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INVESTIGATION OF ^{44}Ti PRODUCTION FOR ^{44}Ti/^{44}Sc RADIONUCLIDE GENERATOR

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^{44}Ti/^{44}Sc RADYONÜKLİD JENERATÖRÜ İÇİN ^{44}Ti ÜRETİMİNİN İNCELENMESİ

Abstract:

As a positron emitter, Scandium-44 (^{44}Sc) having a short half-life of 3.97 (4) h is a promising PET radionuclide which can be produced ^{44}Ti long-lived parent (60.0 (11) y). In this work, a ^{44}Ti/^{44}Sc generator was designed to produce ^{44}Sc. The separation and purification studies were optimized by using ^{46}Sc (83.787 (16) d) as tracer. Hydroxamate and Dowex resins were used for separation process Sc radioisotopes from titanium. Briefly a ^{44}Ti/^{44}Sc generator system may be a source of ^{44}Sc production in hospitals in future. If it is made suitable for hospital use, a hospital will have the opportunity to work with this generator for many years with a single production.

Özet:

Bir pozitron yayıcı olarak, 3,97 (4) h'lik kısa bir yarı ömre sahip olan scandium-44 (^{44}Sc), uzun ömürlü ^{44}Ti ana çekirdeğinden (60.0 (11) y) üretilebilen umut verici bir PET radyonükliddir. Bu çalışmada ^{44}Sc üretmek için ^{44}Ti/^{44}Sc jeneratör sistemi tasarlanmıştır. Ayırma ve saflaştırma çalışmaları, izleyici olarak ^{46}Sc (83.787 (16) d) kullanılarak optimize edildi. Titanyumdan Sc radioizotopları ayırma işlemi için hidroksamat ve dowex reçineleri kullanılmıştır. Kısaca ^{44}Ti/^{44}Sc jeneratör sistemi gelecekte hastanelerde ^{44}Sc üretim kaynağı olabilir. Hastane kullanımına uygun hale getirilirse bir hastane tek üretim ile bu jeneratör ile uzun yıllar çalışma imkanına sahip olacaktır.

Keywords: ^{44}Sc, ^{44}Ti, ^{44}Ti/^{44}Sc generator, cyclotron, ^{45}Sc(p,2n)^{44}Ti, hydroxamate resin.

Anahtar Kelimeler: ^{44}Sc, ^{44}Ti, ^{44}Ti/^{44}Sc jeneratörü, siklotron, ^{45}Sc(p,2n)^{44}Ti, hidroksamat reçinesi.

1. Introduction

PET radionuclides are produced in cyclotron and as generator products. Recently, the production of PET radionuclides has gained an interest to use in nuclear medicine both in terms of being economical and the ease of the applied method. Currently, the search for other radioisotopes that can replace ^{18}F, the most common PET radionuclide produced in particle accelerators, is still ongoing (Ferreira et al., 2012; Jokerst & Gambhir, 2011). It has been proven that especially the new metallic PET radionuclides have better organ involvement and therefore good solubility (Sadeghi, Enferadi & Nadi, 2011; Walczak et al., 2015). Although ^{44}Sc does not have a single production method, there are also different production conditions. Although this radionuclide is a generator product, it can also be produced in accelerators with different targets (Daraban et al., 2009; Hoehr et al., 2014; Severin et al., 2012). However, the general

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method is often the method obtained by irradiating the natural scandium compounds of ^{44}Ti. Due to the economic and physical convenience of this method, studies on this subject have increased in recent years (Kerdjoudj et al., 2016a; Lee, Kong & Hur, 2016; V. Radchenko et al., 2016; Valery Radchenko et al., 2017; Wittwer et al., 2011). As a result of loading the main radioisotope into the system and elution with certain chemicals, this process takes seconds. Another feature of the generators is that they can be used for much longer periods than the half-life of the product radionuclide, depending on the half-life of the main radionuclide. Since the half-life of ^{44}Ti, the main radionuclide, is approximately 60 years in this project, the use of a single generator will be possible for many years (Ayranov & Schumann, 2010; Filosofov, Loktionova, & Rösch, 2010; Lange et al.,1999; Pruszyński et al., 2010; Roesch, 2012). This is of great importance in terms of ease of use and economy.

With its long half-life, ^{44}Ti is promising as a ^{44}Ti/^{44}Sc generator. However, the production of ^{44}Ti can be expensive because the irradiation time to reach higher activities is long. There are two primary production methods of ^{44}Ti: the first is ^{45}Sc(p,2n)^{44}Ti reaction in particle accelerators (Daraban et al., 2009; Yug et al., 2005), and the second is using ^{40}Ca with alpha particles (Alliot et al., 2015; Severin et al., 2012; Szkliniarz et al., 2016). For the first method, the optimum parameters for irradiation are 22 MeV proton acceleration for 10 days in a cyclotron. Yet, with these parameters, only about 1 mCi is achieved because of the low cross-section values. After production, a long cooling time is also needed due to the generation of other products. Nevertheless, such other products are negligible because of their short half-lives and are easily separated using resin systems (Valery Radchenko et al., 2017). After the separation of ^{44}Ti using this method, the ^{44}Ti/^{44}Sc generator can be produced using known ways, e.g., as for a ^{99}Mo/^{99m}Tc generator (Filosofov et al., 2010; Kerdjoudj et al., 2016b; Pruszyński et al., 2010; Valery Radchenko et al., 2017; Roesch, 2012). For the second method, when ^{226}Ra is used as an alpha particle on Ca targets, ^{226}Ra can decay with the same energy levels to ^{44}Ti gamma energy levels. Thus, the separation of ^{44}Ti and other products from ^{226}Ra (such as ^{214}Pb) is essential. Of note, ^{44}Ti and ^{214}Pb are not easily separable with gamma spectroscopy.

2. Material and Method

2.1. Reagents and equipment

As for the chemicals used in this study, thin layer chromatography paper (ITLC-silica), $TiCl_4$, $CaCl_2$, methanol, hydrochloric acid, 2,3,5,6-tetrafluorophenol (TFP), oxalic acid, sodium hydroxide (NaOH, pH adjuster), acetonitrile were purchased from Merck Chemical Co. (Darmstadt, Germany); $CaCl_2$, Dowex 1X8, 8-hydroxyquinoline, EDTA (ethylenediaminetetraacetic acid), 2,3,5,6-tetrafluorophenol (TFP), and N-(3-dimethylamino propyl)-N'-ethyl carbodiimide hydrochloride (EDC) were supplied from Sigma Aldrich (Darmstadt, Germany); and Accell resin in the Sep-Pak cartridge was purchased from Waters Co. (Milford, USA).

The following equipment from Ege University Institute of Nuclear Sciences was used: high-performance liquid chromatography (HPLC) SPD-10AV UV/vis and NaI (Tl) scintillation gamma detector and diode array detector (DAD) (Shimadzu SPD-M20A) systems with LC-10Atvp pump (Shimadzu Corporation, Kyoto, Japan), SIL-20A HT automatic sampler (Shimadzu Corporation, Kyoto, Japan), Inertsil ODS-3 C-18 4.6 × 250 mm HPLC 5 µm column (G.L. Sciences Inc., Tokyo, Japan), column oven (Shimadzu CTO-10ASvp), AR-2000 radio TLC imaging scanner (Eckert & Ziegler, Berlin, Germany), 1024-channel multichannel gamma spectrophotometer with 1 × 1 inch LaBr3(Ce) Detector (ORTEC), and $^{226}RaCl_2$ standard.

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2.2. Separation of $^{46}Sc^{+3}$ and Ti^{+4}

The separation of radioactive [^{46}Sc] Sc^{+3} from Ti^{4+} was achieved using either hydroxamate or Dowex resin

2.3. $^{46}Sc^{+3}$ and Ti^{4+} Separation Using Hydroxamate Resin

Hydroxamate resin was prepared by functionalizing the carboxy groups of silica-based weak cation exchanger resin. Initially, Accell resin (0.42 g) was soaked in 8.0 mL of water in a 15 mL falcon tube for approximately one day. 30 µL of 3 M HCl, a fresh solution of TFP (0.8 g) in 250 µL of acetonitrile, and EDC (0.8 mmol) were added. The reaction mixture was mixed for one hour at room temperature using a magnetic stirrer, and then the reaction was continued by mixing for another 3 hours at room temperature. Afterward, the resin was separated by filtration and washed three times with 10 mL of water and then three times with 10 mL of acetonitrile to separate unreacted impurities. The resin containing TFP ester groups was converted into hydroxamate resin by reacting with hydroxylamine in the next step. After 0.01 mol, 694.9 mg of hydroxylamine hydrochloride was dissolved in a mixture of 1 mL of 1.0 M NaOH and 2 mL of methanol. The pH was adjusted to 5.3–5.4 with 25–50 µL of 1.0 M NaOH. Then, the solution was added to the activated resin in a 15 mL falcon tube, and the reaction (pH 5.0–5.2) was continued at room temperature for 18 hours using a magnetic stirrer. The product was purified by filtration and washed five times with 10 mL of water and 10 mL of acetonitrile, then dried in vacuum. 333 mg of dried resin was placed in an empty syringe. Then, the column was activated by washing with 8 mL of acetonitrile, 15 mL of water, and 2 mL of 2.0 M HCl, respectively. The $Ti^{4+}$and $^{46}Sc^{+3}$ mixture was passed through the prepared resin (200 µL) and its radioactivity was counted.

2.4. $^{46}Sc^{+3}$ and Ti^{4+} Separation Using Dowex 1X8 Resin

Here, 10^{-3} M $ScCl_3$ and 10^{-6} M $TiCl_4$ were dissolved in 5 mL of methanol and mixed in equal volumes. Then, $^{46}Sc^{+3}$ was added, and the resulting solution was saturated with 5 mg of 8-hydroxyquinoline. The resin was activated before the prepared solution was passed through Dowex 1X8 resin. For this, a mixture containing 10% NaCl and 0.2% NaOH was heated at 80 °C for 2 hours, passed through the resin, and the resin was activated by passing through 0.5% HCl immediately afterward.

The mixture of $^{46}Sc^{3+}$ and $TiCl_4$ passed through Dowex 1X8 resin was examined with an ORTEC 1024-channel multichannel gamma spectrophotometer with a 1 × 1-inch $LaBr_3$(Ce) detector. At the first, background activity was measured. Then, background and elution spectra were determined. 5 mg of 8-hydroxyquinoline solution and $^{46}Sc^{3+}$ and $TiCl_4$ solutions were mixed and passed through Dowex 1X8 resin. The radioactivity of the eluents was counted on a multichannel analyzer. Then, 200 µL of the elution profiles were obtained by passing through 12 M HCl and their radioactivity counts were determined using a multichannel analyzer. In the last step, the count and gamma spectrum of the 200 µL sample taken from the elution obtained by passing 2 M HCl were determined. In addition, HPLC analyzes of $^{46}Sc^{3+}$ and Ti^{4+} separated by passing through Dowex 1X8 resin were performed.

3. Results and Discussion

Szkliniarz reported that ^{43}Sc, ^{44g}Sc, and ^{44m}Sc were produced by irradiating alpha particles accelerated in the cyclotron, using Ca and natural K targets, and highly pure ^{43}Sc was obtained (Szkliniarz et al., 2016). Cyclotrons are known to be economical and advantageous. Several studies of nuclear reactions with deuterium and protons in cyclotrons have been

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conducted (Tárkányi et al., 2019). While ^{44}Sc can be produced directly with isotopes of ^{43}Ca and ^{44}Ca, we hypothesized that it is possible to produce a ^{44}Ti/^{44}Sc generator by creating ^{44}Ti by reacting ^{45}Sc with protons or deuterons. The disadvantages of ^{44}Ti that we produced directly under our working conditions compared to cyclotron production are its lower particle energy, lower particle density, and the impurities of ^{226}Ra from other radionuclides in the decay chain. Our results are particularly valuable for individuals or groups that do not have the opportunity to work with a cyclotron within an academic environment. Table 1 presents possible reactions for ^{44}Ti production expect ^{45}Sc.

Table 1. Q-values and threshold energies to produce ^{44}Ti.

Reaction Products	**Q-value** (keV)	Threshold Energy (keV)
^{40}Ca(α,γ)^{44}Ti	5.127	0
^{48}Ti(p,2n+t)^{44}Ti	-36.747	35.477
^{48}Ti(d,3n+t)^{44}Ti	-36.972	38.525
^{51}V(p,4n+ α)^{44}Ti	-42.076	42.908
^{48}Ti(n,5n)^{44}Ti	-43.229	44.139
^{51}V(d,5n+α)^{44}Ti	-44.301	46.052
^{51}V(n,5n+t)^{44}Ti	-61.890	63.116

In these reactions, the simplest isotope, which can be worked with, is 40Ca. Some of the by-products that can be formed according to the ^{40}Ca(α,γ)^{44}Ti reaction are ^{44}Ti(α,p)^{47}V, ^{44}Ti(α,γ)^{48}Cr, ^{40}Ca(α,p)^{43}Sc, ^{43}Sc(p,γ)^{44}Ti, ^{44}Ti(p,γ)^{45}V, and ^{45}V(p,γ)^{46}Cr. Based on these results, there was no chemical or radiochemical damage of any by-product. Gamma energies of the ^{226}Ra isotope (used as an alpha source) and of its decay products are presented in Table 2.

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Table 2. Gamma energies after ^{226}Ra decay chain (Chisté, Bé, & Dulieu, 2007).

Radioisotope	Gamma Energy (keV)	Half-life
^{226}Ra	81.07	1602 years
	83.78	
	186.1	
	600	
^{210}Pb	47	21 years
^{211}Pb	405	36.1 minutes
	832	
^{212}Pb	239	10.64 hours
^{214}Pb	74.81	26.8 minutes
	77.11	
	295	
	352	
	766	
	785	
^{222}Rn	186	3.8 days
^{214}Po	609	162.3 μseconds
	665	
	768	
	934	
	1120	
	1238	
	1764	
	2118	
^{214}Bi	241	19.9 minutes
	295	
	351	
	785	
^{40}K	1460	10^9 years

Gamma energies for the ^{44}Ti isotope and reaction by-products after ^{226}Ra decay are presented in Table 2.

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Table 3. Gamma energies and half-lives of the ^{44}Ti isotope and other primary products after ^{226}Ra alpha particle's reaction with ^{40}Ca.

Radioisotope	Gamma Energy (keV)	Half-life
^{44}Ti	**67.8**	**60 years**
	78.3	
^{46}Sc	889	83.9 days
	1120	
^{52}V	1434	3.76 minutes
^{47}Ca	1308	4.53 days
^{22}Na	511	2.60 years
	1274	
^{24}Na	1369	15 hours
^{38}Cl	1600	37.3 minutes
^{47}V	511	32.6 minutes
^{48}Cr	511	21.6 hours
^{45}V	511	547 mseconds
^{46}Cr	511	0.26 seconds
^{44}Sc	**511**	**3.97 hours**

3.1 Results of Separation with Hydroxamate Resin using ^{46}Sc radiotracer

In this study, we achieved the separation of ^{46}Sc from the target system using hydroxamate and Dowex resins. The results show that hydroxamate resin is suitable for separating ^{46}Sc from the target. With 6 M HCl and hydroxamate resin, 97.4% of the total radioactivity of ^{46}Sc was separated. These results are in line with those reported previously by Gagnon et al., who used hydroxamate resin previously for the separation of ^{45}Sc and who reported that the extraction of ^{45}Ti was possible with > 50% recovery in 1 mL of 1 M oxalic acid (Gagnon et al., 2012). They also reported that this resin could also be used successfully in ^{89}Zr separation. Indeed, in our previous study, the hydroxamate resin was used for the production of ^{89}Zr, whereby 75% of ^{89}Zr was eluted from the hydroxamate resin with oxalic acid (Bulduk et al., 2019).

3.2 HPLC Analysis of the Dowex 1X8 Resin, $ScCl_3$, and $TiCl_4$ Separations

^{46}Sc, a relatively long-lived radionuclide that decays by ß and ɤ radiation with a half-life of 83.8 days of Sc, was used as a carrier to determine Sc separation and purification of ^{46}Sc.

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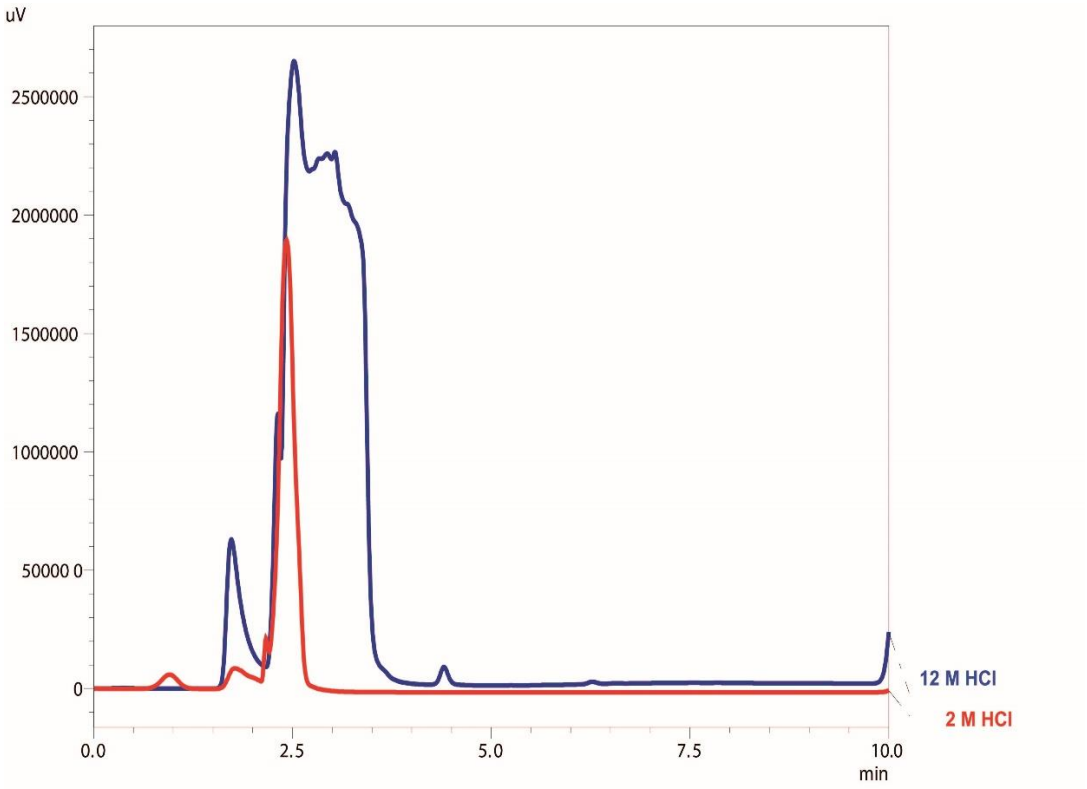

Figure 1. ^{46}Sc elution profile passing through Dowex 1X8 Resin (activity as a percentage).

Figure 1 shows that ^{46}Sc radioactivity can be eluted with 12 M HCl at a rate of 93.86% with Dowex 1X8 resin. Our results agree with Bartos et al. who separated ^{47}Sc with 0.5 M ammonium acetate by adsorbing it on Dowex 50 cation resin. The ^{47}Sc separation efficiency in the proposed procedure is about 90%, with a separation time of fewer than 2 hours. The resulting carrier-free ^{47}Sc was used to label the DOTATATE conjugate (Bartoś et al., 2012).

4. Conclusion

An in-house ^{44}Ti/^{44}Sc generator can be highly valuable for hospitals, making profound contributions to the health system. In addition, such a generator affords the convenience of working with a single generator for many years thanks to the long half-life of ^{44}Ti, dramatically reducing the costs of producing ^{44}Sc.

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