiling point than the produced Lu radionuclides has been evaporated into a special cavity cooled by flowing water, while lutetium remained in the vessel. In the first experiments for the target material evaporation, the oven was kept in the temperature interval of 800-900 °C for the period of one hour in a high vacuum of about 10^{-5} mbar. In Fig. 2, the spectrum with gamma-lines of irradiated ytterbium before (black points) and after (red points) target heating in the quartz vessel is presented. The gamma line with the energy of 396 keV follows ^{175}Yb ($T_{1/2}$=4.2 d) β-decay. This line was used for monitoring the target material evaporation. The gamma line with the energy of 740 keV belongs to ^{171}Lu ($T_{1/2}$=8.24 d) β-decay and a comparison of its intensity before and after heating shows what part of lutetium atoms remains in the vessel after heating. This comparison shows that when the target material (ytterbium) was completely removed, the targeted lutetium remains in the vessel with the efficiency of (94±5) %. The efficiency of lutetium washing away from the internal volume of the quartz vessel by 10% solution of hydrochloric acid is close to 100 % (blue points in Fig. 2). In spite of very efficient separation of lutetium isotopes from the metallic ytterbium target material, the value of separation efficiency has been determined with precision not higher than 5%. To improve the measurement precision, the statistics of accumulated gamma-spectra should be considerably higher.

6. Conclusions

Summarizing the presented results and discussions carried out, we can say that on-line, or semi on-line mass-separator methods can be used for the production of mass-separated, high purity radionuclides for medicine.

The on-line and semi on-line methods give the advantage of production and use radionuclides with considerably shorter lifetimes than the ones used so far. The targets used for on-line or semi on-line mass-separated radionuclide production should be very temperature-resistant and have a very low saturated vapor pressure at high temperature, ensuring a fast enough release (diffusion-effusion) of produced radioactive species from the target material. Usually, these are the targets from refractory metals, metal carbides (YC_2, ThC, UC), liquid metals with high boiling points and some high-temperature resistant metal oxides.

The studies also showed that the thorium carbide of a high density can be used as the target material for the mass-separator method that would enable the simultaneous production of $^{223, 224}$Ra and ^{225}Ac that undergo alpha-decay.

To confirm the first results of the separation of lutetium from the ytterbium target material irradiated by protons, we plan to carry out similar studies for the ^{177}Lu allocation, producing it from the ytterbium metal target in the experiment making use of reaction with the thermal neutrons.

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