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Production of medical Sc radioisotopes with an alpha particle beam

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ABSTRACT

The internal α-particle beam of the Warsaw Heavy Ion Cyclotron was used to produce research quantities of the medically interesting Sc radioisotopes from natural Ca and K and isotopically enriched ^{42}Ca targets. The targets were made of metallic calcium, calcium carbonate and potassium chloride. New data on the production yields and impurities generated during the target irradiations are presented for the positron emitters ^{43}Sc, $^{44\,g}$Sc and $^{44\,m}$Sc. The different paths for the production of the long lived $^{44\,m}$Sc/$^{44\,g}$Sc *in vivo* generator, proposed by the ARRONAX team, using proton and deuteron beams as well as alpha-particle beams are discussed. Due to the larger angular momentum transfer in the formation of the compound nucleus in the case of the alpha particle induced reactions, the isomeric ratio of $^{44\,m}$Sc/$^{44\,g}$Sc at a bombarding energy of 29 MeV is five times larger than previously determined for a deuteron beam and twenty times larger than for proton induced reactions on enriched $CaCO_3$ targets. Therefore, formation of this generator via the alpha-particle route seems a very attractive way to form these isotopes. The experimental data presented here are compared with theoretical predictions made using the EMPIRE evaporation code. Reasonable agreement is generally observed.

1. Introduction

Recently, there has been steadily growing interest in the medical applications of Sc radioisotopes. The longer half-life of the scandium β^+ emitters, $^{44\,g}$Sc and ^{43}Sc ($T_{1/2}$=3.97 h and $T_{1/2}$=3.89 h, respectively), compared to that of other PET radioisotopes like ^{18}F ($T_{1/2}$=109.8 min), ^{68}Ga ($T_{1/2}$=67.7 min), ^{60}Cu ($T_{1/2}$=23.7 min), ^{11}C ($T_{1/2}$=20.3 min), ^{13}N ($T_{1/2}$=10.0 min), ^{15}O ($T_{1/2}$=122.2 s), potentially permits their regional distribution following production at a single central cyclotron facility. Other diagnostic radioisotopes that could be made at a central facility are ^{61}Cu ($T_{1/2}$=3.3 h), ^{64}Cu ($T_{1/2}$=12.7 h), ^{76}Br ($T_{1/2}$=16.2 h), ^{89}Zr ($T_{1/2}$=78.4 h) and ^{124}I ($T_{1/2}$=4.2 d) but, with the exception of ^{61}Cu, all have a positron branch lower than 30%.

Another advantage in the use of Sc as a diagnostic radioisotope lies in the other scandium radioisotope, *i.e.* ^{47}Sc ($T_{1/2}$=3.35 d) which is a promising low-energy β^- emitter for targeted radiotherapy and therefore represents an ideal theranostic pair (Del Vecchio et al., 2007; Baum and Kulkarni, 2012; Verburg et al., 2014; Wright et al., 2015) for the β^+ emitting ^{44}Sc or ^{43}Sc radioisotopes.

The accelerator production routes using proton induced nuclear reactions for the formation of the Sc positron emitters were recently investigated in a number of papers (Krajewski et al., 2012, 2013; Severin et al., 2012; Müller et al., 2013, 2014; Hoehr et al., 2014; Hernandez et al., 2014; van der Meulen et al., 2015; Valdovinos et al., 2015) where natural and isotopically enriched Ca targets were discussed. Besides the "classic" Positron Emission Tomography (PET) application of ^{43}Sc and ^{44}Sc, the latter isotope has also been proposed as an ideal candidate for the new method of three photon PET (Mausner et al., 1998; Grignon et al., 2007; Müller et al., 2014; Thirlof et al., 2015), a method substantially improving the spatial resolution of PET techniques and allowing for patient dose reduction (Lang et al., 2013).

Similarly, deuteron beams were recently used (Huclier-Markai et al., 2014; Alliot et al., 2015a, 2015b; Duchemin et al., 2015) for the production of the $^{44\,m,g}$Sc isomeric pair by the ARRONAX group. In this case the heavier mass of the projectile substantially increased the production efficiency of the high spin, longer lived isomeric state of ^{44}Sc in comparison with the ground state production.

In spite of the fact that some Sc β^+ emitters were already produced by the E.O. Lawrence cyclotron in 1937 using an 11 MeV alpha-particle

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Table 1
Isotopic compositions of natural abundance and enriched calcium targets (Onyx-Met, Sigma-Aldrich and ISOFLEX, USA).

	^{40}Ca (%)	^{42}Ca (%)	^{43}Ca (%)	^{44}Ca (%)	^{46}Ca (%)	^{48}Ca (%)
^{nat}Ca	96.94	0.647	0.135	2.086	0.004	0.187
^{40}Ca	99.99	–	–	0.01	–	–
^{42}Ca	29.9	68	0.4	1.5	0.01	0.2

beam (Walke, 1937), relatively little information is available on this production route for contemporary chemical, biological and medical applications. Pretorius and Schweikert used α activation of natural calcium for determination of ppb level calcium in pure silica and aluminium (Pretorius and Schweikert, 1971). The recently available data on production for nuclear medicine come from six references: (Kupsch and Könnecke, 1988; Kuhn et al., 2013; Coenen et al., 2014; Nagatsu et al., 2015; Szkliniarz et al., 2015a; Walczak et al., 2015) where ^{nat}Ca, ^{nat}CaO or $^{nat}CaCO_3$ targets were irradiated to produce ^{43}Sc. In the present paper we substantially enlarge the available information on the efficiency of ^{43}Sc, ^{44g}Sc and ^{44m}Sc production using an alpha-particle beam and we compare this technique for producing an *in vivo* ^{44m}Sc/^{44g}Sc generator (Huclier-Markai et al., 2014) with those using proton and deuteron induced reactions.

The information contained in this paper was obtained using an alpha-particle beam of relatively low intensity (up to 1 particle·μA) available from the research heavy ion cyclotron operating at the Heavy Ion Laboratory, University of Warsaw. Although the currently produced quantities of the investigated radioisotopes are certainly below the requirements for clinical applications, they largely fulfil the needs of chemical teams working on labelling procedures. The use of the investigated radioisotopes for preclinical tests on animal species is also being considered. It is hoped that the information presented in this paper will be useful for the high current facilities either currently operating [as eg. Duke University, North Carolina; University of Washington, Seattle (Dorman and Emery, 2013); ARRONAX, Nantes (Haddad et al., 2008); Copenhagen, University Hospital], or to become shortly operational [Jülich, Inst. of Neurosciences and Medicine; SPIRAL2, Caen (Ferdinand et al., 2013)] or accepted for funding [Świerk near Warsaw, POLATOM in National Centre for Nuclear Research].

2. Material and methods

2.1. Irradiations with alpha particles

The alpha particle projectiles used in this investigation were accelerated in the Warsaw Heavy Ion Cyclotron (Choiński et al., 2003). The He+ beam produced in a commercial Nanogan ECR ion source can be accelerated up to 32 MeV with intensities currently reaching 1 particle·μA (improvements aimed at increasing this intensity are in progress). After calculation from the cyclotron parameters the highest bombarding energy value can also be experimentally confirmed using the intensity ratio of the ^{210}At/^{211}At saturation activities, produced by the (α,3n) and (α,2n) reactions on a ^{nat}Bi target (Szkliniarz et al., 2015a, 2015b). As an example, the error estimated from this ratio is ± 0.5 MeV at an alpha particle energy of 30 MeV on a Bi target. Decrease of this energy on target is possible in two ways: by a decrease of the cyclotron orbit or by inserting a beam energy degrader before the target material. The second method was selected for the experiments described in this paper.

When aluminium degraders were in use the energy on target was calculated using the SRIM programme (Ziegler et al., 2009). The beam energy spread after the energy degradation was calculated using the GEANT4 (Allison et al., 2006) programme library. As an example, after energy degradation from 32 MeV to 20 MeV the calculated beam energy spread is about 1.6 MeV (FWHM), including 1.5% inherent machine energy resolution. The accelerated beam strikes perpendicularly the target material attached to a water cooled internal target holder. The sample irradiation times were generally in the range of 10 min up to 1.5 h. In total about 30 samples were irradiated with currents ranging from 50 to 200 particle·nA to obtain the whole set of data presented in this paper. The current intensities were obtained from the ^{65}Zn and ^{67}Ga activity produced in a ^{nat}Cu monitor foil placed in front of the target material. The ^{65}Zn and ^{67}Ga production cross sections were obtained from the IAEA compilation (IAEA-TECDOC-1211, 2001).

2.2. Targets

Taking into account the chemical properties of calcium and the chemical form of the separated isotopes of calcium available on the market it was decided to work with targets made of calcium carbonate, both for natural (Sigma-Aldrich, 99.995% purity) and isotopically enriched targets (ISOFLEX, USA). Table 1 shows the isotopic compositions of the natural and enriched calcium targets, whereas Table 2 gives the chemical admixtures in the $^{42}CaCO_3$ target (enrichment 68%) as provided by the target material suppliers.

For the internal alpha-particle beam delivered by the U-200P cyclotron used for Sc production the target has to be of a special shape, *i.e.* it must be frameless at one edge so as not to lose the beam. This excludes impacting of the calcium carbonate powder into a container, as commonly used for powder targets irradiated by an external beam. Therefore, targets with thicknesses of 40–70 mg/cm^2 (depending on the alpha particle energy range) were produced by compacting the powder into pellets wrapped in a thin aluminium foil which reinforces the pellet mechanically. The $CaCO_3$ powder, evenly distributed on the surface of a preformed aluminium foil (20 μm), was wrapped in this foil, forming a rectangular 'candy'. The 'candy' was then compacted using a hydraulic press with a pressure of ~150 bar to compress the powder into a stable pellet. Such a procedure ensures efficient (practically no material loss) production of a thin pellet/target. Thickness was checked with two different tools: a micrometre and an induction thickness gauge. The devices showed the thickness variation to be not larger than 10 μm which, for calcium carbonate pellets manufactured with a pressure of ~150 bar, corresponds to an areal density of ~2–2.5 mg/cm^2. The bundle was placed on the target holder after wrapping with additional aluminium foil (20 μm) and covering (from the beam side) with a 10 μm Cu foil, used for beam intensity monitoring, and was tightly fixed to the holder (thickness of Al and Cu foils as described by the supplier).

A pure metallic rolled ^{nat}Ca target (99.87% purity, Onyx-Met, Poland), was used for the production of ^{43}Sc to determine the highest possible production efficiency with natural Ca. A piece of the metal, packed in an air-tight plastic envelope under an argon atmosphere, was first compressed with a hydraulic press and then rolled in a roller to obtain the desired thicknesses of 51 and 100 mg/cm^2. The target was then brought back to the glove box with an argon atmosphere where the calcium was removed from the plastic and wrapped in an aluminium foil to mimic the composition of the calcium carbonate targets (described above).

The selected target and energy degrader thicknesses reflected, as much as possible, the calculated alpha-particle non-zero cross section in the target material. However, in some cases thinner targets were also

Table 2
Chemical admixtures in the $^{42}CaCO_3$ target (enrichment 68%) (Sigma-Aldrich and ISOFLEX, USA).

Element	Na	Mg	Fe	Al	Si	Ni	Cu	Mn	Pb	Sr	Ba
Content (%)	< 0.002	0.0012	< 0.005	0.001	< 0.005	< 0.001	< 0.0001	0.0026	0.0001	0.013	0.0023

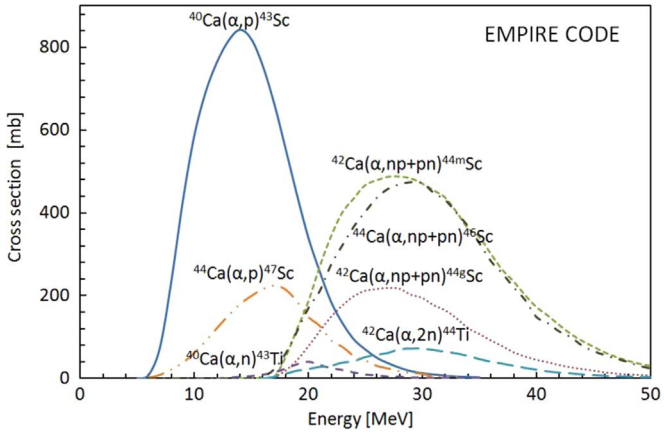

Fig. 1. Calculated cross sections for the production of Sc radioisotopes using Ca targets. The EMPIRE (Herman et al., 2007) evaporation code was employed.

employed in order to decrease the amount of impurities produced.

2.3. Gamma-ray counting

After the irradiation, following the cyclotron safety rules, the targets remained inside the cyclotron for about one hour after EOB (End Of Bombardment) allowing for the decay of short lived radionuclides. After this time samples were placed in front of one of two HPGe gamma-ray counters (EG & G ORTEC, model: GMX, HPGe 49.1 mm×49.5 mm, with a 0.5 mm thick Be window and 15% efficiency and EG & G ORTEC, model: GEM, HPGe 70.1 mm×69.8 mm, 60% efficiency) used with various geometries, depending on the strength of the induced radioactivity. Generally, the first measurements were performed at a distance of about 100 cm, whereas for later counting samples were placed at a shorter distance inside the 10 cm thick Pb shielding (selected for its low background). A supplementary Sn-Cu inner shielding (2.5 mm thickness of Sn and 0.5 mm thickness of Cu) eliminated a large part (around 97%) of the fluorescence Pb X-ray peaks caused by the sample activity. Sometimes weaker samples were produced and measured from the beginning in closer geometry inside the Pb shielding. Data were collected using the DSPEC/ORTEC system or TUKAN8k/National Centre for Nuclear Research system. The gamma-ray spectra were analysed using the Gamma Vision/ORTEC or TUKAN8k/National Centre for Nuclear Research software. The typical dead time during the measurements was below 10%. The energy calibrations and absolute efficiencies of the HPGe detectors were determined before and after the experiments and were found to be stable during many days. Calibrated ^{133}Ba, ^{137}Cs, ^{152}Eu and ^{241}Am sources (with an uncertainty in their activity of below 3%) made by the National Centre for Nuclear Research Radioisotope Centre POLATOM (formerly: POLATOM Isotope Distribution Office) were used.

2.4. Separation of scandium radionuclides from the targets

The method described by Valdovinos et al. (Valdovinos et al., 2015) was employed for separation of the scandium radioisotopes from the calcium targets. Chemical reprocessing of the targets was performed using irradiated natural calcium. A commercially available column packed with UTEVA extraction resin (100 mg) was conditioned with 10 ml of 10 M HCl. Afterwards, the target material was dissolved in 1 ml of 10 M HCl. The dissolved target solution was introduced at the top of the column and after adsorption of the scandium radionuclides the column was washed with 5 ml of 10 M HCl. The scandium radionuclides were eluted with a 0.32 ml portion of H_2O.

2.5. Radiolabelling and stability studies of DOTATATE conjugate

Target radiolabelling studies were performed on ^{43}Sc. The [DOTA0, Tyr3] octreotate (DOTATATE) was used as a model system for radiolabelling of the scandium radionuclide. The ^{43}Sc obtained after separation in a 100 μL ammonia acetate buffer was added to a solution of [DOTA0, Tyr3] octreotate (pH=5) and the mixture was incubated for 35 min at 90 °C. The labelling efficiency was assessed by thin layer chromatography using silica gel plates (ITLC-SG Polygram, Macherey-Nagel) with 0.1 M sodium citrate (pH=5.0) as the mobile phase. The labelled peptide remained at the start while the free radionuclide migrated with the front of the solvent (R_f=0.8–1.0).

2.6. Target material recovery

In order to recover calcium target materials the collected effluent from the UTEVA resin was evaporated to complete dryness and then dissolved in 40 ml of deionized water. The solution acidity was then adjusted to pH=5 with 25% ammonia. Ca was precipitated as $CaCO_3$ by adding 3 ml of 1 M $(NH_4)_2CO_3$ then filtered through a 0.3 μm membrane, washed with water and dried at 140 °C.

3. Evaporation model calculations

The cross sections of the studied reactions were calculated using the EMPIRE (Herman et al., 2007) evaporation code. The default option was used for the model parameters. In Fig. 1 the calculated cross sections of the alpha particle induced reactions on various Ca isotopes are shown. The same programme was used to calculate the cross sections of the alpha particle induced reactions on ^{41}K, which are displayed in Fig. 2.

Once the theoretical values of the investigated reaction cross sections were available the Thick Target Yield (TTY), Target Yield (TY) and Saturation Yield (SY) could be calculated using the formulae derived in Ref. (Krasnov, 1974). It is worth mentioning that in calculating these values the chemical composition of the irradiated samples was taken into account.

3.1. Thick Target Yield (TTY) calculations

The Thick Target Yield (TTY_σ) (the activity of the produced nuclide per unit of beam current during the irradiation time taking into account decay during the irradiation) calculated for a known cross section is given by the following formula (Pedroso de Lima, 2011; Phelps, 2004):

$$TTY_\sigma = \frac{HN_A\lambda}{Mze}\int_{E_{min}}^{E_{max}}\frac{\sigma(E)}{S(E)}dE \quad (1)$$

where: H – isotopic enrichment of the target material, N_A – Avogadro's number, λ – decay constant of the product (in h^{-1} units), M – atomic mass of the target, z – atomic number of the projectile, e – electron charge, σ – reaction cross section, S – stopping power of the projectile in the target material, E – energy of the projectile, E_{max} – maximum

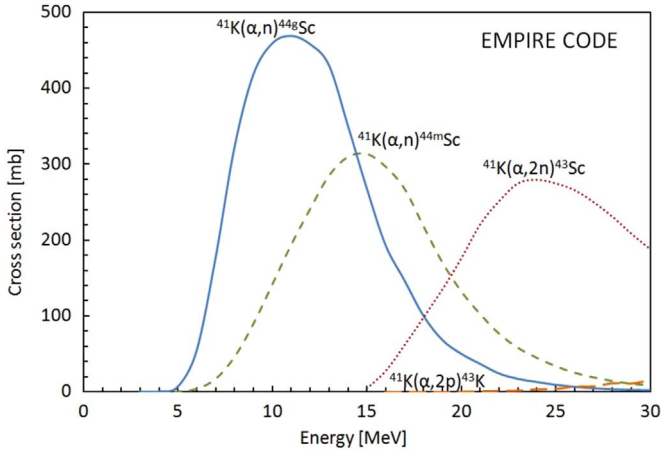

Fig. 2. Calculated cross sections for the production of Sc radioisotopes using a ^{41}K target. The EMPIRE (Herman et al., 2007) evaporation code was employed.

energy of the projectile (at the entry to the target) E_{min} – minimum energy of the projectile (when the reaction cross section becomes equal to zero). In what follows, when the target was not thick enough to cover the reaction cross section range to zero the Target Yield is quoted instead. The most commonly used unit of TTY or TY is [MBq/μAh], (another appropriate unit is the [MBq/C] (Otuka and Takács, 2015).

After calculating the TY or TTY one can calculate the expected activity of the product at the end of the bombardment (EOB) after an irradiation lasting for time t with beam current I [μA]:

$$A_{EOB}(t) = \frac{TTY_{\sigma} \cdot I}{\lambda}\left(1 - e^{-\lambda t}\right) \quad (2)$$

The EOB activity calculated with this formula takes into account the production of the isotope (caused by the nuclear reactions) and the decay of the isotope (during the irradiation). The factor specifying the activity at saturation is called the Saturation Yield (SY). The Saturation Yield is given by:

$$SY_{\sigma} = \frac{TTY_{\sigma}}{\lambda} \quad (3)$$

The Saturation Yield is expressed in [MBq/μA].

3.2. Experimental values of the Thick Target Yield

For an isotope with decay constant λ and experimental activity A at time T after the EOB, the experimental TTY_{exp} value can be calculated from the formula:

$$TTY_{exp} = \frac{\lambda A e^{\lambda T}}{I\left(1 - e^{-\lambda t}\right)} \quad (4)$$

where t and I have the same meaning as above. The values of the TTY and SY as determined in the present work and discussed below are presented in Table 3. As explained above, *TY* in this table indicates determinations of the reaction yield for thick targets, but not covering the whole cross section range. Similarly, SY_{exp} is given as $SY_{exp}=TTY_{exp}/\lambda$.

4. Results and discussion

4.1. ^{43}Sc radioisotope production

The ^{nat}Ca element contains 96.9% of the ^{40}Ca isotope. Therefore, the ^{40}Ca(α,p) and ^{40}Ca(α,n) reactions, the latter leading to the very short lived ^{43}Ti ($T_{1/2}$=0.5 s) which forms almost immediately ^{43}Sc, may constitute a convenient production method for the ^{43}Sc radioisotope. The possibility of ^{43}Sc production using the natural element is, evidently, a very attractive choice due to the low cost of the irradiated material.

In our previous publication (Szkliniarz et al., 2015a) we determined the Thick Target Yield and the Saturation Yield for the production of ^{43}Sc using a ^{nat}CaO target and an alpha-particle beam with an energy of 31 MeV. In the present work natural and enriched $CaCO_3$ target material was used instead, in order to obtain a similar target chemical composition to that available commercially for isotopically enriched isotopes of Ca. Fig. 3 presents the gamma-ray spectrum of the $^{nat}CaCO_3$ thick target (thickness 57.5 mg/cm^2), irradiated for 1.5 h with a 20 MeV α-particle beam of 50 particle·nA intensity, measured 1.5 h after the EOB and, in order to show the impurities, 124 h after the EOB. The ^{58}Co line observed in the 124 h spectrum is due to alpha-particle reactions with ^{55}Mn and ^{56}Fe present as impurities in the Al foil wrapping the target material and counted simultaneously with the $^{nat}CaCO_3$ samples. The determined Thick Target Yields (TTY) (Table 3) are compared with the theoretical values in Fig. 4 (Eqs. (1) and (4)). For comparison results obtained with a metallic ^{nat}Ca target were collected and are also shown in this figure. As expected, much higher production efficiency is observed for such targets.

Fig. 5 shows the deduced evolution in time of the relative activities of Sc radioisotopes produced during a 4 h irradiation of a $^{nat}CaCO_3$ target with a 20–0 MeV alpha-particle beam. The most intense impurities, $^{44\,m}$Sc and $^{44\,g}$Sc are produced by interaction of the beam with ^{42}Ca which corresponds to 0.65% of the Ca present in the target. The ^{44}Ca component present in the natural Ca target at the level of 2% leads to the ^{46}Sc and ^{47}Sc impurities. Although the elimination of the 3.35 d ^{47}Sc is impossible by a change in the bombarding energy (see Fig. 1), irradiation with alpha particles of slightly lower energies should decrease the amount of the 83.8 d ^{46}Sc. This would, however, also diminish the ^{43}Sc production efficiency (see Fig. 4).

Evidently, a complete elimination of the discussed impurities would be possible using an isotopically enriched ^{40}Ca target. Indeed, the irradiation of such a target (composed of 99.99% $^{40}CaCO_3$) with alpha particles of energies 20–0 MeV gave a level of all impurities below $1.5\cdot10^{-5}$% of ^{43}Sc even 20 h after the EOB. Enriched $^{40}CaCO_3$ material with enrichment greater than 99% is commercially available at low price.

However, the observed impurity levels produced in the natural $CaCO_3$ target (activities below 0.05% of ^{43}Sc at EOB and 1.1% 20 h after EOB) already make this production route for the ^{43}Sc PET radioisotope extremely attractive commercially. The present work shows that by irradiating a metallic ^{nat}Ca target with an alpha-particle beam of 25 particle·μA (as available from commercially offered accelerators) a ^{43}Sc activity of 15 GBq could be produced during a 4 h irradiation with a very low level of impurities, at least immediately after EOB.

Reactions induced by alpha particles on ^{41}K were also investigated in this study for the sake of completeness. Natural potassium in the form of KCl was irradiated with a beam of energy 29–19 MeV. In order to limit the production of ^{44}Sc impurities by the (α,n) reaction the target was thin enough not to stop the beam which left the target with an energy of 19 MeV, a value above the reaction threshold (Target Yield and not Thick Target Yield quoted in Table 3). As expected from the calculated cross sections (Fig. 2), the produced ^{43}Sc is contaminated with $^{44\,g}$Sc (13% activity at EOB), $^{44\,m}$Sc (2% at EOB) and ^{43}K (0.4% at EOB). Although the obtained product can be purified from the ^{43}K activity by appropriate chemistry, the ^{44}Sc isomers must be tolerated if this production route has to be selected.

The Target Yield (TY) and Saturation Yield (SY) of the ^{43}Sc radioisotope produced with an alpha-particle beam of energy 29–19 MeV irradiating a ^{nat}KCl target, as determined in this work, is indicated in Table 3 as 4.2 MBq/μAh. This value would be increased up to 60 MBq/μAh if commercially available 95.4% ^{41}KCl were used. However, it should be recalled that besides the high level of contaminants the current price of this target material is very high, making

Table 3
Thick Target Yield (TTY), Target Yield (TY) and Saturation Yield (SY) of Sc radioisotopes produced by alpha particle beams.

Radioisotope	Target chemical form	α-particle energy range (MeV)	TTY or *TY* [MBq/μAh]	SY [MBq/μA]
^{43}Sc	$^{nat}CaCO_3$	29–0 27–0 24–0 20.4–0 20–0	110(20) 92(10) 95(7) 78(8) 84(4)	620(110) 530(60) 540(40) 450(50) 470(20)
	^{met}Ca	29–0 20–0	240(20) 190(30)	1350(100) 1100(170)
	$^{40}CaCO_3$	20–0	88(13)	490(70)
	^{nat}KCl	29–19	*4.2(6)*	24(3)
$^{44\ g}$Sc	$^{42}CaCO_3$ (68%)	29–12	31(5)	180(30)
	$^{42}CaCO_3$ (68%)	29–20	*25(4)*	140(20)
	^{nat}KCl	20–2	4.3(8)	24(5)
$^{44\ m}$Sc	^{42}CaCO3 (68%)	29–12	3.3(6)	280(50)
	^{42}CaCO3 (68%)	29–20	*2.7(4)*	230(40)
	^{nat}KCl	20–2	0.21(3)	19(3)

this production route economically unreasonable too.

4.2. $^{44\ g}$Sc and $^{44\ m}$Sc radioisotope production

Production of the two isomers of the ^{44}Sc radioisotope was investigated using 68% enriched $^{42}CaCO_3$ target material. The isotopic composition of the target material is presented in Table 1. The most abundant admixtures in the target material are presented in Table 2. Bearing in mind the calculated values of the reaction cross sections (see Fig. 1) the irradiations were performed with a beam energy varying from 29 MeV to 12 MeV to obtain the Thick Target Yield values (see Table 3). The experimental results (Eq. (4)) are compared with the theoretical (Eq. (1)) predictions in Fig. 6. From this figure it is evident that the EMPIRE code used for the cross section calculations slightly underestimates the metastable state cross section, whereas the calculated ground state cross section leads to a TTY value lower than the experimental result by a factor of about 1.6. In this energy range ^{43}Sc was abundantly produced due to the ^{40}Ca content in the target material. Its activity at EOB was about 66% of the EOB activity of ^{44}Sc. This contamination would be reduced down to 7% for this energy range if the more expensive 95.9% ^{42}Ca were used.

In order to reduce the amount of radioactive impurities in the irradiated samples, even at the cost of slightly lower activity, an irradiation in the beam energy range 29–20 MeV was performed. The values of the TY and SY obtained (the target was not thick enough to cover the whole cross section range) are presented in Table 3. Table 4 presents the relative intensities of the induced activities for both energy ranges after 12 h of bombardment. The data are normalised to $^{44\ m}$Sc, as the use of an alpha-particle beam for the production of ^{44}Sc is mainly motivated by the higher cross section for the isomer in comparison with (p,n) or (d,2n) induced reactions on a ^{44}Ca target (see the discussion below). Fig. 7 shows the deduced evolution in time of the relative intensities of the Sc radioisotopes produced during a 12 h irradiation of a 68% enriched $^{42}CaCO_3$ target.

In a similar way to the production of the ^{43}Sc radioisotope, formation of the isomeric pair $^{44\ m}$Sc/$^{44\ g}$Sc using the natural KCl target described above was investigated. This time the selected beam energy range was 20–0 MeV. The experimental results are shown in Table 3. In this reaction, due to the lower alpha-particle energy, the theoretical maximum cross section ratio (see Fig. 2) of $^{44\ m}$Sc/$^{44\ g}$Sc calculated with the EMPIRE code is only 0.7, whereas it is 2.2 for the ^{42}Ca target discussed above. Also, the contamination of $^{44\ g}$Sc by ^{43}Sc is of the order of 16% at EOB. Decreasing the bombarding energy (see Fig. 2) would make this contamination smaller, but at the expense of the produced sample intensity.

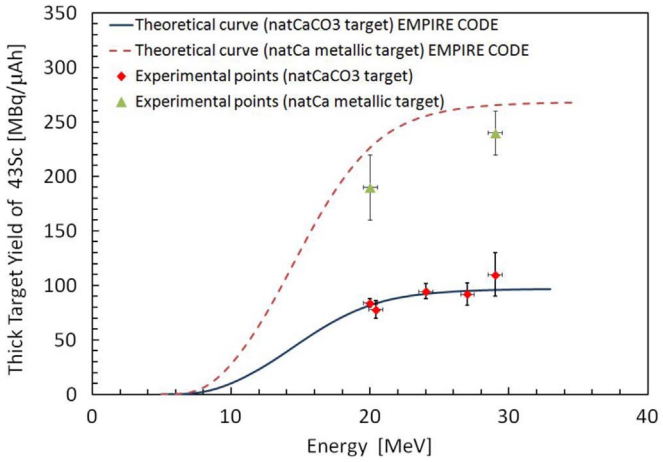

Fig. 4. Comparison of the experimental and theoretical Thick Target Yield (TTY) for the production of the ^{43}Sc radioisotope by an alpha-particle beam incident on $^{nat}CaCO_3$ and metallic ^{nat}Ca targets. The cross sections are calculated with the EMPIRE code (Herman et al., 2007) and the stopping powers using the SRIM code (Ziegler et al., 2009).

In Refs. (Huclier-Markai et al., 2014; Alliot et al., 2015a, 2015b; Duchemin et al., 2015) the feasibility of the formation of an *in vivo* $^{44\ m}$Sc/$^{44\ g}$Sc generator based on a high spin $^{44\ m}$Sc isomer with a 2.4

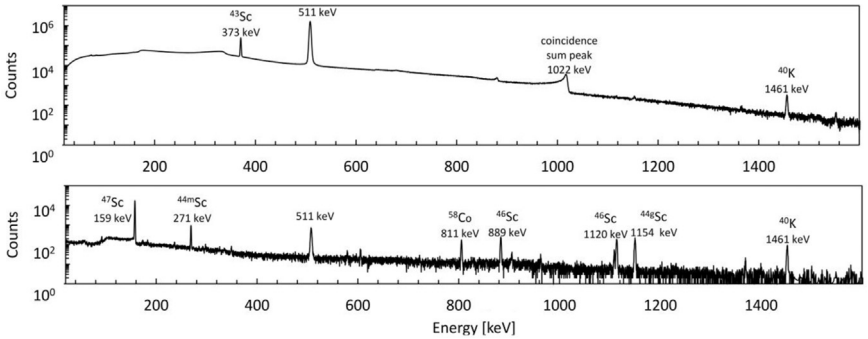

Fig. 3. Upper part: the gamma-ray spectrum of the $^{nat}CaCO_3$ thick target, measured 1.5 h after EOB using a 60% HPGe counter; lower part: the same sample measured 124 h after EOB.

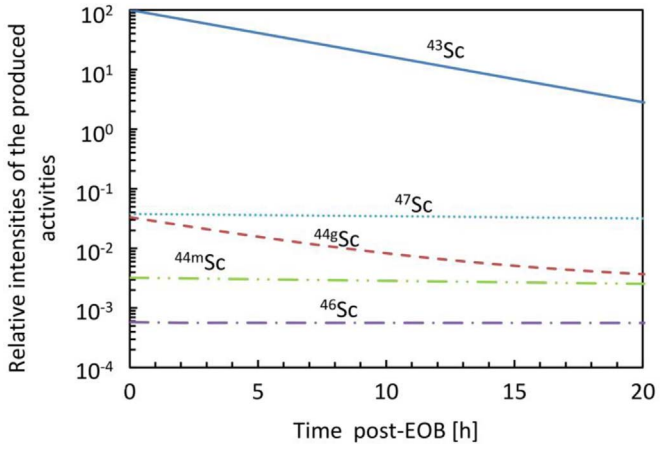

Fig. 5. Evolution with time of the relative intensities of Sc radioisotopes produced during a 4 h irradiation of a $^{nat}CaCO_3$ target with a 20 MeV α-particle beam. A similar plot (not shown) for a $^{40}CaCO_3$ (99.99%) target shows only the ^{43}Sc activity, with impurities below $1.5{\cdot}10^{-5}$% at 20 h after EOB.

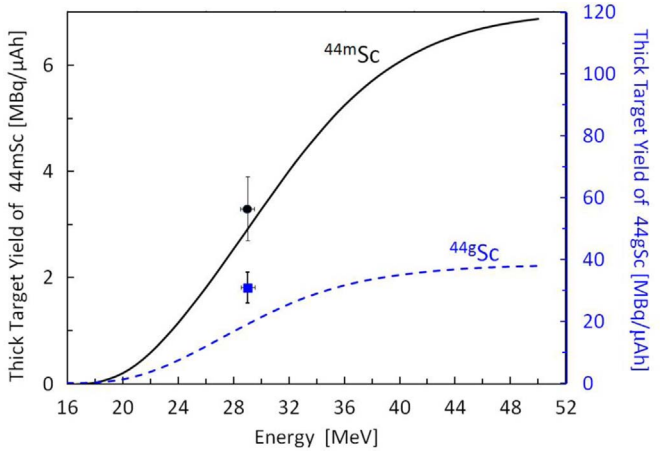

Fig. 6. Comparison of the theoretical (lines) and experimental (points) Thick Target Yields for the production of ^{44}Sc isomers with a $^{42}CaCO_3$ (enriched 68%) target. Note the different scales for $^{44\,m}$Sc and $^{44\,g}$Sc.

Table 4
Relative composition of the activities (EOB) induced by a 12 h alpha particle bombardment of enriched ^{42}Ca targets for two energy ranges.

Isotope	29–12 MeV 68%	29–20 MeV 68%	29–20 MeV 95.9%
$^{44\,m}$Sc	100	100	100
$^{44\,g}$Sc	481(92)	466(93)	466(93)
^{43}Sc	318(46)	157(37)	12(3)
^{46}Sc	0.044(15)	0.053(13)	0.018(4)
^{47}Sc	0.44(20)	0.28(8)	0.09(3)

days half-life, decaying to the 3.97 h $^{44\,g}$Sc by a 271 keV (E4) transition was investigated. Irradiation of ^{44}Ca by a 16 MeV deuteron beam was proposed. The use of this reaction was motivated by the higher $^{44\,m}$Sc/$^{44\,g}$Sc cross section ratio in comparison with proton induced reactions on the same target. As an example, at a bombarding energy of 16 MeV the $^{44\,m}$Sc/$^{44\,g}$Sc cross section ratio is about 0.20 for proton induced reactions and about 0.33 for deuterons (Fig. 2 in Alliot et al., 2015a). This difference is the result of an increase of the angular momentum transfer to the compound nucleus with the increase of the projectile mass. It is evidently also reflected by the larger isomeric ratio of $^{44\,m}$Sc/$^{44\,g}$Sc obtained with deuterons in comparison with protons. The same effect is expected when alpha particles are used for the bombardment instead of deuterons. This is of particular importance since such a generator with a half-life of 58.6 h is well suited for the

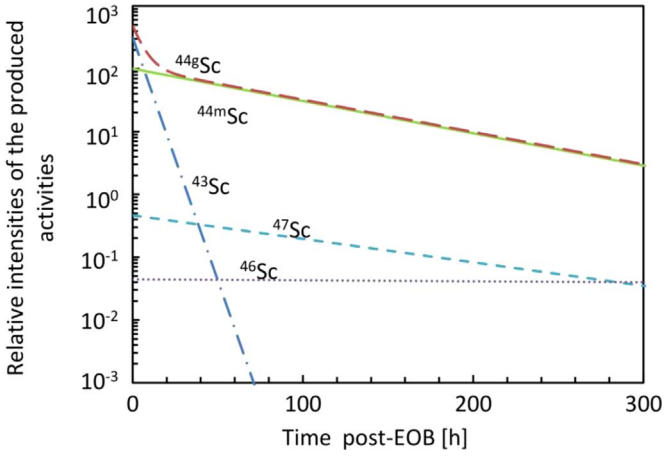

Fig. 7. Evolution with time of the relative intensities of Sc radioisotopes produced during a 12 h irradiation of a 68% enriched $^{42}CaCO_3$, target with a 29–12 MeV α-particle beam. The ^{43}Sc contamination would be decreased by a factor of 11 if commercially available 95.9% $^{42}CaCO_3$ were used.

labelling of proteins such as monoclonal antibodies (mAb). This suitability is related to the immunoPET requirements that the PET isotope can be attached to the mAb with good *in vivo* stability and the decay half-life of the isotope should match the pharmacokinetics of the mAb. Currently, for the labelling of monoclonal antibodies two longer lived radionuclides ^{89}Zr and ^{124}I are mostly used, but the β+ emission of these radionuclides is relatively low (< 25%). Additionally, binding these radionuclides to the vectors is a difficult task.

The experimental thick target yield and cross section (Experimental Nuclear Reaction Data (EXFOR), 2015) data leading to the formation of both isomers of ^{44}Sc are compared in Table 5 for the three projectiles considered here. As expected, due to the much larger stopping power for alpha particles (cf. Section 3.1) the production efficiency of $^{44\,g}$Sc for this projectile, even with 95.9% enriched target material, is much smaller than for proton or deuteron induced reactions. However, for 29 MeV alpha particles the TTY "isomeric ratio" is 5 times larger than for deuterons and 20 times larger than for protons. An increase of the alpha-particle energy up to 50 MeV would lead to a TTY ratio of about 12, as expected from the measured cross section values. The TTY data calculated from the cross sections obtained using the EMPIRE evaporation code overestimate the isomeric ratio for alpha particles, whereas they are in reasonable agreement for proton and deuteron induced reactions.

This result indicates that for the formation of the *in vivo* $^{44\,m}$Sc/$^{44\,g}$Sc generator proposed in (Alliot et al., 2015a), bombardment of a ^{42}Ca target with alpha particles may be one of the preferred routes if a reasonable alpha-particle beam intensity is available. Indeed, for a 25 particle·μA beam and 12 h irradiation time of a highly enriched $^{42}CaCO_3$ target a 1 GBq $^{44\,m}$Sc/$^{44\,g}$Sc generator in radioactive equilibrium would be obtained 24 h after EOB, providing a target holder sustaining almost one kW power on calcium carbonate is available.

4.3. Radiopharmaceuticals labelled with ^{43}Sc and $^{44\,m,g}$Sc

Calcium carbonate is poorly soluble in water, therefore 10 M HCl acid was used to dissolve the target. The separation procedure performed on the UTEVA extraction resin is fast, easy and efficient. Scandium activity was first eluted with water in a 0.32 ml fraction.

The total yield of ^{43}Sc separation was higher than 80%. The elution can be continued until 2000 μL, when recovery will be nearly completed, but specific activity of the solution will be lower. The obtained fraction was Sc radionuclide pure, meaning no other radionuclides were found in the solution.

The target recovery experiments were performed with 100 mg of

Table 5
Thick Target Yield of $^{44\,g}$Sc, $^{44\,m}$Sc ($CaCO_3$ or KCl targets) and the ratio of TTY for $^{44\,m}$Sc/$^{44\,g}$Sc for p, d and α projectiles estimated from Ref. (Severin et al., 2012; Alliot et al., 2015a; Valdovinos et al., 2015) and the present work.

Projectile	p	d	α	α	α
Projectile energy (MeV)	15.6	14.9	20	29	50
Target	^{44}Ca	^{44}Ca	^{41}K	^{42}Ca	^{42}Ca
Target enrichment %	98	96.9	95.4	95.9	95.9
TTY$^{44\,g}$Sc (MBq/μAh)	630[a]	220	60(9)	44(5)	54[d]
TTY$^{44\,m}$Sc (MBq/μAh)	3.4[a]	4.9	3.0(3)	4.8(6)	9.7[d]
TTY$^{44\,m}$Sc/$^{44\,g}$Sc % (exp)[b]	0.54	2.21	5.0(5)	10.9(1.4)	–
TTY$^{44\,m}$Sc/$^{44\,g}$Sc %(exp EXFOR)[c]	0.55	–	3.8	10.6	12.1
TTY$^{44\,m}$Sc/$^{44\,g}$Sc % (th)[d]	0.5	2.34	5.3	15.2	18.2
A(EOB)$^{44\,m}$Sc after 12 h of 1 μA bombardment [MBq][e]	38	55	34	52	–

[a] Metallic target experimental data converted to $CaCO_3$;
[b] From the thick target data;
[c] From the experimental cross sections and SRIM stopping powers;
[d] Calculated using EMPIRE cross sections and SRIM stopping powers.
[e] From the experimental data.

natural $CaCO_3$. The recovery yield in the UTEVA separation process exceeds 90%.

The high chemical purity of the obtained scandium fraction was verified by labelling the DOTATATE bioconjugate. The labelling yield was 98.3% for 25 nmol of DOTATATE, evidence that high purity and n.c.a. (no carrier added) $^{43,44\,g,44\,m}$Sc may be obtained.

High chemical purity of the final radioactive scandium fraction is important, since the presence of other metals may interact with the DOTA-chelator. The most dangerous is Fe^{3+} for which the stability with the DOTA ligand is greater than that for Sc^{3+}. The influence of divalent metal cations is negligible due to the much lower stability of DOTA complexes.

The final product from this separation was analysed with ICP-MS for trace metal contaminants. The results of this analysis indicated that the level of calcium, iron, zinc, nickel, aluminium, and manganese was less than 5 ppb. In the dissolved targets the concentration of Fe was 38 ppm, so the decontamination factor for Fe exceeds $7{\cdot}10^3$.

4.4. The quality of the obtained scandium radionuclides

The separation procedure using UTEVA resin gives high purity scandium radionuclides in a small volume of eluate (0.32 ml) which can be used for labelling of biomolecules. High efficiency of labelling DOTATATE with ^{43}Sc was achieved as shown by the labelling yield exceeding 87% for amounts of the bioconjugate equal to or higher than 17 nmol. The recovery of the expensive ^{42}Ca and ^{44}Ca at higher than 90% makes the process cost effective.

5. Summary and conclusions

The alpha-particle beam from the cyclotron at the Heavy Ion Laboratory, University of Warsaw was used to produce quantities of medically interesting Sc isotopes sufficient for chemical and animal studies using natural and isotopically enriched Ca targets and natural K targets. The production efficiency and the generated impurities were determined for the prospective positron emitters ^{43}Sc, $^{44\,g}$Sc and $^{44\,m}$Sc. It was demonstrated that a highly pure (purity of $4{\cdot}10^{-4}$ at EOB) ^{43}Sc positron emitter can be produced with a natural Ca target and an extremely pure one (purity better than 10^{-6} at EOB) with a cheap, enriched ^{40}Ca target. It was also demonstrated that the production of the recently proposed *in vivo* $^{44\,m}$Sc/$^{44\,g}$Sc generator can benefit from the substantially larger angular momentum transfer with alpha particles in comparison with deuteron induced reactions. However, the large scale production of these isotopes will be only possible if a high power target device for calcium carbonate is available.

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