CONVERTERLESS CONVERSION OF RADIUM-226 TO ACTINIUM-225

Description

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to US application Serial No. 63/523992, filed on June 29, 2023, whose disclosures are incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to the preparation of ^{225}Ac from ^{226}Ra target by the bombardment of that radium isotope with a high energy electron beam to produce virtual photons electromagnetic radiation that transmutes the ^{226}Ra to ^{225}Ra and ^{225}Fr both of which decay to ^{225}Ac. This photonuclear reaction is carried out without the use of an intervening *Bremsstrahlung*-converter between the electron beam and the target ^{226}Ra.

BACKGROUND ART

The quest for bridging the gap between the severely constrained ^{225}Ac (which has a half-life $T_{1/2}$= 9.92 days) supply and the large worldwide demand for that isotope is a key factor in nuclear medicine. The demand for ^{225}Ac stems from the use of that isotope in targeted alpha therapy (TAT). Radioisotope ^{225}Ac and its daughter ^{213}Bi ($T_{1/2}$= 45.61 minutes) are used in medicine for the treatment of several cancers, including prostate, brain, and neuroendocrine cancers.

In one of the usual methods of production, ^{225}Ac is produced via the β^--decay of ^{225}Ra ($T_{1/2}$= 14.9

days), which is itself produced by the (γ,n) reaction on a high-purity ^{226}Ra ($T_{1/2}$= 1600 years) target. The photons are produced by a solid converter of high atomic number (high-Z) material, such as tantalum, via the braking-radiation (*Bremsstrahlung*) mechanism that can result from slowing down very energetic accelerated electrons impinging on the converter material. The *Bremsstrahlung* thereby produced are high energy photons that impinge upon the target ^{226}Ra and cause the ^{226}Ra to transmute into another radioisotope, ^{225}Ra that decays via the β^--decay to ^{225}Ac.

However, the typical photon spectrum generated using a converter is widely dispersed in terms of energy (see Fig. 1) and also to an extent in terms of the emission angle (see Fig. 2). Moreover, around 80% of the photon flux spectrum is below the neutron separation energy (e.g., S_n) of ^{226}Ra (S_n= 6.39 MeV), which makes those photons sterile, but can catastrophically overheat the target and its surrounding materials. Such overheating requires enhanced cooling and, consequently enhanced radio-waste removal systems.

Two tantalum disk converters were used previously to enhance cooling and heat removal. They are shown in Figs. 1 and 2 as illustrative of difficulties found when using converters. The use of more than a single converter was proposed by Diamond et al., *J Appl Phys* **129**:104901 (March 09, 2021).

In addition, with the use of converters, the proton-removal channel that produces an important precursor of the ^{225}Ra, i.e., ^{225}Fr ($T_{1/2}$= 3.95 m), via photon bombardment (irradiation) of the ^{226}Ra target is not feasible. The deficiency stems from the

anticipated very low yield due to the very low photon flux level at the energy where the (γ,p) reaction cross-section has its peak value σ_{max}(30 MeV)= 0.2 mb.

Alternatively, without a converter, and as a result of the electrons traveling with an ultra-relativistic speed (Energy >>M_o) and hitting the high-Z $^{226}_{88}Ra$ target, a new class of interaction with the time-varying Coulomb field takes place. This interaction, named Coulomb Dissociation (CD), can be interpreted as an absorption of a virtual photon [Bertulani et al., *Physics Reports* **163**:299-408, 1988; and *International Atomic Energy Agency, Handbook on Photonuclear Data for Applications: Cross sections and Spectra,* I.A.E.A TECDOC **1178** (2000), Sections 3.1.4 and 4.4].

The absorption probability can be translated into (γ,n) and (γ,p) cross-sections, which can be experimentally measured using several techniques. One of these techniques is the activation and delayed counting method. Many measurements were performed in the past using this technique on a variety of different beam-target systems. The work reported in [Gerab et al., *Phys Rev C*, **48(1)**:105-108 (1993); Martins et al;., Phys. Rev. C, **16**:613 (1977); and Shotter et al., *Nucl Phys* **A330**:325 (1979)] for accelerated electrons incident on ^{238}U are of special interest due to their seeming similarity to the reactions here for the production of $^{225}Ra/^{225}Ac$ via (e^-,n) and (e^-,p) on ^{226}Ra.

The similarity in the nuclear structures between both target nuclear systems, i.e., ^{238}U and ^{226}Ra, suggests using the same optical model potential (OPM) parameters for the distorted-wave Born approximation (DWBA) calculation as the reaction

model for both systems when interacting with E1 and E2 virtual photons generated from the ultra-relativistic electrons. As noted in Fig. 3, which is adopted from Gerab et al., above, and replotted here using the JANIS database [JANIS Database (Nuclear Energy Agency (NEA) - JANIS (oecd-nea.org)], the cross-section for removing a neutron from a ^{238}U nucleus at 40 MeV of beam energy is about 2.5 mb. ^{226}Ra is believed to exhibit a similar value of the (e^-,n) reaction cross-section. However, a slightly lower value for the (e^-,p) reaction cross-section is believed to be present due to the need for protons to tunnel out of the radium nucleus Coulomb barrier when absorbing a virtual photon.

As discussed in detail hereinafter, the present invention contemplates a converterless approach for the production of ^{225}Ac by direct bombardment of an encapsulated ^{226}Ra target with electron beams with an average power of about 20 to 250 kW. In this method, the well-established and validated CD mechanism of nuclear disintegration is employed when electrons impinge on a thin-target of ^{226}Ra.

BRIEF SUMMARY OF THE INVENTION

The present invention contemplates the production of ^{225}Ac by the absorption of virtual photons by ^{226}Ra, followed by spontaneous neutron or proton removal to produce ^{225}Ra and ^{225}Fr, respectively, and then the formation of ^{225}Ac, which is produced following a beta-minus decay of ^{225}Ra and ^{225}Fr. The photons are generated from the direct bombardment of a high-purity ^{226}Ra enclosed target using a high-intensity electron beam current with

about 25 to about 100 MeV of energy. In this implementation, the virtual photons are responsible for the Coulomb Dissociation (CD) of the target, and with the neutron or proton removals from the ^{226}Ra target, ^{225}Ac can be produced following the naturally occurring beta-minus decay of ^{225}Ra and ^{225}Fr, respectively. The average electron beam intensity is at about 20 to 250 kW of effective beam power at about 25 to about 100 MeV. The higher efficiency is a result of having a focused and mono-energetic beam of electrons.

Previous methods for ^{225}Ac production with photons use beam converters to convert the electron beam energy into bremsstrahlung photons, from which about 81% are produced below the neutron-removal threshold. Such previous methods utilize converters of high-Z material to produce photons that are emitted with a large angle. This type of production reduces the number of photons on target. The result is a low production yield. Moreover, the efficiency of these methods is very low, and the designs of such setups are complex.

In this embodiment, there is no actual beam converter. The ^{226}Ra is directly bombarded with about 25 to about 100 MeV electrons. Optionally, a thin layer (about 120 to about 220 microns) of a high-Z material as are well-known, such as gold (Au), tantalum (Ta) or tungsten (W), present on the inner wall of the enclosure lid produces *Bremsstralung* photons [Gerab et al., *Phys Rev C*, **48(1)**:105-108 (1993)].

More specifically, the present invention contemplates a method for converting ^{226}Ra to ^{225}Ac by electron stream bombardment with high energy

electrons that comprises the following steps. The words "bombardment" and "irradiation" are used interchangeably herein. ^{226}Ra present within a hermetically sealed capsule is bombarded with an electron beam with an average electron intensity of about 20 to about 250 kW of effective beam power at about 25 to about 100 MeV electrons.

The capsule has a lid 232 through which the beam of electrons passes prior to impacting the ^{226}Ra. The capsule lid 232 can include high-Z material coating having a thickness of about 120 to about 220 microns (μ) on its internal capsular surface through which the beam of electrons also passes prior to impacting said ^{226}Ra, but that high-Z material coating is insufficiently thick to provide transmutation reaction-causing amounts of *Bremsstrahlung*.

The bombardment is maintained for a time period sufficient to remove a neutron or proton from the ^{226}Ra to form ^{225}Ra or ^{225}Fr, respectively. The ^{225}Ra and ^{225}Fr that are formed decay into ^{225}Ac, which is typically recovered from the irradiated target material and is also typically separated from any remaining ^{226}Ra and formed ^{225}Ra or ^{225}Fr. The ^{225}Ra and ^{225}Fr can be separated through an elution process.

Additionally, any ^{227}Ac byproduct, which is a decay product of ^{227}Ra (half-life = 42 ± 0.5 minutes) that is produced via a less probable neutron capture reaction on ^{226}Ra, can be eliminated by discarding a first eluted fraction of actinium a few hours after the end of the bombardment. A few hours of wait time is adequate for the vast majority of the ^{227}Ra to decay away.

Although bombardment of the ^{226}Ra does not form ^{225}Ac directly, the intermediate ^{225}Fr has a half-

life of only about 3.95 hours and is therefore generally absent from the ^{226}Ra or ^{225}Ra reaction mixture when the actinium product is obtained. Similarly, although not to the same extent, produced ^{225}Ra also decays to ^{225}Ac, albeit more slowly, as shown in Fig. 4. In view of the disappearance of some intermediate product formed from ^{226}Ra and the obtention of the desired ^{225}Ac, this method is described as a method for converting ^{226}Ra into ^{225}Ac for ease of description.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings forming a part of this disclosure,

Fig. 1 is a graph of a *Bremsstrahlung* photon flux profile produced by a two-tantalum disk converter that illustrates that any photon with energy below 6.4 MeV does not have the required energy to produce $^{225}Ra/^{225}Ac$;

Fig. 2 is a MCNP-Simulated spatial distribution of the photons produced by the above two-disk converter, illustrating that a large fraction of the photons do not hit the target, where the target is shown as a black rectangular box in the middle of the circle.

Fig 3 is a graph showing the virtual-photon induced reaction cross section on a ^{238}U target (thickness = 150 µg/cm^2) measured using the (e^-,n) activation reaction with electron beam energies between 12 and 60 MeV as reported in [Gerab et al., *Phys Rev C*, **48(1)**:105-108 (1993)], the plot is generated using the JANIS EXFOR Database [Nuclear Energy Agency (NEA) - JANIS (oecd-nea.org)].

Fig. 4 is a graph showing the relative activities of ^{225}Ac to ^{225}Ra over a time of storage as calculated in Maslov et al., *Radiochemistry*, **48(2)**:195-197 (2006).

Fig. 5 is a schematic depiction of an exemplary system 100 for producing an isotope such as ^{225}Ac.

Fig. 6 is a schematic drawing of a target capsule enclosure that illustrates five ^{226}Ra target-containing capsules with the electron beam entering through a window in the enclosure with an electron-absorbing tantalum beam stop to capture the flow of electrons passing into the air-filled enclosure.

Fig. 7 illustrates a block diagram of a beamline according to an exemplary embodiment.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention contemplates a method for converting ^{226}Ra to ^{225}Ac by electron beam bombardment with high energy, about 25 to about 100 MeV, electrons to impact a ^{226}Ra target. In this reaction, ^{226}Ra is transformed by neutron loss to ^{225}Ra, which naturally decays into ^{225}Ac by beta-minus decay with a half-life of 14.9 days. ^{226}Ra is also transformed by electron beam bombardment to ^{225}Fr by proton loss and then to ^{225}Ac with a half-life of 3.95 hours.

Contrary to prior electron-based bombardment methods, the present method is carried out without a converter of the electron beam energy into *Bremsstrahlung* photons but rather into the production of virtual photons. In a contemplated method, the estimated yield of ^{225}Ac using the disclosed systems and methods is about three times

higher than the yield that results from the *Bremsstrahlung* bombardment of the ^{226}Ra using a converter. This exceptional feature of the converter-less concept makes the need for a higher accelerator beam power less important because similar yields are achievable using about one-third of the power needed when using a converter.

A contemplated method is basically a neutron or proton removal process. Conventionally, a neutron removal process for producing an isotope, and particularly a radioisotope, involves firing a linear electron accelerator (linac) or Rodotron® at a target along a common axis. However, the conventional method results in a low yield rate of the desired isotope and creates backstreaming radiation that is harmful to equipment downrange from the beamline.

Referring to Fig. 5, an exemplary system 100 is shown for producing an isotope, particularly ^{225}Ac. Specifically, the system 100 to produce the isotope can comprise an accelerator 110 connected to a first beamline 130. The beamline 130 impacts on a target holder 150. The target holder 150 can be an apparatus where a target isotope, such as ^{226}Ra, is held for irradiation. The target holder 150 can further engage with a target cooling system 160 (also known as a process cooling system) and a hot cell 170.

The accelerator 110, the beamline 130, and the target holder 150 can be shielded within an accelerator vault 180. In an exemplary embodiment, the accelerator vault 180 can further be separated into a first radiation zone 182, which houses the accelerator 110 and the beamline 130 therein, and a

second radiation zone 186, which houses the target holder 150 therein.

In an exemplary embodiment, the accelerator vault 180 together with the interior walls used to form the radiation zones 182 and 186 and any other building rooms can be constructed out of high-density (HD) concrete blocks supplied by Veritas Medical Solutions, Harleysville, PA, USA. HD concrete is better per unit volume at shielding gamma rays, which are the primary source of prompt radiation created in the process, than regular-density concrete.

Specifically, prompt radiation refers to radiation emitted instantaneously during an operation of the accelerator 110, which is different from residual or induced radiation caused by activated components in the accelerator vault 180 or the beamline 130. Although other materials, such as steel or lead, can also be used for the accelerator vault, those materials are more expensive and are not as efficient in stopping prompt neutrons, which are also produced during the process, as HD concrete.

The accelerator 110 generates accelerated electrons to irradiate ^{226}Ra held in the target holder 150. In an exemplary embodiment, the electron accelerator 110 is capable of supplying about 20 to about 250 kW of average power with about 25 to about 100 MeV electrons. Preferably, the average power value is about 60 to about 200 kW, and more preferably about 80 to about 125 kW. Preferably, the electrons are at about 25 to about 55 MeV.

In order to irradiate the target holder 150, a specialized beamline (as shown in Fig. 7) can be used to bend a respective electron beam at an angle toward the target holder 150. In an exemplary

embodiment, the beamline 130 bends the electron beam by 90 degrees toward the target holder 150. The invention is not limited to 90 degrees but can include other angles to result in beamlines irradiating the target holder 150 from different directions or degrees. As a result, the target holder 150 may not be placed on a common axis with the accelerator 110. In one exemplary embodiment, the accelerator 110 is offset from the target holder 150, as shown in FIG. 5. In another exemplary embodiment, the accelerator 110 can be placed on a common axis with the target holder 150.

Further, a control system can be provided that integrates individual control systems of the accelerator 110, the beamline 130, the target cooling system 160, the hot cell 170, and other system components for producing a radioisotope such as ^{225}Ac. For example, the combined control system can be used to time a production of beam pulses by the accelerator 110 such that the beam pulses arrive at the target holder 150 at a desired interval.

As discussed in more detail in FIG. 7, the beamline 130 can accept the electron beam from the accelerator 110 in operation. Then the beamline 130 can bend the respective beam to hit the target holder 150 at a desired spot and avoid backstreaming radiation. After the bend, the beamline 130 aims the beam to that desired spot at the target holder 150, analyzes the energy of the beam, or passes the beam straight through to a waiting beam analyzer and dump.

According to an exemplary embodiment, a Rhodotron® electron beam (e^--beam) accelerator, produced by IBA Industrial, Louvain-La-Neuve, Belgium, can be used as the accelerator 110. Unlike

a conventional linear accelerator (e.g., linac), a Rhodotron® E-beam accelerator is a pulse wave electron beam accelerator combining high power and high energy. The high-power and high energy properties of a Rhodotron® e^--beam accelerator help to improve the production efficiency of ^{225}Ac, previously unattainable using a linac. Moreover, a Rhodotron® e^--beam accelerator is more compact in size, allowing the accelerator setup to take up less square footage in an isotope production facility.

The preferred Rhodotron® e^--beam accelerator can provide an electron beam whose diameter is either 7 mm (Full Width at Half Max; FWHM) or 12 mm FWHM. A Gaussian beam with 3 sigma of standard deviation corresponds to 8.9 mm and 15 mm of diameter, respectively. The size of the target in all the simulations used for this disclosure is 25 mm in diameter, with 0.060198 mm of thickness ($RaBr_2$).

FIG. 6 illustrates a target capsule enclosure system 200. The target capsule enclosure system 200 can be included in, or part of, the target holder 150 of FIG. 1.

The target capsule enclosure system 200 comprises an enclosure 210 designed to encase one or more target capsules 220. The enclosure 210 is comprised of a wall 212, including a window 214 where an electron beam 216, such as an electron beam produced by the accelerator 110 and beamline 130 of FIG. 5, passes through to irradiate the one or more target capsules 220.

As shown in one embodiment, the target capsule enclosure system 200 includes five target capsules 221-225. However, in other embodiments, the

target capsule enclosure system 200 can include more or fewer target capsules 220.

Each of the one or more target capsules 220 can be identical. In instances where the target capsule enclosure system 200 includes multiple target capsules 220, each of the target capsules 220 can be arranged along a common axis with a pathway of an electron beam designed to bombard the target capsules 220.

In an exemplary embodiment, as shown in FIG. 6, a long axis of the one or more target capsules 220 are arranged perpendicular to the axis along which the electron beam 216 passes. In other words, the electron beam 216 passes through a "short side" or "short axis" of the one or more target capsules 220. In other embodiments, the long axis of the one or more target capsules 220 can be arranged on the same axis as the electron beam 216.

Many geometries for the one or more target capsules 220 can be utilized. Illustrative examples include a cylindrical-shaped capsule with generally rounded ends where a ^{226}Ra target 230 is made of $RaBr_2$, $RaCl_2$, or $Ra(NO_3)_2$ salt and present on the inner surface of the capsule base, with a lid 232 coated on its internal surface with a thin layer of tantalum 234 (e.g., the tantalum layer is on an internal capsular surface).

Another embodiment utilizes a cone-shaped or frusto-conical capsule, where the ^{226}Ra target 230 is on the inner walls of the capsule, whereas an inner surface of the lid 232 is coated only with tantalum. The cone-shaped capsule provides a significant surface area for heat transfer to a coolant fluid (water-based liquid or a chemically

inert gas), while distributing and spreading the volumetric heating induced by the electron beam. The coolant flow direction can be perpendicular or parallel to the electron beam.

The ^{226}Ra metal is preferably electroplated or liquid-deposited as a salt onto the inner surface of the target capsule, followed by drying. Solid radium salt particles are preferably used as the target, and are preferably prepared *in situ* by drying a solution of a water-soluble radium salt such as a nitrate or halide.

The one or more target capsules 220 are generally referred to herein as a "capsule" for ease of expression and not because of having the shape of a medicinal capsule. Similarly, capsules used in space travel were not shaped like medicinal capsules but were shaped as truncated cones.

The word "lid" is also used here for convenience as such a covering is typically present at the top of a chamber when viewed in the longest vertical axis of the chamber and covers an opening at the top in that position. In the present invention, the capsule lid 232 can be at a first end of the capsule opposite a second end of the capsule, where each of the first end and the second end are generally positioned along a common axis of the capsule.

In a preferred embodiment, as shown in Fig. 6, the common axis along which the first and second capsule ends are positioned is a "short" axis of the capsule that is parallel to the direction of the electron beam. That "short axis" is a different axis from a "long" axis of the depicted capsule and is usually perpendicular to the axis of the electron

beam. In other embodiments, the common axis along which the first and second ends are positioned is the "long" axis of the capsule. In other words, the capsule can be provided in the form of a shape having different lengths, heights, and thicknesses. Further, the lid can be positioned along any of these axes.

Here, the capsule "lid" is, in most instances, a portion of the capsule whose inner surface, relative to the capsule, is coated with the tantalum layer that is impacted by the electron beam.

The word "lid" here is usually used to close and hermetically seal the target-containing capsule, although other sealing devices at other locations can also be used to sealingly-close the capsule. The lid 232 and its sealingly-closing of the capsule helps prevent radon gas and radium (and any other radioactive material) from escaping outside the capsule after a long irradiation period and heating.

The one or more target capsules 220 are preferably made out of aluminum (e.g., an aluminum wall 236) due in part because of its weld-ability (e.g., the ability to join with a hermetic seal). Aluminum also has good mechanical properties (yield strength/ultimate strength) and, to a lesser extent, high thermal conductivity and high melting temperature. The latter two properties should not be of great import as because the conduction length scales (wall thickness) are small to keep the volumetric generation minimized.

Diamond et al., *J Appl Phys* **129**:104901 (March 09, 2021) report that one-half mm of aluminum on both sides of a radium target produces little