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Review

Research Progress on Major Medical Radionuclide Generators

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Abstract: As the concept of integrated diagnosis and treatment gains increasing prominence, the utilization of radiopharmaceuticals in personalized medicine has garnered unprecedented attention. However, the production of these radiopharmaceuticals continues to encounter numerous technical challenges. It plays an important role in improving the efficiency and convenience of nuclear medicine services and can quickly and conveniently provide the required radioactive isotopes to meet the needs of integrated clinical diagnosis and treatment while reducing dependence on external supplies and improving safety and the economy. At present, commonly used medical radioactive isotope generators include ^{99}Mo/^{99}mTc, ^{68}Ge/^{68}Ga, ^{90}Sr/^{90}Y, ^{188}W/^{188}Re, etc. This article reviews the latest research progress on three main medical radioactive isotope generators of ^{99}Mo/^{99}mTc, ^{68}Ge/^{68}Ga, and ^{90}Sr/^{90}Y. It also evaluates the highly anticipated new ^{44}Ti/^{44}Sc generator and proposes research prospects for current medical radioactive isotope generators, providing exploration directions for the future development of nuclear medicine.

Keywords: radionuclide; generator; nuclear medicine; radio pharmaceuticals

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1. Introduction

With the continuous advancement of modern medicine and nuclear medicine technology, radioactive isotopes are playing an increasingly vital role in the diagnosis and treatment of diseases. Statistics indicate that approximately one-fifth of patients in developed countries require treatments involving medical radioactive isotopes [1]. Commonly used isotopes in clinical applications include ^{99}mTc, ^{44}Sc, ^{68}Ga, and ^{90}Y. Among these, ^{99}mTc is particularly favored due to its short half-life and the emission of low-energy gamma rays, which enhances safety. It is widely utilized for organ imaging and clinical drug development. On the other hand, ^{44}Sc and ^{68}Ga are primarily employed in positron emission tomography (PET) for diagnosing conditions such as cancer and inflammation. Furthermore, ^{90}Y shows promising potential in the field of radioimmunotherapy for tumors. Despite the considerable potential of radiopharmaceuticals in clinical applications, their production and translation processes are fraught with numerous challenges.

Currently, there are three primary methods for the production of medical radioactive isotopes. The first method is the traditional reactor production technique, which includes fission and neutron activation approaches. This method offers advantages such as a wide variety of isotopes, minimal radioactive waste, and low production costs. However, the isotopes produced by traditional methods do not fully meet the demands of the medical field. The second method involves the use of accelerators for the production of isotopes. This approach partially addresses the limitations in the variety of radioactive isotopes available. High-energy charged particles generated by the accelerator bombard specific

stable isotope targets, resulting in the production of a diverse range of radioactive isotopes. Currently, isotopes produced using accelerators account for over 60% of the known radioactive isotopes. Despite this, the high construction costs of accelerators pose significant challenges, as does the logistics of transporting isotopes with short half-lives.

The third way is through the medical radionuclide generator [2], a device that can separate the daughter radionuclide from the parent radionuclide. One radionuclide can produce another radionuclide by decay. The former is usually called parent radionuclide/mother radionuclide, and the latter is called daughter radionuclide. A parent–daughter radionuclide pair can be considered to build a radionuclide generator system to produce daughter radionuclides when needed.

The working principle of the medical radionuclide generator is based on the radioactive decay process; that is, the parent isotope decays into the daughter isotope. In the generator, with the decay of the parent nuclide, the daughter nuclide continues to grow and decay until the radioactivity balance is reached (as shown in Figure 1). Carrier-free progeny nuclides can be obtained from the parent by appropriate separation methods. Since the matrix decays continuously, the above separation process can be repeated, so the generator can be reused within a certain time. This phenomenon is similar to milking cows, so radionuclide generators are commonly known as "cows" Not all radionuclides can be assembled into generators. The parent and daughter isotopes of radionuclide generators need to meet the following conditions: the parent radionuclide should have a relatively long half-life to achieve long-term balance with the daughter isotope; the parent and daughter isotopes should be two different elements for effective separation by physical and chemical methods; parent isotopes should be easily prepared by nuclear reactors or accelerators for easy access; daughter isotopes should have a short half-life to meet the needs of specific applications. These conditions jointly ensure the efficient operation and practicability of a radionuclide generator.

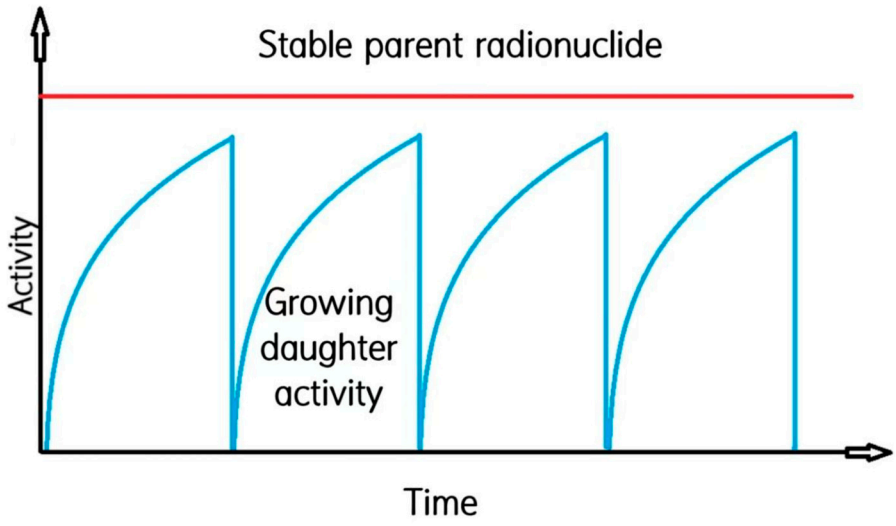


Figure 1. Principle of generator.

Medical radionuclide generators can regularly separate short-lived daughter isotopes from long-lived parent isotopes(Table 1), which provides convenience for its application in medicine, especially in areas far away from reactors or without accelerators. At present, common medical radionuclide generators include ^{99}Mo/^{99}mTc, ^{68}Ge/^{68}Ga, ^{44}Ti/^{44}Sc, and ^{90}Sr/^{90}Y generators. The parent isotopes used by these generators can be produced by reactors or accelerators, which can provide carrier-free, high nuclear purity, and high specific activity short half-life isotopes safely and conveniently many times, and are widely used in medical, industrial, and scientific research fields. This paper summarizes and com-

ments on the existing research on common medical radionuclide generators and discusses the challenges and directions of the development of medical radionuclide generators in the future.

2. ^{68}Ge/^{68}Ga Generator

In the field of cancer diagnosis, although traditional imaging techniques such as X-ray, CT, and MRI provide information about the size and location of tumors, they are often not sensitive enough in early diagnosis and are difficult to accurately identify small lesions. Nuclear medicine imaging technology shows higher sensitivity and specificity by virtue of its characteristics of integrating computer, physics, biology, and nuclear science. Through the radiation generated by the decay of medical radionuclides, nuclear medical imaging can provide insight into tumors and other diseases from the molecular level, with the advantages of real-time monitoring, accuracy, and noninvasive nature, and become an important tool for early diagnosis of tumors. Among them, pet (positron emission tomography) technology stands out with its excellent sensitivity and spatial resolution, especially suitable for detecting small lesions.

^{68}Ga has a half-life of 68 min and emits positrons during the decay process, which is conducive to PET imaging. A ^{68}Ge/^{68}Ga generator is one of the main ways to produce ^{68}Ga. As the parent isotope, ^{68}Ge has a half-life of 271 days, which is suitable for the ^{68}Ge/^{68}Ga generator (Figure 2).

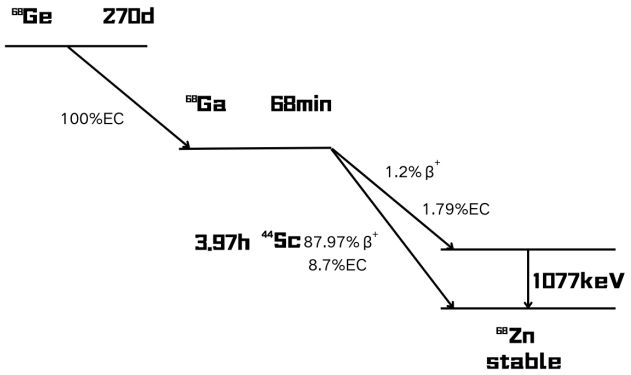


Figure 2. The decay diagrams of ^{68}Ge and ^{68}Ga.

^{68}Ga has regained attention due to the new ^{68}Ge/^{68}Ga generator and its complex radioactive drugs combined with PET/CT for clinical diagnosis. Although ^{68}Ga has been used for imaging since the 1960s, its application has gradually decreased due to the rise of other diagnostic methods in the late 1970s. However, researchers continue to explore and optimize ^{68}Ge/^{68}Ga generator technology. At the beginning of the 21st century, the ^{68}Ge/^{68}Ga generator based on hydrochloric acid was commercialized and successfully generated ^{68}Ga in the form of a cation, which prompted it to achieve remarkable results in the design of MRI and SPECT imaging probes, especially in neuroendocrine tumor imaging.

^{68}Ge/^{68}Ga generators are usually divided into extraction types and chromatographic types.

2.1. Extraction Type ^{68}Ge/^{68}Ga Generator

In 1960, Gleason [2] first introduced the solvent extraction ^{68}Ge/^{68}Ga generator, nicknamed "positron cow". ^{68}Ga was extracted from a ^{68}Ge aqueous phase at pH 4.5 by liquid–liquid extraction, extracted with acetylacetone cyclohexane solution, and then back extracted with 0.1 mol/L HCl to obtain ^{68}Ga. Ehrhardt et al. [3] extracted ^{68}Ga from a ^{68}Ge aqueous phase at pH 5 with 8-hydroxyquinoline chloroform solution to obtain ^{68}Ga oxine complex, which can be converted into ^{68}Ga EDTA, etc. However, the complex operation

and residual organic solvents limit its application. These early developments opened up a new path for molecular imaging and radiopharmaceutical chemistry in nuclear medicine and promoted the application of radionuclides in medical diagnosis.

2.2. Chromatographic $^{68}Ge/^{68}Ga$ Generator

The $^{68}Ge/^{68}Ga$ generator used in early liquid–liquid extraction was replaced by chromatographic separation technology due to its defects. The solid-phase chromatography generator (Figure 3) developed by Greene [4] and Yano [5] uses an alumina column and EDTA eluent, which can elute ^{68}Ga in 95% yield, while ^{68}Ge remains in the column. This process is simple and fast. Sterile eluent is used to ensure sterility through a millipore filter. It is widely used to prepare ^{68}Ga EDTA, which is suitable for brain tumor localization, etc. When the concentration of ^{68}Ge is lower than 1.4×10^{-6}, add 0.5 mL of 18% NaCl solution and then inject it. However, due to the strong complexation ability of EDTA, ^{68}Ga needs to be converted to an ionic state by solvent extraction, which may prolong the operation time and affect the yield.

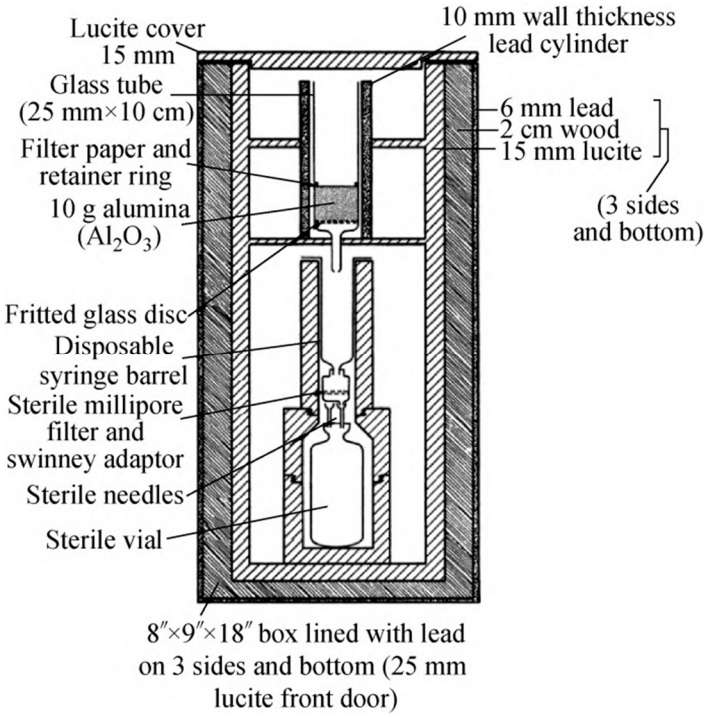


Figure 3. $^{68}Ge/^{68}Ga$ generator [4].

In order to solve the problem that ^{68}Ga exists in the form of a complex, Schuhmacher et al. [6] studied an organic ion exchanger that can separate $^{68}Ga^{3+}$ from ^{68}Ge and elute it with a 4.5 mol/L HCl solution. However, the volume of the eluent obtained is large and the acidity is high. It needs AG 1-x8 resin to concentrate ^{68}Ga and reduce the acidity. Neirinckx et al. [7] used AG 1-x8 resin to separate ^{68}Ge and ^{68}Ga. By controlling the eluent, the yield of ^{68}Ga was 90% and the leakage of ^{68}Ge was less than 0.01%. However, the resin may decompose under radiation, affecting the adsorption performance and generator performance.

Nakayama et al. [8] used a resin containing N-methylglucamine (NMG), referred to as R-MGlu, which effectively adsorbed ^{68}Ge and eluted ^{68}Ga using a sodium citrate solution at pH levels greater than 5. With a sodium citrate concentration of 0.1 mol/L, the recovery rate of ^{68}Ga exceeded 90%, while the leakage of ^{68}Ge was below 0.0004%. Subsequently, over a period of six months, the elution of ^{68}Ga was repeatedly performed using 0.1 mol/L sodium citrate, with the efficiency maintained at 69–80% [9]. Although

the adsorption capacity of R-MGlu for non-radioactive germanium decreased under high doses of gamma radiation, indicating possible decomposition, its stability was preserved during long-term use.

Chinese scholars successfully developed a $^{68}Ge/^{68}Ga$ isotope generator for the first time in 1980 and optimized the separation process of ^{68}Ge and ^{68}Ga adsorbed by acidic Al_2O_3 [10]. ^{68}Ge was produced by irradiating the zinc target with a cyclotron. After chemical separation, ^{68}Ge was loaded onto the chromatographic column. The high-efficiency elution of ^{68}Ga was achieved by fine-tuning the eluent, simplifying the extraction process, improving the yield, and reducing the risk of ^{68}Ge leakage. Songming et al. [11] found that when the pH value was about 5, the SnO_2 carrier had the best adsorption for ^{68}Ge, and the adsorption capacity for ^{68}Ga was low. A total of 0.1 mol/L sodium citrate washing solution could achieve a recovery rate of more than 90% of ^{68}Ga, and the leakage of ^{68}Ge was very low. There are no other radioactive impurities in the eluent with high chemical purity, and SnO_2 is stable without dissolution. Lizongquan et al. [12] studied the adsorption properties of different SnO_2 materials and pointed out that the physical and chemical properties of SnO_2, such as crystal structure and particle size, had a significant impact on the adsorption properties, and the adsorption capacities of SnO_2 from different manufacturers were different.

The first commercial $^{68}Ge/^{68}Ga$ generator [13] developed by Russia's cyclotron Ltd. (Kaluga, Russia) to modify TiO_2 solid carrier provides ^{68}Ge active substances up to 3.7 GBq. The ^{68}Ga extraction yield is about 80%, and the ^{68}Ge penetration is controlled at 10^{-3}%. Since then, commercial $^{68}Ge/^{68}Ga$ generators have emerged in succession (Table 2). Eckert&Ziegler also produces TiO_2-based generators, which also contain ^{68}Ge of 3.7 GBq. $^{68}Ga^{3+}$ is obtained in the form of a 0.1 M HCl solution. The initial elution yield is about 80%, the ^{68}Ge leakage is between 3×10^{-5}% and 5×10^{-3}%, and the level of chemical impurities is between 1 and 10 ppm [14].

Table 1. Half-lives of parent and daughter isotopes.

Parent Isotope	Half-Life	Daughter Isotope	Half-Life	References
^{68}Ge	270 d	^{68}Ga	68 min	[3]
^{99}Mo	65.94 h	^{99}mTc	6.01 h	[15]
^{90}Sr	28.79 y	^{90}Y	64 h	[16]
^{44}Ti	60 y	^{44}Sc	3.927 h	[17]

Table 2. Adsorption material for new $^{68}Ge/^{68}Ga$ generators.

Manufacturer	Adsorbing Material	Eluent	Initial Yield of ^{68}Ga/%	Leakage of ^{68}Ge/%
Cyclotron Ltd. (Kaluga, Russia; https://www.cyclotron.com/ accessed on 8 February 2025)	TiO_2	0.1 M HCl	80	1×10^{-3}
Eckert & Ziegler (Berlin, Germany; https://www.ezag.com/ accessed on 4 February 2025)	TiO_2	0.1 M HCl	80	1×10^{-3}
iThemba Labs (Cape Town, South Africa; https://tlabs.ac.za/ accessed on 4 February 2025)	SnO_2	0.05 M HCl	80	2×10^{-3}
ITM (Munich, Germany; https://www.itm-radiopharma.com/ accessed on 3 February 2025)	SnO_2	0.05 M HCl	80	5×10^{-3}

Table 2. *Cont.*

Manufacturer	Adsorbing Material	Eluent	Initial Yield of ^{68}Ga/%	Leakage of ^{68}Ge/%
IRE EliT (Fleurus, Belgium; https://www.ire.eu/en/ accessed on 4 February 2025)	Unknown	0.1 M HCl	70	3×10^{-5}
PARS Isotope (Tehran, Iran; https://parsisotope.com/ accessed on 1 February 2025)	SnO_2	0.6 M HCl	80	1×10^{-3}

The ^{68}Ge/^{68}Ga generator manufactured by ithemba labs in South Africa is based on a SnO_2 solid-phase support material [14]. The eluent of the SnO_2-based generator was 0.6 M HCl. The initial ^{68}Ga elution yield was about 75–85%. During one year of use, the ^{68}Ge leakage of the SnO_2-based generator increased from 10^{-3}% to 10^{-1}%. The level of chemical impurities in the ^{68}Ga eluent is between 1 and 20 ppm.

The ^{68}Ge/^{68}Ga generator developed by the German ITM company (isoope technologies Garching GmbH) uses hydrophobic dodecyl-3,4,5-trihydroxybenzoate to bind to SnO_2 resin (C-18) as an adsorbent [18]. Using 3–4 mL of 0.05 M HCl solution as the eluent, the average elution yield of ^{68}Ga was 80% (range 72.0–95.1%), and the leakage of ^{68}Ge was less than 0.006%, which decreased to 0.001% with the increase in time.

Recently, the ^{68}Ge/^{68}Ga generator developed by the Belgian ire elit company has also entered the market [19], but the adsorption material used is unknown. Using 0.1 M HCl as the eluent, the volume of each elution of the generator was 5 mL. The elution yield of ^{68}Ga is 70–80%, and the yield will gradually decrease over time. The leakage of ^{68}Ge is very low, which is 0.00003% for the new generator. With the use of the generator, the leakage of ^{68}Ge will increase slightly, but it is usually kept below 0.001%.

The adsorption material used in the ^{68}Ge/^{68}Ga generator [20] developed by pars isotope in Iran is SnO_2. The average yield of ^{68}Ga was 80%, and the yield was never less than 70% during the whole year of the study. The leakage of ^{68}Ge was 0.006% at the beginning and decreased to 0.001% over time.

In the reported literature, the performance of the ^{68}Ge/^{68}Ga generator can be improved by using SnO_2 as the adsorbent. It is mentioned in the literature that the content of Sn ions in ^{68}Ga eluted by a SnO_2-based generator is low (about 0.03 ppm), but there is still a potential risk of metal ion pollution. In order to further improve the purity of ^{68}Ga, it is necessary to use a cation exchange resin column for post-treatment. Other types of adsorbents, such as TiO_2 and SiO_2, are also mentioned in the literature. Similar to SnO_2, these adsorbents may also introduce metal ion pollution. Appropriate post-treatment steps are required to ensure the purity of ^{68}Ga [21,22].

Chakravarty et al. [23] synthesized nano-ceria polyacrylonitrile (CeO_2-PAN) composites. XRD and bet showed that the particle size was about 10 nm, the specific surface area was 72 m^2/g, and the pore size was 3.8 Å. In 0.01 n HCl, CeO_2-PAN has a high Kd value for ^{68}Ge, which can quantitatively retain ^{68}Ge and effectively elute ^{68}Ga. The developed ^{68}Ge/^{68}Ga chromatographic generator can elute high-purity ^{68}Ga (^{68}Ge < 1×10^{-5}%) with a yield of >80%, Ce, Fe, Mn < 0.1 ppm), The performance was stable within 7 months.

Subsequently, Chakraborty et al. [24–26] successfully prepared ^{68}Ga-labeled dota-e[c(RGDFK)]$_2$ at Bhabha Atomic Research Center in Mumbai, India, using a self-developed CeO_2-PAN-based ^{68}Ge/^{68}Ga generator (Figure 4), which achieved a radiochemical purity of more than 98% without post-treatment and showed excellent in vitro stability in 0.1 M EDTA solution at room temperature. A one-year evaluation showed that the ^{68}Ga yield of the generator was over 70%, and the ^{68}Ge leakage was less than 10^{-4}%, maintaining

high purity. The $^{68}GaCl_3$ solution provided meets the chemical requirements of most ^{68}Ga complexation, and the yield of the compound with a variety of ligands and dota coupling peptides is more than 95%. ^{68}Ga dota NOC injection passed the sterility and pyrogen tests and met the drug standards. ^{68}Ga dota NOC PET/CT showed a high positive rate in patients. Although only one patient changed the treatment plan, the overall application results were satisfactory.

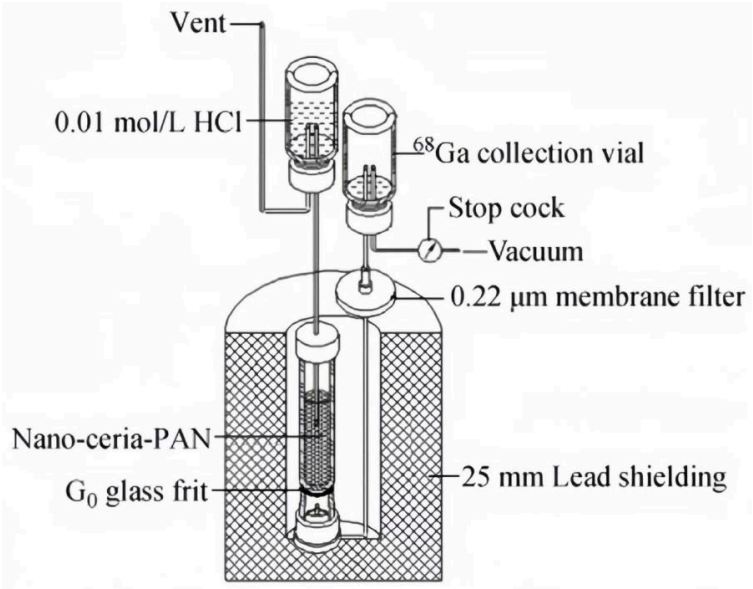


Figure 4. $^{68}Ge/^{68}Ga$ generator (CeO_2-PAN as column adsorbent) [26].

On the original basis, Chakravarty et al. [27] developed a $^{68}Ge/^{68}Ga$ generator based on nano-zirconia to meet the needs of the clinical environment and facilitate the preparation of radioactive drugs. The nano-zirconia in the generator was synthesized by an in situ reaction of zirconia and ammonium hydroxide in an alkaline medium, and the physical properties of the material were studied by analytical technology. The 740 MBq (20 mCi) $^{68}Ge/^{68}Ga$ generator performed well during the one-year evaluation period. The yield of ^{68}Ga was more than 80%, the leakage of ^{68}Ge was less than 10^{-5}%, and the concentration of Zr, Fe, and Mn ions was <0.1 ppm. The labeling yield of dota-tate, a ^{68}Ga-labeled biomolecule, also exceeded 99%. In addition, Chakravarty et al. [28] also reported a kind of mesoporous tin oxide (MTO) nanoparticles synthesized by solid-state mechanochemical method as a new generation of nano-adsorption material for $^{68}Ge/^{68}Ga$ generator. The synthesized MTO nanoparticles have a grain size of 6–12 nm and a large specific surface area of 265 $\pm$ 16 m^2/g. The mechanism of adsorption and separation was studied by measuring zeta potential under different pH conditions. The adsorption capacity of the nano-adsorbent is 85 $\pm$ 5 mg Ge/nm/g adsorbent under column flow conditions. Using this material, a 740 MBq clinical scale $^{68}Ge/^{68}Ga$ generator was developed. The regular elution was successfully carried out for more than one year, and the elution yield was more than 70%, which met the requirements of clinical use.

SnO_2 and its calcined form were characterized in detail by XRD, SEM, and BET surface area analysis, and its radiation stability was tested [29]. On this basis, two $^{68}Ge/^{68}Ga$ generators were developed and evaluated at 100 and 200 elution cycles, using different concentrations of hydrochloric acid as the eluent. The results showed that the generator based on calcined SnO_2 exhibited a higher ^{68}Ga elution yield and lower ^{68}Ge content in the elution solution than the unheated SnO_2 generator. Specifically, the ^{68}Ga elution yield of calcined SnO_2 is 75–80%, while the 68Ge content is less than 3 $\times$ 10^{-3}%;. The elution yield

of ^{68}Ga without heating SnO_2 was only 60–65%, and the content of ^{68}Ge was higher than 1×10^{-1}%.

A new ^{68}Ge/^{68}Ga generator column material chitosan titanium dioxide (C-TOM) composite was proposed [30]. C-TOM showed excellent physical and chemical stability in 0.01 M HCl. During the pre-evaluation period of about two months, the yield of ^{68}Ga remained above 95%, and the leakage rate of ^{68}Ge was 2×10^{-4}%. Due to its high specific surface area and porosity, c-tom is an efficient solid-phase extraction agent, which can routinely elute more than 99.99% ^{68}Ga in a small volume (about 1.5 mL) of 0.01 M HCl.

The ^{68}Ge/^{68}Ga generator plays a significant role in nuclear medicine, particularly in PET imaging, where it demonstrates high sensitivity and specificity for detecting small lesions. The relatively long half-life of the parent isotope ^{68}Ge (271 days) allows the generator to stably supply ^{68}Ga over an extended period, reducing the need for frequent replacements. Modern generators typically achieve a yield of over 80% for ^{68}Ga while maintaining extremely low leakage rates of ^{68}Ge (less than 0.001%), enhancing the purity and safety of radiopharmaceuticals. However, the preparation process is complex, involving chemical separation and purification, requiring specialized technology and equipment. Early solvent extraction generators used organic solvents, which could pose environmental pollution and operational safety issues. Certain resins may decompose under radiation, affecting long-term stability. Additionally, high costs and the high demands on operators also limit its widespread application.

3. ^{99}Mo/^{99}mTc Generator

The first ^{99}Mo/^{99}mTc generator was developed by Tucker et al. [15] at Brookhaven National Laboratory, but it did not meet the pharmacopeia standard and was not put into medical use. ^{99}mTc is the most critical isotope in nuclear medicine, accounting for more than 80% of nuclear medicine applications. It is used in more than 40 million medical procedures every year, involving heart disease, cancer, and other diseases. The 6.01 h half-life of ^{99}mTc and 140 keV gamma ray are suitable for the SPECT camera. ^{99}mTc is mainly produced by the ^{99}Mo/^{99}mTc generator, and ^{99}Mo is usually manufactured by a nuclear reactor as the parent. Since 2007, the global supply has been interrupted many times, especially in 2009 and 2010. The shutdown of two key reactors affected two-thirds of the global supply [31]. In order to deal with the shortage of ^{99}Mo/^{99}mTc, a variety of separation technologies were developed, including column chromatography, solvent extraction, and electrochemical separation to separate ^{99}Mo and ^{99}mTc.

3.1. Chromatographic Generator

The chromatographic ^{99}Mo/^{99}mTc generator uses a chromatographic column to adsorb the parent isotope ^{99}Mo, while its daughter isotope ^{99}mTc is not adsorbed due to different charges. ^{99}mTc can be eluted in the form of ^{99}mTcO^{4-} by adding an appropriate eluent.

This ^{99}Mo/^{99}mTc generator [32] simplifies the production process by using the low adsorption capacity of acidic Al_2O_3 at pH 5–6, avoiding pretreatment and post-treatment of Al_2O_3. At pH 5–6.2, the adsorption capacity of Al_2O_3 for ^{99}Mo is about 2 mg Mo/g. The preparation method is simple. Using 4 mL of normal saline, more than 95% of ^{99}mTc yield can be obtained under the ^{99}Mo load of 1 mCi to 20 Ci, and the aluminum leakage is less than 100 ppb. This design makes the new generator simpler in production and better in operating characteristics [33].

Tetragonal nano-zirconia (t-ZrO_2), as the adsorbent of the new ^{99}Mo/^{99}mTc generator [34], has a high specific surface area and large adsorption capacity and can strongly retain ^{99}Mo under acidic pH conditions, while ^{99}mTc can be eluted by 0.9% sodium chloride solution. The generator based on t-ZrO_2 eluted repeatedly within 10 days, and the yield of ^{99}mTc

was more than 85%. Nanocrystalline γ-Al_2O_3 (Figure 5) as an adsorbent [35] has a selective adsorption capacity of up to 200 ± 5 mg Mo/g for ^{99}Mo, a total yield of more than 80% for ^{99}mTc, and a radioactive purity and radiochemical purity of more than 99%. The ^{99}mTc yield of the generator was stable within six days, which was suitable for the preparation of radiopharmaceuticals, and the labeling yield was more than 98%.

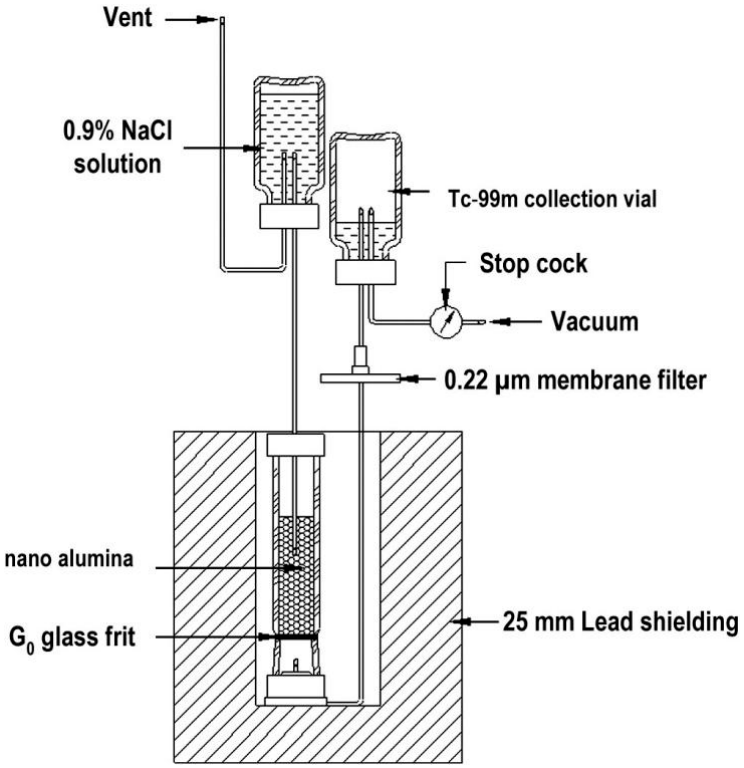


Figure 5. Schematic diagram of ^{99}Mo/^{99}mTc generator assembly [35].

Chakravarty et al. [36] developed a new type of ^{99}Mo/^{99}mTc generator using neutron-activated low specific activity ^{99}Mo and mesoporous nano-Al_2O_3 (MA). MA was synthesized by glucose template with a grain size of 2–3 nm and a specific surface area of 230 ± 10 m^2/g. In an acidic environment, MA can strongly and selectively retain ^{99}Mo, while ^{99}mTc can be easily eluted by 0.9% NaCl solution with adsorption capacities of 225 ± 20 and 168 ± 12 mg Mo/g, respectively. The concept of a series column generator [37] was proposed to improve the radioactive concentration and purity of ^{99}mTc. A generator of 26 GBq (700 mCi) was developed. The eluted ^{99}mTc has high purity and is suitable for the preparation of ^{99}mTc-labeled drugs.

Nanostructured materials have attracted much attention due to their large specific surface area, changed physical properties, customized surface chemical properties, favorable adsorption properties, and enhanced surface reactivity. These characteristics make nanomaterials a new adsorbent in column chromatography separation, showing potential in the development of radionuclide generators in nuclear medicine. A recently reported novel silica zirconia sulfate inorganic polymer adsorbent (SZ) was synthesized by the sol–gel method [38] and was polymerized with tetraethoxysilane (TEOS), forming in situ tetra (n-octyloxy) zirconium sulfate ($Zr(OCT)_4$). SZ adsorbent was characterized by FT-IR SEM, XRD. It was found that the maximum adsorption capacity of MoO_4^- could reach 450 mg/g. When a small amount of normal saline was used to elute ^{99}mTc, the elution yield was about 75%, and the leakage rate of ^{99}Mo was less than 0.02%. The study of different calcination temperatures, Zr/Si, and Si/Zr molar ratios showed that under the conditions of 180 °C calcination, a Zr/Si molar ratio of 0.1, and a SO_4^{2-}/Zr molar ratio

of 0.6, the SZ adsorbent showed the best Mo adsorption capacity, showing the potential application value in ^{99}Mo/^{99}mTc generators.

3.2. Gel Generator

The first gel type ^{99}Mo/^{99}mTc generator is made of zirconium molybdate gel as the matrix [39], which overcomes the complex treatment and waste storage problems faced by the traditional generator when using high specific activity ^{99}Mo. The gel contains about 25% Mo, which is much higher than the 0.2% adsorption capacity of Al_2O_3. Therefore, ^{99}Mo with low specific activity can be used to make the generator smaller in physical size but can accommodate up to 37gBq (1Ci) or more activity. This gel is mainly used as a cation exchanger, and its open structure allows TcO_4^- to diffuse freely, thus achieving a high yield elution in a small volume. Unlike the chromatographic generator, ^{99}Mo is chemically bound to the gel structure and cannot be eluted.

Subsequently, Guzman et al. [40] studied the effect of the molar ratio of Zr to Mo in zirconium molybdate gel on the performance of the ^{99}Mo/^{99}mTc generator. The research team prepared a series of gels with a zr:mo molar ratio from 0.5:1 to 2.3:1 and characterized them by TGA, IR, XRD, and UV. The results show that the change in the Zr: Mo ratio will affect the arrangement of polymolybdate in the octahedral unit around Zr and then affect the elution efficiency. Although a high Mo concentration can improve the elution efficiency, it also increases the leakage of ^{99}Mo, so it is necessary to balance the two. Subsequent studies discussed the effects of the concentration and aging time of ^{99}Mo molybdate solution and zirconate solution with different pH values on the gel properties [41]. The results showed that using a more alkaline ^{99}Mo molybdate solution can significantly improve the elution efficiency by up to 81%. The concentration of zirconate and aging time have little effect on the elution curve, but they are related to the leakage of ^{99}Mo. The radiochemical purity of ^{99}mTc in all gels exceeded 93%, indicating that ^{99}mTc was eluted mainly in the form of ^{99}mTcO_4^-. A semi-automatic equipment named disigeg [42] was further studied and designed to produce a zirconium molybdate gel generator, and the effect of drying conditions on its performance was evaluated. It was found that the temperature, time, and air flow during the drying process directly affected the porosity and permeability of the gel and then affected the diffusion properties of ^{99}mTcO_4^-. The gel eluent was prepared at the following conditions: 80 °C, 5 h, and 90 mm/s gas flow. The yield of ^{99}mTc was 70–75%, the leakage rate of ^{99}Mo was less than 3×10^{-3}%, and the radiochemical purity was about 97%. Combined with the characterization results from the infrared spectrum and X-ray diffraction, all gels showed amorphous structures, similar chemical composition, and increased porosity with the increase in drying time, which further affected the performance of the generator.

The study of the ^{99}Mo/^{99}mTc column generator based on Ce (IV) molybdate gel shows that [43] when the molar ratio of Mo:Ce is 2:1, the precipitation yield of ^{99}Mo in the gel is the highest, reaching 63%. When 10 mL of 0.9% NaCl solution was used for elution, the yield of ^{99}mTc was 75.4 ± 2.2%, and the radiochemical purity was 97.3 ± 0.8%. In the ^{99}mTc eluent, the activity contribution of ^{99}Mo is very low, and the concentrations of Mo and CE are not more than 2 ppm and 0.5 ppm, respectively.

A new Cerium (IV) tellurium molybdate gel material is used to prepare a ^{99}Mo/^{99}mTc column generator [44]. The gel has attracted much attention due to its high molybdenum content and excellent precipitation yield of ^{99}Mo (up to 97.6%). The results showed that the yield of ^{99}Mo was the highest when the molar ratio of Ce:Te:Mo was 1:0.2:1. The generator showed good performance. The elution yield of ^{99}mTc was 77.8 ± 3.0%, the radioactive nuclear purity was not less than 99.99%, the radiochemical purity was 96.5 ± 1.3% (in the form of ^{99}mTcO_4^-), and the pH value of the eluent was between 5 and 7. In addition,

the contents of molybdenum and cerium in the eluate were less than 1 ppm and 0.3 ppm, respectively, and tellurium was not detected.

Amin et al. [45] studied the effect of different molar ratios of Al and Mo on the elution performance of the ^{99}Mo/^{99}mTc generator based on Al^{99}Mo gel. Al^{99}Mo gel was prepared by dissolving non-radioactive MoO_3 and $AlCl_3 \cdot 6H_2O$ in the NaOH solution with different Al:Mo molar ratios, adding ^{99}Mo radioactive tracer, and then using HCl acid precipitation. It was found that the change in the al:^{99}Mo ratio would lead to the formation of different polymolybdate (VI) structures around fine alumina particles and then affect the elution efficiency of ^{99}mTc from the gel matrix with normal saline. With the increase in Mo content, the elution efficiency increased, but the leakage value of ^{99}Mo increased slightly.

Subsequently, Guzman [46] studied the ^{99}Mo/^{99}mTc generator based on magnesium molybdate. The results show that the performance of the generator is the best in the following conditions: 0.1 mol/L $MgCl_2 \cdot 6H_2O$ solution, pH 7 ammonium molybdate solution, and the Mg: Mo molar ratio is 1:1. It was found that the non-crystalline matrix had a higher elution efficiency of ^{99}mTc, while the crystalline matrix showed a lower leakage rate of ^{99}Mo. The separation mechanism of ^{99}Mo and ^{99}mTc is the free diffusion of $^{99}mTcO_4^-$, which is not adsorbed by the matrix and can be eluted by normal saline while ^{99}Mo remains in the matrix.

3.3. Extraction Generator

Solvent extraction technology has become a common method for the separation of ^{99}mTc because of its high efficiency and high purity. This method can produce ^{99}mTc purity equivalent to that of a high specific activity ^{99}Mo-based generator. At present, there are many extraction systems, including ketones, crown ethers, trioctylamine, trioctylmethyl ammonium chloride (Aliquat-336), liquid ion exchangers, and ionic liquids. Among them, methyl ethyl ketone (MEK) is considered the best choice for extracting ^{99}mTc because of its high extraction yield, high radiation stability, and low boiling point [47].

The working principle of the ^{99}Mo/^{99}mTc generator based on MEK extraction (Figure 6) is that MEK containing 1% hydrogen peroxide is mixed with 5 M NaOH solution of ^{99}Mo, and ^{99}mTc is extracted to MEK phase by stirring. Hydrogen peroxide is used to maintain the oxidation state of ^{99}Mo and ^{99}mTc. After separation, the MEK/^{99}mTc phase was sucked out and ^{99}Mo was removed by the acid alumina column. After MEK evaporation, ^{99}mTc is dissolved in normal saline and stored in a sterile bottle after aseptic filtration for subsequent use.

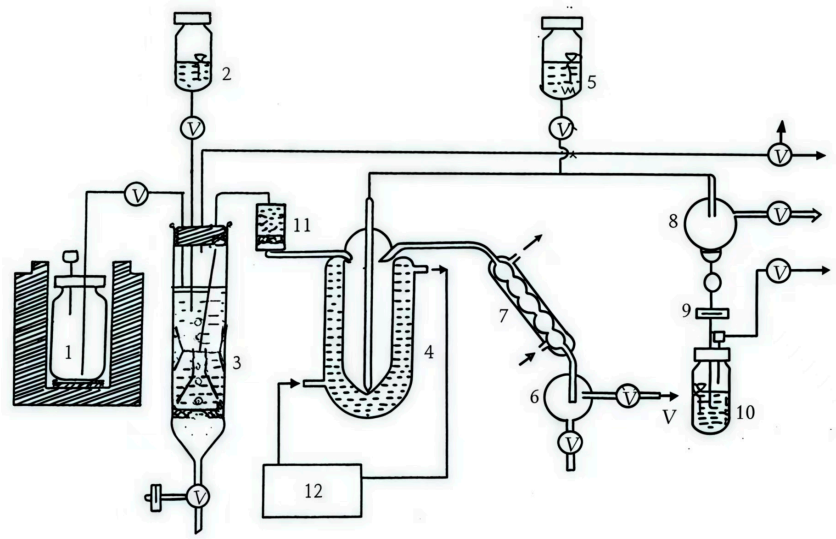


Figure 6. Diagram of MEK extraction-based ^{99}Mo/^{99}mTc generator [47].

Studies using trioctylamine (TOA) as the extractant, cyclohexane as the organic phase, and HCl as the aqueous phase show that under the concentration of 10^{-5} M HCl and 0.5 m TOA, ^{99}mTc can be quantitatively transferred to the organic phase, while ^{99}Mo remains in the aqueous phase, achieving high efficiency and a high separation factor [48]. With the increase in acidity, the extraction rates of ^{99}mTc and ^{99}Mo increased and then decreased sharply after reaching the peak because negative ion complexes were formed under high acidity. At lower acidity, Mo forms a neutral complex and is not extracted by toa. The optimal separation conditions were 10^{-5} M HCl and 0.5 M TOA. At this time, the extraction rate of ^{99}mTc was 100%, and ^{99}Mo remained in the aqueous phase.

A new MEK-based solid–liquid extraction technology was developed to extract ^{99}mTc from ^{99}Mo solution into MEK and purify it by acid alumina column to remove ^{99}Mo [49]. This process is carried out in a closed circulation system without MEK evaporation, simplifying operation and improving safety. This method can improve the extraction and purification efficiency of ^{99}mTc, the yield is 85–97%, and the purity is high, which is suitable for the preparation of radioactive drugs. The technology reduces the operation complexity and safety risk and provides a low-cost and efficient source of ^{99}mTc.

Skuridin et al. [50] reported an automatic unit for extracting ^{99}mTc from the ^{99}Mo/^{99}mTc generator. This miniaturized chromatographic unit can be operated automatically without manual control. It transfers the solution through air dilution technology, uses MEK as the extraction agent, separates ^{99}mTc from the molybdenum solution, and then obtains sodium technetium perchlorate through distillation and elution with normal saline. The unit shortens the preparation time from 50 to 90 min to about 25 min, improves the efficiency and safety of ^{99}mTc preparation, and is convenient for direct use in the radiation laboratory.

3.4. Electrochemical Generator

Using the electrochemical method [51], after optimizing the voltage, ^{99}mTc was selectively deposited from the ^{99}Mo/^{99}mTc mixture to the platinum cathode and stripped back to normal saline (Figure 7). The purity of ^{99}mTc product was more than 99%, which was used to label DMSA and EC, and the labeling yield was more than 98%. Under the voltage of 5V, the selective deposition of ^{99}mTc was achieved within 1 h, the overall yield was over 90%, and the performance of the generator was stable within 10 days.

Subsequently, a ^{99}Mo/^{99}mTc generator was developed [52], containing ^{99}Mo up to 29.6gBq (800 mCi), and its performance was evaluated within 10 days. The generator can provide a high radioactive concentration of $^{99}mTcO_4^-$ with a yield of more than 90%, which can meet the needs of hospital Radiopharmacy, and ^{99}mTc products show high compatibility and labeling yield in the preparation of ^{99}mTc DMSA, ^{99}mTc EC, and other labeled drugs. An electrochemical method (Figure 8) [53] for concentrating ^{99}mTc from a zirconium molybdate gel generator was also reported. ^{99}mTc was electrodeposited on a small platinum electrode in an oxalic acid bath and then recovered with normal saline. The overall recovery and purity were more than 99%. The parameters affecting the electrodeposition of ^{99}mTc were systematically optimized, including pH value, potential, and deposition time. The results showed that the electrodeposition efficiency of ^{99}mTc was the highest at 8V potential, 25 min electrolysis time, and pH of about 3. The electrochemical concentration process has good repeatability and can concentrate 20 mL of ^{99}mTc to about 1 mL. The yield and purity are stable, and the radionuclide purity is more than 99.99%.

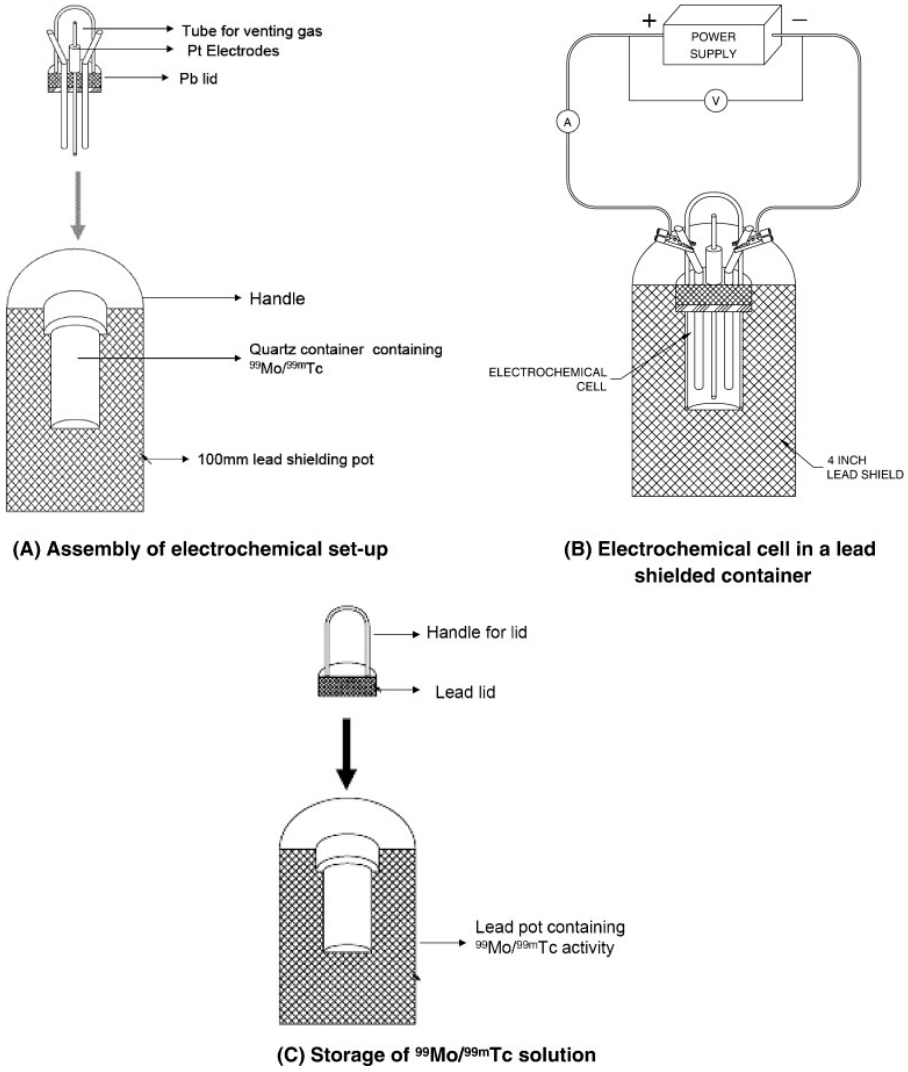


Figure 7. Schematic diagram of electrochemical device [51].

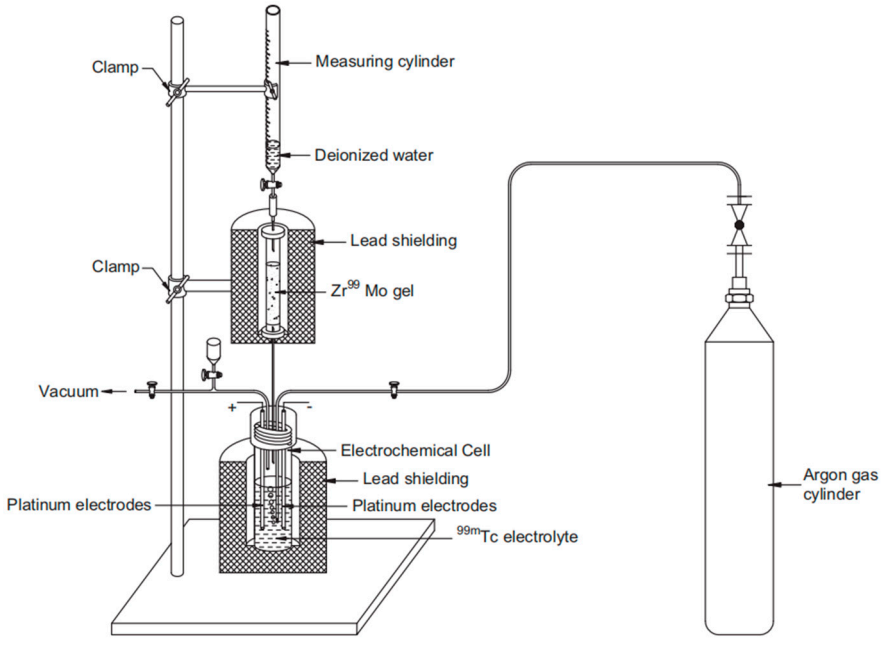


Figure 8. Schematic diagram of the electrochemical set-up [53].

The ^{99}Mo/^{99}mTc generator is a crucial tool in nuclear medicine, with ^{99}mTc being the most widely used radionuclide, accounting for over 80% of nuclear medicine applications. Its 6.01 h half-life and 140 keV gamma ray emission make it ideal for SPECT imaging. The generator efficiently produces ^{99}mTc from ^{99}Mo, simplifying the production process and enhancing accessibility. Various separation techniques, including column chromatography, solvent extraction, and electrochemical separation, have been developed to meet diverse production and application needs. Despite these advantages, the global supply of ^{99}Mo/^{99}mmTc has faced interruptions, notably in 2009 and 2010, due to reactor shutdowns. The production process is complex, requiring precise control of parameters like pH and the flow rate. Radioactive waste generated from the generator needs proper disposal to prevent environmental and personnel contamination. Operating and maintaining the generator requires specialized equipment and skilled personnel. Additionally, strict control of ^{99}Mo leakage and impurities is necessary to ensure the purity and quality of radiopharmaceuticals. Future research and development should focus on improving supply stability, simplifying production, reducing waste, and enhancing operational safety.

4. ^{90}Sr/^{90}Y Generator

^{90}Y is an important medical radionuclide with a half-life of about 64.0 h. During the decay process, ^{90}Y mainly emits beta particles (i.e., electrons). These beta particles have high energy and can penetrate biological tissues. The beta particle energy of ^{90}Y is 2.3MeV. ^{90}Y can be separated from its long-lived parent isotope ^{90}Sr, with a half-life of 28 years. ^{90}Y is mainly used for radiation immunotherapy, especially for liver cancer, colorectal cancer, prostate cancer, etc. [16]. ^{90}Y is mainly produced by a ^{90}Sr/^{90}Y generator. The types of ^{90}Sr/^{90}Y generators include extraction generators, precipitation generators, electrodeposition generators, and chromatographic generators.

4.1. Extraction Generator

Several extraction generator methods for the efficient separation of ^{90}Y and ^{90}Sr were reported. One is a process based on semi-countercurrent extraction separation and phase inversion [54], which can separate high-purity ^{90}Y from parent ^{90}Sr in 30 to 60 min, with a purity of 99.3% to 99.9%, and has almost unlimited output capacity. Another method [55] can significantly improve the extraction efficiency of ^{90}Sr in 0.1–7 m nitric acid and 0.1–2 m yttrium nitrate solution, with a distribution ratio of up to 40, while the distribution ratio of ^{90}Y is not more than 0.05. There is also a method for rapid separation of trace Sr^{2+} and Y^{3+} by extraction system [56], and the separation factor α (Sr/Y) is about 10.5.

The separation of ^{90}Y and ^{90}Sr was achieved in a nitrobenzene solution using sodium dicarboxy cobalt complexes, p-nonylphenol-9-ethyleneglycol, and the tetrakisodium salt of ethylenediamine-N,N,N′,N′-tetraacetic acid, with a separation factor of ^{90}Sr/^{90}Y greater than 10^2 within the pH range of 3.3 to 4.3 [57].

The study also found that benzo-15-crown-5 showed significant extraction and separation effects for ^{90}Sr and ^{90}Y in nitrobenzene solution [58].

Du et al. [59] reported the efficient separation of ^{90}Y and ^{90}Sr from aqueous solutions using Bisphenyl-18-crown-6-oxoacetic acid as a novel extractant, achieving a separation factor α(Sr/Y) greater than 10^6, with a recovery rate of approximately 85% and good radiation resistance.

4.2. Precipitation Type Generator

Kanapilly et al. [60] developed a cost-effective method to separate a large amount of ^{90}Y from ^{90}Sr by forming colloidal yttrium hydrophosphate and filtering. The recovery rate was close to 100%, and the pollution level was very low, lower than 1×10^{-6}% of

^{90}Y. This process is fast, completed in about 1 h, and the ^{90}Sr solution can be reused. Even when treating ^{90}Sr/^{90}Y with up to 40 Ci, there is no effect of radiation on the formation of colloids.

Although this method is simple, economical, and efficient, it needs to accurately control pH and phosphate concentration, has certain requirements for equipment and chemical reagents, and requires special attention to storage and treatment. Although the design minimizes pollution, improper operation or other factors may still lead to pollution risk. Therefore, the actual operation needs to strictly abide by the operating procedures and radiation safety measures to ensure high efficiency and purity.

4.3. Electrodeposition Generator

Electrodeposition is a technology used to reduce target ions such as ^{90}Y in solution by electrolysis and depositing them on the cathode. In the separation of medical ^{90}Y, the high deposition rate of ^{90}Y was achieved by electrodeposition in 0.1 mol/L ammonium sulfate solution with pH 2.5 at a current density of 0.5 A/cm^2 for 50 min and then eluted and purified with hot nitric acid to achieve a high separation with ^{90}Sr. The separation coefficient was more than 8×10^{-5}, which improved the purity and yield of ^{90}Y, and the mother liquor of ^{90}Sr could be reused, which was a cost-effective separation technology [61].

Xu et al. [62] studied the process conditions of electrodeposition of ^{90}Y from a ^{90}Sr/^{90}Y solution and found that current density and electrodeposition time had significant effects on the electrodeposition rate, and 0.63 A/cm^2 current density and 40 min electrodeposition time were the optimal conditions. The electrodeposition method is simple, low-cost, and can achieve high-purity separation, which is suitable for a variety of materials.

However, the electrodeposition method needs to accurately control the current density and time and requires high equipment accuracy and stability. Samples with high salt concentration may be disturbed by salt, and the purity may be affected by side reactions and impurity codeposition.

4.4. Chromatographic Generator

The working principle of the chromatographic ^{90}Sr/^{90}Y generator usually involves fixing the parent isotope ^{90}Sr on an adsorption material of a chromatographic column, while the daughter isotope ^{90}Y produced by its decay is eluted from the chromatographic column through an eluent. This method allows ^{90}Y to be collected in high-purity form for further medical applications. In some designs, the double column system and reverse carrier method are used to improve the separation efficiency of Sr and Y and ensure the high purity and high yield of ^{90}Y.

A semi-automatic program based on the sequential injection method (SIA) was developed [63] for the rapid determination of ^{90}Sr and ^{90}Y in water samples. This method can complete radiochemical separation within 30 min and determine the total β activity through the α-β proportional counter to calculate the initial concentrations of the two isotopes. In the experiment, the medium with a pH of 6.5 and the cotton filter impregnated with MnO_2 were used to preferentially enrich ^{90}Y and then the hydroxylamine was used to extract ^{90}Y. The whole process includes the formation of MnO_2, washing the filter, the adsorption of water samples, and the elution of ^{90}Y. The results showed that the existence of common ion pairs had little effect on the yield, and the yield remained at about 90%. The method has been successfully applied to the determination of ^{90}Sr/^{90}Y in mineral water and hot mineral water. Even at high salt concentrations, the radiochemical yield is still more than 80%.

Su et al. [64] studied the selectivity and stability of inorganic ion exchangers such as antimony silicate and tin pyrophosphotungstate for ^{90}Sr and ^{90}Y. The results show that

antimony silicate is suitable for $^{90}Sr/^{90}Y$ generators because of its simple preparation, strong selectivity to ^{90}Sr, good thermal stability and irradiation stability, and its separation coefficient can reach 5.5×10^4. Dowex 1-x8 anion exchange resin and dilute hydrochloric acid, lactic acid, and ammonium oxalate at different pH values were used as eluents to study the separation effect of Sr^{2+} and Y^{3+}ions [65].

Diethylenetriamine pentaacetic acid (DTPA) was developed as a new eluent for $^{90}Sr/^{90}Y$ generators [66], and its separation efficiency was systematically studied. DTPA can effectively separate ^{90}Y, improve separation efficiency, and reduce the leakage rate. Compared with the traditional citric acid lotion, DTPA has a narrower elution peak and lower leakage rate, which improves the safety and effectiveness of radioimmunotherapy. The generator using DTPA lotion can provide high-purity ^{90}Y, which is suitable for radioimmunotherapy.

The carrier-free ^{90}Y in the $^{90}Sr/^{90}Y$ generator can be effectively separated by extraction chromatography using a new crown ether-coated silica gel [67]. The results showed that DC18C6-coated silica gel was more effective than DB18C6, and its ^{90}Sr extraction capacity was 5.6 mg Sr/g silica gel. The yield of ^{90}Y was over 95%, the radionuclide purity was more than 99.9% after elution with wild acid solution, and the performance was stable after multiple elutions.

A new type of $^{90}Sr/^{90}Y$ generator [68] has been developed, which uses the supported liquid membrane (SLM) technology to directly separate ^{90}Y (III) suitable for direct complexation from high-level liquid waste. The generator uses a PTFE membrane and ksm-17 as transport agents to transfer ^{90}Y (III) ions to the receiving chamber filled with acid, while impurities remain in the feed chamber.

Ma et al. [69] studied the application of extraction resin in the separation of Sr and Y and determined the optimal adsorption conditions and the ability to separate elements with similar properties. It was found that strontium and yttrium could be effectively separated by controlling the pH value of the feed solution, and the extraction resin showed good effect in analytical separation and hydrometallurgy.

The $^{90}Sr/^{90}Y$ generator is a vital tool in radiopharmaceutical therapy, particularly for treating cancers like liver, colorectal, and prostate cancer, due to ^{90}Y's high-energy beta particle emission. The long half-life of ^{90}Sr (28 years) ensures a stable supply of ^{90}Y over extended periods, enhancing the generator's usability. Various separation techniques, including extraction, precipitation, electrodeposition, and chromatography, have been developed to optimize the yield and purity of ^{90}Y. However, the generator's operation involves complex processes and stringent requirements for equipment precision and operator skill, increasing costs and operational challenges. Additionally, the management of radioactive waste and the need for high purity in ^{90}Y production add to the complexity. Future advancements should focus on simplifying production, reducing waste, improving equipment stability, and enhancing operational safety to broaden the application of $^{90}Sr/^{90}Y$ generators in medical treatments.

5. $^{44}Ti/^{44}Sc$ Generator

^{44}Sc is a radionuclide with excellent PET imaging characteristics, with a half-life of 3.927 h. It is suitable for labeling biological molecules such as peptides and antibody fragments. Compared with ^{68}Ga, ^{44}Sc has a lower average positron energy and better image resolution, and its half-life is slightly longer, allowing a longer imaging time. Dota chelates are commonly used to attach ^{44}Sc to biomolecules [17,70–72].

The main methods for preparing ^{44}Sc include irradiating calcium targets with protons or deuterons. The ^{44}Ca (P, n) ^{44}Sc reaction is more popular because of its higher physical yield and lower isomer ratio [73,74]. These methods have high yields but need daily

irradiation to maintain supply. The production process will also produce the nuclear isomer ^{44}mSc, which can be used as an in vivo generator of ^{44}Sc [75]. ^{44}Sc needs to be separated and recovered from a calcium target. The separation methods based on ion exchange and solid-phase extraction chromatography can meet the purity requirements of biomarkers.

Another method to obtain ^{44}Sc is to decay the long half-life parent isotope ^{44}Ti (60 years) and provide high-purity ^{44}Sc through the ^{44}Ti/^{44}Sc generator system without daily irradiation, which is suitable for PET facilities lacking irradiation capacity. However, this system faces challenges, including the requirements of high beam current and long-time irradiation, complex separation processes, and efficient separation. To solve these problems, researchers have proposed solid-supported ion exchange and chelating resin adsorption methods to ensure the long-term reliability and stability of the generator system [76–79].

5.1. Development Status of ^{44}Ti/^{44}Sc Generator

The advantage of ^{44}Sc as a PET imaging isotope is that it can be produced and separated by a generator, providing a convenient short-lived isotope source for hospitals and research institutions. Compared with the cyclotron costing about USD 1.6 million to USD 2.1 million, the generator is a more economical option, especially in places where there is a lack of accelerator facilities. In addition, the isotopes produced by cyclotron need post-treatment and purification, and the generator simplifies this process.

Although there are many PET imaging facilities in the world, relatively few are equipped with cyclotrons. In 2008, there were about 700 cyclotrons in the world [80], and by 2015, there were 1218 cyclotrons, most of which were for medical use [81]. At the same time, there are about 2000 pet/ct scanners in the United States and 350 in Europe [82]. The gap between these facilities and the number of accelerators highlights the need for on-site generators to produce imaging isotopes [13,83,84].

Since the 1960s, the generator design based on ^{44}Ti/^{44}Sc has been studied to explore medical applications. Modern generators usually use commercial anion exchange resins or hydroxy acid/base chelating resins. The anion exchange generator is eluted with a mixture of oxalic acid and hydrochloric acid, which has a long service life but requires a large amount of eluent. Oxalic acid may inhibit radioactive labeling. The Zr resin generator can effectively elute ^{44}Sc without oxalic acid, but the leakage rate of ^{44}Ti is high. The development of these technologies is crucial to the long-term stability of the generator system.

5.2. Accelerator Direct Production ^{44}Sc

The direct production of ^{44}Sc can increase production and reduce radioactive impurities [85]. However, ^{44}Sc produced by the accelerator will produce the excited isotope ^{44}mSc with a half-life of 58.61 h, which will decay mainly through internal transformation and emit high-energy gamma rays, or decay to ^{44}Ca through electron capture (Figure 9). The long half-life of ^{44}mSc may cause an additional dose for short-term research, which is mostly useless for diagnostic imaging. Therefore, the direct production of ^{44}Sc needs to minimize the ^{44}mSc/^{44}Sc ratio.

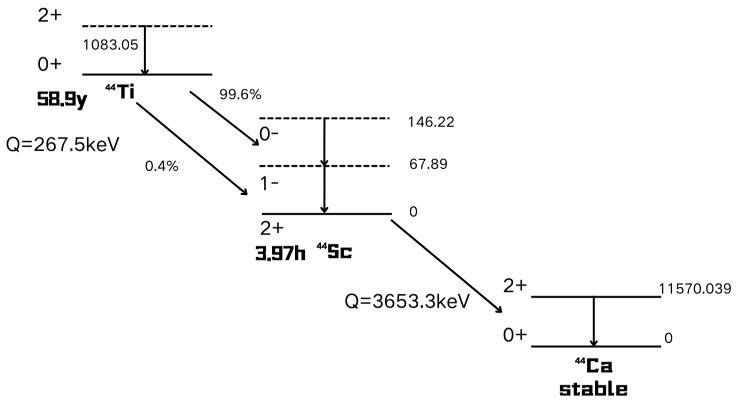


Figure 9. The decay diagrams of ^{44}Ti and ^{44}Sc.

5.3. Production of Parent ^{44}Ti

The success of all ^{44}Ti/^{44}Sc generator systems depends on the availability of the parent isotope ^{44}Ti. Table 3 shows two different ^{44}Ti accelerator production methods, both of which use cheap, single isotope natural Sc targets.

Table 3. Different production methods of ^{44}Ti.

Reaction	Target	Target Purity	Incident Beam Energy (MeV)	Yield (MBq/(μA·h))	References
^{45}Sc(p,2n)^{44}Ti	$^{45}Sc_2O_3$	99.5%	38	5.04	[86]
^{45}Sc(d,3n)^{44}Ti	^{45}Sc Foil	99.5%	50	2.5	[87]

The main route is through the ^{45}Sc (P, 2n) ^{44}Ti reaction because of the availability of a high-energy proton beam. Daraban et al. [86] measured 40 MB with a maximum section of 23–25 MeV. The irradiation time required to produce the maximum yield of radionuclides is proportional to its half-life, so it needs more than 60 years of irradiation to obtain the maximum yield of ^{44}Ti. The second ^{44}Ti production route, ^{45}Sc (D, 3n) ^{44}Ti, has a lower cross-section (21 MB) and requires a higher beam energy (21–50 MeV) [87]. Although the cross-section of these ^{44}Ti production routes is relatively low, the production reaction only needs to be carried out once, which can provide a lasting ^{44}Sc source for the life of the generator system. The amount of ^{44}Ti produced by these irradiations is enough to serve as the clinically relevant amount of ^{44}Sc produced by the parent isotope decay. The main advantage of using a ^{44}Ti/^{44}Sc generator over the direct accelerator production of ^{44}Sc is the long half-life of ^{44}Ti, which allows production and transportation from the central accelerator facility and then assembling and using the generator in other locations without access to the local medical cyclotron.

5.4. Existing ^{44}Ti/^{44}Sc Generator

In the 1860s, several ^{44}Ti/^{44}Sc generator designs were studied for potential medical applications. The generators in the current literature use commercial anion exchange (Ag 1-x8 and Teva) or ZR resins. The anion generator uses a diluted mixture of oxalic acid and hydrochloric acid to elute ^{44}Sc, which has a longer life, but usually uses a very large elution dose. Oxalate will compete with the ligand in the ^{44}Sc eluent to inhibit direct radioactive labeling. Zr resin generator can elute ^{44}Sc in diluted hydrochloric acid without oxalic acid, but the leakage of ^{44}Ti in these systems is much earlier than that of anion exchange resin generator. This section will discuss in depth the comparison of current generators in the literature and the potential improvement to the more clinically relevant ^{44}Ti/^{44}Sc generator.

Dowex/AG 1×8 Resin ^{44}Ti/^{44}Sc Generator

In 1967, Brookhaven National Laboratory designed the ^{44}Ti/^{44}Sc generator for the first time [88]. The device uses the Dowex 1-x8 anion exchange resin, which is poured into a 2 cm diameter pipe, with a coarse hole glass sand core at the bottom and powdered quartz on the top to prevent the liquid from flowing out. Before loading, flush the resin column with water until there is no chloride ion. Add 3% hydrogen peroxide to the ^{44}Ti solution and evaporate to dryness. Dissolve the residue with 0.1 M $H_2C_2O_4$ and pour it into the resin. Rinse the above solution with 0.1 M $H_2C_2O_4$-0.2 M HCl. ^{44}Sc was eluted by the same solution flowing naturally, and the yield was 60–70%. Oxalate ions can be removed by adding hydrogen peroxide after evaporation. At first, the leakage of ^{44}Ti was only 0.02%, but after 40 times of 50 mL elution, it increased to 0.1%.

This design is based on previous anion exchange research, and it is found that SC (III) is adsorbed on anion exchange resin [89] in oxalate or citrate complexes and can be eluted by dilute hydrochloric acid. In the presence of oxalate, the adsorption of Ti (IV) on anion exchange resin is enhanced, indicating that the ratio of $H_2C_2O_4$ to HCl can effectively separate titanium and scandium [90].

Subsequent studies systematically analyzed the distribution coefficient of Ti (IV) and SC (III) on Ag 1-x8 and Ag 50w-x8 resins [78] and optimized the separation conditions: elute with 0.2 M HCl/0.1 M $H_2C_2O_4$ or more diluted mixed solution. The use of eluent mixtures with low salt concentrations seems to be more suitable for radiopharmaceutical synthesis.

In another study, two peek columns with a diameter of 3 mm and a length of 40 mm were fabricated and filled with Ag 1-x8 resin. After a series of washing, the sample with activity of 300 kBq was loaded into two generators. After elution, "reverse" elution in alternate directions is used for regeneration. After the first 15 times of elution, the yield of the direct elution generator gradually decreased to less than 50 kBq, and the leakage amount increased. After 50 times of elution, almost all ^{44}Ti was eluted, while the generator with reverse elution maintained a stable yield of ^{44}Sc, and the leakage amount slightly increased to 0.2%.

In the follow-up study, larger peek columns were prepared and filled with Ag 1-x8 resin. A total of 54 elutions were performed with 0.07 M HCl/0.005 m $H_2C_2O_4$. The total elution activity was 97%, showing a good separation efficiency. However, this method also has some disadvantages, such as the amount of 20 mL eluent is too large for radioactive labeling, and $H_2C_2O_4$ as a competitive ligand affects the radioactive labeling reaction. Before ^{44}Sc is suitable for radiopharmaceutical labeling reaction, it needs to be purified many times, which reduces the final activity.

5.5. TiO_2 Bead ^{44}Ti/^{44}Sc Generator

Recently, a new type of ^{44}Ti/^{44}Sc radiochemical generator has been developed [91]. The generator (Figure 10) is designed based on porous TiO_2 beads. This study comprehensively evaluated the optimal conditions of generator construction (^{44}Ti loading) and use (^{44}Sc elution) through three steps. It was found that heat treatment at 180 °C for 90 min was effective in stabilizing ^{44}Ti loaded on titanium dioxide, and 0.3 M HCl was the preferred medium for ^{44}Sc elution. Under the optimized conditions, the two 3.6 MBq generators used different protective substrates (TiO_2 beads and ZR resin) to minimize the leakage of ^{44}Ti. The results showed that both of them could provide nearly 50% recovery of ^{44}Sc, but the leakage rate of the Zr resin protective matrix was significantly lower than 0.0002% in ^{44}Ti transmission. This represents a new design method for inorganic/organic ^{44}Ti/^{44}Sc generators that combines the durability of TiO_2 and the advantages of ZR resin in reducing ^{44}Ti leakage.

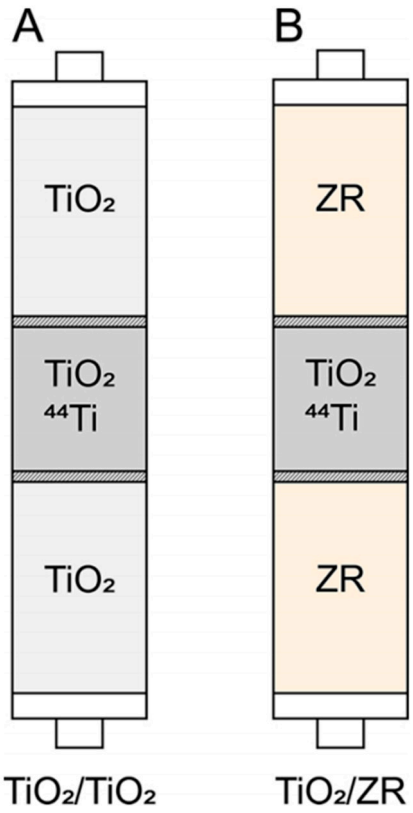


Figure 10. TiO_2 generator: (**A**) TiO_2 microbeads, and (**B**) ZR resin [91].

5.5.1. ZR Resin $^{44}Ti/^{44}Sc$ Generator

ZR hydroxy ester resin (ZR resin) is specially developed for the separation of zirconium (Zr) and yttrium (Y). It has a high selective adsorption capacity for Zr, titanium (Ti), and niobium (Nb) in a hydrochloric acid medium, especially for ferric iron at low and high hydrochloric acid concentrations but has weak adsorption capacity for SC and Y [92]. This makes ZR resin suitable for separating Ti from Sc and Zr from Y.

ZR resin has strong adsorption selectivity for Ti in a solution containing Sc, especially for Ti in 10 M HCl, but weak adsorption for Sc. At least 3 mL of 0.1 M citric acid is required to elute Ti from the resin, and hydrogen peroxide or oxalic acid can also be used to elute. The Zr resin titanium scandium generator designed by Radchenko et al. [93] shows that Zr resin has a strong adsorption effect on titanium and a weak affinity for Sc, which is suitable for use as a ^{44}Ti retention stationary phase in a $^{44}Ti/^{44}Sc$ generator.

Radchenko's experiment showed that 6 M HCl was the best eluent, and the elution effect of 0.1 M oxalic acid, 1 M oxalic acid, 0.1 M citric acid, and a 0.65 M H_2O_2/6 M HCl mixture on titanium decreased in turn. ZR resin showed a low ^{44}Ti leakage rate in the reverse elution method, which was helpful in prolonging the service life of the generator, but the service life was relatively short. The advantages of ZR resin include the use of dilute hydrochloric acid to elute ^{44}Sc in a small volume without oxalic acid, which is conducive to the direct radiolabeling experiment, and the low leakage rate of ^{44}Ti in the reverse elution method, which is conducive to long-term operation.

5.5.2. Teva Resin $^{44}Ti/^{44}Sc$ Generator

Recent studies mentioned that the $^{44}Ti/^{44}Sc$ generator uses Teva resin [93], which is a chromatographic extraction resin with an aliphatic quaternary ammonium salt functional group, and is good at anion exchange. Similar to strong base anion exchange

resin, Teva resin has the fluidity of functional groups, providing better flexibility and coordination ability.

Larenkov et al. optimized the eluent concentration and found that 0.1 M $H_2C_2O_4$/0.05~0.2 M HCl and 0.025 M $H_2C_2O_4$/0.125 M HCl were the most suitable for the separation of ^{44}Ti and ^{44}Sc. They tested different $H_2C_2O_4$/HCl mixed solutions on a column containing 150 mg Teva resin and 1.5 MBq ^{44}Ti, finding that at least 0.1 M oxalic acid concentration was required to obtain a recovery of more than 90% of ^{44}Sc, and the effect of HCl concentration on the recovery was less than that of $H_2C_2O_4$. Larenkov prepared a 5 MBq generator for long-term evaluation. The generator was eluted 120 times regularly in a year. At first, it was eluted manually and then switched to a vacuum pump to improve consistency. The results showed that the yield of ^{44}Sc was 91 $\pm$ 6%, the leakage rate of ^{44}Ti was less than 1.5 $\times$ 10^{-5}%, 95% of ^{44}Sc was in the first 0.5 mL eluent, and the leakage rate of ^{44}Ti was mainly in the part of 1.5~2.0 mL. This shows that the Teva resin generator maintains high separation efficiency and a low leakage rate in long-term operation.

5.5.3. SnO_2 Resin ^{44}Ti/^{44}Sc Generator

Christine et al. [94] reported a ^{44}Ti/^{44}Sc generator based on SnO_2. Christine et al. synthesized and characterized SnO_2 as an inorganic resin for the stationary phase of a ^{44}Ti/^{44}Sc generator. Through batch experiments, the adsorption behavior of ^{44}Ti/^{44}Sc on SnO_2 was studied, and the effects of different acidity, concentration, and time on the adsorption effect were tested. The experimental results showed that the retention rate of ^{44}Ti to the resin was more than 88% at low acid concentrations (0.05 M HNO_3 and 0.05 M HCl). Further dynamic column separation experiments showed that under the condition of 5 M HNO_3, the elution yield of ^{44}Sc was 85.3 $\pm$ 2.8%, and the leakage rate of ^{44}Ti was 0.71 $\pm$ 0.14%. In order to evaluate the stability of SnO_2 resin and the efficiency of eluting ^{44}Sc, Christine et al. constructed a 7.4 MBq (200 μ Ci) amplification generator. The results showed that the system could regularly elute ^{44}Sc from the generator, and the overall average yield was 84.7 $\pm$ 9.5%. In addition, after the post-treatment of DGA normal resin, all the existing ^{44}Ti was removed, and the yield of ^{44}Sc dota labeling was up to 94.2 $\pm$ 0.5%.

The ^{44}Ti/^{44}Sc generator has significant advantages in the PET imaging field, such as excellent imaging characteristics, cost-effectiveness, and the absence of daily irradiation, providing high-purity ^{44}Sc for PET imaging, especially suitable for areas lacking accelerator facilities. However, its preparation process is complex, requiring high standards for equipment and technical personnel, strict purity and quality control, and long-term stability, which needs further optimization. Future research should focus on simplifying production, improving stability, reducing equipment dependence, and optimizing operating conditions to promote the widespread application of the ^{44}Ti/^{44}Sc generator in nuclear medicine.

6. Summary

Although there have been dispersion studies on various types of medical radionuclide generators, the comprehensive analysis of ^{68}Ge/^{68}Ga, ^{99}Mo/^{99}mTc, ^{90}Sr/^{90}Y, and ^{44}Ti/^{44}Sc is still rare. The ^{68}Ge/^{68}Ga generator has attracted much attention for its application in PET imaging, especially the importance of ^{68}Ga in the diagnosis of cancer and neuroendocrine tumors; the ^{99}Mo/^{99}mTc generator is very important because of its wide application in nuclear medicine program. The ^{90}Sr/^{90}Y generator shows great potential in radiation immunotherapy, especially for some types of cancer treatment. The ^{44}Ti/^{44}Sc generator has attracted attention because of its characteristics in PET imaging. As a new radionuclide, ^{44}Sc has excellent imaging characteristics. This review fills this gap and provides a systematic and comprehensive perspective for researchers to deeply understand the characteristics of these generators and their clinical applications. This paper not only summarizes the

latest research progress of each generator but also evaluates their potential in practical medical treatment, providing a valuable reference for future research and promoting the development of new technologies and methods.

The continuous evolution of medical radionuclide generators is driven by the need for more efficient, sustainable, and clinically adaptable technologies. Several key areas of research are poised to shape the future of this field:

(1) Technological Innovations in Generator Design:

Future advancements will likely focus on developing more compact, efficient, and user-friendly generator systems. Innovations in materials science and engineering could simplify production processes, reduce operational costs, and enhance the yield and purity of generated isotopes. For instance, the integration of microfluidic technologies or novel adsorbent materials could revolutionize the design and functionality of radionuclide generators.

(2) Advances in Separation and Purification Techniques:

The development of advanced separation techniques, including novel chromatographic materials and automated purification systems, will be critical for improving the efficiency and scalability of radionuclide production. These advancements could minimize the need for post-treatment purification, thereby reducing costs and enhancing the practicality of generators in clinical settings.

(3) Exploration of Novel Radionuclides and Applications:

The discovery and utilization of new radionuclides, such as ^{44}Sc, could expand the diagnostic and therapeutic capabilities of nuclear medicine. Additionally, the development of innovative radiopharmaceuticals and targeting molecules could unlock new applications for existing radionuclides, enabling more precise and effective disease management.

(4) Sustainability and Environmental Considerations:

As the demand for radionuclides grows, sustainable production practices and improved waste management solutions will become increasingly important. Research into eco-friendly production methods, such as the use of renewable energy sources or recycling of generator materials, will be essential for reducing the environmental impact of radionuclide production.

(5) Regulatory and Safety Enhancements:

Strengthening regulatory frameworks and safety standards will be crucial for the widespread adoption of radionuclide generators. Improved guidelines for production, handling, and disposal will ensure safer and more reliable use in clinical practice, fostering greater acceptance and integration into healthcare systems.

(6) Interdisciplinary Collaboration:

The future of radionuclide generator technology will depend on increased collaboration between academia, industry, and regulatory bodies. Multidisciplinary partnerships can accelerate the translation of research findings into practical applications, ensuring that advancements are implemented more quickly and effectively.

Through a comprehensive evaluation of current technologies, this review identifies critical research directions for the future, particularly in the development of high-purity and high-efficiency isotopes. This forward-looking analysis provides valuable guidance for both academia and industry, fostering advancements in related fields. As nuclear medicine continues to play an increasingly pivotal role in disease diagnosis and treatment, the optimization of isotope generators will significantly enhance the efficiency, safety, and accessibility of medical services. The insights presented in this work aim to empower

researchers and clinicians to leverage these technologies more effectively in clinical practice, ultimately improving patient outcomes.

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References

1. Glenn, D.; Heger, A.S.; Hladik, W.B. Comparison of characteristics of solution and conventional reactors for ^{99}Mo production. *Nucl. Technol.* **1997**, *118*, 142–150. [CrossRef]
2. Gleason, G.I. A Positron Cow. *Int. J. Appl. Radiat. Isot.* **1960**, *8*, 90–94. [CrossRef] [PubMed]
3. Ehrhardt, G.J.; Welch, M.J. A new germanium-63/gallium-68 generator. *J. Nucl. Med.* **1978**, *19*, 329–332.
4. Greene, M.W.; Tucker, W.D. An improved gallium-68 cow. *Int. J. Appl. Radiat. Isot.* **1961**, *12*, 1–2. [CrossRef]
5. Yano, Y.; Anger, H.O. A Gallium-68 Positron Cow for Medical Use. *J. Nucl. Med.* **1964**, *5*, 484–487.
6. Schuhmacher, J.; Maier-Borst, W. A new ^{68}Ge/^{68}Ga radionuclide generator system for production of ^{68}Ga in dilute HCl. *Int. J. Appl. Radiat. Isot.* **1981**, *32*, 31–36. [CrossRef]
7. Neirinckx, R.D.; Davis, M.A. Potential column chromatography for ionic Ga-68. II: Organic ion exchangers as chromatographic supports. *J. Nucl. Med. Off. Publ. Soc. Nucl. Med.* **1980**, *21*, 81.
8. Nakayama, M.; Haratake, M.; Koiso, T.; Ishibashi, O.; Harada, K.; Nakayama, H.; Sugii, A.; Yahara, S.; Arano, Y. Separation of ^{68}Ga from ^{68}Ge using a macroporous organic polymer containing N-methylglucamine groups. *Anal. Chim. Acta* **2002**, *453*, 135–141. [CrossRef]
9. Nakayama, M.; Haratake, M.; Ono, M.; Koiso, T.; Harada, K.; Nakayama, H.; Yahara, S.; Ohmomo, Y.; Arano, Y. A new Ge-68/Ga-68 generator system using an organic polymer containing N-methylglucamine groups as adsorbent for Ge-68. *Appl. Radiat. Isot.* **2003**, *58*, 9–14. [CrossRef]
10. Wang, Z.Y. Ge-68-Ga-68 radionuclide Generator. *At. Energy Sci. Technol.* **1980**, *14*, 183.
11. Song, M.; Bao, B. New Type ^{68}Ge/^{68}Ga Generator Study II: Preparation Conditions of CeO_2 Support. *Isotopes* **1995**, *1*, 27–31.
12. Li, Z.Q.; Wang, Y.X. Study on ^{68}Ge-^{68}Ga Generator with SnO_2 as the Support. *Isotopes* **1997**, *18*, 35–39.
13. Dash, A.; Chakravarty, R. Radionuclide generators: The prospect of availing PET radiotracers to meet current clinical needs and future research demands. *Am. J. Nucl. Med. Mol. Imaging* **2019**, *9*, 30–66.
14. Chakravarty, R.; Chakraborty, S.; Ram, R.; Vatsa, R.; Bhusari, P.; Shukla, J.; Mittal, B.R.; Dash, A. Detailed evaluation of different ^{68}Ge/^{68}Ga generators: An attempt toward achieving efficient ^{68}Ga radiopharmacy. *J. Label. Compd. Radiopharm.* **2016**, *59*, 195–204. [CrossRef] [PubMed]
15. Tucker, D.; Greene, M.W.; Weiss, A.J.; Murrenhoff, A.P. Methods of preparation of some carrier-free radionuclide involving sorption of alumina. *Rep. BNL* **1958**, 3746.
16. Washburn, L.C. ^{90}Y-labeled monoclonal antibodies for cancer therapy. *Nucl. Med. Biol.* **1986**, *13*, 453–456. [CrossRef]
17. National Nuclear Data Center. *Nudat 2 Database [Online]*; National Nuclear Data Center: Upton, NY, USA, 2016.
18. Amorcoarasa, A.; Schoendorf, M.; Meckel, M.; Vallabhajosula, S.; Babich, J.W. Comprehensive Quality Control of the ITG ^{68}Ge/^{68}Ga Generator and Synthesis of ^{68}Ga-DOTATOC and ^{68}Ga-PSMA-HBED-CC for Clinical Imaging. *J. Nucl. Med.* **2016**, *57*, 1402. [CrossRef]
19. Fernández-Barahona, I.; Muñoz-Hernando, M.; Pellico, J.; Ruiz-Cabello, J.; Herranz, F. Molecular Imaging with ^{68}Ga Radio-Nanomaterials: Shedding Light on Nanoparticles. *Appl. Sci.* **2018**, *8*, 1098. [CrossRef]
20. Aghanejad, A.; Jalilian, A.R.; Ardaneh, K.; Bolourinovin, F.; Yousefnia, H.; Bahrami Samani, A. Preparation and Quality Control of ^{68}Ga-Citrate for PET Applications. *Asia Ocean. J. Nucl. Med. Biol.* **2015**, *3*, 99–106. [PubMed]
21. Cressier; Oelsner, S.; Hunter, G.; Quarin, L.; Methot, N.; Westerd, D.; Barré, L. Smoothened titania particles to improve radionuclide separation and their application to the development of a novel [Ge-68]/[Ga-68] generator. *RSC Adv.* **2015**, *5*, 29319–29324. [CrossRef]
22. Das, S.S.; Chattopadhyay, S.; Alam, M.N.; Madhusmita; Barua, L.; Das, M.K. Preparation and evaluation of SnO_2-based ^{68}Ge/^{68}Ga generator made from ^{68}Ge produced through (nat)Zn(α,xn) reaction. *Appl. Radiat. Isot.* **2013**, *79*, 42–47.

23. Chakravarty, R.; Shukla, R.; Ram, R.; Venkatesh, M.; Dash, A.; Tyagi, A.K. Nanoceria-PAN composite-based advanced sorbent material: A major step forward in the field of clinical-grade ^{68}Ge/^{68}Ga Generator. *ACS Appl. Mater. Interfaces* **2010**, *2*, 2069–2075. [CrossRef]
24. Chakraborty, S.; Chakravarty, R.; Sarma, H.D.; Dash, A.; Pillai, M.R.A. The practicality of nanoceria-PAN-based ^{68}Ge/^{68}Ga generator toward preparation of ^{68}Ga-labeled cyclic RGD dimer as a potential PET radiotracer for tumor imaging. *Cancer Biother. Radiopharm.* **2012**, *28*, 77–83. [CrossRef]
25. Chakravarty, R.; Chakraborty, S.; Ram, R.; Dash, A.; Pillai, M.R.A. Long-term evaluation of 'BARC ^{68}Ge/^{68}Ga Generator' based on the nanoceria-polyacrylonitrile composite sorbent. *Cancer Biother. Radiopharm.* **2013**, *28*, 631–637. [PubMed]
26. Chandra, P.; Shetye, B.; Chakravarty, R.; Mukherjee, A.; Pandey, U.; Jha, A.; Purandare, N.; Shah, S.; Agrawal, A.; Ram, R.; et al. Initial clinical experience with ^{68}Ga-DOTA-NOC prepared using ^{68}Ga from nanoceria-polyacrylonitrile composite sorbent-based ^{68}Ge/^{68}Ga generator and freeze-dried DOTA-NOC kits. *World J. Nucl. Med.* **2017**, *16*, 140–144. [CrossRef] [PubMed]
27. Chakravarty, R.; Shukla, R.; Ram, R.; Tyagi, A.K.; Dash, A.; Venkatesh, M. Development of a nano-zirconia based ^{68}Ge/^{68}Ga generator for biomedical applications. *Nucl. Med. Biol.* **2011**, *38*, 575–583. [CrossRef] [PubMed]
28. Chakravarty, R.; Chakraborty, S.; Shukla, R.; Bahadur, J.; Ram, R.; Mazumder, S.; Sarma, H.D.; Tyagi, A.K.; Dash, A. Mechanochemical synthesis of mesoporous tin oxide: A new generation nanosorbent for ^{68}Ge/^{68}Ga generator technology. *Dalton Trans.* **2016**, *45*, 13361–13372. [CrossRef] [PubMed]
29. Romero, E.; Morcillo, M.A. Inorganic oxides with potential application in the preparation of a ^{68}Ge/^{68}Ga generator system. *Appl. Radiat. Isot.* **2017**, *119*, 28–35. [CrossRef] [PubMed]
30. Vyas, C.K.; Lee, J.Y.; Hur, M.G.; Yang, S.D.; Kong, Y.B.; Lee, E.J.; Park, J.H. Chitosan-TiO_2 composite: A potential ^{68}Ge/^{68}Ga generator column material. *Appl. Radiat. Isot.* **2019**, *149*, 206–213. [CrossRef]
31. Metello, L. ^{99m}Tc-Technetium shortage: Old problems asking for new solutions. *Med. Imag. Radiat. Sci.* **2015**, *46*, 259–261. [CrossRef] [PubMed]
32. Arino, H.; Kramer, H.H.; McGovern, J. Fission product 99 Tcm generator. *Appl. Radiat. Isot.* **1975**, *26*, 301–303. [CrossRef] [PubMed]
33. Molinski, V.J. A review of ^{99m}Tc generator technology. *Int. J. Appl. Radiat. Isot.* **1982**, *33*, 811–819. [CrossRef]
34. Chakravarty, R.; Shukla, R.; Ram, R.; Tyagi, A.K.; Dash, A.; Venkatesh, M. Practicality of Tetragonal Nano-Zirconia as a Prospective Sorbent in the Preparation of ^{99}Mo/^{99m}Tc Generator for Biomedical Applications. *Chromatographia* **2010**, *72*, 875–884. [CrossRef]
35. Chakravarty, R.; Ram, R.; Dash, A.; Pillai, M.R.A. Preparation of clinical-scale ^{99}Mo/^{99m}Tc column generator using neutron activated low specific activity ^{99}Mo and nanocrystalline γ-Al_2O_3 as column matrix. *Nucl. Med. Biol.* **2012**, *39*, 916–922. [CrossRef]
36. Chakravarty, R.; Ram, R.; Mishra, R.; Sen, D.; Mazumder, S.; Pillai, M.R.A.; Dash, A. Mesoporous Alumina (MA) Based Double Column Approach for Development of a Clinical Scale ^{99}Mo/^{99m}Tc Generator Using (n,γ)^{99}Mo: An Enticing Application of Nanomaterial. *Ind. Eng. Chem. Res.* **2013**, *52*, 11673–11684. [CrossRef]
37. Chakravarty, R.; Dash, A. Nanomaterial-based adsorbents: The prospect of developing new generation radionuclide generators to meet future research and clinical demands. *Radioanal. Nucl. Chem.* **2014**, *299*, 741–757. [CrossRef]
38. Sharbatdaran, M.; Farzaneh, F.; Larijani, M.M. Sol-gel synthesis and characterization of silica-zirconia inorganic polymer as ^{99}Mo/^{99}Tcm generator. *Sol-Gel Sci. Technol.* **2015**, *74*, 613–620. [CrossRef]
39. Evans, J.V.; Moore, P.W.; Shying, M.E.; Sodeau, J.M. Zirconium molybdate gel as a generator for technetium-99m-I: The concept and its evaluation. *Appl. Radiat. Isot.* **1987**, *38*, 19–23. [CrossRef] [PubMed]
40. Monroy-Guzman, F.; Díaz-Archundia, L.V.; Contreras Ramírez, A. Effect of Zr: Mo ratio on ^{99m}Tc generator performance based on zirconium molybdate gels. *Appl. Radiat. Isot.* **2003**, *59*, 27–34. [CrossRef]
41. Monroy-Guzman, F.; Díaz-Archundia, L.V.; Hernández-Cortés, S. ^{99}Mo/^{99m}Tc generators performances prepared from zirconium molybdate gels. *J. Braz. Chem. Soc.* **2008**, *19*, 380–388. [CrossRef]
42. Monroy-Guzman, F.; Rivero Gutiérrez, T.; López Malpica, I.Z.; Hernández Cortes, S.; Rojas Nava, P.; Vazquez Maldonado, J.C.; Vazquez, A. Production optimization of ^{99}Mo/^{99m}Tc zirconium molybdate gel generators at semi-automatic device: DISIGEG. *Appl. Radiat. Isot.* **2012**, *70*, 103–111. [CrossRef] [PubMed]
43. Mostafa, M.; Ramadan, H.E.; El-Amir, M.A.; El-Said, H. ^{99}Mo/^{99m}Tc chromatographic column generator based on cerium(IV) molybdate gel. *Radiochemistry* **2013**, *55*, 272–275. [CrossRef]
44. El-Amir, M.A.; Mostafa, M.; Ramadan, H.E. Preparation and characterization of cerium(IV) tellurium molybdate gel and its application as a bed for chromatographic ^{99}Mo/^{99m}Tc generator. *Nucl. Radiochem. Sci.* **2014**, *14*, 1–5. [CrossRef]
45. Amin, M.; Abdel-Galil, E.A.; El-Kenany, W.M. Effect of Al:Mo molar ratio on elution performance of ^{99}Mo/^{99m}Tc generators based on Al^{99}Mo gels. *Radioanal. Nucl. Chem.* **2015**, *309*, 485–492. [CrossRef]
46. Monroy-Guzman, F.; Martinez, T.S.J.; Arriola, H.; Longoria Gandara, L.C. Magnesium molybdate compounds as matrix for ^{99}Mo/^{99m}Tc generators. *Pharmaceuticals* **2011**, *4*, 215–232. [CrossRef]
47. Le, V.S. ^{99m}Tc Generator Development: Up-to-Date ^{99m}Tc Recovery Technologies for Increasing the Effectiveness of ^{99}Mo Utilisation. *Sci. Tech. Nucl. Inst.* **2014**, *2014*, 345252.

48. Maiti, M.; Lahiri, S. Separation of ^{99}Mo and ^{99m}Tc by liquid-liquid extraction using trioctylamine as extractant. *Radioanal. Nucl. Chem.* **2010**, *283*, 661–663. [CrossRef]
49. Chattopadhyay, S.; Barua, L.; De, A.; Das, S.S.; Kuniyil, R.; Bhaskar, P.; Pal, S.S.; Sarkar, S.K.; Das, M.K. A computerized compact module for separation of ^{99m}Tc-radionuclide from molybdenum. *Appl. Radiat. Isot.* **2012**, *70*, 2631–2637. [CrossRef]
50. Skuridin, V.S.; Stasyuk, E.S.; Rogov, A.S.; Nesterov, E.A.; Sadkin, V.L.; Varlamova, N.V.; Larionova, L.A. Development of an Automated Unit for Extraction-Chromatographic Separation of the ^{99}Mo/^{99m}Tc Generator Couple. *Radiochemistry* **2014**, *56*, 189–193. [CrossRef]
51. Chakravarty, R.; Dash, A.; Venkatesh, M. A novel electrochemical technique for the production of clinical grade ^{99m}Tc using (n,γ) ^{99}Mo. *Nucl. Med. Biol.* **2010**, *37*, 21–28. [CrossRef] [PubMed]
52. Chakravarty, R.; Venkatesh, M.; Dash, A. A novel electrochemical ^{99}Mo/^{99m}Tc generator. *Radioanal. Nucl. Chem.* **2011**, *290*, 45–51. [CrossRef]
53. Chakravarty, R.; Sarkar, S.K.; Venkatesh, M.; Dash, A. An electrochemical procedure to concentrate ^{99m}Tc availed from a zirconium [^{99}Mo] molybdate gel generator. *Appl. Radiat. Isot.* **2012**, *70*, 375–379. [CrossRef] [PubMed]
54. Kodina, G.E.; Korpusov, G.V.; Filyanin, A.T. Production of high-purity ^{90}Y on specially developed centrifugal semicounterflow extractors. *Radiochemistry* **2002**, *44*, 63–66. [CrossRef]
55. Kuznetsov, R.A.; Han, H.S.; Park, U.J.; Park, S.J.; Pakhomov, A.N. Separation of strontium from yttrium nitrate solutions by solvent extraction with dicyclohexano-18-crown-6. *Radiochim. Acta* **2001**, *89*, 461–467. [CrossRef]
56. Vanura, P.; Makrlik, E. Mathematical modeling of separation of microamounts of strontium from yttrium in the water-HCl-nitrobenzene-15-crown-5-hydrogen dicarbollylcobaltate extraction system. *J. Radioanal. Nucl. Chem.* **2006**, *268*, 437–439. [CrossRef]
57. Makrlík, E.; Vaňura, P. Separation of microamounts of yttrium from strontium by using sodium dicarbollylcobaltate, Slovafol 909 and ethylenediamine-N,N,N′,N′-tetraacetic acid in the water-nitrobenzene extraction system. *J. Radioanal. Nucl. Chem.* **2006**, *268*, 645–649. [CrossRef]
58. Vanura, P.; Jedináková-Křížová, V.; Yoshioka, A. Extraction separation of strontium and yttrium radionuclides by hydrogen heptachlorodicarbollylocobaltate in the presence of benzo-15-crown-5. *J. Radioanal. Nucl. Chem.* **2002**, *251*, 511–514. [CrossRef]
59. Du, H.S.; Wang, Y.X. Extraction of ^{90}Sr-^{90}Y with Diphenyl-16-crown-5-oxyacetic Acid. *Isotopes* **1995**, *16*, 105–109.
60. Kanapilly, G.M.; Newton, G.J. A new method for the separation of multicurie quantities of ^{90}Y from ^{90}Sr. *Int. Fission Prod. Inhal. Proj.* **1969**, *11*, 75–81. [CrossRef]
61. Liang, J.F.; Hou, X.F.; Ouyang, Q. Experimental Study on Electrodeposition of ^{90}Y. *Isotopes* **2007**, *20*, 159–163.
62. Xu, H.-C.; Zhou, J.-B.; Wu, Y.-T.; Cui, Y.-S.; Tang, Y.; Huang, L.-L. Study on the Separation of ^{90}Y by Electrodeposition and Measurement of Its Content by Weighing Method. *Appl. Chem. Ind.* **2023**, *52*, 662–664+670.
63. Mateos, J.J.; Gomez, E.; Garcias, F.; Casas, M.; Cerdà, V. Rapid ^{90}Sr/^{90}Y determination in water samples using a sequential injection method. *Appl. Radiat. Isot.* **2000**, *53*, 139–144. [CrossRef]
64. Su, Z.-M.; Liu, X.-Q.; Wang, Y.; Chu, T.-W.; Wang, X.-Y. Preparation of ^{90}Sr-^{90}Y Generator Using Inorganic Ion Exchanger. *Ion Exch. Adsorp.* **2003**, *19*, 481–488.
65. Jin, X.-H.; Yu, H.-B.; Zhang, J.-M.; Zhang, P.-X.; Lin, Q.-F. Development of ^{90}Sr-^{90}Y Generator. *Isotopes* **1990**, *3*, 161–168.
66. Cheng, Z.Y.; Li, M.L. Study on DTPA as a Leaching Agent for ^{90}Sr/^{90}Y Generator. *Nucl. Power Eng.* **1993**, *14*, 543–546.
67. Chuan, J.T.; Lo, J.G. Extraction chromatographic separation of carrier-free ^{90}Y from ^{90}Sr generator by crown ether coated silica gels. *J. Radioanal. Nucl. Chem.* **1996**, *204*, 83–93. [CrossRef]
68. Venkatesh, M.; Pandey, U.; Dhami, P.S.; Kannan, R.; Achuthan, P.V.; Chitnis, R.R.; Gopalakrishnan, V.; Banerjee, S.; Samuel, G.; Pillai, M.R.A.; et al. Complexation studies with ^{90}Y from a novel ^{90}Sr-^{90}Y generator. *Radiochim. Acta* **2001**, *89*, 413–417. [CrossRef]
69. Ma, Z.Q.; Yang, H.X. Performance of P507 Resin and Its Study on Separation of ^{90}Sr-^{90}Y. *Ion Exch. Adsorp.* **1991**, *7*, 277–280.
70. Honarvar, H.; Müller, C.; Cohrs, S.; Haller, S.; Westerlund, K.; Eriksson Karlström, A.; van der Meulen, N.P.; Schibli, R.; Tolmachev, V. Evaluation of the first ^{44}Sc-labeled Affibody molecule for imaging of HER2-expressing tumors. *Nucl. Med. Biol.* **2017**, *45*, 15–21. [CrossRef]
71. RoeSch, F.; Baum, R.P. Generator-based PET radiopharmaceuticals for molecular imaging of tumours: On the way to THERANOSTICS. *Dalton Trans.* **2011**, *40*, 6104–6111. [CrossRef] [PubMed]
72. Domnanich, K.A.; Mueller, C.; Farkas, R.; Schmid, R.M.; Ponsard, B.; Schibli, R.; Türler, A.; van der Meulen, N.P. ^{44}Sc for labeling of DOTA- and NODAGA-functionalized peptides: Preclinical in vitro and in vivo investigations. *EJNMMI Radiopharm. Chem.* **2016**, *1*, 8. [CrossRef] [PubMed]
73. Alliot, C.; Kerdjoudj, R.; Michel, N.; Haddad, F.; Huclier-Markai, S. Cyclotron production of high purity Sc-44m,Sc-44 with deuterons from ($CaCO_3$)-Ca-44 targets. *Nucl. Med. Biol.* **2015**, *42*, 524–529. [CrossRef]
74. van der Meulen, N.P.; Bunka, M.; Domnanich, K.A.; Müller, C.; Haller, S.; Vermeulen, C.; Türler, A.; Schibli, R. Cyclotron production of ^{44}Sc: From bench to bedside. *Nucl. Med. Biol.* **2015**, *42*, 745–751. [CrossRef]

75. Huclier-Markai, S.; Kerdjoudj, R.; Alliot, C.; Schmid, R.M.; Ponsard, B.; Schibli, R.; Türler, A.; van der Meulen, N.P. Optimization of Reaction Conditions for the Radiolabeling of DOTA and DOTA-Peptide with $^{44m/44}$Sc and Experimental Evidence of the Feasibility of an In Vivo PET Generator. *Nucl. Med. Biol.* **2014**, *41*, e36–e43. [CrossRef]
76. Roesch, F. Scandium-44: Benefits of a long-lived PET radionuclide available from the (44)Ti/(44)Sc generator system. *Curr. Radiopharm.* **2012**, *5*, 187–201. [CrossRef] [PubMed]
77. Lange, R.; D'Auria, J.; Giesen, U.; Vincent, J.; Ruth, T. Preparation of a radioactive ^{44}Ti target. *Nucl. Instrum. Methods Phys. Res. Sect. A Accel. Spectrometers Detect. Assoc. Equip.* **1999**, *423*, 247–255. [CrossRef]
78. Filosofov, D.V.; Loktionova, N.S.; Roesch, F. A Ti-44/Sc-44 radionuclide generator for potential application of Sc-44-based PET-radiopharmaceuticals. *Radiochim. Acta: Int. J. Chem. Asp. Nucl. Sci. Technol.* **2010**, *98*, 149–156. [CrossRef]
79. Gagnon, K.; Severin, G.W.; Barnhart, T.E.; Engle, J.W.; Valdovinos, H.F.; Nickles, R.J. ^{45}Ti extraction using hydroxamate resin. *AIP Conf. Proc.* **2012**, *1509*, 211–214.
80. Synowiecki, M.A.; Perk, L.R.; Nijsen, J.F.W. Production of novel diagnostic radionuclides in small medical cyclotrons. *EJNMMI Radiopharm. Chem.* **2018**, *3*, 3. [CrossRef]
81. Goethals, P.E.; Zimmermann, R.G. *Cyclotrons Used in Nuclear Medicine World Market Report & Directory*; MEDraysintell: Louvain-la-Neuve, Belgium, 2015.
82. Buck, A.K.; Herrmann, K.; Stargardt, T.; Krause, B.J.; Schreyögg, J. Economic evaluation of PET and PET/CT in oncology: Evidence and methodologic approaches. *J. Nucl. Med. Technol.* **2010**, *38*, 6–17. [CrossRef] [PubMed]
83. Schmor, P. Review of cyclotrons for the production of radioactive isotopes for medical and industrial applications. *Rev. Accel. Sci. Technol.* **2011**, *4*, 103–116. [CrossRef]
84. Braccini, S.; Alves, F. Special issue "instruments and methods for cyclotron produced radionuclides". *Instruments* **2019**, *3*, 60. [CrossRef]
85. Krajewski, S.; Cydzik, I.; Abbas, K.; Bulgheroni, A.; Simonelli, F.; Holzwarth, U.; Bilewicz, A. Cyclotron production of ^{44}Sc for clinical application. *Radiochim. Acta* **2013**, *101*, 333–338. [CrossRef]
86. Daraban, L.; Rebeles, R.A.; Hermanne, A.; Tarkanyi, F.; Takacs, S. Study of the excitation functions for, 43K, 43,44,44mSc and ^{44}Ti by proton irradiation on ^{45}Sc up to 37MeV. *Nucl. Instrum. Methods Phys. Res. B* **2009**, *267*, 755–759. [CrossRef]
87. Hermanne, A.; Rebeles, R.A.; Tarkanyi, F.; Takacs, S.; Takacs, M.P.; Csikai, J.; Ignatyuk, A. Cross sections of deuteron induced reactions on ^{45}Sc up to 50MeV: Experiments and comparison with theoretical codes. *Nucl. Instrum. Methods Phys. Res. B* **2012**, *270*, 106–115. [CrossRef]
88. Greene, M.W.; Hillman, M. A scandium generator. *Int. J. Appl. Radiat. Isot.* **1967**, *18*, 540–541. [CrossRef]
89. Vickery, R.C. The Extraction and Purification of Scandium. *J. Chem. Soc.* **1955**, *31*, 2435–2438. [CrossRef]
90. Walter, R.I. Anion exchange studies of Sc(III) and V(IV). Separation of scandium, titanium and vanadium. *J. Inorg. Nucl. Chem.* **1958**, *6*, 58–62. [CrossRef]
91. Klouda, J.; Fassbender, M.E.; Mocko, V. A combined inorganic-organic titanium-44/scandium-44g radiochemical generator. *J. Chromatogr. A* **2023**, *1711*, 464438. [CrossRef] [PubMed]
92. Dirks, A.; Rebeles, R.A.; Hermanne, A.; Tarkanyi, F.; Takacs, S.; Takacs, M.P.; Csikai, J.; Ignatyuk, A. On the development and characterisation of an hydroxamate based extraction chromatographic resin. In Proceedings of the 61st RRMC, Iowa City, IA, USA, 25–30 October 2015.
93. Larenkov, A.A.; Makichyan, A.G.; Iatsenko, V.N. Separation of ^{44}Sc from ^{44}Ti in the context of a generator system for radiopharmaceutical purposes with the example of [^{44}Sc]Sc-PSMA-617 and [^{44}Sc]Sc-PSMA-I&T synthesis. *Molecules* **2021**, *26*, 6371. [CrossRef]
94. Schmidt, C.E.; Groveman, S.; Sanders, V.A.; Cutler, C.S.; Shusterman, J.A.; Deri, M.A. Development of a SnO_2-based ^{44}Ti/^{44}Sc generator for medical applications. *J. Chromatogr. A* **2024**, *1732*, 465245. [CrossRef]

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