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(54) Title: PROCESS FOR THE RECOVERY OF A RADIOISOTOPE FROM AN IRRADIATED TARGET

(57) **Abstract:** The present invention relates to an improved process for the recovery of a radioisotope from an irradiated target which comprises a solid surface material. The improvement comprises sonication of the target dissolution medium using either external sonication (e.g. a sonication bath), or internal sonication (e.g. a sonication probe immersed in the dissolution medium). The method provides faster and more efficient recovery of radioisotope under milder conditions.

Target Process

Field of the Invention.

The present invention relates to an improved process for the recovery of a radioisotope from an irradiated target, such as a target from a cyclotron. The improvement comprises sonication of the target dissolution medium.

Background to the Invention.

It is known to prepare radioisotopes by bombardment of a non-radioactive target with particles, especially protons in a cyclotron, to convert a small percentage of the irradiated target surface into one or more radioisotopes. The radioisotope is then separated from the target by either:

(i) complete dissolution of the target plus radioisotope,

(ii) partial dissolution of the target plus radioisotope, such that only the target surface containing the radioisotope is removed, leaving the target ready for further irradiation and purification cycles.

In both cases, the dissolution medium is subjected to further purification steps involving one or more selective separation techniques such as ion exchange chromatography, solvent extraction or precipitation. Method (ii) may employ controlled conditions such as limited concentrations or amounts of chemicals, or solvents in which only the target surface has significant solubility. Method (ii) is preferred where the target is relatively precious, eg. an artificially enriched level of a particular isotope to improve the yield of the desired radioisotope product, or the target comprises a precious metal. Method (ii) also has the advantage that there are lower levels of the non-radioactive target material present in solution. This makes the subsequent separation and purification of the radioisotope more straightforward. This is particularly useful when the radioisotope is to be used for medical applications involving administration to the human body (ie. a radiopharmaceutical), where removal of the potentially toxic levels of the non-radioactive target material (typically a heavy metal) is highly desirable.

US 4487738 discloses that carrier-free ^{67}Cu can be produced by proton spallation of a zinc oxide target with subsequent chemical separation and purification. The zinc oxide target is irradiated with protons having an energy of 800 MeV, and the irradiated target dissolved in concentrated acid. The ^{67}Cu is then separated by a series of ion exchange chromatography and precipitation procedures.

US 3993538 discloses that ^{201}Tl suitable for use as a myocardial imaging radiopharmaceutical can be prepared by bombardment of a thallium target with 20-30 MeV protons *via* the reaction ^{203}Tl (p,3n) ^{201}Pb. The ^{201}Pb radioisotope formed has a half-life of 9.4 hours, and decays to the desired ^{201}Tl. After irradiation, the target is completely dissolved in concentrated nitric acid forming soluble lead and thallium nitrates. Evaporation and further chemical purification steps gave the desired ^{201}Tl product.

Use of target materials comprising two or more metals is known. Thus, US 4297166 discloses a thallium target for the production of the radioisotope ^{201}Tl, in which the ^{203}Tl target material is electroplated onto an electroconductive support such as copper or silver. The electroconductive support has two advantages. First, it can be used to provide efficient cooling of the thallium layer (*via* a circulating fluid such as water or gas). Second, it can facilitate target processing, since only the thallium target layer and radioisotope formed is dissolved during processing. This makes the purification of the ^{201}Tl radioisotope more straightforward, since the processed target solution does not contain substantial amounts of the non-radioactive electroconductive support (eg. copper). After chemical processing, the target electroconductive support can then simply be reused by electroplating with more thallium, and subsequent proton bombardment.

JP 04-326096 A (1992) discloses a cyclotron target which comprises silver plated onto a copper support. The desired target material (^{68}Zn) is plated onto the silver, and then irradiated with a proton beam. The silver layer means that no copper is present in the acid processing solutions, ie. the recovery and purification of the desired ^{68}Zn radioisotope is simplified.

US 6011825 discloses a cyclotron method for the production of radioisotopes, especially ^{64}Cu. The ^{64}Cu is produced by proton bombardment of a target which comprises ^{64}Ni deposited onto a gold substrate. The irradiated ^{64}Ni together with the ^{64}Cu product are dissolved off the gold disk in 6.0 M hydrochloric acid at 90 °C.

Prior art chemistry used to process targets therefore typically employs concentrated solutions of mineral acids (eg. hydrochloric acid), or powerful oxidising agents such as hydrogen peroxide. Acids which are also powerful oxidising agents, such as concentrated nitric acid may also be used. Heating is often also applied. Such forcing conditions are understandable given that the target material to be dissolved may be a relatively unreactive metal such as rhodium. The difficulty of achieving the required dissolution of the target may also mean that extended contact times are required. For radioisotopes, all such target processing time is time during which radioactive decay of the desired product is occurring, ie. product is being lost. The shorter the half-life of the radioisotope product, the bigger the potential problem this represents.

An additional problem with the use of such prior art forcing conditions is that careful handling of the radioactive process solution is required due to the chemical hazard as well as the radioactive hazard. In addition, when it is intended that only the surface of the irradiated target should be dissolved, such conditions increase the likelihood of dissolution of other elements of the target e.g. the electroconductive support. It is also the case that the process solutions consequently require more chemical processing, eg. to neutralise the strong acid, before proceeding further with the isolation and purification of the radioisotope.

There is therefore a need for an improved method of processing such radioisotope targets under milder conditions.

The Present Invention

In a first aspect, the present invention provides a process for the production of a preparation containing a radioisotope from an irradiated target comprising:

(i) providing an irradiated target having
 a support material comprising silver; and
 a surface solid material comprising said radioisotope;
 wherein the surface solid material is disposed on said support material;

(ii) treating the irradiated target with a dissolution medium;

(iii) applying sonication to the dissolution medium whilst it is in contact with the surface solid material of said irradiated target so that a portion of the radioisotope in the surface solid material dissolves in the dissolution material;

(iv) isolating the dissolution medium containing the radioisotope;

(v) subjecting the dissolution medium to purification, thereby producing a preparation containing the radioisotope; and

(vi) optionally repeating steps (ii) to (v);

wherein the applying step is carried out under milder conditions compared to other conditions without sonication.

The target of the present invention suitably comprises a 'surface solid material' which, when irradiated with charged particles reacts to give one or more radioisotopes. The surface solid material is thus that part of the irradiated target which reacts during the irradiation to give the desired radioisotope product. The charged particles are suitably derived from an accelerator, preferably a cyclotron. The charged particles may be protons, deuterons, alpha, ^{3}He or electrons, and are preferably protons. Suitable surface solid materials include metals such as thallium, cadmium, rhodium, molybdenum or zinc, or metal oxides such as zinc oxide, strontium oxide or gallium oxide, plus such materials containing an artificially enriched level of a particular isotope. Preferred surface solid materials are those which are suitable for plating (eg. by electroplating or electroless deposition) onto a support material.

The target comprises a 'support material' onto which is provided an outer coating of the surface solid material to be irradiated. The support material functions to provide effective cooling of the irradiated surface solid material during the irradiation, and permits separation of the radioisotope product, leaving the support material substantially unchanged, ready to be reused. The 'support material' comprises a material which is a good conductor of heat and/or electricity, ie. electroconductive such as silver. The support material is suitably of a shape and size that permits facile production, as well as ease of attachment and detachment from the target assembly. A preferred shape of the support material is a plate.

The support material may comprise silver, but most preferably is made entirely of silver, since silver has advantages over copper. The non-radioactive copper of a copper support material can dissolve in acidic dissolution media (especially nitric acid). This makes purification and isolation of the radioisotope more difficult, by eg. increasing the viscosity of the dissolution medium, making solvent extraction of the radioisotope product more difficult. Hence one advantage of the use of silver as the support material is that silver does not dissolve readily in nitric acid, which makes subsequent purification of the radioisotope easier. Silver does, however, have a finite solubility in concentrated hydrobromic acid, hence is less advantageous when the dissolution medium comprises concentrated hydrobromic acid.

In addition, when copper is the support material, and the target is subjected to proton bombardment, any protons which penetrate the surface solid material and are captured by the copper lead to the production of the potential impurity radioisotope ^{65}Zn. At least a portion of any ^{65}Zn formed may dissolve in the dissolution medium, especially when the dissolution medium comprises aqueous acid, since Zn(0) dissolves in acid. ^{65}Zn has a half-life of 244 days, and hence both the copper target support material and the dissolution medium are, in effect, contaminated for a prolonged period. For the copper support plate, the period necessary to await radioactive decay of the ^{65}Zn is so long (minimum 10 half-lives), that corrosion of the copper support is likely to occur during the storage period to allow for decay. Hence, in effect the copper plate cannot be reused. Also, any ^{65}Zn contamination of the dissolution medium means that, even after the desired radioisotope product has been isolated or extracted, the dissolution medium must be kept for prolonged periods to await decay of the ^{65}Zn. In contrast, when the support material comprises silver, any protons captured by the silver generate the radioisotopes ^{105}Ag and ^{106m}Ag, which have half-lives of 41.3 and 8.5 days respectively. The result is that such silver target supports can be reused after an appropriate decay period (suitably of approximately one year).

Radioisotopes which can be prepared using the present process include ^{201}Tl, ^{83}Rb, ^{88}Y, ^{88}Zr, ^{96}Tc, ^{97}Ru, ^{111}In, ^{67}Ga, ^{68}Ge, ^{57}Co, ^{103}Pd, ^{62}Cu and ^{67}Cu. The process is especially useful for ^{201}Tl, ^{111}In, ^{67}Ga, ^{103}Pd, ^{57}Co and ^{62}Cu, particularly ^{201}Tl. The present invention may also be applied to the production of parent radioisotopes which decay to give positron emitters useful as radiopharmaceuticals, as used in so-called radioisotope generators. Suitable parent radioisotopes (with positron-emitting daughter) include: ^{82}Sr (^{82}Rb), ^{68}Ge (^{68}Ga) and ^{62}Zn (^{62}Cu).

When the target of the present invention includes a support material, the support material may optionally further comprise an 'inert layer' at its' outer surface. The inert layer suitably forms an unreactive layer interspersed between the surface solid material and the bulk of the support material. The inert layer comprises a material which is essentially insoluble in the dissolution medium, and thus protects the support material from partial dissolution when the irradiated target is processed. Preferably, the inert layer is provided at a thickness of less than 10 μm, to maximise the transparency of the inert layer to the charged particles used in the target irradiation, and hence minimise potential radioisotopic impurities arising due to capture of the charged particles by the inert layer itself. The inert layer functions to minimise dissolution of the target support material, together with any radioisotopic impurities formed *via* irradiation of the target support material (eg. the low energy gamma emitters ^{105}Ag or ^{106m}Ag from a silver support material), into the dissolution medium. Any such dissolution could introduce potential impurities into the desired radioisotope product. Suitable inert layers comprise unreactive metals such as silver, gold, platinum, tungsten, tantalum or nickel. When the surface solid material is zinc, and the support material is copper, then nickel represents a preferred inert layer material. Preferably the inert layer comprises gold or silver, most preferably gold. Gold has the advantage that it has greater passivity (ie. is less reactive chemically), and is most suitable for accepting the plated solid material of the target.

The sonication of the present invention may suitably be provided either by an ultrasonic probe which is immersed in the dissolution medium, or *via* external sonication of the container or bath containing the dissolution medium. Suitable sonication probes and sonication baths are commercially available.

The sonication apparatus converts the frequency of the power supply (eg. 50 to 60 Hz) to high frequency 20 kHz electrical energy. This high frequency electrical energy is in turn converted *via* a transducer in the sonication apparatus to mechanical vibrations (either of the sonication probe or sonication bath). The mechanical vibrations are intensified by the sonication apparatus, thus creating pressure waves within the dissolution medium. These pressure waves form microbubbles in the dissolution medium, which expand during the negative pressure phase, and implode violently during the positive pressure phase. This phenomenon is known as cavitation, and causes the molecules in the dissolution medium to become intensely agitated. Suitable sonication probes have a level of cavitation at the horn tip of ca. 500 W/cm², and a frequency of ca. 20 kHz, whereas suitable sonication baths may have a lower cavitation level of ca. 1 W/cm² at the horn tip, with a frequency of 36-42 kHz.

The sonication bath may comprise any material compatible with the dissolution medium, but is preferably Teflon^{TM}. For the production of ^{201}Tl, it has been found that there are separation distance effects (see Examples 1 and 2). Thus, whilst the dissolution can be accelerated using an ultrasonic immersion probe, the irradiated ^{203}Tl-enriched target material in proximity to the probe was found to be dissolved smoothly, whereas those parts of the irradiated target more distant from the probe were harder to dissolve. Thus, an immersion probe gives less uniform effects due to inhomogeneity, whereas ultrasonic baths give more uniform or homogeneous performance. It is therefore preferred that, when the size and geometry of the target is suitable for immersion of the whole target in a sonication bath, that such a sonication bath is used, ie. that external sonication of the dissolution medium is applied. External sonication also gives shorter dissolution times (see Example 1), and is more convenient since there is no need to wash or decontaminate the immersion probe between preparations. Internal sonication may, however, be the best option when the size and geometry of the target is such that only a portion of the target can be immersed in a sonication bath.

The shorter dissolution times of the present invention are believed to result from improved kinetics of mixing the dissolution medium with the surface solid material, due to the cavitation of the dissolution medium. This confers particular improvements where the solubility of the irradiated target material in the dissolution medium is low, especially when it is necessary to dissolve the whole irradiated target. For the radioisotope product, any reduction in the target processing time results in an improved yield, because there is reduced loss due to radioactive decay during target processing. Clearly, this problem is exacerbated the shorter the half-life of the radioisotope, such as positron emitters which may have half-lives of the order of a few hours. Shorter processing times also reduce the risk of radiation dose to the operator, by reducing the time spent in target processing.

The process of the present invention also permits the use of much milder conditions for processing the irradiated target. This includes the use of more dilute solutions of acids and/or oxidants, lower temperatures, and shorter reaction times. In the case of a ^{203}Tl target for the production of ^{201}Tl, dilute aqueous nitric can be used as the dissolution medium instead of the conventional concentrated nitric acid solution (7 molar). By the term 'dilute aqueous nitric acid' is meant an aqueous solution which is 0.5 to 1.5

molar; preferably 0.8 to 1.2 molar, most preferably about 1 molar. The use of such dilute nitric acid results in a significant reduction in the undesirable dissolution of the silver or copper support of the irradiated target, and thus facilitates purification of the ^{201}Tl product. The use of such milder dissolution media also has the advantage that it presents less of a corrosion hazard to the plant used to carry out the process.

In a second aspect, the present invention provides an improved process for the production of ^{201}Tl. The improved process comprises the use of the sonication process as described above, together with a target which comprises ^{203}Tl as the surface solid material, where the target is irradiated with protons, and the dissolution medium is 'dilute nitric acid' as defined above. The support material preferably comprises silver, and most preferably is made entirely of silver metal. The use of silver as the support medium has the advantages described above, and the sonication method provides a shorter processing time, which gives improved yields of ^{201}Tl.

The radioisotope ^{201}Tl illustrates an additional reason why shorter processing times are important. It is typically produced by proton beam irradiation of a ^{203}Tl-enriched solid target material, giving ^{201}Pb *via* a (p,3n) nuclear reaction, and subsequent extraction of the trace amount of ^{201}Pb produced. The ^{201}Pb initial product decays to ^{201}Tl with a half-life of 9.4 hours. This means that the ^{201}Pb must be chemically separated from the target ^{203}Tl before the desired ^{201}Tl can be obtained, since once the ^{201}Tl decay product has formed, it is chemically identical to the ^{203}Tl target material, and hence impossible to separate therefrom. Therefore it is critically important to decrease the loss of ^{201}Tl by shortening the time period necessary to achieve the separation of the ^{201}Pb initial product from the ^{203}Tl-enriched target material after the completion of the proton irradiation. Thus, in the case of ^{201}Tl, there is a chemical separation reason why shorter irradiated target dissolution times are important. Theoretical calculations indicate that every one hour increase in the processing period results in a 7.7 % loss of yield of the final product ^{201}Tl.

The invention is illustrated by the following Examples:

Example 1: Sonication of ^{203}Tl Targets (Comparative Example).

Three identical silver target plates (ie. targets where solid silver is used as the support material, in the shape of a plate, without an inert layer) were electroplated with 1200mg of ^{203}Tl, and immersed into a dissolution medium of 5% aqueous nitric acid solution (molarity ca. 1M) in three separate baths. The dissolution of the ^{203}Tl-thallium target material was carried out:

(a) without sonication,

(b) with a 100 W ultrasonic probe,

(c) with an ultrasonic bath (300 W).

Dissolution of all the ^{203}Tl target material took 20 minutes using internal sonication with the immersed probe (b), and 13 minutes using external sonication *via* the bath (c). Without sonication, ie. method (a), the thallium target material could not be dissolved even at 30 minutes after the addition of the dilute nitric acid.

Example 2: Production of ^{201}Tl Using a Silver-containing Target.

A target having solid silver in the shape of a plate as the support material, and having 1200 mg of ^{203}Tl-enriched material plated thereon as the surface solid material, was attached to a target support assembly made of aluminium. The target was irradiated for 8 hours with protons, using a proton beam of about 30 MeV. The dissolution of the irradiated ^{203}Tl-enriched target material was carried out in an ultrasonic bath of 300 W sonication power, with 5% aqueous (ie. ca. 1M) nitric acid as the dissolution medium. The dissolution was complete in about 10 minutes. Hydrochloric acid was then added to the solution.. The separation of the ^{201}Pb radioisotope produced was achieved by solvent extraction of the irradiated ^{203}Tl-enriched target material using diisopropylether.

The ^{201}Pb separation from the end of the proton bombardment took 1.6 hours to complete. Thus the total processing times compared to those without sonication are as follows:

	Without sonication (Prior art)	Example 2
Dissolution time (min)	25-30	10-15
Evaporation time for the nitric acid (min)	40	0
Total processing time	2.4 hours	1.6 hours

Thus, the method of the present invention saves ca. 0.8 hours.

The yield of radioactivity of ^{201}Tl obtained *via* this method was 21.9 GBq per target plate at 15 hr after the completion of the ^{201}Pb separation.

Example 3: Production of ^{201}Tl using a Copper-containing Target.

A target plate made of copper as the support material, and having ^{203}Tl-enriched target material plated onto its' surface was attached to a target support assembly made of aluminium for ^{201}Tl preparation, and irradiated with protons as per Example 2. After dissolution of the target material in a bath using 7 M nitric acid as the dissolution medium, the extraction of the irradiated ^{203}Tl-enriched target material was performed in the same way as Example 2; except that the separation sequence was as follows:

(i) evaporation of the nitric acid,

(ii) dissolution of the precipitate (which includes a copper salt) with a small volume (ca. 10 ml) of aqua regia,

(iii) addition of hydrochloric acid, and

(iv) solvent extraction.

Using this method, it took 2.5 hours to complete the ^{201}Pb separation from the end of the bombardment. The amount of radioactivity of ^{201}Tl obtained using this method was 18.8 GBq per plate at 15 hr after the separation of ^{201}Pb in this reference method. The lower yield of ^{201}Tl compared to Example 2 can be attributed to:-

(a) the process period for the ^{201}Pb separation is longer than that of Example 2 by 1 hour,

(b) the dissolution of significant amounts of the copper plate into the nitric acid dissolution medium reduces the efficiency of the process after the separation of the ^{201}Pb.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process for the production of a preparation containing a radioisotope from an irradiated target comprising:
   (i) providing an irradiated target having
   a support material comprising silver; and
   a surface solid material comprising said radioisotope;
   wherein the surface solid material is disposed on said support material;
   (ii) treating the irradiated target with a dissolution medium;
   (iii) applying sonication to the dissolution medium whilst it is in contact with the surface solid material of said irradiated target so that a portion of the radioisotope in the surface solid material dissolves in the dissolution material;
   (iv) isolating the dissolution medium containing the radioisotope;
   (v) subjecting the dissolution medium to purification, thereby producing a preparation containing the radioisotope; and
   (vi) optionally repeating steps (ii) to (v);
   wherein the applying step is carried out under milder conditions compared to other conditions without sonication.

2. The process of claim 1, where only the surface solid material is dissolved.

3. The process of claim 1 or 2, where the irradiated target further comprises an inert layer interspersed between the surface solid material and the support material.

4. The process of any one of claims 1 - 3, where the irradiated target is irradiated with protons.

5. The process of any one of claims 1 - 4, where the dissolution medium comprises an oxidising agent.

6. The process of any one of claims 1 - 5, where the dissolution medium comprises an acid.

7. The process of any one of claims 1 - 6, where the sonication is applied *via* a sonication probe immersed in the dissolution medium.

8. The process of any one of claims 1 - 6, where the sonication is applied *via* external sonication of the dissolution medium.

9. The process of any one of claims 1 - 8, where the surface solid material comprises molybdenum, nickel, rhodium, zinc, zinc oxide, copper, thallium, cadmium or gallium oxide.

10. The process of any one of claims 1 - 9, where the radioisotope is ^{201}Tl, ^{83}Rb, ^{88}Y, ^{88}Zr, ^{96}Tc, ^{97}Ru, ^{62}Cu, ^{67}Cu, ^{111}In, ^{67}Ga or ^{68}Ge.

11. A process for the production of a preparation containing a ^{201}Tl radioisotope from an irradiated target comprising:
    (i) providing an irradiated target having a surface solid material which comprises ^{203}Tl and ^{201}Pb on a support material;
    (ii) treating the irradiated target with a dissolution medium which comprises dilute aqueous nitric acid;
    (iii) applying sonication to the dissolution medium whilst it is in contact with the ^{203}Tl and ^{201}Pb surface solid material of said irradiated target so that a portion of the ^{201}Pb radioisotope in the surface solid material dissolves in the dissolution medium;
    (iv) isolating the dilute nitric acid dissolution medium containing the ^{201}Pb radioisotopes;
    (v) subjecting the dissolution medium to purification, thereby producing a preparation containing the ^{201}Tl radioisotope; and
    (vi) optionally repeating steps (ii) to (iv).

12. The process of claim 11, where the support material is silver.

13. The process of claim 11 or 12, where the sonication is applied *via* external sonication of the dissolution medium.

14. A process for the separation of a radioisotope from an irradiated target substantially as herein described with reference to either example 2 or 3.