MEDICAL ISOTOPE PRODUCTION USING ACCELERATOR NEUTRONS

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Abstract

We describe a new method for the generation of radioisotopes with accelerator neutrons by deuterons (GRAND) by discussing medical radioisotopes, such as ^{99}Mo, ^{90}Y, ^{64}Cu, and ^{67}Cu. We use intense accelerator neutrons with a most probable energy of 14 MeV from the ^{nat}C(d,n) reaction with 40 MeV deuteron beams. The characteristic feature of the method lies in its capability to produce a wide variety of high-quality, carrier-free, carrier-added radioisotopes with a minimum level of radioactive waste without using uranium for medical, research, and industrial applications.

MEDICAL RADIOISOTOPE

The medical use of radioisotopes (RIs) for diagnostic and therapy accounts for the majority of RIs applications. In reactors, neutron-rich RIs, which decay by emitting β^--rays and/or γ-rays, are produced. Radiopharmaceuticals with β^--ray emitting radionuclides are used in radioimmunotherapy (RIT), and those with γ-ray emitting radionuclides are used in nuclear medicine imaging (NM). ^{90}Y is a typical example of the former application and ^{99m}Tc is the latter one. In accelerators, a variety of RIs including proton-rich light RIs are produced using protons in the energy between 10 and 200 MeV. These RIs decay by emitting β^+-rays or α-rays. Radiopharmaceuticals with β^+-rays and α-rays emitting radionuclides are used in NM and RIT, respectively. ^{18}F is a typical example of the former application and ^{225}Ac is the latter one [1].

Among medical RIs, ^{99m}Tc, the daughter nuclide of ^{99}Mo with a half-life ($T_{1/2}$) of 66 h, is the most common radioisotope used in diagnosis. More than 25-30 million procedures are carried out every year in the world. Therefore, a reliable and constant supply of ^{99}Mo is the key issue to ensure the routine application of ^{99m}Tc. Note that ^{99m}Tc has unique characteristic for diagnosis. Because of a short half-life of $T_{1/2}$ = 6.0 h of ^{99m}Tc, ^{99m}Tc is routinely produced in ^{99}Mo/^{99m}Tc generators, and one can use a large quantity of ^{99m}Tc with a low radiation dose to the patient. A low γ-ray energy of 141 keV can be detected by a gamma camera with high efficiency using a low-energy collimator [2].

^{99}Mo has been mostly produced by the fission reaction of highly enriched ^{235}U (HEU) in five research reactors in the world. However, a number of incidents of the reactors in 2008, caused a worldwide shortage of ^{99}Mo, which triggered widespread discussions on the medium- and long-term supplies of ^{99}Mo.

A variety of production methods of ^{99}Mo and/or ^{99m}Tc in reactors or accelerators without HEU have been studied, since the use of HEU is an issue of public concern due to the proliferation of nuclear weapons. In fact, a conversion from HEU to low-enriched ^{235}U (LEU) was made, and succeeded in small-scale ^{99}Mo production in Argentina, Brazil, and Australia [3]. However, it is considered that in order to maintain the same production rate of ^{99}Mo using LEU as HEU, about 5 times more uranium targets (LEU) than HEU are required. Therefore, it is important to develop an alternative production method of medical radioisotopes without the use of ^{235}U.

The ^{99}Mo production by the neutron capture of enriched ^{98}Mo or natural Mo targets in reactors was demonstrated to be an attractive alternative. Note that ^{99}Mo produced by fission reaction of ^{235}U has a high-specific-activity (~370 TBq/(g ^{99}Mo)), but ^{99}Mo by the neutron capture reaction is as low as ~37 GBq/(g Mo). Hence, one has to develop a method to separate high-quality ^{99m}Tc from ^{99}Mo of low-specific activity, as discussed later.

A charged-particle induced reaction, such as the ^{100}Mo(p,x)^{99}Mo, ^{100}Mo(d,x)^{99}Mo, and ^{100}Mo(p,$2n$)^{99m}Tc reactions, has been investigated by a number of researchers. ^{99}Mo productions by the ^{235}U(n,fission)^{99}Mo or ^{98}Mo(n,γ)^{99}Mo reactions using spallation neutrons, and by the ^{238}U(γ,fission)^{99}Mo or ^{100}Mo(γ,n)^{99}Mo reactions using bremsstrahlung photons have also been studied [3].

Contrary to the studies using charged particle-induced or photon-induced reactions on Mo isotopes, ^{99}Mo production by neutron-induced reactions using fast neutrons from an accelerator had not yet been studied. We proposed a new route to produce ^{99}Mo by the ^{100}Mo(n,$2n$)^{99}Mo reaction [4].

^{99}Mo PRODUCTION BY ACCELERATOR NEUTRONS

To the best we know, fast neutrons from an accelerator have not yet been used for producing any radioisotopes. We found that fast neutrons have a great potential to produce a large quantity of high-quality ^{99}Mo with a minimum level of radioactive wastes. In fact, the cross section of the ^{100}Mo(n,$2n$)^{99}Mo reaction at 11≤ E_n ≤18 MeV is quite large, 1.5 barn, which is 10-times larger than the thermal neutron capture cross section of ^{98}Mo. On the other hand, the cross sections of the (n,α), (n,$n'p$), and (n,p) reactions on ^{100}Mo producing impurity radionuclides other than ^{99}Mo, are less than a few mb at E_n ~ 14 MeV. Because of high neutron penetration power, a large amount of ^{100}Mo sample (> 100 g) can be used in the ^{100}Mo(n,$2n$)^{99}Mo reaction.

It should be also noted that intense neutrons with 11≤ E_n ≤18 MeV, necessary to produce ^{99}Mo with good specific-activity, are available. In fact, significant progress has been achieved in obtaining high-flux fast neutrons from accelerators. At SPIRAL2 in GANIL, neutrons with a high flux of 10^{15} n/s with a most probable energy of 14 MeV are planned to be produced by ^{nat}C(d,n) using 40 MeV 5 mA deuterons using a linear accelerator

[5]. Neutrons are used to produce a large range of exotic neutron-rich radioactive nuclei via the fission reaction of a natural uranium target. Emitted neutrons from the reaction peak at forward angles with respect to the deuteron beam direction. On the other hand, at a cyclotron facility of Paul Scherrer Institute in Switzerland, a high-intensity proton beam of 2.2 mA with energy of 72 MeV has already been used for experiments [6]. Hence, one could obtain a high-intensity deuteron beam with energy of ~36 MeV. A marked advance has been also achieved with the development of a neutron converter that can withstand the high power of the 40 MeV 5 mA deuteron beam. For example, a rotating carbon converter was selected in the SPIRAL2 project by taking into account the neutron yield, thermal properties, toxicity, production of long-lived radioactive nuclides, and cost [7]. It should be noted that a carbon converter with a rotation frequency of 10-20 Hz has been shown to accept a deuteron beam of 200 kW power.

The yield of ^{99}Mo for an enriched ^{100}Mo sample (100% enriched in ^{100}Mo) with a cylindrical shape was evaluated for an irradiation time of two days at different distances (d) between the neutron production target and the ^{100}Mo sample position, and with different ^{100}Mo sample radii (r) and thicknesses (t) [8]. In the calculation, we used the latest data of neutrons from ^{nat}C(d,n) at E_d = 40 MeV, assuming a beam intensity of 5 mA, and the evaluated cross section of ^{100}Mo(n,2n)^{99}Mo given in the Japanese Evaluated Nuclear Data Library (JENDL). We assumed the deuteron beam size to be 1 cm in diameter. Typically, 6.8 TBq of ^{99}Mo was obtained at d = 2 cm for a ^{100}Mo sample with a thickness of 2 cm and a radius of 2 cm (251g ^{100}Mo). Note that the ^{99}Mo yield decreases rather smoothly with increasing d as expected, since the emitted intense neutrons peak at forward angles. Consequently, if one could obtain 40 MeV 5 mA deuteron beams and place an enriched ^{100}Mo sample at d = 2 cm away from a carbon neutron converter, about 20-25% of the demand of ^{99}Mo in Japan, for example, could be obtained constantly with a single facility.

REQUIREMENTS FOR ^{99}Mo PRODUCTION

There may be several requirements in the domestic production of ^{99}Mo (^{99m}Tc). Any method of ^{99}Mo production must have a potential to meet all, or a significant part, of the domestic demand of ^{99}Mo. The safety and efficacy of the ^{99m}Tc radiopharmaceutical preparation should be ensured. The United States Pharmacopeia (USP) contains requirements concerning the radionuclide purity of ^{99m}Tc; the ^{99}Mo in the ^{99m}Tc product must be less than 5.6 kBq per 37 MBq of ^{99m}Tc, and the total concentration of all other β- and γ-emitters must be less than 3.7 kBq per 37 MBq of ^{99m}Tc. The labelling efficiency of the ^{99m}Tc radiopharmaceutical complex, which reflects the chemical purity of ^{99m}Tc, is also required to be above 90% [9]. Note that ^{99}Mo produced by any alternative production method, including the ^{100}Mo(n,2n)^{99}Mo one, has a low-specific-activity (~37 GBq/(g Mo), as discussed before. In order to separate high-quality ^{99m}Tc from ^{99}Mo of low-specific activity, several methods have been successfully developed to separate high-quality ^{99m}Tc from ^{99}Mo of low-specific activity by using any methods of chromatography, sublimation, and solvent extraction. Here, the sublimation method is based on a different volatility of technetium heptoxide (Tc_2O_7) and molybdenum trioxide (MoO_3); ^{99m}Tc produced in MoO_3 volatilizes at a temperature lower than that of the sublimation of MoO_3, which is 790°C [10].

R & D WORKS FOR ^{99}Mo PRODUCTION

^{99}Mo was produced by irradiating an enriched $^{100}MoO_3$ sample with ~14 MeV neutrons from the ^{3}H(d,n)^{4}He reaction at the Fusion Neutronics Source (FNS) facility of Japan Atomic Energy Agency (JAEA). Taking the γ-ray spectrum of an irradiated $^{100}MoO_3$ sample, we observed γ-rays from ^{99m}Tc, ^{99}Mo, ^{97}Zr, and ^{97}Nb. ^{97}Zr with $T_{1/2}$ = 16.7 h, produced by ^{100}Mo(n,α)^{97}Zr, and ^{97}Nb with $T_{1/2}$ = 1.20 h, the decay product of ^{97}Zr, were impurity radionuclides [11]. However, their yields were much smaller than that of ^{99}Mo, and therefore an irradiated $^{100}MoO_3$ sample can be recycled.

In order to separate ^{99m}Tc from the $^{100}MoO_3$ sample, the sublimation separation was performed by using an electric furnace. The irradiated $^{100}MoO_3$ sample was placed in a platinum boat in the furnace, and heated at around 820 °C so as to form gaseous materials containing vaporized $^{99m}Tc_2O_7$ in a stream of oxygen carrier gas. The separation process of ^{99m}Tc was performed within one hour. By taking a γ-ray spectrum of the separated ^{99m}Tc with a HPGe detector, the upper limits of γ-rays from any impurity isotopes, such as ^{99}Mo, ^{97}Zr and ^{97}Nb, were found to fulfil the USP requirement of the radionuclide purity of ^{99m}Tc. Labelling efficiency was shown to be higher than 99% by formulating a radiopharmaceutical by using commercially available methylene diphosphonate (MDP) (FUJIFILM RI Pharma) kits. The efficiency was above the USP requirement (>90%) [11]. Note that a sublimation method allows us to recycle any irradiated enriched ^{100}Mo sample.

OTHER MEDICAL RI PRODUCTION

A radiopharmaceutical agent containing a radionuclide ^{90}Y ($T_{1/2}$ = 64 h), a pure β^--ray emitter with a maximum energy of 2.28 MeV, has been used for cancer therapy. ^{67}Cu ($T_{1/2}$ = 61.8 h) is a promising radionuclide to treat small distant metastases in RIT, since ^{67}Cu decays to excited states of ^{67}Zn by emitting β^--rays. Note that ^{67}Cu emits low-energy γ-rays, it can be used simultaneously for diagnostic and therapy. ^{64}Cu ($T_{1/2}$ = 12.7 h) is a promising radionuclide suitable for PET imaging, since it decays by positron (β^+) emission. Currently, a carrier-free grade of ^{90}Y used for radiopharmaceuticals is obtained from the ^{90}Sr/^{90}Y generator. Note that large amounts of ^{90}Sr with $T_{1/2}$ = 28.8 y can be obtained by the fission reaction of

^{235}U at reactors. As for the production of ^{64}Cu, the generally adopted route of ^{64}Cu production is ^{64}Ni(p,n)^{64}Cu. The ^{68}Zn(p,2p)^{67}Cu reaction is currently used to produce ^{67}Cu. Note that the proton energy used in the ^{68}Zn(p,2p)^{67}Cu reaction is high, a large amount of impurity radionuclide of ^{64}Cu is produced by ^{68}Zn(p,αn)^{64}Cu.

Here, it should be noted that a charge exchange reaction, such as (n,p), (n,np+d), and (n,α), of a sample nucleus with a medium-weight mass (<100) has a sizable cross section of from ~50 to ~500 mb at ~ 10 < E_n < 18 MeV. Therefore, a wide variety of carrier-added and carrier-free radioisotopes can be produced using neutrons from the ^{nat}C(d,n) reaction at E_d = 40 MeV. In fact, we have proposed new routes to produce carrier-free medical radioisotopes of ^{90}Y [12], ^{64}Cu, and ^{67}Cu [13] using neutrons from an accelerator. The production yield of ^{90}Y via the ^{90}Zr(n,p)^{90}Y reaction was estimated to be 220 GBq using neutrons from the ^{nat}C(d,n) reaction with 40 MeV 5 mA deuteron beams. A ^{90}Zr sample (100% enriched in ^{90}Zr) with a radius of 2 cm and a thickness of 2 cm, which was placed at d = 2 cm downward from the neutron target position, was irradiated with neutrons for 2-days. The calculated ^{64}Cu yield is 1.8 TBq (175 g ^{64}Zn) for 12 h of irradiation; the yields of ^{67}Cu by ^{67}Zn(n,p)^{67}Cu and ^{68}Zn(n,x)^{67}Cu were 249 GBq (184 g ^{67}Zn) and 287 GBq (186 g ^{68}Zn) at the end of 2 days of irradiation, respectively. Note that three medical isotopes of ^{90}Y, ^{64}Cu, and ^{67}Cu can be produced using neutrons from the ^{nat}C(d,n) reaction at E_d = 40 MeV.

Here, we discuss a potential of accelerator neutrons for other isotopes co-production at the same time, which was discussed in the OECD report in considering alternative production method of medical RI [14]. This criterion provides an indication of the economic sustainability, demand risk mitigation and the ability to avoid creating other isotope shortage. We showed that co-production of other radioisotopes is possible using accelerator neutrons. As a typical example, we calculated the yields of ^{99}Mo and ^{90}Y produced by irradiating ^{100}Mo and ^{90}Zr samples with neutrons. ^{100}Mo and ^{90}Zr samples (100% enriched in ^{100}Mo and in ^{90}Zr) with the same size of a radius of 2 cm and a thickness of 2 cm were placed at d = 2 cm between the neutron production target and the ^{100}Mo sample position. ^{90}Zr was placed behind ^{100}Mo. The calculated yield for the two-days of irradiation is 6.8 TBq for ^{99}Mo and 130 GBq for ^{90}Y, respectively. Note that the maximum dose of ^{90}Y injected to a patient is limited to be 1.184 GBq.

PROTOTYPE FACILITY FOR GRAND

On the basis of the results of all the important steps necessary to obtain high-quality ^{99m}Tc together with the potential of accelerator neutrons for producing important medical RIs, we present our proposal for a prototype facility for the generation of radioisotopes with accelerator neutrons by deuterons (GRAND) [15]. The facility consists of an azimuthally variable field (AVF) cyclotron with a deuteron beam intensity of 2 mA and with a carbon converter to produce intense accelerator neutrons with a most probable energy of 14 MeV. Note that a fixed radiofrequency cyclotron is robust in operation and compact in size. Here, negative deuteron D^- ions are accelerated up to 40 MeV because of the ease and low loss in extraction by the stripping of negative deuteron ions into positive deuteron (D^+) ions on a thin carbon foil with a thickness of about 500 μg/cm^2.

The system has unique features in the production of a wide variety of radioisotopes, including ^{99}Mo, ^{90}Y, ^{64}Cu, and ^{67}Cu useful for nuclear medicine with a minimum level of radioactive waste. The system has a potential for the co-production of other radioisotopes at the same time. A single prototype facility can produce ^{99}Mo, which meets about 10% of the ^{99}Mo demand in Japan.

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