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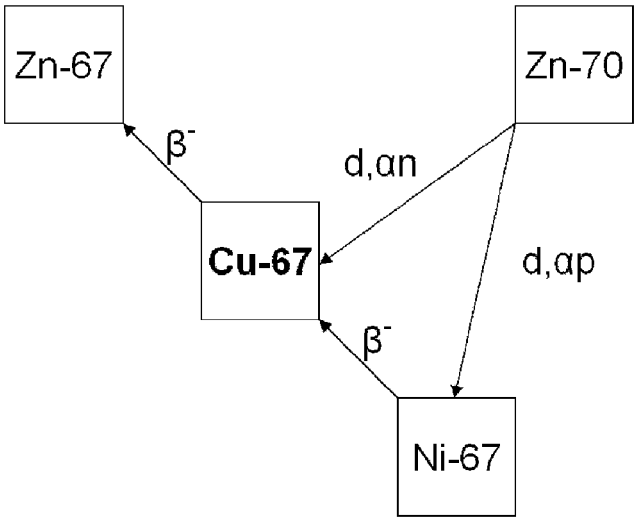
(54) **Method for the production of copper-67**

(57) A method for the production of copper-67 comprising the provision of a zinc-70 enriched target and the irradiation of at least a portion of the target with deuteron particles, thereby producing an irradiated target portion comprising copper-67, which can than be isolated from the target.

Fig. 1



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Description

Technical field

[0001] The present invention generally relates to a method for the production and the separation of copper-67 (^{67}Cu).

Background Art

[0002] Radionuclides of copper are of sustaining interest in biology, chemistry, nuclear medicine, and other industrial applications. They are used as radiotracers, radiotherapy agents or as industrial ionizing radiation sources. Especially they are used in vivo either in ionic form or as part of molecules of target selective tracers (mainly copper-61, -64 and -67). Their decay modes, with different decay radiation emissions, favour their multi-purpose use (e.g. radiotherapy, PET & SPECT imaging, etc.). Particularly copper-67, which is β^- emitter with half-life of 61.8 h, emits also 93 keV and 185 keV y peaks and is therefore suitable for radiotherapy and/or SPECT imaging. Copper-64 and copper-61 are positron emitters and can be used for PET imaging.

[0003] It was shown recently, that the copper-67 has superior therapeutic effects over copper-64 [1], iodine-125 [2] or iodine-131 [3] and is a radionuclide of preference for targeted radio-immunotherapy. The main limitation factor however is still the lack in copper-67 worldwide supply. Copper-64 and copper-61 are mainly produced from enriched nickel targets [4, 5] or zinc [e.g. 6].

[0004] Current state-of-art production methods of copper-67 are summarized in Table 1.

[0005]

Table 1.

Method	Reference
^{70}Zn(p,α)^{67}Cu	[7], [8]
^{nat}Zn(p,x)^{67}Cu	[9]
^{64}Ni(α,p)^{67}Cu	[10]
^{68}Zn(p,2p)^{67}Cu	[11]
^{nat}Zn(d,x)^{67}Cu	[12]
^{75}As(p,spall.)^{67}Cu	[13]

[0006] In the above Table 1, e.g. ^{70}Zn(p,α)^{67}Cu in the well known nuclear reaction notation means that ^{70}Zn is the target nucleus, p represents the incident particle, in this case a proton, α denotes the emitted particle, and ^{67}Cu is the residual nucleus.

Technical problem

[0007] It is the object of the present invention to provide an alternative method for producing copper-67 (^{67}Cu). The method should preferably yield the copper-67 radionuclide in commercially significant amounts and at specific activities which are suitable for use in diagnostic and therapeutic applications. Preferably, the method should further be feasible using low or medium energy charged-particle accelerators, such as a cyclotron commonly found on-site at major medical treatment and/or research facilities. Finally, the method of the invention should be such to minimize the expense of preparing said radionuclide.

[0008] This object is achieved by a method as claimed in claim 1.

General Description of the Invention

[0009] The present invention therefore proposes a method for the production of copper-67 comprising the provision of a zinc-70 enriched target and the irradiation at least a portion of the target with deuteron particles, thereby producing an irradiated target portion comprising copper-67. The reactions leading to copper-67 following irradiation of enriched zinc-70 with deuteron particles may be represented by the following nuclear reaction notations: ^{70}Zn(d,αn)^{67}Cu and/or ^{70}Zn(d,αp)^{67}Ni wherein ^{67}Ni decays almost immediately ($t_{½}$ = 21 s) to ^{67}Cu (see also Fig. 1).

[0010] Hence, the method of the invention concerns a preparation method of copper-67 by the deuteron irradiation of targets containing zinc-70 in enriched form, i.e. in relative amounts greater than the natural isotopic occurrence.

[0011] In the method described herein, the zinc-70 enriched target is generally a target enriched with respect to zinc-70 content, which contains at least 25 at-%, preferably at least 50 at-%, even more preferably at least 70 at-%, still more preferably at least 75 at-%, in particular at least 85 at-% of zinc-70 relative to total zinc content. In particular embodiments of the invention, the zinc-70 enriched target advantageously contains at least 90 at-%, preferably even at least 95 at-% of zinc-70 relative to total zinc content.

[0012] Hence, the present invention first provides for an alternative production method of copper-67. Second, a major advantage of this invention compared to known methods is the fact that low energy deuteron accelerator is sufficient to produce adequate quantities of copper-67.

[0013] In fact, the inventors have found that surprisingly, and compared to the known methods presented above, low energy deuteron accelerator is sufficient to produce significant quantities of copper-67. Indeed, the inventors' experiments lead to the conclusions that advantageous cross-section data are obtained with the present method. The comparison of cross-section data for different known production methods of copper-67 and that of the present invention are shown in Fig. 2.

[0014] The nuclear cross-section of a nucleus is used to characterize the probability that a nuclear reaction will occur. The concept of a nuclear cross-section can be quantified physically in terms of "characteristic area" where a larger area means a larger probability of inter-

action. The standard unit for measuring a nuclear cross-section (denoted as σ) is the barn, which is equal to 10^{-28} m^2. Nuclear cross-sections are used in determining the nuclear reaction rate, and are governed by the reaction rate equation for a particular set of particles.

[0015] Although the method of Skakun et al. slightly advantages in cross-section values, high current alpha particle beam is not readily available in common cyclotrons. Furthermore, compared to proton irradiation of zinc-70, the present method exhibits higher cross-sections at lower energies.

[0016] As a conclusion, the method presented herein allows for a high production yield of copper-67 even at relatively low incident energies.

[0017] In practice, the deuteron particles in the present method generally need incident energy of at least about 5 MeV, commonly between 7 and 35 MeV. Preferred values are comprised between 10 and 30 MeV, especially between 10 and 25 MeV, still more preferably between 14 and 22 MeV, although incident energies < 20 MeV will generally be sufficient.

[0018] Hence, in one embodiment, the invention is directed to a method for producing a copper-67 radionuclide from a zinc-70 enriched target using an accelerator capable of generating a beam of deuterons at energies ranging from about 7 MeV to about 20 MeV.

[0019] The solid target comprising the target zinc-70 nuclide is generally loaded in a target holder adapted for use with the accelerator. The zinc-70 enriched target nuclide is in any appropriate form, preferably in metal or oxide form. The deuteron beam is preferably generated using an accelerator, such as in a cyclic and/or linear accelerator, e.g. a biomedical cyclotron.

[0020] The irradiation can thus be accomplished by inserting the target into any particle accelerator capable of producing deuteron beams of the desired energy and beam current. A beam current of greater than about 1 pA, but generally less than about 100 pA, is generally preferred to maximize production. In practice, the current will usually be selected between 5 - 50 pA.

[0021] In one embodiment of the method of the present invention, a copper product essentially free of any copper-64 can be produced as the reaction with enriched zinc-70 produces only copper-67 if the target contains no or essentially no zinc-67.

[0022] This leads to a product that avoids the presence of a second radioisotope thus eliminating the unnecessary exposure to that radioisotope while using the targeted radioisotope copper-67. Further, as essentially only copper is produced, the specific activity of the product is naturally greater.

[0023] By "essentially copper-64 free" is meant that the ratio of copper-64 : copper-67 is about 0.1 or less : 1, preferably about 0.01 or less : 1.

[0024] Another embodiment of this invention proposes the simultaneous production of copper-67 (useable for therapy and SPECT imaging) together with copper-64 (useable for therapy and PET imaging) and/or copper-61 (useable for PET imaging). When the mixture with variable content of zinc-70, zinc-67 and/or zinc-64 is irradiated with a deuteron beam, copper-64 and copper-61 isotopes may be produced along with copper-67.

[0025] Thus, in a further embodiment of the invention, the zinc-70 enriched target may further contain zinc-67 or zinc-64 or both, the method thereby producing an irradiated target portion comprising additionally to copper-67, either copper-64 or copper-61 or both.

[0026] This approach advantages in the simultaneous production of PET/SPECT imaging and therapeutical radionuclides, the possibility to modify the ratio of produced copper isotopes and therefore set precise therapeutical/imaging dose (as a radionuclidic cocktail) for nuclear medicine applications. The ratio of the above zinc-67 and/or zinc-64 isotopes to zinc-70 can be varied in order to prepare irradiated target portion comprising not only copper-67, but also copper-64 and/or copper-61 at correspondingly varied ratios.

[0027] The method preferably further comprises at least one physical and/or chemical separation step for separating the resulting copper isotope(s) from the irradiated target portion in order to yield on the one hand copper isotopes and on the other hand a target portion essentially purified from copper. Further separation steps may be included if necessary to eliminate possible further impurities or unwanted compounds and elements.

[0028] In the case where more than one zinc isotope is present in the zinc-70 enriched target, a plurality of copper isotopes will be obtained after irradiation. The above physical and/or chemical separation step will thus generally yield a composition comprising all the copper isotopes. One or more further isotope isolation step(s) can thus be envisaged if desired for isolating one or more of the different copper isotopes, e.g. copper-67, copper-64 and copper-61 using any appropriate method or combination of different methods, such as for example laser isotope separation techniques [14].

[0029] This is of particular interest in view of the different fields each of these isotopes can be used in, as mentioned above.

[0030] The physical and/or chemical separation step (s) are preferably chosen among ion exchange, electrolysis, extraction, sublimation or any combination of two or more of them.

[0031] In a further advantageous embodiment, the method further comprises a step of recycling the purified target portion in the preparation of the zinc-70 enriched target for use in the irradiation step.

[0032] A further aspect of the invention relates to the use of the copper isotopes obtained as claimed in any of claims 1 to 9 in the preparation of radiopharmaceuticals and/or radiation sources, which contain copper-67 or copper-67 in combination with copper-64 and/or copper-61.

[0033] As a conclusion, the different aspects of the present invention describe the deuteron irradiation of an enriched zinc target material, the selective recovery of

radioisotopes of copper from the enriched zinc target material, as well as the fabrication of new targets from such recovered target material. Such a method can produce sufficient quantities of such radioisotopes for use in the fields on nuclear medicine and/or nuclear chemistry. The method can further be effected using low or medium energy charged-particle accelerators, such as those commonly found at major medical treatment and/or research facilities. Finally, the above presented method allows to minimize the expenses in relation with preparing said radionuclide(s).

Brief Description of the Drawings

[0034] Preferred embodiments of the invention will now be described, by way of example, with reference to the accompanying drawings in which:

Fig. 1 is a schematic diagram of reactions which can occur in a method of the invention; and

Fig. 2 is a figure showing the comparison of cross-section data for different known production methods of copper-67 and that of the present invention.

[0035] Further details and advantages of the present invention will be apparent from the following detailed description of not limiting embodiments.

Examples

Example 1

[0036] 97 % enriched zinc-70 metal foil target of diameter of about 1 cm, mass of about 56 mg and thickness of about 100 μm is placed together with/or without thin catcher protecting metallic foil (e.g. 30 μm Ti) into a dedicated holder equipped with appropriate water or helium cooling loop and irradiation with deuteron beam of 15 pA of incident energy of 20 MeV is performed for 3 hours as continuous single irradiation. Deuterons can be accelerated to incident energy of 20 MeV on a cyclic (e.g. cyclotron) and/or linear accelerator (e.g. tandem electrostatic accelerator). All chemicals used in the preparation process should be of highest available purity, particularly with respect to Cu and Zn contaminants content. The target is dissolved in appropriate concentrated acid (e.g. HCl) and produced copper-67 is separated by ion exchange chromatography from other activation by-products and the zinc-70 target, which is then recycled for next irradiations by electrolysis.

Example 2

[0037] A powder mixture of about 200 mg of enriched zinc-70 oxide and zinc-67 oxide is placed into metallic target holder or capsule (e.g. made of Platinum) with appropriate water or helium cooling loop and with cavity of diameter of about 0.8 cm and thickness of about 300 μm. The cavity may be closed with a metallic foil (e.g. 30 μm Al, Havar®, Ti, etc.). The target is then placed into beam and irradiated with deuterons of selected incident energy of 19 MeV, accelerated on a cyclotron. Irradiation is performed in 12 hours or in a series of shorter-time irradiations to give 12 hours of total irradiation time. After the end of bombardment the zinc mixture target is transferred to appropriate radiation shielding container, hot-cell or a glovebox for further processing. All chemicals used in the preparation process should be of highest available purity, particularly with respect to Cu and Zn contaminants content. Target is dismantled and zinc oxides are placed into oven with temperature gradient from 300 to 1200°C, equipped with gas flow washing system. Produced nuclides of copper and others are separated thermochromatographically from the zinc oxide mixture target, which is recovered and recycled for next irradiations using known chemical processes.

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[0038]

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Claims

1. A method for the production of copper-67 comprising providing a zinc-70 enriched target; and irradiating at least a portion of the target with deuteron particles, thereby producing an irradiated target portion comprising copper-67.

2. The method as claimed in claim 1, wherein the zinc-

70 enriched target is a zinc-70 enriched target containing at least 50 at-%, preferably at least 60 at-%, still more preferably at least 75 at-%, in particular at least 85 at-% of zinc-70.

3. The method as claimed in any one of claims 1 or 2, wherein said deuteron particles have an incident energy between 5 and 35 MeV, preferably between 10 and 25 MeV and still more preferably between 14 and 22 MeV.

4. The method as claimed in any one of claims 1 to 3, wherein the irradiation is effected in a cyclic and/or linear accelerator.

5. The method as claimed in any one of claims 1 to 4, wherein the zinc-70 enriched target further contains zinc-67 and/or zinc-64, thereby producing an irradiated target portion comprising copper-67, as well as copper-64 and/or copper-61.

6. The method as claimed in any one of claims 1 to 5, further comprising one or more physical and/or chemical separation step(s) for separating copper isotopes from the irradiated target portion to yield copper isotopes and a purified target portion.

7. The method as claimed in claim 6, further comprising one or more isotope isolation step(s) for isolating one or more of the different copper isotopes, preferably using laser separation.

8. The method as claimed in claim 6 or 7, wherein the physical and/or chemical separation step(s) are chosen among ion exchange, electrolysis, extraction and sublimation or combinations thereof.

9. The method as claimed in any one of claims 6 to 8, further comprising a step of recycling the purified target portion in the preparation of the zinc-70 enriched target for use in the irradiation step.

10. Use of the copper isotopes obtained as claimed in any of claims 1 to 9 in the preparation of radiopharmaceuticals and/or radiation sources, which contain copper-67 and/or copper-64 and/or copper-61.

Fig. 1

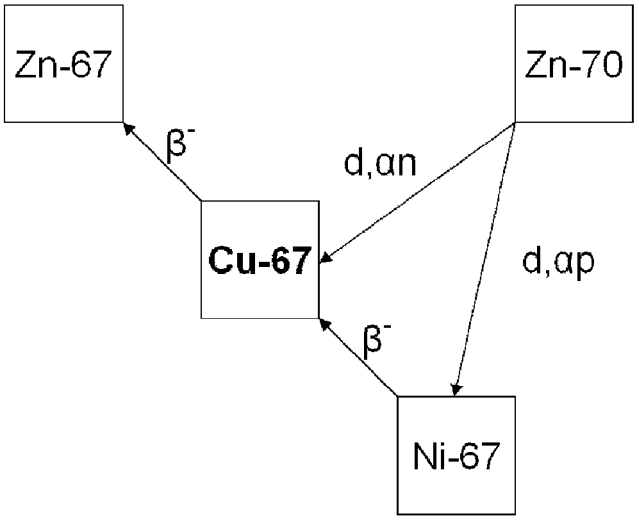
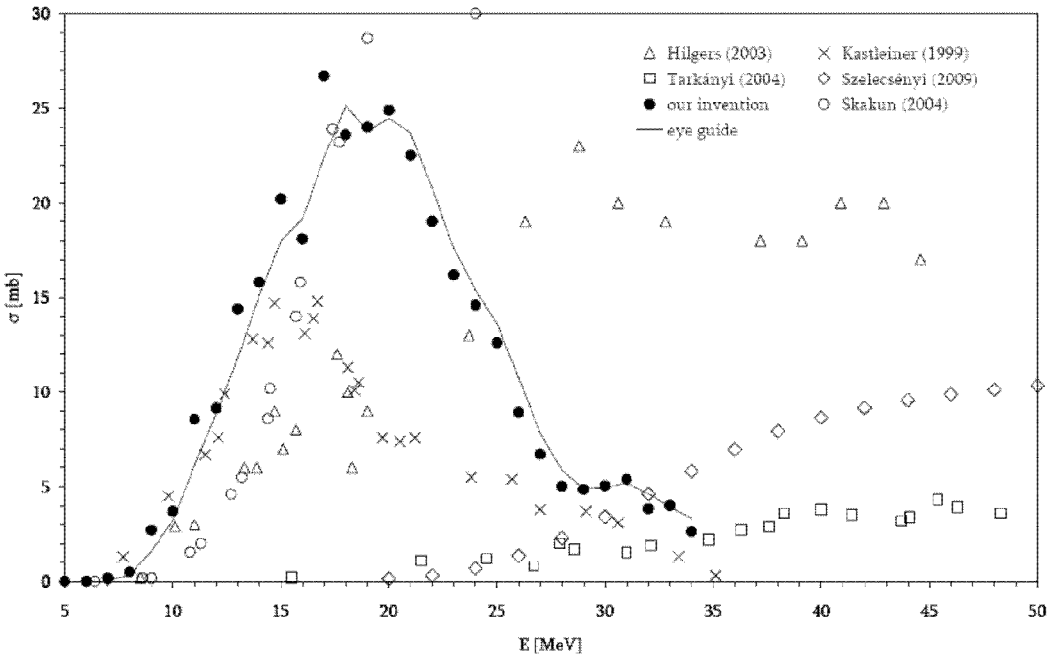

Zn-67
Zn-70
β-
d,αn
Cu-67
d,αp
β-
Ni-67

Fig. 2


Hilgers (2003)
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Kastleiner (1999)
Szelecsényi (2009)
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EUROPEAN SEARCH REPORT

Application Number
EP 10 15 8461

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	TARKANYI F ET AL: "Excitation functions of deuteron induced nuclear reactions on natural zinc up to 50 MeV" NUCLEAR INSTRUMENTS & METHODS IN PHYSICS RESEARCH, SECTION - B:BEAM INTERACTIONS WITH MATERIALS AND ATOMS, ELSEVIER, AMSTERDAM, NL LNKD- DOI:10.1016/J.NIMB.2003.11.089, vol. 217, no. 4, 1 June 2004 (2004-06-01), pages 531-550, XP004505943 ISSN: 0168-583X * page 549, left-hand column, line 22 - line 27; figure 8 *	1-10	INV. G21G1/10 ADD. G21G1/00
A	US 6 490 330 B1 (JAMRISKA SR DAVID J [US] ET AL) 3 December 2002 (2002-12-03) * abstract; paragraph [0011] *	1-10	
A	US 4 487 738 A (O'BRIEN JR HAROLD A [US] ET AL) 11 December 1984 (1984-12-11) * abstract; figure 1 *	1-10	TECHNICAL FIELDS SEARCHED (IPC) G21G

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	15 June 2010	Smith, Christopher

CATEGORY OF CITED DOCUMENTS

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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