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Citation style: Stolarz Anna, Sitarz Mateusz, Szkliniarz Katarzyna, Choiński Jarosław, Jastrzębski Jerzy, Trzcińska Agnieszka, Zipper Wiktor. (2020). Calcium targets for production of the medical Sc radioisotopes in reactions with p, d or α projectiles. "EPJ Web of Conferences" (2020), Vol. 229, art. no. 06004, s. 1-14. DOI: 10.1051/epjconf/202022906004

Calcium targets for production of the medical Sc radioisotopes in reactions with p, d or α projectiles

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Abstract. The scandium radioisotopes for medical application can be produced in reactions of calcium with proton, deuteron or alpha projectiles. Enriched isotopic calcium material is commercially available mainly as calcium carbonate which can be used directly for production of Sc radioisotopes or can be converted into other calcium compounds or into metallic form. The superiority of application of calcium oxide is shown throughout analysis of use of each target chemical form.

1 Introduction

Majority of medically interested radioisotopes are produced in reactions induced by neutrons i.e. in reactors. Nevertheless, the alternative methods of their production are being extensively developed. The advantages and drawbacks of each production route are well presented by M. A. Synowiecki et al in [1].

The studies on the alternative methods were triggered by unplanned shut-downs of reactors several years ago which caused the shortage of isotopes (i.e. ^{99}Tc) widely used in medical applications. These studies are also stimulated by development of the diagnostic techniques and by search for replacements having longer half-live then isotopes recently used in PET scanning. One of the alternative method of these radioisotopes production is use of the reactions induced by accelerated projectiles such as protons, deuterons or alpha particles.

These studies cover search for replacements of PET isotopes such like ^{18}F ($T_{1/2}$≈110 min), ^{68}Ga ($T_{1/2}$≈68 min, ^{60}Cu ($T_{1/2}$≈24 min), ^{61}Cu ($T_{1/2}$≈20 min) and ^{15}O ($T_{1/2}$≈122 s). The scandium isotopes are among potential replacements. The scandium radioisotopes which are β^+ emitters (^{44g}Sc and ^{43}Sc, $T_{1/2}$=3.97 h and 3.89 h, respectively) can replace currently used PET scanning isotopes mainly due to their longer half-life. Another interesting scandium isotope, ^{47}Sc ($T_{1/2}$=3.35 d) with its low energy β^- emission, is a good candidate for targeted radiotherapy. This isotope coupled with one of the Sc β^+ emitters may represent an ideal theranostic pair. The ^{44}Sc is as well considered a good candidate to be applied in the new β^+-γ coincidence PET method [2].

Majority of the studies on the scandium isotopes production via reactions induced by p, d or α projectiles are performed using calcium as a target nucleus. The alternative nucleus is Ti as the source of Sc isotopes but comparison of the cross sections for reactions of both nuclei (Table 1) shows that reaction with Ca nucleus promises much higher production efficiency. As can be found from these data production of ^{43}Sc with very high efficiency can be achieved even applying target composed of the natural calcium employing reaction of ^{40}Ca (96.94 % of nat. abundance) with α particles [3].

Table 1. Example of cross sections for production of ^{43}Sc and ^{44g}Sc on reactions of Ca or Ti with p, d or α [4].

isotope produced	Calcium isotope cross section [mb]/ (beam energy [MeV])			Titanium isotope cross section [mb]/ (beam energy [MeV])	
	p	d	α	p	d
^{43}Sc	^{43}Ca 400/(9) ^{44}Ca 200/(24)	^{42}Ca 270/(5)	^{40}Ca 700/(15)	^{46}Ti 60/(15) 80/(60) ^{47}Ti 70/(25)	
^{44g}Sc	^{44}Ca 700/(10)	^{43}Ca 380/(5)	^{42}Ca 750/(25) ^{43}Ca 600/(35)	^{46}Ti 240/(35) ^{47}Ti 70/(15) ^{48}Ti 80/(25)	^{46}Ti 110/(10); 310/(75) ^{47}Ti 140/(22); 200/(100)

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Table 2. Advantages (+) and drawbacks (-) of use of various chemical form of calcium targets.

Chemical form	$CaCO_3$	CaO	Ca
	(+) The form of the enriched materials easily available commercially; (+) Ready to be used for target preparation by encapsulation, pellets formation, etc.	(+) Achievable by thermal decomposition of $CaCO_3$; (-) Unstable in air , quick manipulation is required or best to be handled in the inert atmosphere.	(-) Have to be prepared by $CaCO_3$ conversion; it is a two steps procedure; (-) unstable in the air, it requires handling in the inert atmosphere.
under the beam	(-) Thermal insulator; Decomposes producing $CaO+CO_2$. The target cracks when exposed to intensive beams due to this process (see Fig. 1); (-) Production of large amount of ^{13}N (decaying in ~10 min via β^+ to ^{13}C).	(-) Thermal insulator; (+) Low production of ^{13}N.	(-) If not sufficient cooling can melt in the beam.
Treatment after irradiation	(+) Dissolves very easily in a weak acids.	(+) Dissolves easily in a weak acids; only slightly more difficult than carbonate.	(++) Dissolves even in water.
Efficiency	see next table		

2 Chemical form of the target

Production of the Sc medical radioisotopes in reaction of Ca nucleus can be done working with unprocessed enriched material i.e. with calcium carbonate ($CaCO_3$, the chemical form of the enriched Ca isotopes mostly available commercially) or with material converted into either calcium oxide (CaO) or metal (Ca). Work with each target form has advantages and drawbacks (Table 2). The thermal damages mentioned in Table 2 for calcium carbonate can be eliminated by mixing the target material with a good heat conductor e.g. graphite or aluminium as discussed in [5].

Fig. 1. $CaCO_3$ target after 2 h irradiation with 15 μA proton beam of 16 MeV.

Taking into account only the level of produced activity which is proportional to the nuclei number per cm^2 as expressed in the formula

$$A = \Phi\, n\, \chi\, \sigma\, (1-e^{-\lambda t}) \quad (1)$$

where:

A - activity [Bq]
Φ - beam intensity [projectiles/s]
n - number of nuclei per mg of the target material
χ - target thickness [mg/cm^2]
σ - reaction cross section [cm^2]
λ - decay constant (=$\ln 2/T_{1/2}$) [s^{-1}]
t - irradiation time [s]

working with metallic form of Ca would be the most favourable. The activity of the Sc radioisotopes produced during the same time of irradiation of Ca metallic target would be nearly tripled comparing to activity produced while using $CaCO_3$ (or doubled if working with CaO). This is due to the number of nuclei per cm^2 (N) in targets with thicknesses covering the projectile range in $CaCO_3$, CaO and Ca. The ratio of nuclei numbers in these targets is ~ 1:2:3, respectively, and thus is the produced activity.

Table 3. 16 MeV proton and 25 MeV alpha ranges and stopping powers in calcium targets

Chemical form, density	Range* of projectile in material [mg/cm^2]		Stopping power* MeV/(mg/cm^2)		N [nuclei/cm^2]	
	16 MeV p	25-8 MeV α**	16 MeV p	25 MeV α	16 MeV p	25 MeV α
$CaCO_3$ 2.71 g/cm^3	348.59	56.94	0.02576	0.2157	$3.48\times A_v\times 10^{-3}$	$0.57\times A_v\times 10^{-3}$
CaO 3.35 g/cm^3	368.50	72.025	0.02450	0.2028	$6.58\times A_v\times 10^{-3}$	$1.28\times A_v\times 10^{-3}$
Ca 1.55 g/cm^3	389.05	77.068	0.02345	0.1922	$9.72\times A_v\times 10^{-3}$	$1.92\times A_v\times 10^{-3}$

Av – Avogadro constant = $6.022140857\times 10^{23}$ mol^{-1};
* calculated using SRIM 2013 code;
** example energy for ^{43}Sc isotope production in ^{40}Ca reaction with α;

However, conversion of $CaCO_3$ into metallic Ca is a time-consuming two steps reduction process [6,7]. The process can be done under vacuum by decomposing carbonate to oxide, followed by the oxide reduction into Ca using metallic (Me) reductants such as e.g. Zr, Ti.

$$CaCO_3 \Rightarrow CaO + CO_2 \quad \text{(heating at temp. > 700 ºC)} \quad (2)$$

$$2CaO + Me \Rightarrow Ca + MeO \quad \text{(reduction)} \quad (3)$$

In addition, process may as well introduce additional contaminants to the target apart from those present in the available starting material. Also the process efficiency (lower than 80%) has to be kept in mind considering metallic target. Therefore, it is better to avoid this conversion if it's not vital.

Working with metallic Ca would also require a special vacuum containers and/or construction of a transfer vacuum line to the cyclotron to prevent the contact of Ca with air.

Taking these difficulties into account it is much better to work with calcium oxide as target. Although activity produced is only doubled comparing to activity produced with $CaCO_3$ target of adequate thickness (see Table 3) but conversion to CaO is much easier than conversion to Ca. It can be done either by heating the oxide in flow of the inert gas [8] or in vacuum using the resistant heating. The advantages of the second method are: the instant/online control on the decomposition process via controlling the vacuum and gives the possibility of cooling down the produced CaO in the air free atmosphere. Conversion carried in a special vessel/crucible with the perforated cover (Fig. 2.) and venting-in the vacuum apparatus after completion of the procedure, with inert gas allows the transfer of the produced CaO to the glove box for manipulations needed to produce the final target (e.g. pressing the pellet, encapsulating into container, etc.) without special precautions.

Fig. 2. Crucible with perforated cover used for calcium carbonate conversion in vacuum by resistant heating.

In addition decrease of the oxygen content in the target results in a significant decrease of the side radioactivity in the irradiation area related to the production of ^{13}N in $^{16}O(p,x)^{13}N$ or $^{16}O(d,x)^{13}N$ reaction.

The oxide targets prepared as inserts into graphite bed as described in [5] survived 45 min irradiation with 15 μA proton beam very well. There were no signs of thermal damage of the target. The irradiation conditions are sufficient to produce ~8 GBq of ^{44g}Sc irradiating the CaO converted from enriched up to 99.2 % $^{44}CaCO_3$. Taking into account the activity loses during isotope separation and labelling process, such amount of ^{44}Sc should be enough for diagnosing ~ 75 patients (the estimation based on clinical studies for ^{44}Sc [9] where 50.5 MBq of ^{44}Sc-PSMA-617 were applied for single diagnosis).

3 Conclusions

Production of the research quantities of Sc radioisotopes can easily be performed using targets made directly from calcium carbonate. However, for clinical application when higher activities are required more favourable is to work with targets made from calcium oxide.

Conversion of carbonate into oxide is one step process practically without loses of the often expensive, enriched calcium material.

As it has been shown using the calcium oxide instead of carbonate gives nearly double activity within the same time of irradiation and much less undesirable radioactivity (originating from decay of ^{13}N formed in the side reaction) is produced in the irradiation area.

Studies on Sc radioisotopes production presented in this paper were partly supported by NCBiR (National Centre for Research and Development), grant no. DZP/PBS3/2319/2014 and was partly performed within the framework of the EU HORIZON 2020 project RIA-ENSAR2.

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