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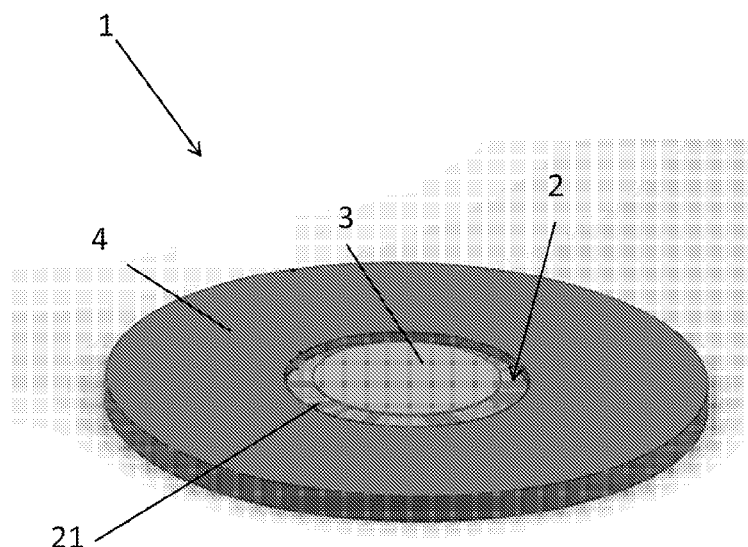


Fig. 1

(57) **Abstract:** Method (100) for obtaining a solid target for radionuclides production by cyclotron, comprising the steps of : - arranging at least one first supporting element (2), having at least one first surface (21) intended to support at least one precursor isotope (3), and at least one second surface (22) opposed thereto (step 110); and - applying said at least one precursor isotope (3) on said at least one first surface (21) of said at least one first supporting element (2). The at least one first supporting element (2) is a chemically inert material at conditions of dissolution of said at least one precursor isotope (3) and at least one radioactive isotope of interest produced upon irradiation of said target (1) by said cyclotron.



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## METHOD FOR OBTAINING A SOLID TARGET FOR RADIOPHARMACEUTICALS PRODUCTION

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## BACKGROUND

The present invention relates to the field of radionuclides production and, in particular, to a method for obtaining a target or solid state target, for use in the production of radiopharmaceuticals for diagnostic and therapeutic purposes, through use of a particle accelerator, more particularly a cyclotron.

The present invention also relates to a system for production of said radionuclides.

## STATE OF THE ART

Nuclear Medicine is a branch of medicine that uses radiopharmaceuticals both for diagnostic and therapeutic purposes.

One of these,  $^{99m}\text{Tc}$ , is an extremely important radioactive isotope, used in almost all types of traditional diagnostic exams.

$^{99m}\text{Tc}$  is currently extracted from portable generators containing the precursor radioactive isotope  $^{99}\text{Mo}$  coming from fission reactors, which use highly enriched  $^{235}\text{U}$ . As of today, 95% of  $^{99}\text{Mo}$  is produced by five plants which are over 50 year old and, since the stable supply of  $^{99}\text{Mo}$  cannot be guaranteed in the future, alternative routes for the production of  $^{99m}\text{Tc}$  based on particle accelerators (cyclotrons) were developed.

Currently, the reaction  $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$  is considered to be the most favourable for the direct production of  $^{99m}\text{Tc}$  by means of a cyclotron, starting from the precursor isotope  $^{100}\text{Mo}$ , and it was found that, in order to obtain the maximum production of  $^{99m}\text{Tc}$  with minimal impurities by means of small medical cyclotrons (e.g., GE PETtrace supporting a standard current of about 100  $\mu\text{A}$ ), it is necessary to impart the protons in the cyclotron, intended to hit a target formed by a layer of enriched  $^{100}\text{Mo}$  and having a thickness of the order of about 100  $\mu\text{m}$ , applied to a corresponding supporting element (in technical jargon also backing), an energy optionally comprised between about 10 MeV and about 22 MeV.

In this regard, various targets for different types of cyclotron have been developed and tested and various irradiation tests with  $^{100}\text{Mo}$ , metal oxide and carbide natural Mo, applied to different supporting elements [1, 2] have been conducted.

The radiopharmaceutical production requires that the targets to be used in combination with a cyclotron meet two fundamental requirements: they must guarantee a high level of heat dissipation, so as to be able to apply the maximum current that can be

delivered by the cyclotron, during the irradiation of the target, and obtain the maximum production yield; and they must also ensure a high inertia of the supporting element in (standard) conditions of the target dissolution, to guarantee the chemical and radiochemical purity of the final product.

5           Although oxides [1-5], carbides [1, 2], and also targets in solution [1, 2] have been studied, metal Mo targets are considered the most suitable for the purpose, since the metal Mo target provide high production yields of  $^{99m}\text{Tc}$ .

          This is due to the high level of heat dissipation, associated with a good thermal conductivity of metal. In fact it was noted that just the presence of oxygen traces drastically  
10       reduces the thermal conductivity of the material.

          For the production of a target having the above mentioned characteristics of heat dissipation and chemical inertia, two different approaches have been taken into consideration at present. According to a first approach, one target can be manufactured by means of a preparation step of a coin or pellet of precursor isotope of Mo, followed by a subsequent step  
15       of adhesion to a supporting element. According to a second approach, the precursor isotope of Mo is directly deposited on a supporting element.

          With reference to the first approach,  $^{100}\text{Mo}$  is commercially available in the form of metal powder, therefore different research groups have proposed the transformation of the powder of  $^{100}\text{Mo}$  in a dense and not porous pellet or sheets - using different methods,  
20       including pressing, sintering and lamination - to be applied to a respective supporting element.

          However, the targets produced only by hydraulic pressing of metal powder [1, 2, 6-8] have proven to be able to support only low cyclotron currents, because the density of the pellets thus produced is much less than that of the bulk material.

25           With the sintering technique of Mo powders [2, 9, 10] in reduced or inert atmosphere [1, 2, 6-8] followed by pressure bonding [1, 2, 6-8] or vacuum brazing [2, 9, 10] targets of Mo were made which support currents of the order of hundreds of  $\mu\text{A}$  and standard procedures are considered rolling, starting from dust or beads of Mo, produced by melting the powder through e-beam [1, 2, 11], or recasting of the Mo powders followed by remodelling through  
30       rolling.

          The targets produced according to the first approach have shown, however, not to be fully satisfactory. In fact, they showed to be adequate for manufacturing, since it is very

difficult to provide a good thermal contact between the pellets or sheets of Mo and the supporting element, during irradiation by the cyclotron.

With reference to the second approach for manufacturing a target for the production of  $^{99m}\text{Tc}$ , direct deposition of Mo on a supporting element was obtained by direct fusion of the powders of Mo on the support material (backing) itself [12]. This approach, however, has shown that it does not guarantee an acceptable uniformity of the layer of Mo.

It has also been considered also the technique of electrodeposition of metals in aqueous solutions, which is a well known industrial process, but it has proved to be difficult to deposit refractory metals such as Mo, with standard techniques of electrodeposition, due to their great affinity with oxygen. Techniques have been disclosed of electrodeposition, in particular alkaline solutions [13] or acetates [14]. This type of deposition has shown a high level of oxidation and a thickness no greater than about 20  $\mu\text{m}$ .

In addition, the electrodeposition process from aqueous solution is very inefficient. In fact, only a percentage quantity of Mo below 2% remains deposited onto the support material, due to the high affinity of Mo with the oxygen of the aqueous solution. Moreover, it has been reported [15] that the co-deposition of molybdenum with zinc is much more efficient. The electrodeposition in ionic liquids or molten salts [2, 16, 17] provides for a better quality of the layer of Mo, but requires expensive equipment and more difficult protocols.

With the electrophoretic deposition from a mixture of powders of Mo and additives, followed by sintering at high temperature, Mo films were obtained having a sufficient thickness, resistant to a current of 300  $\mu\text{A}$ , at conditions of target inclined, at power density reduced with respect to an orthogonal target and same intensity of current delivered [1, 18]. Through further improvements to the sintering process in inert atmosphere [2] the actual targets support up to 500  $\mu\text{A}$ .

The main disadvantage of all electrochemical deposition methods mentioned above is, however, the incapacity of avoiding impurities coming from the electrolytic bath in the manufactured target, which is a serious limit for medical applications relating to the present invention.

PVD methods of direct deposition of Mo have also been considered, which include a thermal spray (Thermal spray) [19], cathodic arc [2], argon [20] and xenon [21] sputtering FIB.

At the moment information regarding tests under cyclotron beam are not available for target obtained by the arc sputtering and FIB technique and, although with the FIB-sputtering

technique thicknesses of Mo films more than a few microns have not been reported, the method seems very interesting because it allows: the use of minimum quantities of isotope, to have very low losses of the expensive material (enriched<sup>100</sup>Mo ) during deposition, and to obtain a high purity of the target thus manufactured.

5 With reference to the supporting element to which enriched <sup>100</sup>Mo is to be directly applied or deposited for the production of <sup>99m</sup>Tc, at the moment the materials tested for its production are many and among them is copper [1, 2, 19, 22], aluminium [1, 2, 6-8, 11], the tantalum [1, 2, 6-8, 12, 18]GLIDCOP[2, 9, 10] and platinum [1, 2, 13].

10 The process of standard production of <sup>99m</sup>Tc with the reaction <sup>100</sup>Mo(p, 2n)<sup>99m</sup>Tc, provides, as mentioned above, for the irradiation by a cyclotron of a target comprising enriched <sup>100</sup>Mo and, after such irradiation, a standard step of dissolution of Mo and of the mixture of Tc in H<sub>2</sub>O<sub>2</sub> at a high temperature, optionally comprised between 60°C and 90°C. However, since the transition, post transition and refractory metals used up to now as support materials are not perfectly chemically inert under these conditions, even very small  
15 amounts of impurities in the mixture of Mo, Tc, H<sub>2</sub>O<sub>2</sub> can compromise the production of the radiopharmaceutical.

Therefore, there is a continuing demand for innovation regarding the manufacturing of targets for the production of radiopharmaceuticals by use of particle accelerators, in particular for the production of <sup>99m</sup>Tc.

20 The need to develop a method for obtaining a target that can be used in the production of radiopharmaceuticals is therefore felt, in particular for the production of <sup>99m</sup>Tc, allowing to minimize or eliminate the above mentioned drawbacks.

#### OBJECTS OF THE INVENTION

25 The main object of the present invention is to improve the state of the art in the field of production, through small sized particle accelerators (for example GE PETtrace), of radionuclides in general and <sup>99m</sup>Tc, in particular.

30 More particularly, it is an object of the present invention to provide for a method for obtaining a target, which target can be used in the production of a radionuclide, allowing for heat dissipation, during the irradiation step, which is higher with respect to traditional targets.

Another object of the present invention is to provide for a method for obtaining a target, which target can be used in the production of a radionuclide, allowing obtaining a high

thickness and a high uniformity of the precursor isotope coupled to the respective supporting element, with respect to the traditional targets.

A further object of the present invention is to provide for a method for obtaining a target, which target can be used in the production of a radionuclide, allowing obtaining low  
5 oxidation levels and a high adhesion of the precursor isotope coupled to the respective supporting element, with respect to the traditional targets.

A further object of the present invention is to provide for a method for obtaining a target, which target can be used in the production of a radionuclide, allowing reducing impurities generated in the production process, with respect to the traditional targets.

10 A still further object of the present invention is to provide for a system for the production of a radiopharmaceutical, allowing optimizing the radiopharmaceutical production, with respect to the traditional systems.

These and further aspects of the present inventions will be obtained by a method for obtaining a target, which target can be used in the production of a radionuclide, according to  
15 claim 1.

The dependent claims refer to preferred and advantageous embodiments of the invention.

#### BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be now described, for illustrative but not limiting purposes,  
20 according to its preferred embodiments, with particular reference to the drawings in the accompanying Figures, wherein:

Figure 1 shows a target which can be obtained by means of a preferred embodiment of the method of the present invention;

Figure 2 shows the main steps of the preferred embodiment of the method for  
25 obtaining the target of Figure 1;

Figure 3 shows process parameters relating to a step of the method of Figure 2;

Figure 4 illustrates the main elements of a system for dissolving the target of Figure 1;

Figure 5 is a scaled-up representation with parts in cross-section and in transparency,  
of some elements of the dissolution system of Figure 4; and

30 Figures 6a and 6b show some images relating to results of experimental tests conducted on a target obtained according to the method of the present invention.

#### EMBODIMENTS OF THE INVENTION

Before going into the merits of the invention, it is of note that in the description and in the claims which follow, explicit reference is made and will be made to radioactive isotope  $^{99m}\text{Tc}$ , but it is clear that the teachings of the present invention can be used for the production of other radioactive isotopes of medical interest, among which, purely by way of example,  $^{68}\text{Zn}$  for the production of  $^{64,67}\text{Cu}$ , radioactive isotopes  $^{68}\text{Ga}$ ,  $^{89}\text{Y}$  or  $^{\text{nat}}\text{Y}$  for the production of  $^{89}\text{Zr}$ ,  $^{52}\text{Cr}$  for the production of  $^{52}\text{Mn}$ ,  $^{\text{nat}}\text{Ti}$  for the production of  $^{48}\text{V}$ , the  $^{\text{nat},63}\text{Cu}$  for the production of  $^{62,63}\text{Zn}$ , etc. are mentioned.

It is also of note that the use of the terms "for example", "etc.", "or" indicates not exclusive alternatives without limitation, unless otherwise indicated, and the use of the term "includes" means "includes but is not limited to" unless otherwise indicated.

This being said, with reference to the accompanying drawings, it will be noted that a method for obtaining a solid target (represented in Figure 1 with reference numeral 1) for the production of at least one radionuclide by cyclotron, according to the present invention, is indicated with reference numeral 100 and comprises at least one first step (step 110) of providing at least one first supporting element 2, having at least one first surface 21, intended to support in use at least one precursor isotope 3, and at least one second surface 22 opposite to the first surface 21; and at least one second step (step 120) of application of said at least one precursor isotope 3 on the first surface 21.

The first supporting element 2 typically has a substantially flat configuration, for example circular or elliptical or rectangular in plan, with opposite surfaces 21 and 22 theirbetween, and can be obtained in bulk material, or in the form of layer, applicable, as will be explained hereinafter, to one second supporting element 4.

The first supporting element 2 is advantageously made of a chemically inert material (dielectric) under the conditions of dissolution of the precursor isotope 3 applied thereto and of the radioactive isotope produced after the irradiation by the cyclotron, in a deprived or not oxygen atmosphere), more in particular it is a material that is chemically inert with respect to a dissolution mixture with which it is intended to come into contact for further chemical separation between precursor isotope and radioactive isotope obtained, following the irradiation by the cyclotron.

In the specific case of production of radioactive isotope  $^{99m}\text{Tc}$  produced starting from  $^{100}\text{Mo}$ , the chemically inert material (dielectric) at the conditions of dissolution, which makes up the first supporting element 2, comprises a material chosen among sapphire, synthetic



diamond, quartz, glass, silicon, carbon compounds, glassy carbon, silicon oxide, aluminium oxide, magnesium oxide, zirconium oxide, advanced ceramics, or DLC (Diamond-like carbon or synthetic diamond), graphene, polymeric materials and the like or combinations thereof. The first supporting element 2 can also be made of copper or copper and diamond or copper electrodeposited on a goretex net, with the first surface 21, intended to support at least one precursor isotope 3, gold covered by sputtering or galvanic plating.

With reference to step 120 of the method according to the present invention, of application of at least one precursor isotope 3 on the first surface 21 of the first supporting element 2, it comprises at least one step of magnetron sputtering of said at least one precursor isotope 3 on the first surface 21, allowing to obtain one film of precursor isotope 3 having a high density level.

In this regard, preliminary tests have demonstrated that with said magnetron sputtering technique, it is possible to obtain a film of precursor isotope 3 having a density greater than 98% of bulk density, while with pressing and sintering techniques density ranging between 80% and 95% (the maximum density is obtained at particularly specific sintering conditions in a reducing atmosphere) are obtained, and with other conventional techniques, the density of the in the precursor isotope 3 film is the following:

- with pressing, less than 80% of bulk density,
- with electrodeposition, less than 80% of bulk density; and
- with electrophoresis, comprised between 40% and 60% of bulk density.

Moreover, thanks to the magnetron sputtering technique, a film of precursor isotope 3 having uniformity, thickness and adhesion to the first supporting element 2 is obtained.

In this respect, the method of the present invention comprises one step 125 of setting the process parameters for said step 120, so that, in said deposition step, the total stress of the system, composed by the first supporting element 2 and the film by precursor isotope 3, is minimized.

The total stress of the system, as is well known, is given by the residual stress (intrinsic) of the film of precursor isotope 3 applied to the first supporting element 2, and by the stress associated with the thermal discrepancy (in technical jargon also thermal mismatch or  $\sigma_{\text{mismatch}}$ ) between the film of isotope precursor 3 and the first supporting element 2.

The use of the magnetron sputtering technique is particularly advantageous in the present invention, because it can be used for direct deposition of isotopes on fragile - i.e.

inclined to break, if subjected to an external force, with no deformation or stretching occurring beforehand - first supporting elements, i.e. the dielectric, ceramic, non-metallic materials mentioned above, including: DLC, quartz, sapphire, etc.

The intrinsic stress ( $\sigma_{\text{intrinsic}}$ ) in the deposited films depends, as is known, by the energy  
5 supplied to the surface of the precursor isotope 3 film, increasing thickness during the deposition. The variables significantly involved in the change of energy and, therefore, in the mechanism for the growth of the thickness of said film, are the sputtering gas, the temperature of the sample stage, the bias (i.e. a potential applied to sample holder), etc. Theoretically there is one sputtering gas pressure marking the passage from the traction to  
10 the compression stress. At relatively high pressures, the frequency of collisions between the atoms of the gaseous phase increases, reducing the kinetic energy of the sputtered atoms and of reflected neutral atoms bombarding the film of precursor isotope 3 during its thickness growth, thereby providing a porous microstructure; the interatomic attraction forces between the edges of the grain, therefore produce a traction stress. At low pressures, the  
15 atoms of the precursor isotope 3 that are deposited on the first supporting element 2 have a high kinetic energy and the resulting film of precursor isotope 3 has a dense microstructure, promoting compression stress. The temperature of the substrate influences, moreover, the kinetic energy of the particles of precursor isotope 3 already deposited on the first supporting element 2. A low temperature, which depends on the material, the pressure and that,  
20 according to the Structure Zone Model is given by  $T_h < 0.2$  with  $T_h = T_{\text{depos}}/T_{\text{melt}}$  (in Kelvin) where  $T_{\text{depos}}$  is the temperature of the substrate (sample carrier) during the process and  $T_{\text{melt}}$  is the melting temperature of the material to be deposited, promotes, in fact, a microstructure of columnar type with microscopic voids, associated with a traction stress. A high temperature, which always depends on the material and the pressure and that, according to the Structure  
25 Zone Model is given by  $T_h > 0.3$ , corresponds to an increase in the mobility of the atoms of the precursor isotope 3, which leads to a structure of type bulk and a negligible "thermally induced" stress.

According to a particularly advantageous aspect of the method of the present invention, the step 120 of applying the precursor isotope 3 on said first supporting element 2  
30 comprises a multilayer deposition of said at least one precursor isotope 3, and between a deposition step and the next at least one relaxation time period is optionally provided for, optionally comprised between a few milliseconds to a few hours, during which the layer of

precursor isotope 3 applied to the first supporting element 2 is hardening.

With reference to the aforementioned second component of the total stress of the system, i.e. the stress due to thermal mismatch ( $\sigma_{\text{mismatch}}$ ) between precursor isotope 3 and first supporting element 2, it is detected, in general, in structures having very different coefficients of thermal expansion, subject to a uniform change of temperature. When a film of precursor isotope 3 is deposited on one first supporting element, usually at high temperature, i.e.  $T_h > 0.3$  as defined above and, in the case of Mo, higher than 500°C, and is subsequently cooled and brought to room temperature, the difference between the coefficients of thermal expansion between the film of precursor isotope 3 and the first supporting element 2 determines the generation of a stress. If the coefficient of thermal expansion of the film of precursor isotope 3 is smaller than that of the first supporting element 2, a compressive stress will result or, vice versa, a traction stress.

This being said, since the coefficients of thermal expansion which cause the stress due to the mismatch  $\sigma_{\text{mismatch}}$ , vary in function of the material used for the first supporting element 2, the intrinsic stress of the film of precursor isotope  $\sigma_{\text{intrinsic}}$  is adapted to minimise the total stress of the system ( $\sigma_{\text{tot}} = \sigma_{\text{mismatch}} + \sigma_{\text{intrinsic}}$ ), in the method of the present invention.

Purely by way of example and with reference to obtaining a target for the production of  $^{99\text{m}}\text{Tc}$ , starting from  $^{100}\text{Mo}$ , the process parameters set at step 125 of the method according to the present invention, for the application, by magnetron sputtering, of a layer of  $^{100}\text{Mo}$  having a thickness of about 110  $\mu\text{m}$  on a substrate of sapphire ( $\varnothing$  13 mm x 0.5 mm, quality IR, with optical finish) and wherein the total stress of the system is minimized, are reported below.

The film of  $^{100}\text{Mo}$  was deposited by DC magnetron sputtering with a source of planar cathode (2 inches). The deposition was performed on a planar sample holder, heated to 500°C, 6 cm away from the cathode. The optimized sputtering parameters are shown in Table 1 (Figure 3 attached). Experimental tests have demonstrated that the film of Mo deposited with this technique of magnetron sputtering, under conditions shown in Table 1, advantageously possesses the same density of the bulk material, good adhesion to the substrate, greater than 98% of bulk density, and no signs of oxidation.

The method for obtaining a solid target, usable in the production of at least one radionuclide, according to the present invention, may also comprise a further step (step 130) of coupling between said at least one first supporting element 2 and at least one second

supporting element 4, at the second surface 22 of the first supporting element 2, said at least one second supporting element 4 comprising at least one material having a high thermal conductivity and mechanical stability, even chemically not inert at the conditions of dissolution of the precursor isotope 3 and of the radioactive isotope produced as a result of irradiation, by a cyclotron.

Such a second supporting element 4 can be made of a material selected between copper, silver, aluminium and/or their compounds.

The coupling between the first and second supporting element (2, 4) allows compensating, in part, the low thermal conductivity, for example less than 50W/(mK), of the first supporting element 2 made of dielectric material and obtaining, therefore, for target 1 thereby manufactured, higher levels of heat dissipation during the irradiation of the same, by the cyclotron. By way of example, consider in fact that the thermal conductivity of the sapphire is approximately equal to 40W/(mK) and that of quartz is equal to about 8W/(mk).

The second supporting element 4 has a flat shape, and delimits a seat 41, suitably configured and provided for coupling with the second surface 22 of the first supporting element.

The second supporting element 4 may have any configuration, provided it is suitable for insertion in a respective housing seat of the cyclotron used for the production of the radionuclide.

According to a particularly advantageous aspect of the present invention, this step 130 of coupling between the first supporting element 2 and the second supporting element 4 comprises at least one step of vacuum brazing between the first supporting element 2 and at least the second supporting element 4.

This vacuum brazing step is particularly advantageous for the present invention since it allows obtaining a high thermal and mechanical stability between the first and the second supporting element.

The brazing step 130 may occur, alternatively, in an inert atmosphere and this helps to prevent oxidation of the metal part and the brazing material used and, therefore, it guarantees a better thermal contact between the two supporting elements 2 and 4.

The person skilled in the art will have no difficulty in understanding that the brazing material, selected for use in step 130 of the method according to the present invention, will be different depending on the materials of which the first and the second supporting element

are made and will be selected in such a way as to reduce to the minimum the stress due to thermal mismatch ( $\sigma_{\text{mismatch}}$ ) generated during the brazing process.

According to a further alternative of the present invention, step 130 of coupling, between the first supporting element 2 and the second supporting element 4, comprises the direct deposition of the first supporting element 2 on at least the second supporting element 4 and in particular, the direct deposition of any one of the materials mentioned above for the first supporting element 2 (among which, DLC, aluminium oxide, zirconium oxide, silicon oxide, etc.) on the second supporting element 4 having a high conductivity, by means of appropriate methods such as CVD, PECVD, reactive sputtering.

Optionally, the method according to the present invention further comprises a metallization step (step 115) of at least one second surface 22 of the first supporting element 2, before the coupling step between the second surface and the second supporting element 4 and, optionally, before step 120 of deposition of the film of precursor isotope 3 on the supporting element.

The metallization is carried out according to known metallization techniques, for example through chemical, electrochemical deposition, PVD deposition, mechanical deposition, etc., using appropriate metals, such as Ti or Ni.

Purely by way of example and with reference to obtaining a target for the production of  $^{99\text{m}}\text{Tc}$ , starting from the precursor isotope of  $^{100}\text{Mo}$ , a target comprising both the first supporting element 2 and the second supporting element 4, coupled by means of vacuum brazing was obtained and composed as follows:

- the first supporting element is made of sapphire ( $\emptyset$  13 mm x 0.5 mm, quality IR, optical finish) or synthetic diamond ( $\emptyset$  13.5 mm x 0.4 mm, with thermal conductivity 1500W/(mK);
- the second supporting element is made of copper ( $\emptyset$  32 mm x 1 mm) having high thermal conductivity; the brazing material used is a paste of Cu-Ag-Ti, obtained by mixing the powder of the corresponding elements with a binder, the Coccoina i.e. a glue of partially hydrolysed potato starch, and water. By way of example, the percentages of the various components of the brazing material can be the following: metal powder 82%, Coccoina, 7.3% and water 10.7% by weight, with the metal powder thus composed: Cu 35.3 % - Ag 63 % - Ti 1.7 % by weight;
- the second surface 22 of the first supporting element 2 in sapphire or synthetic

diamond, destined to come into contact with the second supporting element 4, has previously been metallised with a layer of approximately 1 µm of Ti, deposited by magnetron sputtering.

The brazing process was carried out in vacuum, at 950°C, maintaining a heating rate of 3°C/min and cooling rate of 2°C/min, to minimize thermomechanical stress in the final target.

This being said, the above described method allows to obtain one target that achieves the objects mentioned above, since it allows a high heat dissipation during the irradiation step, has a high thickness and high uniformity of the precursor isotope 3 coupled to the respective supporting element by magnetron sputtering, low levels of oxidation and a high adhesion of the precursor isotope coupled to the respective first supporting element.

It is advantageously usable in a dissolution system, which also forms the object of the present invention, of at least one precursor isotope 3 and at least one radioactive isotope produced as a result of irradiation by cyclotron - shown, in particular, in Figures 4 and 5.

Such a dissolution system is indicated in the figures by reference 200 and comprises:

- at least one target 1, obtained as described above, and
- at least one vial 210, intended to come into contact with the target 1 and defining with it at least one containment cavity 220, for at least one dissolution solution of the precursor isotope 3 and of the produced radioactive isotope, included in the target 1, as a result of irradiation by cyclotron.

Advantageously, the vial 210, for example made of PEEK, and the target 1 are mutually configured in such a way that the containment cavity 220 remains, in use, delimited between the vial 210 and the first supporting element 2 of the target 1, which is chemically inert under the conditions of dissolution of the precursor isotope 3 and the radioactive isotope produced as a result of irradiation, so that a dissolving solution for that precursor isotope 3 and for its products never comes into contact with the second supporting element 4, during the dissolution step of the target.

In the specific case of obtaining of a solid target for the production of <sup>99m</sup>Tc, starting from <sup>100</sup>Mo, the standard dissolution procedure of the target after irradiation provides for the dissolution of the isotope <sup>100</sup>Mo and the radioactive isotope produced <sup>99m</sup>Tc, in a solution of concentrated H<sub>2</sub>O<sub>2</sub>, for further chemical separation.

In these conditions of dissolution, the second supporting element 4, for example made of copper, would release chemical contamination which would compromise the effectiveness

of the method of production of the radioactive isotope  $^{99m}\text{Tc}$ .

The system described above, instead, avoiding contact between the dissolution solution and the second supporting element 4 of the target 1, chemically not inert with respect thereto, allows obtaining a produced radioactive isotope  $^{99m}\text{Tc}$  of high purity.

5 As a demonstration of the effectiveness of the method and system described above, results of experimental tests conducted under the conditions set out below are reported.

A solid target 1 obtained by the method of the present invention and comprising a film of thickness equal to 110  $\mu\text{m}$  of precursor isotope  $^{\text{nat}}\text{Mo}$  deposited by magnetron sputtering on a first supporting element 2 in sapphire or synthetic diamond, vacuum brazed according to  
10 the method explained above, and with the second supporting element 4 made of copper with a high thermal conductivity, was tested subjected to a proton beam with energy of 16 MeV, using a cyclotron GE PETtrace.

The target 1 showed an excellent mechanical stability during the irradiation up to 60  $\mu\text{A}$  current.

15 Experimental tests conducted, inter alia, on a target 1 composed of a layer of Mo having a thickness of 110  $\mu\text{m}$ , applied by sputtering to a first supporting element 2 in sapphire, having diameter of 12.7 mm and thickness of 0.5 mm, in turn brazed on a second supporting element 4 made of copper, have shown a high mechanical stability (absence of cracks or other deformations of the target) at irradiation conditions at the maximum  
20 deliverable energy (15.6MeV), for 1 min, at 30  $\mu\text{A}$ , 40  $\mu\text{A}$  and 60 $\mu\text{A}$  (Figure 6a).

Excellent mechanical stability has been verified experimentally also on targets 1 having the same characteristics indicated above but one layer of Mo of greater thickness, equal to about 125  $\mu\text{m}$ .

Experimental tests were also conducted also on a target 1 composed of a layer of Mo  
25 having a thickness of 125  $\mu\text{m}$ , applied by sputtering to a first supporting element 2 made of synthetic diamond, having diameter of 13 mm and a thickness of 0.3 mm, in turn brazed on a second supporting element 4 made of copper. The tests results demonstrated a high mechanical stability (absence of cracks or other deformations of the target) at irradiation conditions at the maximum deliverable energy (15.6MeV), for 1 min, at 30  $\mu\text{A}$ , 40  $\mu\text{A}$  and  
30 60 $\mu\text{A}$  (Figure 6b).

Excellent mechanical stability has been verified experimentally even on one target 1 having the same characteristics but at conditions closer to working conditions. The irradiation

of the cyclotron lasted for 30 min at 60 $\mu$ A and at 15.6 MeV of energy delivered. The target 1 has demonstrated excellent resistance without any sign of mechanical damage.

The dissolution of the irradiated material was carried out in a vial in 1 ml of H<sub>2</sub>O<sub>2</sub> at 30% by weight, 70°C and 10 $\mu$ l of this solution was analysed with a gamma spectrometer of  
5 the Research Laboratory of the Department of Medical Physics of the Sant'Orsola Hospital of Bologna.

Between the radioactive isotopes identified with the gamma spectrometry only products of the irradiation of the natural Mo were present: <sup>92m</sup>Nb, <sup>94</sup>Tc, <sup>95m</sup>Tc, <sup>96</sup>Tc, <sup>99</sup>Mo, <sup>99m</sup>Tc.

10 The chemical inertia, in particular, of the sapphire and synthetic diamond was proven because no contaminant was present in the solution, and especially the effectiveness of the solid target obtained according to the method of the present invention.

In the foregoing the preferred embodiments were described and some modifications of this invention have been suggested, but it should be understood that those skilled in the  
15 art can make modifications and changes without departing from the relative scope of protection, as defined by the appended claims.

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## CLAIMS

1. Method for obtaining a solid target for radionuclides production by cyclotron, comprising the steps of:

- 5 - arranging at least one first supporting element (2), having at least one first surface (21) intended to support at least one precursor isotope (3) - (step 110);
- applying said at least one precursor isotope (3) on said at least one first surface (21) of said at least one first supporting element (2) - (step 120);

characterized by the fact that

10 said at least one first supporting element (2) is a chemically inert material at conditions of dissolution of said at least one precursor isotope (3) and at least one radioactive isotope of interest produced upon irradiation of said target (1) by said cyclotron.

2. Method according to claim 1, wherein said step (120) of applying said at least one precursor isotope (3) on said at least one first surface (21) of said at least one first supporting element (2) comprises at least one magnetron sputtering step of said precursor isotope (3) on  
15 at least one said first surface (21).

3. Method according to claim 1, wherein said magnetron sputtering step comprises at least one multi-layer deposition step of said at least one precursor isotope (3), on said at least one first supporting element (2), providing at least one relaxation time between a deposition step and the next one, optionally ranging from few milliseconds up to few hours.

20 4. Method according to any one of the preceding claims, wherein said magnetron sputtering step comprises at least one preliminary step (125) of process parameter setting, such that during said magnetron sputtering step the total stress of a system, comprising said at least one first supporting element (2) and said at least one radioactive precursor isotope (3), is minimized, said total stress of the system comprising the intrinsic residual stress of said  
25 at least one precursor isotope (3) applied to said at least one first element (2) and the stress associated with the thermal mismatch between said at least one first supporting element (2) and said at least one precursor isotope (3).

5. Method according to any one of the preceding claims, wherein said at least one first supporting element (2) comprises a non-metallic material in a layer form, applicable on at  
30 least one second supporting element (4).

6. Method according to any one of the preceding claims, wherein said at least one first supporting element (2) is made of a dielectric material selected out of sapphire, synthetic

diamond, quartz, glass, silicon, carbon compounds, glassy carbon, silicon oxide, aluminium oxide, magnesium oxide, zirconium oxide, advanced ceramics, or DLC, graphene, polymers and the like.

7. Method according to any one of claims 1 to 4, wherein said at least one first supporting element (2) is made of copper or copper and diamond or copper electrodeposited on a goretex net, with said at least one first surface (21) gold covered by sputtering or galvanic plating.

8. Method according to any one of the preceding claims, comprising the step (130) of coupling between said at least one first supporting element (2) and at least one second supporting element (4), in correspondence of at least one second surface (22) of said at least one first supporting element (2) opposite to said at least one first surface (21), said at least one second supporting element (4) comprising at least one material having high thermal conductivity and mechanical stability, and being chemically non inert at conditions of dissolution of said at least one precursor isotope (3) and at least one radioactive isotope of interest produced on said at least one first supporting element (2) upon irradiation by said cyclotron, said material of said at least one second supporting element (4) being optionally selectable out of copper, silver, aluminium and/or their compounds.

9. Method according to claim 8, wherein said step (130) of applying said at least one first supporting element (2) on said at least one second supporting element (4), comprises at least one step of brazing in vacuum or inert gas, between said at least one first supporting element (2) and said at least one second supporting element (4).

10. Method according to claim 8 or 9, comprising one step (115) of plating at least said second surface (22) of said at least one first supporting element (2), before said step (130) of applying said at least one first supporting element (2) on said at least one second supporting element (4) and optionally before said step (120) of applying said precursor isotope (3) on said supporting element.

11. Method according to claim 8, wherein said step (130) of applying said at least one first supporting element (2) on said at least one second supporting element (4), comprises at least one step of direct depositing said at least one first supporting element (2) on said at least one second supporting member (4) by a technique selected out of CVD, PECVD or reactive sputtering.

12. Target for the production of radionuclides by cyclotron, comprising at least one first

supporting element (2) and at least one isotope precursor (3), applied on said at least one supporting element (2), said target being obtained by the method according to any one of the preceding claims, wherein said at least one first supporting element (2) is a chemically inert material at the conditions of dissolution of said at least one precursor isotope (3) and at least  
5 one radioactive isotope of interest produced upon irradiation of said target (1) by said cyclotron.

13. Target according to claim 12, wherein said at least one precursor isotope (3) is optionally comprised among  $^{100}\text{Mo}$ ,  $^{\text{nat}}\text{Mo}$  or other Mo isotopes,  $^{68}\text{Zn}$ ,  $^{68}\text{Ga}$ ,  $^{89}\text{Y}$  or  $^{\text{Y Nat}}$ ,  $^{\text{nat},52}$ ,  
10  $^{53}\text{Cr}$ ,  $^{\text{NAT},48}$ ,  $^{50}\text{Ti}$ ,  $^{\text{nat},63}\text{Cu}$ .

14. Dissolution system (200) of at least one precursor isotope (3) and at least one  
15 radioactive isotope of interest produced upon irradiation by means of a cyclotron of said at least one precursor isotope (3), comprising:  
at least one target (1) according to claim 12 or 13, and  
at least one vial (210), intended in use to get in contact with said at least one target (1) and  
20 delimiting along with the same at least one containment cavity (220) for at least one solution for dissolution of said at least one precursor radioactive isotope (3) and at least one produced radioactive isotope of interest, characterized in that said at least one containment cavity (220) is delimited between said vial (210) and said at least one first supporting element (2) chemically inert at conditions of dissolution of said at least one precursor isotope (3) and said  
at least one produced radioactive isotope of interest, so that said at least one solution for  
dissolution of said radioactive isotopes gets in contact with only said at least one first supporting element (2) of said target (1).