Production of Scandium Radioisotopes

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The concept of theranostics is based on the use of radioisotopes of the same or chemically similar elements to label biological ligands in a way that allows the use of diagnostic and therapeutic radiation for a combined diagnosis and treatment regimen. For scandium, radioisotopes -43 and -44 can be used as diagnostic markers, while radioisotope scandium-47 can be used in the same configuration for targeted therapy.

Keywords: theranostics ; scandium radioisotopes ; radiolabeling ; radiopharmaceuticals

1. Introduction

The development of technologies related to nuclear medicine requires providing new solutions in the field of imaging and the production of radioisotopes that can perform specific functions. One of them is the concept of personalized medicine, where the treatment process is matched based on individual screening of tumor phenotypes [1]. In this approach, dedicated compounds with a high affinity for cancer cells are designed based on test results [2]. These compounds can be labeled with diagnostic or therapeutic radioisotopes to obtain information about the development and progression of the disease or the implementation of a therapeutic process [3].

The concept of theranostics is based on the use of radioisotopes of the same or chemically similar elements to label biological ligands in a way that allows the use of diagnostic and therapeutic radiation for a combined diagnosis and treatment regimen. Despite several theranostic pairs being present in clinical practice, theranostic pairs based on the same element are relatively rare [4]. However, when using radionuclides of two different elements, differences in the pharmacokinetic and pharmacodynamic profile could be observed. For scandium, the radioisotopes -43 and -44 can be used as diagnostic markers, while radioisotope scandium-47 can be used in the same configuration for targeted therapy [5]; therefore, theranostic agents that incorporate the matched-pair radionuclides of scandium-43/scandium-47 or scandium-44/scandium-47 would guarantee identical chemistries and pharmacologic profiles.

Another interesting property of the scandium-44 radioisotope is the relatively rare decay consisting of the co-emission of a positron and a gamma quantum. This feature was used in the development and validation of diagnostic methods that, to refine the imaging, use the detection of two gamma quanta originating from positron annihilation in the coincidence mode, supported by the detection of a single gamma quantum, the so-called 3γ positron emission tomography (PET). The work in [6] supports improvement in the resolution and imaging characteristics of PET.

2. Scandium Radioisotopes

The chemical properties of scandium are similar to the group of lanthanides, while its ionic radius in the range of about 68–74 pm classifies it among the elements with chemical properties most similar to yttrium. In macrocyclic systems, Sc has a coordination number from three to nine and due to its similarity to other M^{3+} radiometals, such as gallium, yttrium, and lutetium, forms complexes with ligands by connecting through oxygen, nitrogen, and halogen. Acid–base equilibria strongly influence the chemical form in which scandium occurs in aqueous solutions. The distribution of individual chemical forms of scandium indicates that, at pH < 4, the hydrated Sc^{3+} cation is the dominant form. Due to the ease of forming hydroxy complexes together with increasing pH, $ScOH^{2+}$ and $Sc(OH)_2^{+}$ ions appear in the solution. At a pH value around 4, gradual precipitation of $Sc(OH)_3$ begins, but other ions present in the solution can influence scandium solubility: acetates increase the solubility, while phosphates reduce via coprecipitation of $ScPO_4$ [7]. Depending on the source of literature data, the solubility constant (K_{sp}) ranges from 10^{-29} to 10^{-33} and could be used for selective separation of Sc via precipitation [8][9].

Naturally occurring scandium is composed of one stable isotope: scandium-45 [10]. Other scandium radioisotopes are characterized by short half-lives, with only five having half-lives exceeding seconds. Among these five, scandium-43, scandium-44, scandium-47, and scandium-48 exhibit favorable emission profiles for radiopharmaceutical applications.

The last of the relatively stable scandium radioisotopes, scandium-46, is a low-energy beta emitter with a half-life of 83.8 days and is complementarily used in basic research. Specifically, scandium-47 and scandium-48 are β^- emitters with a half-life of 3.3492 days and 43.67 h, while scandium-43 and scandium-44 are positron emitters with half-lives of 3.891 h and 4.0421 h, respectively [10]. These radioisotopes have shown promising prospects for theranostic systems and may be effectively employed in diagnostic and therapeutic procedures in the realm of nuclear medicine.

3. Production of Scandium Radioisotopes

Due to their properties, scandium radioisotopes can be produced in different ways: using cyclotrons, accelerators, or reactors. In the case of cyclotron production, it is possible to use standard proton or deuteron beams with moderate energies available in medical cyclotrons (p,d, 10–20 MeV per particle) or cyclotrons providing α beams.

The starting elements for the production of scandium are calcium, scandium, titanium, and vanadium isotopes. Three of them in their natural form have a promising property, i.e., a very significant dominance of one of the isotopes: natural calcium contains 96.9% calcium-40, natural scandium contains 100% scandium-45, and vanadium is composed of 99.75% vanadium-51. This makes it possible to irradiate naturally occurring materials, which increases availability and reduces costs (see **Table 1**). The abundance of titanium isotopes is less favorable, where 73.7% is titanium-48, 8.25% titanium-46, 7.4% titanium-47, and just over 5% are isotopes of titanium-49 and -50. Therefore, it is necessary to use separated isotopes enriched in a specific isotope as target materials. This causes a significant increase in target costs (tens or hundreds of EUR/mg) and difficulties in obtaining appropriately enriched separated isotopes. Another issue is the need to reuse the target material; thus, the target processing has to include a recovery step and not introduce any additional impurities. Examples of production methods are presented in **Table 1**.

Table 1. Production of scandium radioisotopes.

Isotope	Irradiation Data			Activity	Radionuclidic Purity (%)	Ref.
	Reaction	Abundance (%)	Beam Energy (MeV)			
Target materials with natural isotopic abundance						
Scandium-43	$^{40}Ca(\alpha,n)^{43}Ti- > {}^{43}Sc$	96.9	12.5–17.5	240 MBq/μAh	>98.9	[11]
	$^{40}Ca(\alpha,n)^{43}Ti- > {}^{43}Sc$	96.9	34	54.8 MBq/μAh	99.7	[12]
		96.9	28	102.7 MBq/μAh	99.9	[13]
Scandium-44	$^{44}Ca(p,n)^{44}Sc$	2.1	12	6.2 MBq/μAh	N/a	[14]
	$^{44}Ca(p,n)^{44}Sc$	2.1	12.8	10.0 MBq/μAh	N/a	[15]
	$^{45}Sc(p,2n)Ti^{44}- > {}^{44}Sc$	100	Generator	185 MBq/elution	N/a	[16]
Scandium-47	$^{51}V(p,x)^{47}Sc$	99.75	20–30	1.7 MBq/μAh		[17]
	$^{51}V(\gamma,p)^{47}Sc$	99.75	20	N/a	>99.99	[18]
	$^{51}V(\gamma,p)^{47}Sc$	99.75	38	3.7 GBq	98.2	[18]
Isotopically enriched target materials						
Scandium-43	$^{46}Ti(p,\alpha)^{43}Sc$	97	15.1	225 MBq	>98.2	[19]
	$^{42}Ca(d,n)^{43}Sc$	93.58	5.8	30.4 MBq/μAh	99.4	[20]
	$^{43}Ca(p,n)^{43}Sc$	83.9	13.6	229.0 MBq/μAh	87.8	[20]
Scandium-44	$^{44}Ca(p,n)^{44g}Sc$	98.9	13.6	433.3 MBq/μAh	99.7	[20]
	$^{43}Ca(d,n)^{44g}Sc$	83.9	5.8	34.4 MBq/μAh	98.1	[20]
Scandium-47	$^{46}Ca(n, \gamma)^{47}Ca- > {}^{47}Sc$	5.0		2.14 GBq	99.99	[21]
	$^{47}Ti(n,p)^{47}Sc$	95.7		4.9 MBq	88–99	[21]

Another potentially attractive pathway for the production of scandium radioisotopes is production from a generator by the decay of the parent radionuclide, which is immobilized on the solid phase and then selectively eluted on the scandium

radioisotope. It replicates the concepts of technetium-99 m and gallium-68 generators commonly and successfully introduced in nuclear medicine, significantly facilitating the availability of radioisotopes in clinical applications [22]. Scandium-44 is produced as a decay product of titanium-44 formed in the reaction $^{45}Sc(p,2n)^{44}Ti$, while scandium-47 is a decay product of calcium-47 produced in ^{46}Ca (n,γ)^{47}Ca or $^{48}Ca(\gamma,n)^{47}Ca$ reactions. The status of generator systems for scandium-44 was recently reviewed [22]. In its current state, the concept is very interesting, but it has not been possible to create a generator that would provide enough activity for clinical applications. The first solutions [23] offered 185 MBq of activity suitable for simple preclinical studies, but the eluate required an additional purification step for effective labeling [24]. However, the availability of scandium-44 from the generator enabled a significant development of preclinical work aimed at searching for appropriate macrocyclic ligands for scandium [25]. Work is being carried out to increase the efficiency of the $^{44}Ti/^{44}Sc$ generators, significantly increasing the quality of the eluate [26][27][28][29], but at present no generator solution has been presented that could routinely and commonly provide access to the radioisotope similar to technetium or gallium generators.

The idea supporting the development of scandium generators is proof of the concept of the $^{47}Ca/^{47}Sc$ generator, which would supplement the theranostic pair with a therapeutic radioisotope from the generator. One approach is to irradiate ^{46}Ca (n,γ)^{47}Ca- > ^{47}Sc. Although the cross-section of this reaction is 740 mb, which is promising, the natural abundance of calcium-46 (0.004%) and low enrichment (~30% ^{46}Ca) combined with the ~4000 EUR/mg price of enriched material make this technology extremely expensive. Chemical isolation of scandium-47 from the target material enabled the formulation of up to 1.5 GBq of scandium-47 with high radionuclidic purity (>99.99%) in a small volume (~700 µL) [21]. Another approach is production via photonuclear reaction $^{48}Ca(\gamma,n)^{47}Ca$- > ^{47}Sc, but the effects of irradiation of the $^{nat}CaCl_2$ target reached only 1–1.5 MBq of scandium-47 in eluate [30]. Using an enriched calcium-48 target increases results up to tens of MBq activity of scandium-47 [31]. The potential drawback is the relatively short half-life of the produced calcium-47 ($T_{1/2}$ = 4.5 d), resulting in a 10–15-day shelf life of the generator, which poses challenges similar to the logistics of technetium generators.

The possibility of creating complementary $^{44}Ti/^{44}Sc$ diagnostic and $^{47}Ca/^{47}Sc$ therapeutic generators would be an ideal solution from the point of view of clinical theranostics, but this vision is quite distant yet.

In conclusion, the comparison of scandium radioisotope production methods reveals a wide range of techniques and available hardware platforms. However, a notable challenge lies in the mismatch between cost-effective and readily available target materials, which demand specialized and less common irradiation systems. Conversely, the more widely used irradiation systems necessitate separated materials and, in certain cases, the production conditions for specific radioisotopes are at the limits of the hardware capabilities.

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