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^{225}Ac/^{213}Bi radionuclide generators for the separation of ^{213}Bi towards clinical demands

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Bismuth-213 (^{213}Bi) is a promising radionuclide for clinical application in targeted alpha therapy of cancers. ^{225}Ac/^{213}Bi radionuclide generators are of particular interest for the production/separation of ^{213}Bi. This review aims to give an overview of the current status of ^{225}Ac production, ^{225}Ac/^{213}Bi radionuclide generator systems, the types of adsorbents, separation conditions, separation mechanisms, and critical challenges. The review also provides guidance for investigating emerging new sorbents that can be developed to overcome the limitations of currently used sorbents.

1. Introduction

The use of radionuclides is becoming increasingly important for medical diagnosis, and therapeutic applications.[1,2] The diagnostic imaging can enable precise visualization of physiological processes.[1,2] Radiopharmaceutical therapy (RPT), in particular, is a safe and effective method to treat various cancers *via* delivering radioactive atoms to tumor-associated targets (Fig. 1).[2] The radiation emitted by the radionuclides kills cancer cells locally, which ensures targeted therapeutic outcomes while minimizing radiation exposure to non-targeted tissues.[3] RPT offers several advantages over conventional therapeutic techniques, including targeted therapy, metastatic disease treatment, high efficacy, and minimal toxicity.[4] These benefits make it an attractive alternative or complementary option to traditional cancer treatments like chemotherapy, radiotherapy, and surgery.[2] The therapeutic efficacies of radionuclides vary based on their fundamental nuclear properties, including their decay pathway, energy emissions, effective range, half-life, and chemical behavior.[5] The penetration range

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Stephan Heinitz

Stephan Heinitz (born in 1982) obtained his PhD in 2013 from the University of Berne, Switzerland, in collaboration with PSI. The work was devoted towards purification of irradiated liquid metal targets and behaviour of polonium in lead–bismuth eutectic. He continued as PSI PostDoc in radioactive target development where he was involved in lanthanide purification for different research institutes such as CERN and INFN. In 2018, he joined SCK CEN as project leader for the production of the medical isotope ^{225}Ac. He published 120 papers in international journals (h-index = 17) and is co-inventor of 2 patents (applications).

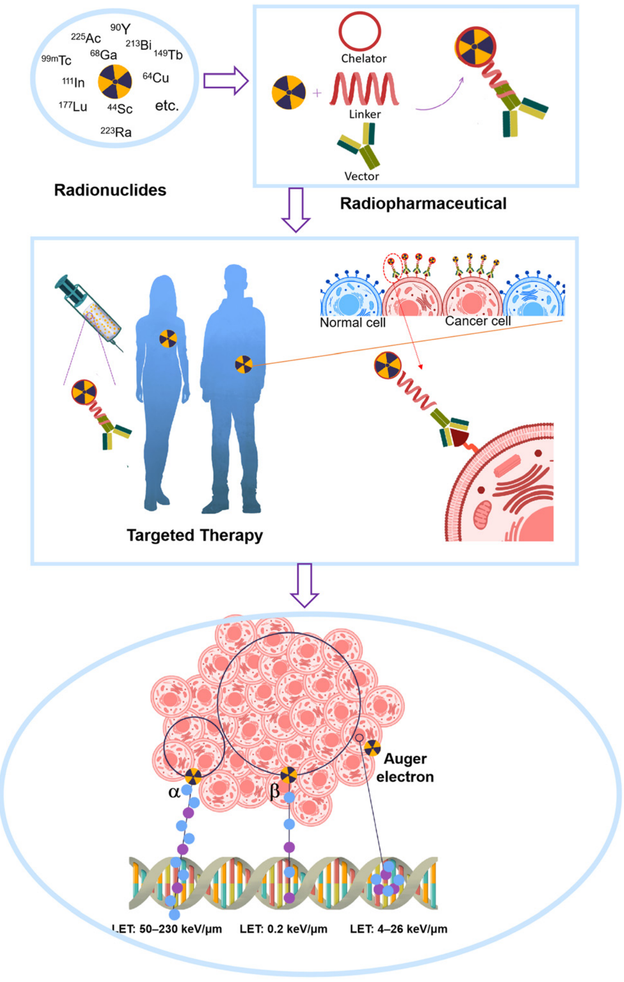

Fig. 1 Simplified illustration of how radiopharmaceutical targeting works and damage from radioactive emissions: α-emitters, β-emitters, and Auger-electron emitters.

and the linear energy transfer (LET) are critical factors, as the potent pathway of malignant cell destruction is related to the direct interaction between ionization events and the DNA string in the nucleus.[6] The emitted particles should possess a suitable penetration range (usually several cell diameters).[1,2,6] A more extensive penetration range can result in the death of the surrounding healthy cells and induce unnecessary dose. Alternatively, a low penetration range is insufficient for damaging malignant cells.[1,2,6] The LET indicates the energy deposited per unit length of the track. The LET radiations are usually divided into two classes.[1,2,6] High LET radiations, like neutrons and alpha particles, have stronger biological effects due to their higher ionization events within tissues, while low LET radiations (*e.g.*, X-rays and gamma rays) produce fewer biological effects. However, the biological effects are also impacted by other factors, as described in previous reviews.[7–9]

Radionuclides used in radiopharmaceutical therapy are typically classified as alpha, beta, and Auger-electron emitters (Fig. 1).[10,11] Alpha particles, positively charged helium nuclei, are highly effective ionization agents with a short penetration range of 40–100 μm, corresponding to roughly 2–6 cell diameters. They possess a high LET of 50–230 keV μm^{-1}, which enables maximum malignant cell destruction with reduced cytotoxicity to surrounding normal cells.[12,13] Moreover, the distance between two strands in a DNA structure coincides with the distance between two consecutive alpha ionizations, indicating that a single alpha particle can kill one cell.[14] In contrast, beta particles (electrons) with a long penetration range of 0.3–12 mm (several hundred cells in diameter) may damage healthy tissues surrounding the malignant cells. Additionally, beta particles also have a low LET of only 0.2 keV μm^{-1}.[11] Hundreds of beta particles are possibly needed to break a double-stranded DNA structure.[13] Although Auger electrons possess a higher LET of 4–26 keV μm^{-1}, their limited penetration range of 2–500 nm restricts their efficacy to a single cell, as they must cross the malignant cell membrane to reach

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Steven Mullens

Steven Mullens (born in 1972) is a senior researcher at the Flemish Institute for Technological Research. His research focusses on shaping and surface modification of ceramic, metallic and hybrid materials by 3D-printing, coatings and granulation. These structures are utilized in various applications, including biomaterials, advanced sorbent materials, and as structured catalysts. He has been involved for more than 20 years in several academic and industrial projects. He has published 120 papers in international journals (h-index = 34) and is co-inventor of 14 patents (applications).

the nucleus.[15] Auger elections can damage the cancer cells *via* cross-dose effect, bystander effect, generation of hydroxyl free radicals, cell membrane damage, and direct or indirect DNA damage.[16] Consequently, more recent research has focused on radiopharmaceuticals with alpha particles because of their more favorable radiobiological properties.[13]

The alpha-emitting radiopharmaceuticals for targeted alpha therapy (TAT) (Fig. 1) are primarily made of radioactive isotopes, chelating agents, linkers, and biological-targeting vectors.[17] Chelator is used to attach the isotope to the vector, while linkers can connect the radionuclide-chelator to the vector. Disease-targeting vectors can act as carriers of radionuclides to the targeted cancer cells.[18] The chemical purity of ^{213}Bi should be high, as impurities can affect chelation and reduce stability and effectiveness. The half-life of radionuclides should be suitable for the therapeutic window (referring to the drug dose needed), which should match the biological kinetics of the targeted malignant cells without producing toxic effects in any patients.[13] Typically, the half-life of radionuclides needs to be carefully balanced to avoid overexposure on one hand, and on the other hand allow adequate time for radionuclide and radiopharmaceutical production and delivery to the patients while ensuring cancer cells receive a sufficient dose.[13] Other preferred characteristics are related to the decay process, in which radionuclides must undergo alpha decay, preferably with a high alpha decay ratio, and produce no long-lived intermediates, ultimately decaying into a stable, non-hazardous element. Additionally, they should have high specific activity (the activity per unit mass of a radionuclide) and abundance (significant quantities of the radioactive substance present within a sample).[19] However, the potential detachment of daughter radionuclides due to recoil effects resulting from multiple alpha decays should be mentioned to reduce unnecessary dose for patients.

Thomas Cardinaels

Thomas Cardinaels (born in 1979) obtained his PhD in Chemistry in 2006 at KU Leuven where he continued research in the field of metal-containing liquid crystals as PostDoc. In 2009 he moved to SCK CEN expanding expertise in nuclear fuel materials. Since 2015 he is head of the Radiochemistry group at SCK CEN which he combines with a position as Associate Professor in Chemistry at KU Leuven. His research aims at developing radiochemical process technology for sustainable radioactive waste solutions, and to produce medical radioisotopes and radiopharmaceuticals. He published 100 papers (h-index = 24) and is co-inventor of 6 patents (applications).

While there are over 100 radionuclides capable of emitting alpha particles, only a handful of alpha-emitter radionuclides are suitable for therapeutic applications.[13,20–23] These radionuclides have suitable characteristics, including the correct nuclear properties, chemical properties (*e.g.*, stable complexes with biomolecules), or accessibility (*e.g.*, regularly available and affordable). ^{223}Ra was the first therapeutic alpha-emitting radionuclide approved by the Food and Drug Administration (FDA) for clinical prostate cancer treatment in 2013.[24] Among all radionuclides, ^{225}Ac and its daughter ^{213}Bi have been attractive candidates for TAT because of their high specific activity, effective half-life, high alpha decay ratio (the ratio of alpha particles emitted by a radioactive substance relative to other types of radiation), absence of long-lived intermediates, and stable complexes with the availability of chelators.[25] Geerlings M. W. *et al.* suggested the use of ^{225}Ac and ^{213}Bi for therapy in 1993.[26] Clinical applications of ^{225}Ac have been reported for treating targeted leukemia, glioma, neuroendocrine tumors, and prostate cancer, whereas ^{213}Bi has shown potential in clinical trials of leukemia, lymphoma, malignant melanoma, glioma, neuroendocrine tumors, fungal infections and infectious diseases.[25,27] However, the limited availability and accessibility of ^{225}Ac for clinical use pose a significant challenge, as its production and purification can be both challenging and expensive.[28–30] Being less cytotoxic than ^{225}Ac, the chemical properties and the presence of an alpha-emitting daughter (^{213}Po) make ^{213}Bi much easier to incorporate into future clinical trials.[19] The supply of ^{225}Ac also impacts the application of ^{213}Bi for TAT since ^{213}Bi is obtained by the ^{225}Ac decay (Fig. 2). While ^{213}Bi is a valuable radionuclide for TAT, currently its application is very limited mainly due to the availability of its parent ^{225}Ac. Furthermore, the application of ^{213}Bi is the cost as it requires about 1000 times more activity per patient dose compared to ^{225}Ac.[28,31,32] As a result, research efforts have been focused on developing more efficient and cost-effective routes to produce larger quantities of ^{225}Ac.[28–30,33] Additionally, the separation of ^{213}Bi from ^{225}Ac is also crucial. The chemical and radiochemical purity is indispensable for precise labeling at high specific activity, ensuring optimal diagnostic accuracy and therapeutic efficacy while minimizing radiation exposure in nuclear medicine applications.

^{213}Bi is generally separated by the ^{225}Ac/^{213}Bi radionuclide generators. These generators are widely used to produce and separate daughter radionuclides with short half-lives from their long-lived parent radionuclides.[34] A schematic diagram of the representative radionuclide generator is shown in Fig. 2, composed of shielding containers, adsorbent material, radionuclide(s), and eluent.[34] Their use can ensure the availability of short-lived daughter radionuclides for medical applications in hospitals that are located far away from nuclide production facilities (*e.g.*, nuclear reactors, accelerators, and actinide stocks).[34,35] Moreover, radionuclide generators are capable of providing short-lived daughter radionuclides with high specific activity and in a carrier-free form at a relatively low cost.[35,36] The choice of separation systems for separating ^{213}Bi

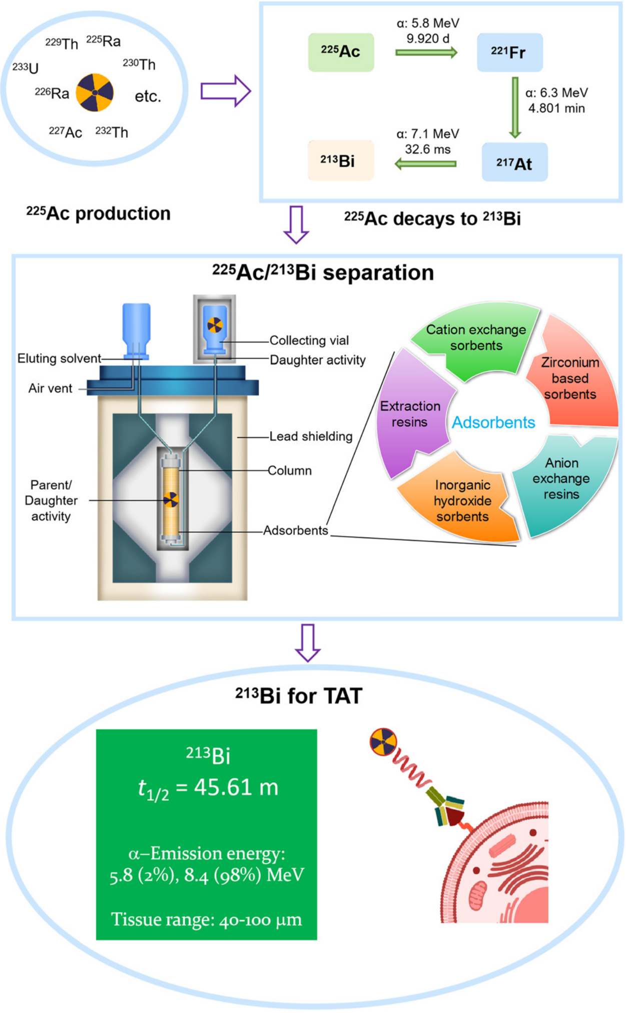

Fig. 2 Schematic diagram of the process from ^{225}Ac production to ^{213}Bi for targeted alpha therapy.

depends on the adsorption and desorption performance of the adsorbents used.[37,38] This review sheds light on the various separation techniques used in previous studies, offering insights into selecting appropriate separation systems for specific isotopes of interest.

The adsorbent is the crucial component that plays a key role in facilitating the separation of radionuclides, and a variety of adsorbent materials have been utilized in the ^{225}Ac/^{213}Bi radionuclide generators.[37–49] While these materials can be suitable for certain conditions, most of them still have drawbacks such as limited shelf-life (*e.g.*, less than one day), radiolytic damage (*e.g.*, scission of functional groups), nanoparticle aggregation, insufficient active sites, low adsorption capacity, long diffusion time, poor structural stability, and difficulties in their regeneration.[37–49] Therefore, there is still an urgent need to investigate new emerging adsorbents that can meet the stringent requirements posed in clinical applications. The advantages and disadvantages of the reported adsorbents are introduced in this review.

This review aims to consolidate current knowledge and provide a comprehensive overview of ^{225}Ac/^{213}Bi radionuclide generators, their working principles, and the adsorbents involved (Fig. 2). The present paper provided a brief overview of the current status of ^{225}Ac production, highlighting its current limitations and prospects for the future. The physical and chemical properties of ^{225}Ac and ^{213}Bi are introduced to facilitate a better understanding of the separation mechanisms employed in ^{225}Ac/^{213}Bi radionuclide generators. A detailed discussion of previously used generator systems and adsorbents provides the readers with a historical context and helps them understand the evolution of the separation techniques used for ^{213}Bi from ^{225}Ac, as well as identify the advantages and limitations of such adsorbents. By covering these aspects, this review serves as a valuable resource for researchers, clinicians, and other stakeholders involved in ^{225}Ac/^{213}Bi radionuclide generators and radiopharmaceutical development.

2. Actinium-225 production

Currently, there is limited availability of carrier-free ^{225}Ac for preclinical and clinical trials.[50] Approximately 4 TBq (216 Ci) of ^{225}Ac per year is required to meet the demand for cancer treatment, and the activity for ^{213}Bi should be increased accordingly.[51] Various approaches have been considered or examined to produce ^{225}Ac, which can be broadly divided into two categories: direct and in-direct production routes.[50] In the direct route, ^{225}Ac is the primary product of a nuclear reaction. In contrast, the indirect route involves the production of either ^{229}Th or ^{225}Ra, which subsequently decay to create ^{225}Ac.[50] Fig. 3 illustrates the numerous relevant nuclear reactions involved in ^{225}Ac production.[33,52–62]

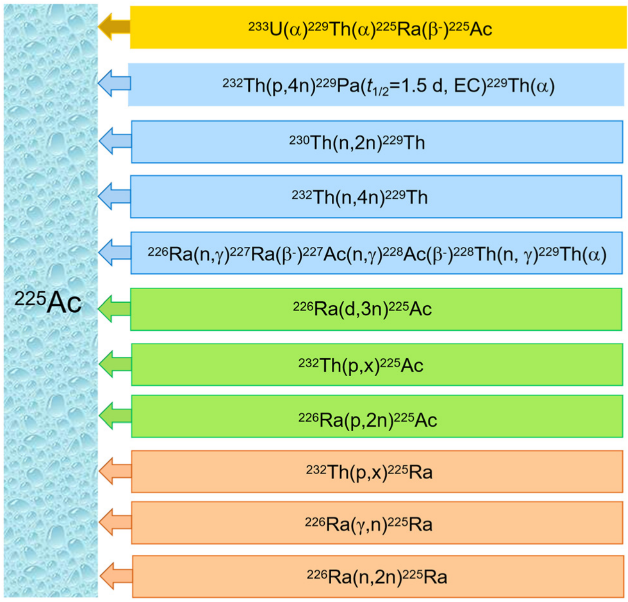

Fig. 3 Nuclear reactions for ^{225}Ac production.

Currently, the primary global supply of ^{225}Ac is facilitated by the decay of ^{229}Th sources with a long half-life of 7920 (34) years, primarily from the decay of fissile ^{233}U with a half-life of 159 200 years.[41,50,63–66] ^{233}U is produced by the neutron irradiation of ^{232}Th for its applications in advanced fuel cycles for Th-breeders.[52] Fig. 4 depicts the decay chain starting from ^{233}U.[41,50,64–66] However, only a limited number of ^{229}Th and ^{233}U stocks are available because of non-proliferation restrictions on the management of fissile material.[67] It is estimated that no more than 63 GBq (1.7 Ci) per year of ^{225}Ac can be produced worldwide by the decay of ^{229}Th.[52,68] Several institutions can generate limited quantities of ^{225}Ac by this method; for instance, 26.6 GBq (720 mCi) per year produced by Oak Ridge National Lab (ORNL) in Oak Ridge, USA, ∼26.4 (715 mCi) per year produced by Institute of Physics and Power Engineering (IPPE) in Obninsk, Russia, and 13.1 GBq (350 mCi) per year produced by the Institute for Transuranium Elements (ITU) in Karlsruhe, Germany.[30,31,62,67,69,70] In addition, the Belgian Nuclear Research Centre (SCK CEN) in Mol, Belgium, has a limited quantity of high-purity ^{229}Th became available from legacy thorium sources originating from reactor irradiated ^{226}Ra. ^{225}Ac from this material has been used to evaluate the alternative adsorbents in ^{225}Ac/^{213}Bi generators and preclinical studies.[31,47,71,72] There is also an additional small source of ^{229}Th that is currently becoming available at Canadian Nuclear Laboratories.[73] The separation process of ^{225}Ac from ^{225}Ra and ^{229}Th was illustrated in the previous review[52] and will thus not be covered within this work.

Several alternative strategies to produce ^{229}Th have been considered or investigated over time. ^{229}Th can be produced from the proton irradiations of ^{232}Th with the reaction of ^{232}Th(p,4n)^{229}Pa ($t_{1/2}$ = 1.5 d, EC) ^{229}Th.[33,53] However, this process produces a limited supply of ^{229}Th because of the low cross-sections (*e.g.*, 162 ± 14 mb at a proton energy of 29.7 ± 0.5 MeV), and the concerns regarding co-production of ^{230}Th.[29,53,74] Furthermore, the handling and separation process is challenging due to a broad range of interfering isotopes such as ^{228}Pa and ^{230}Pa. The irradiation of ^{230}Th and ^{232}Th using fast neutrons was also considered for ^{230}Th(n,2n)^{229}Th or ^{232}Th(n,4n)^{229}Th, but these methods only provide isotopically diluted ^{229}Th and further investigations must be conducted to verify their feasibility.[29] Yet another approach is the thermal neutron irradiation of ^{226}Ra, described as follows: ^{226}Ra(n,γ)^{227}Ra(β$^-$)^{227}Ac(n,γ)^{228}Ac(β$^-$)^{228}Th(n, γ)^{229}Th, which involves three neutron captures and two beta(−) decays *via* a series of alternative pathways.[54] However, the production of ^{229}Th *via* this approach can only be efficiently conducted in high flux reactors and requires significant infrastructure due to the complicated process and the handling of large activities of intermediate products, such as ^{227}Ac and ^{228}Th. Likewise, ^{229}Th can also be produced by the irradiation of ^{227}Ac, ^{228}Ra and ^{228}Th, based on the irradiation route of ^{226}Ra.[54]

The production of ^{225}Ac by the proton-induced irradiation of ^{232}Th *via* ^{232}Th (p,x)^{225}Ac or ^{232}Th(p,x)^{225}Ra(β$^-$)^{225}Ac in a proton accelerator at energies between 66 and 500 MeV is widely considered a promising method.[52,55–57] The preparation of ^{232}Th targets does not pose difficulties, and this method is currently efficiently applied for the production of a higher amount of ^{225}Ac (*e.g.*, 11.2 TBq of ^{225}Ac per month in TRIUMF

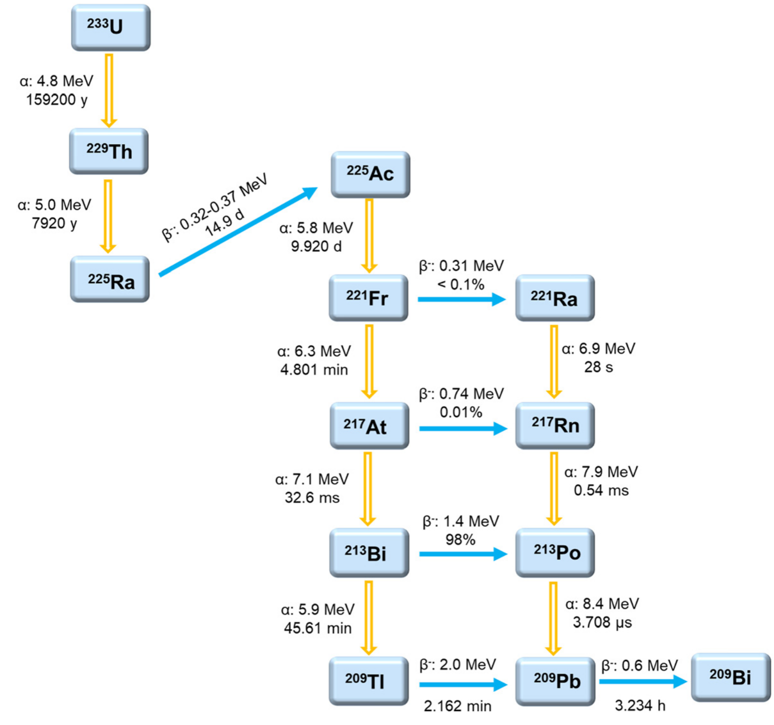

Fig. 4 Decay chain of ^{233}U.[41,50,64–66]

in principle).[52] However, it should be noted that the high energy proton spallation produces a broad variety of other radionuclides that require complex chemical separation procedures. Additionally, co-production of ^{227}Ac with a half-life of 21.772 years is inevitable and hampers the radionuclidic purity of ^{225}Ac ($^{225/227}$Ac atom ratio 1 : 1 at end of irradiation).[58,59] To circumvent this, separating ^{225}Ra from ^{232}Th can be used as the mother isotope for ^{225}Ac, which can significantly enhance the radionuclidic purity of ^{225}Ac.[58] However, the activity of ^{225}Ac obtained from ^{225}Ra this way is an order of magnitude lower than that directly produced from ^{232}Th irradiation.[55,59] The presence of small amounts of ^{227}Ac and its descendants (*e.g.* ^{227}Th) within ^{225}Ac appears to be acceptable for maintaining the purity of ^{213}Bi from ^{225}Ac/^{213}Bi radionuclide generators.[31,48,58,75] Hence, the production of ^{225}Ac in this manner might be beneficial for the application of ^{213}Bi.[58]

The irradiation of ^{226}Ra ($t_{1/2}$ = 1600 years) with protons, deuterons, fast neutrons and gamma rays can be applied or suggested to create ^{225}Ac through different nuclear reactions, which has also garnered much attention from scientists.[60] However, the ^{226}Ra targets also face a series of challenges with respect to the limited availability of the starting material, high infrastructure costs and considerable safety hazards (*e.g.*, ^{222}Rn gas and emission of high energy gamma rays).[76,77] Proton-irradiation of ^{226}Ra, resulting in the ^{226}Ra(p,2n)^{225}Ac reaction, is the most promising direct method for the large-scale production of ^{225}Ac, which can generate ^{225}Ac with significantly less interference from ^{227}Ac.[62] The co-production of ^{226}Ac (29.37 h) and ^{224}Ac (2.78 h) probably exerts less effect than the ^{227}Ac contaminant because of their relatively short half-lives, but increases the cooling time after irradiation to achieve the required ^{225}Ac isotopic purity.[52] Additionally, the ^{226}Ra(p,2n)^{225}Ac reaction has a high cross-section (710 mb [maximum] at 16.8 MeV beam energy) by comparison to ^{232}Th(p,x)^{225}Ac production.[52,62,70] Irradiating ^{226}Ra by deuterons, resulting in the reaction ^{226}Ra(d,3n)^{225}Ac, has been suggested as a promising approach.[60,61] This reaction can produce relatively high production yields compared to ^{226}Ra(p,2n)^{225}Ac, as predicted by model calculations.[60] However, this method is hampered by the availability of suitable accelerators that offer deuteron beams of sufficiently high energy.[61] Similarly, the fast neutron reaction pathway *via* ^{226}Ra(n,2n)^{225}Ra has a promisingly high cross-section (860 mb at 16.6 MeV), but the challenge remains in the availability of a suitable facility providing the required fast neutron fluxes.[78]

The use of photonuclear reactions to induce ^{226}Ra(γ,n)^{225}Ra(β$^-$)^{225}Ac reaction is another potential route for ^{225}Ac production.[77,79] This reaction involves irradiating ^{226}Ra with bremsstrahlung photons to generate ^{225}Ra. Based on the properties of the target configuration to thermalize emitted neutrons, the obtained ^{225}Ac will be free from other actinium isotopes after a series of consecutive milking operations of the irradiated target. However, the production yield is relatively low compared to other methods, and the efficiency of this production method will depend on factors such as target mass, the energy and intensity of the electron/bremsstrahlung used *etc*.

Other potential methods have also been discussed in previous reviews.[52] Moreover, studies have demonstrated the separation of ^{225}Ac from large target masses.[52,80] In summary, the production and separation of ^{225}Ac with large quantities and high purity are crucial for developing the ^{225}Ac- and ^{213}Bi-radiopharmaceuticals.

3. Physical and chemical properties of ^{225}Ac and ^{213}Bi

Understanding the physical and chemical characteristics of ^{225}Ac^{3+} and ^{213}Bi^{3+} ions is crucial for identifying the separation mechanisms of the adsorbents and optimizing the separation procedures. These insights can be exploited to develop improved separation methods and alternative adsorbents for separating ^{225}Ac and ^{213}Bi.

3.1. Decay characteristics of ^{225}Ac

^{225}Ac is a highly cytotoxic radiometal with a half-life of 9.920 days and is considered a pure alpha emitter.[64,81] It undergoes decay *via* a cascade involving six short-lived radionuclide daughters (^{221}Fr, ^{217}At, ^{213}Bi, ^{213}Po, ^{209}Pb, and ^{209}Bi), ultimately resulting in the long-lived ^{209}Bi ($t_{1/2}$ = 1.9 × 10^{19} years) (Fig. 4).[25,64] The ^{225}Ac decay process predominantly involves the emission of four alpha and two beta particles. Most intermediates in the decay path have high energies, demonstrated by the significant radiations of 5.8–8.4 MeV for alpha emitters and 0.6–2.0 MeV for beta emitters.[64] The cumulative energy of four alpha particles can reach about 28 MeV, which can be harnessed for cancer treatment.[82] However, the leaching of its daughters from chelating agents is a concern regarding the potential toxicity to healthy cells. The high recoil energy of an alpha particle, ranging from 100–200 keV, is challenging for the radiation stability of chelating agents, as it exceeds the binding energy of the coordination complex.[64] In addition to alpha particles emission, two useful gamma emissions are produced by the disintegration of ^{221}Fr (218 keV, 11.6% emission probability) and ^{213}Bi (440 keV, 26.1% emission probability), which can be applied for *vivo* imaging.[25]

3.2. Actinium/lanthanum chemistry

Non-radioactive lanthanum is usually used as a surrogate of actinium, owing to its several similar chemical behaviors in aqueous.[81,83] Here, the properties of actinium and lanthanum together were displayed. The stable valence for actinium ions is +III (Ac^{3+}), and Ac^{3+} (an electronic configuration of [Rn]5f^0) is considered the largest trivalent cation among the elements in the periodic table.[83] The stable lanthanum valence is also +III (La^{3+} with an electronic configuration of [Xe]4f^0). The first hydrolysis constant of the Ac^{3+} is in the pH range of 8.6–10.4, and the La^{3+} is at pH = ∼8.5.[81,84–86] Fig. 5a shows the distribution species of La as a function of pH.[87] Typically, the separation of ^{225}Ac and ^{213}Bi occurs under acidic conditions (pH <

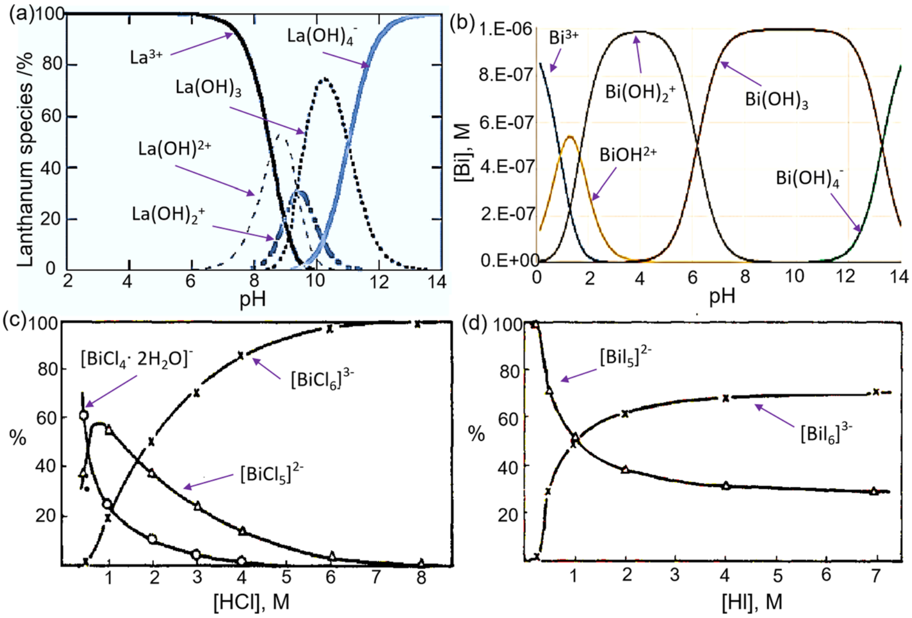

Fig. 5 Distribution species of La^{3+} as a function of pH (a) (reproduced from ref. 95 with permission from the Royal Society of Chemistry, copyright 2006); distribution species of Bi^{3+} (10^{-6} mol L^{-1}) as a function of pH (b) (reproduced (adapted) from ref. 96. with permission from the American Chemical Society, Copyright 2022); and distribution species of Bi^{3+} as a function of HCl (c) and HI concentrations (d) (reproduced (adapted) from ref. 97 with permission from Elsevier, copyright 1979).

5), where hydrolysis of ^{225}Ac minimally impacts on the separation process. According to the hard and soft acids and bases (HSAB) theory, the Ac^{3+} and La^{3+} both belong to hard Lewis acids, and the absolute chemical hardness for Ac^{3+} and La^{3+} is 14.4 and 15.4 eV, respectively.[88–91] Hence, such metal ions are possibly preferred to "hard" nonpolarizable, electronegative Lewis bases.[83] One of the main differences between Ac^{3+} and La^{3+} is the ionic radius, with a 6-coordinate ionic radius of 0.112 nm for Ac^{3+} and 0.103 nm for La^{3+}.[83] Due to its larger size, Ac^{3+} possesses a lower charge density.[83] Ferrier *et al.* reported that the Ac^{3+} could directly coordinate with 10.9 ± 0.5 water molecules, and Ac–O(H_2O) distance is about 2.63 Å.[92,93] The detailed information on coordination properties for actinium can be found in a review paper.[81] Allen *et al.* proposed that the hydration number of La^{3+} is 9.2 at low chloride concentrations, whereas the distance of the La–O(H_2O) bond is 2.54 Å.[94]

3.3. Decay characteristics of ^{213}Bi

The radiometal ^{213}Bi, with a half-life of 45.61 min, is a mixed alpha/beta emitter.[64] It decays *via* a branched pathway involving alpha and beta disintegration to the near-stable ^{209}Bi.[25,64] In particular, ^{213}Bi (97.8%) decays primarily *via* the beta emission to a pure alpha-emitter ^{213}Po with an ultra-short half-life of 3.708 μs (Fig. 4). ^{213}Po emits alpha particles with a high energy of 8.4 MeV and a path length of 85 μm in human tissue, which is mainly responsible for the therapy's efficacy.[25] Moreover, the ^{213}Bi decay is accompanied by the emission of 440 keV gamma rays (26%), which is possibly beneficial for quantitative tumor uptake and dose calculations for clinical medical treatment.[25] Approximately 2.2% of ^{213}Bi decays *via* alpha emission to ^{209}Tl, a beta-emitting isotope. The decay of ^{209}Tl follows with the emission of high-energy gamma rays (~1567 keV). Indeed, it has a low probability, which might exhibit a limited effect on patients. When working with a high amount of ^{213}Bi, shielding is a possible consideration to protect personnel and the environment from these potentially harmful gamma rays.

3.4. Bismuth chemistry

Bismuth, with an electronic configuration of [Xe] $4f^{14}5d^{10}6s^{2}6p^{3}$, is readily able to accept electron pairs due to the poor shielding of the f-orbital electrons and has a high affinity for extended coordination due to its unoccupied orbits.[98,99] The trivalent cation (Bi^{3+}), with an ionic radius of 0.096–0.117 nm (CN = 5–8), is the most stable oxidation due to the inner pair effect. Even the pentavalent cation is recognized as an oxidative reagent.[1,100] Bi^{3+} is usually classified as a borderline acid, and it has a high affinity for oxygen and nitrogen donors and forms strong complexes with sulfur and halogens.[100,101] Chelating agents, including oxygen, nitrogen or thiolate donors, have the ability to form very stable complexes with Bi^{3+}, with coordination numbers ranging from three to nine.[100] The first pK_a of Bi^{3+} is approximately 1.1, indicating that the Bi^{3+} undergoes hydrolysis in acidic solutions, which is an important consideration when separating ^{213}Bi from ^{225}Ac.[102] The speciation diagram of Bi^{3+} as a function of pH is shown in Fig. 5b. The eluents with halide ions are usually utilized to elute ^{213}Bi due to the formation of negatively charged Bi-halide complexes (Fig. 5c and d) from cation exchange platforms, and the strength of Bi-halide complexes increases in the expected order of $F^- < Cl^- < Br^- < I^-$.[101] In a 0.1 M NaI/0.1 M HCl solution, often used as an elution solution, the dominant species include BiI_4^- and BiI_5^{2-}.[69]

4. Principle of ^{225}Ac/^{213}Bi radionuclide generators

4.1 Ingrowth of ^{225}Ac and ^{213}Bi

Generally, ^{229}Th and ^{225}Ra serve as the grandparent and parent for the indirect production of ^{225}Ac, respectively. The optimal elution frequency and schedule may vary depending on the decay properties of the radionuclides and the specific clinical needs of patients. The ingrowth of ^{225}Ra (from 0) and ^{225}Ac (from 0) from ^{229}Th was calculated, and the results are shown in Fig. 6a.[34,103] Clearly, ^{225}Ac and ^{225}Ra can reach secular equilibrium with ^{229}Th after four months, while more than 80% of ^{225}Ac are available after two months. Fig. 6b shows the decay of ^{225}Ra to ^{225}Ac, with a transient equilibrium time of 17 days. The optimal elution time for ^{225}Ac is about every 10 days. Fig. 6c displays the ingrowth of ^{213}Bi from the decay of ^{225}Ac. The secular equilibrium time is about 5 h, whereas more than 80% and 90% of ^{213}Bi can be obtained in about 2 and 3 h, respectively.[42] Typically, the generators are eluted every 2–3 h.[37,104]

4.2 Adsorption mechanisms

Understanding the separation mechanisms of adsorbents is crucial for selecting suitable adsorbents for radionuclide generators that produce high-purity radioisotopes with optimal efficiency and selectivity. These separation mechanisms can be divided into two categories: adsorption and desorption.[34] Unfortunately, there is limited research on the adsorption and desorption mechanisms of adsorbents towards ^{225}Ac, possibly due to the absence of stable, non-radioactive isotopes of this element. In this review, the general sorption mechanisms have been illustrated by using previous studies on the separation of similar metal ions and radionuclides. The primarily sorption mechanisms are as follows: electrostatic interactions, ion exchange, and surface complexation.[105,106] Physical adsorption mechanisms may also occur, such as pore filling, hydrolysis, and precipitation; however, current literature indicates that these mechanisms have a limited impact on Ac^{3+}/Bi^{3+} adsorption.[105,106] Additionally, the primary objective of this section is to shed light on the role of surface functional groups. As such, a detailed discussion on these physical adsorption mechanisms is not included in this section.

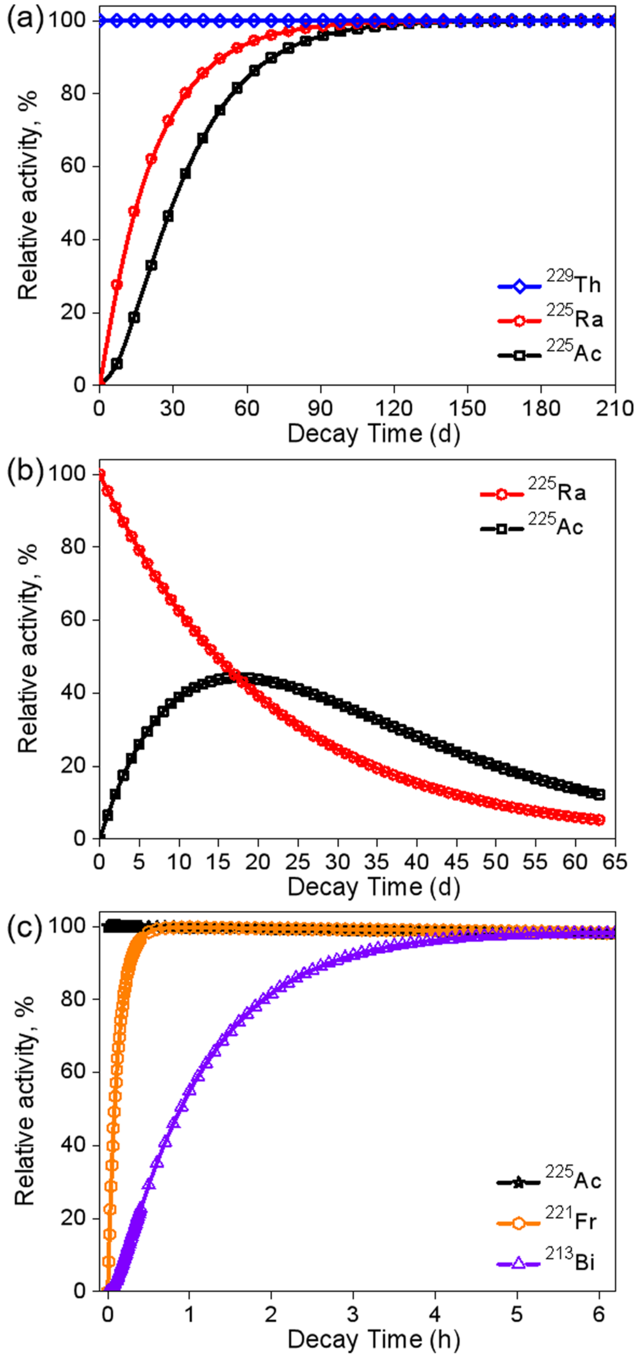

Fig. 6 Theoretical ^{229}Th-decay and ^{225}Ra/^{225}Ac-ingrowth (a); theoretical ^{225}Ra-decay and ^{225}Ac-ingrowth (b); theoretical ^{225}Ac-decay and ^{221}Fr/^{213}Bi-ingrowth (c).

Electrostatic attractive and repulsive interactions, mainly occurs between the protonated/deprotonated function groups and metal ion species (Fig. 7a).[105] Positively charged metal ions (*e.g.*, Ac^{3+}, La^{3+}, and Bi^{3+}) are attracted by negatively charged functional groups (*e.g.*, $–SO_3^-$, $–PO_3^-$, and $–COO^-$) and are repelled by positively charged functional groups (*e.g.*, $R\text{-}N(CH_3)_3^+$, $R\text{-}N(CH_2CH_3)_3^+$, and $R\text{-}NH(CH_2CH_3)_2^+$).[38,39,47,107–114] This type of interaction is highly governed by the solution pH. Typically, the surface charge of the adsorbents becomes negative when the solution pH exceeds the point of zero charges (pH_{pzc}), which is beneficial for the adsorption of cations. If the pH of the solution is lower than the pH_{pzc}, the surface charge becomes positive.[105] Apart from the impact on the charge of the functional groups, the solution pH also influences the metal ion speciation.[47,114,115] This is because the concentration of H^+ ions can affect the oxi-

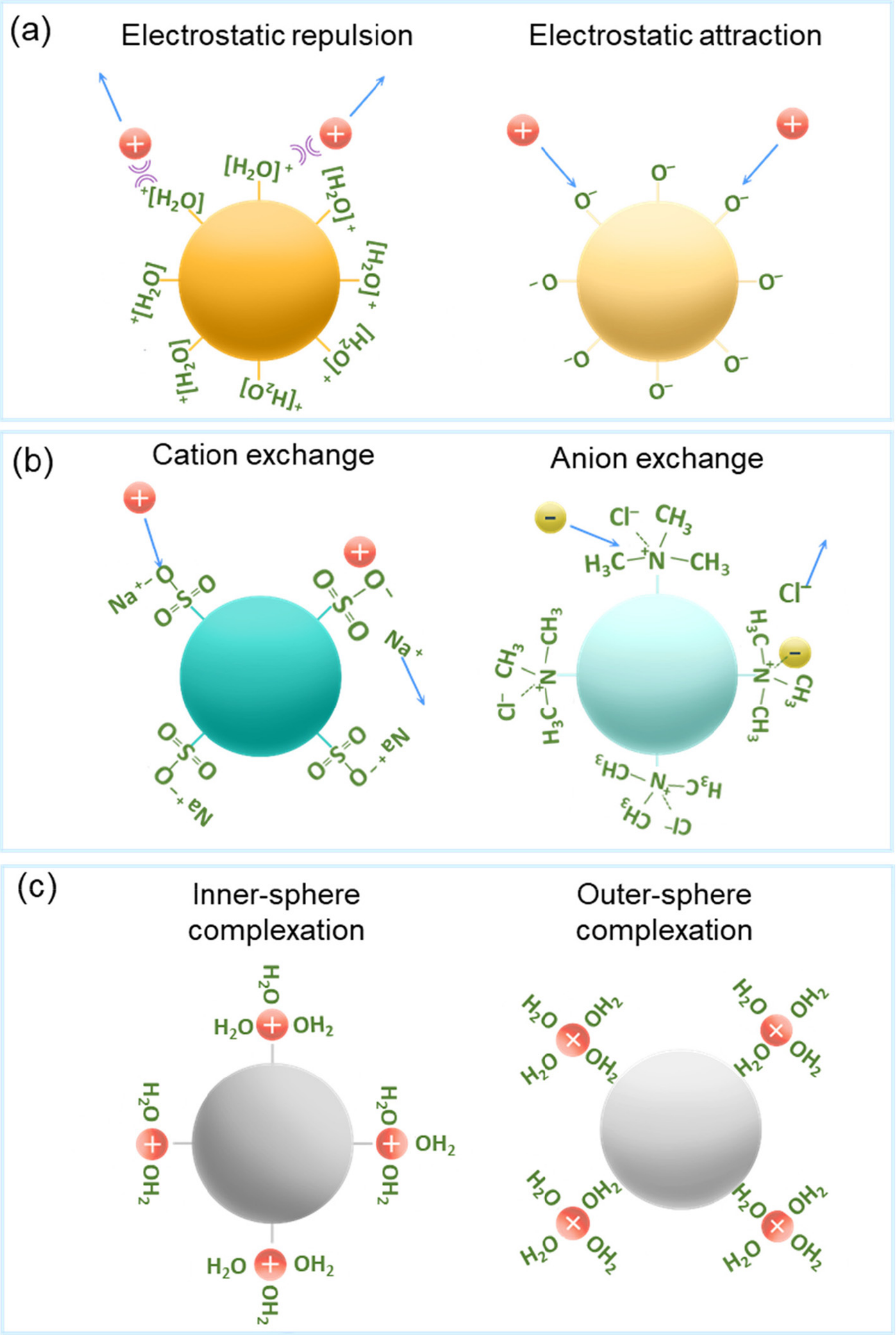

Fig. 7 Schematic diagrams of the adsorption mechanisms: electrostatic interaction (a), ion exchange (b), and surface complexation (c).

dation states, solubility, ionization, and forms of metal ions. Apart from the pH, other solution parameters, including the ionic strength, and the presence of co-existing ions that can complexate, play a major role in the type of interaction.[116]

Ion exchange is a process in which cations (or anions) in a solution replace dissimilar and displaceable ions of the same charge contained in a solid materials (Fig. 7b). During cation exchange, cations from the liquid can replace positively charged metal ions attached to the adsorbents.[105] Conversely, during anion exchange, anions from the liquid can replace negatively charged metal ions attached to the adsorbents. For a number of commercially available ion exchange resins, a selectivity series is available to indicate the affinity to converse from one ion form to the other. In cation exchange resins, sulfonic acid groups (strong acidity), phosphonic (medium acidity), and carboxylic (weak acidity) acid groups are the main functional groups.[39,47,107–110,112–114,117] Meanwhile, anion exchange resins utilize quaternary ammonium and amine groups to facilitate ion exchange.[38,111] For example, Ac^{3+} ions are adsorbed onto the cation exchange resin by cation exchange, while the Bi-halide complexes are adsorbed onto the anion exchange resins *via* the anion exchange.[26,38,111,118]

Surface complexation is a crucial adsorption mechanism involving inner- and outer-sphere complexation (Fig. 7c).[105,116,119] Inner-sphere complexation occurs when metal ions bind to specific active adsorption sites on a surface, owing to a strong bond between the adsorbing species and active adsorption sites.[105] In contrast, outer-sphere complexation occurs when adsorbing metal ions interact with active adsorption sites *via* water molecules. This interaction is highly sensitive to the ion strength, which can alter the inner and outer-sphere complexations.

The adsorption of metal ions which preferably interact by inner-sphere complexation, is less impacted by changes in the ionic strength.[116] This is in contrast to metals that predominantly interact by outer-sphere complexation, for which the adsorption decreases with increasing ionic strength, due to the increased competition with other ions that are present in solution.[116]

The contribution of the three main types of interaction in the total adsorption process will be dependent on numerous factors, including the pH, the ionic strength, the type of ions, and the introduction of competing or complexing ions and chelators.[39–41,69,107,120–125] The desorption mechanism is illustrated when introducing the previously used adsorbents for ^{225}Ac and ^{213}Bi separation.

4.3 Types of ^{225}Ac/^{213}Bi radionuclide generators

Understanding the separation process of ^{225}Ac/^{213}Bi radionuclide generators is crucial for selecting or designing the appropriate adsorbents to use in these generators. This knowledge enables researchers to optimize the efficiency and effectiveness of the separation process, thereby ensuring high purity (*e.g.*, the ^{225}Ac impurity less than 10^{-4}%) for the desired radionuclides and prolonging the lifespan of the generators. Fig. 8a presents several general requirements for radionuclide generators that can be used as a guide to evaluate the advantages and disadvantages of current ^{225}Ac/^{213}Bi radionuclide generators.[34] Various types of radionuclide generators have been examined for their efficacy in ^{225}Ac and ^{213}Bi separation.[28,48,100,120] The generator columns for the ^{225}Ac and ^{213}Bi separation can be typically classified into two types based on the method of operation and properties of the adsorbents: regular (direct) and inverse columns.[34,39,44,48] Considering the number of columns involved, the generator systems can be primarily classified into single-column and double-column systems. The second column is typically used to concentrate and further purify the ^{213}Bi eluate from the first column in order to fulfill radiopharmaceutical requirements.[49,107] In this review, the generator types (Fig. 8b) are divided into the following categories: (1) single-column direct ^{225}Ac/^{213}Bi generators; (2) two-column direct ^{225}Ac/^{213}Bi generators; (3) single-column inverse ^{225}Ac/^{213}Bi generators; (4) multicolumn selectivity inversion generators (MSIGs); and (5) millifluidics-controlled electrodeposition-based ^{225}Ac/^{213}Bi generators.[37,39,41–47,49,107,108,126–130]

4.3.1 Single-column direct ^{225}Ac/^{213}Bi generators. Direct radionuclide generators, which are the most popular generators for the separation of medical radionuclides, can simplify the separation process and shorten the separation time.[34,43] The adsorbents in a direct column should have a strong adsorption affinity for the mother isotope, while the daughter isotope can be selectively eluted at regular intervals using appropriate eluents, which must be devoid of the mother isotope. The separation process of the direct generator systems typically consists of the following several steps (Fig. 9a): (1) column preconditioning, (2) column rinsing, (3) ^{225}Ac/^{213}Bi stock solution loading, (4) elution of ^{213}Bi, and (5) column regeneration.[26]

Column preconditioning is an essential but easily overlooked step because it removals any impurities that can interfere with the separation process. During the preconditions, the adsorbent materials are activated in order to have an optimal performance in both ad- and desorption. This step is typically performed using solutions such as HCl (*e.g.* 1.5 M HCl for AG MP-50) and HNO_3 (*e.g.* 8 M HNO_3 for AG 50WX4).[41,45,120,131] Afterward, any excess acid attached to the column can be removed by rinsing the column to ensure that the adsorbent is within the appropriate pH range for optimal separation and to remove any impurities introduced during the preconditioning process.[45]

There are various methods for loading ^{225}Ac onto an adsorption column. The most straightforward method is to pass the ^{225}Ac stock solution through the column, allowing the ^{225}Ac to be adsorbed on the adsorbent (Fig. 9a). In case the adsorbent has a very high affinity, such as cation exchange resins with sulfonic acid groups, ^{225}Ac adsorption will predominantly occur at the top layer of the column. This localized adsorption might lead to severe radiolytic damage of the adsorbents.[48] For example, the AG MP-50 column can be irreversibly damaged within a few hours when more than 4 GBq of ^{225}Ac is loaded on the top layer of the sorbents, which was mainly due to the scission of sulfonic acid groups, discoloration, and the damage of polymer structures.[48,71] In an alternative loading method, about two-thirds of the adsorbent is removed from the column, mixed with the ^{225}Ac solution, and shaken for a period to ensure a more homogeneously spreading of ^{225}Ac on the adsorbent (Fig. 9b).[39] Thereafter, the column is filled with the adsorbent material onto which ^{225}Ac solution is more uniformly loaded. This method aims to lengthen the lifetime of the adsorbents by increasing the contact area between the radionuclides and sorbents. However, it can also lengthen the handling time of the radionuclides and probably increases the risk of personnel and the environment being exposed to radiation. Hence, a novel strategy is to distribute the ^{225}Ac throughout a large mass of adsorbents by reducing the sorption capacity for ^{225}Ac. This can be achieved by increasing the acid or salt concentrations of the ^{225}Ac stock solution (Fig. 9b).[69] Similarly, another method for dispersing ^{225}Ac across a large mass of adsorbents is to use a

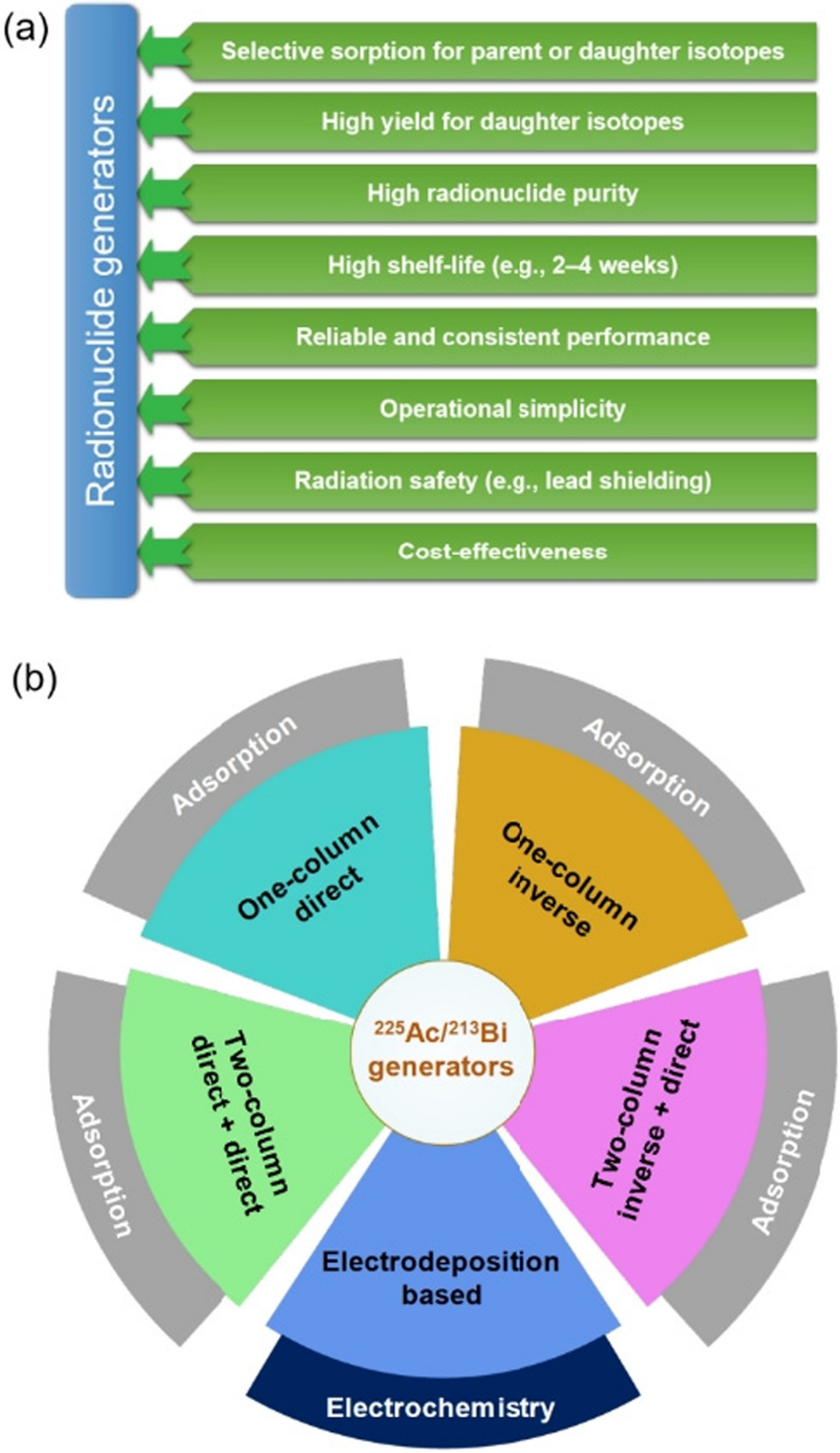

Fig. 8 Requirements of radionuclide generators (a) and the types of ^{225}Ac/^{213}Bi radionuclide generators (b).

high-acid solution to elute the column. For example, a 2 M HCl solution can be used to distribute ^{225}Ac throughout half of the AG MP-50 column.[107] Additionally, introducing ^{225}Ac surrogates, such as La^{3+}, is expected to reduce the sorption capacity of sorbents for ^{225}Ac because of the increased adsorption competition between La^{3+} and Ac^{3+} (Fig. 9b).

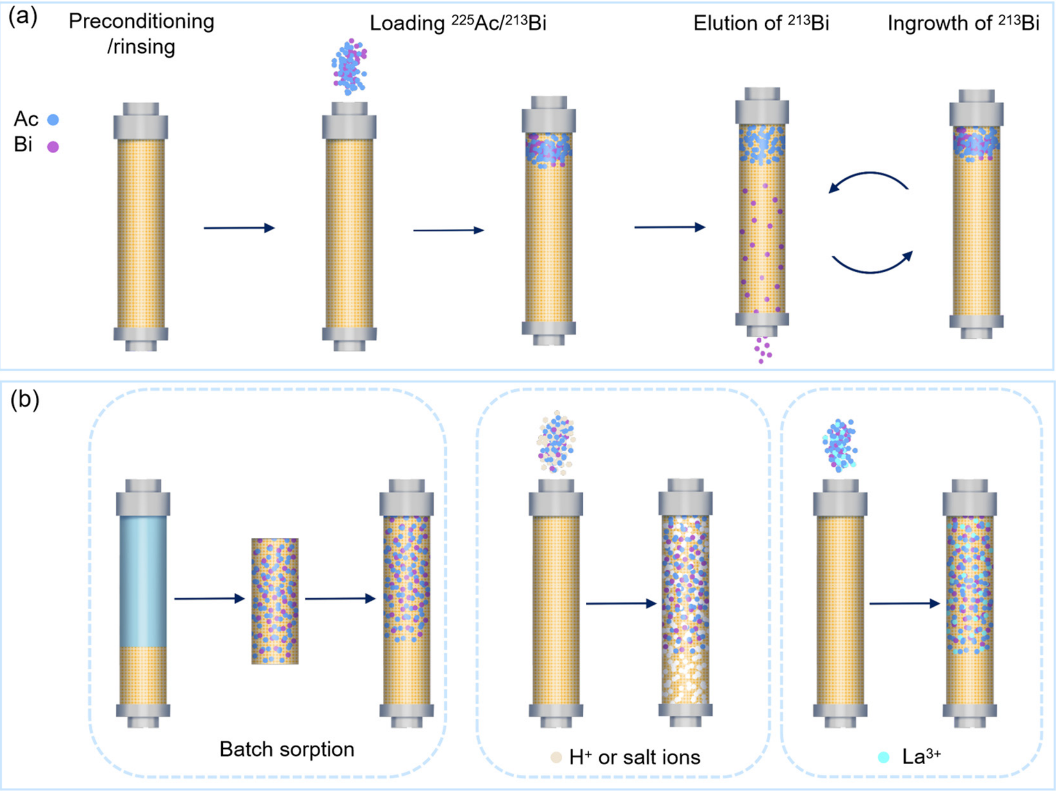

Fig. 9 Separation process of the direct generator system (a) and the loading process to distribute the ^{225}Ac in a large mass of sorbents (b) (La^{3+} acted as a competition ion for Ac^{3+} sorption).

The fourth step in the process is the selective desorption of ^{213}Bi. Therefore, a stripping solution is used to selectively desorb ^{213}Bi without desorbing the ^{225}Ac. As explained above, elution with halide ions is typically used to milk ^{213}Bi owing to the formation of ^{213}Bi-halide complexes.[43,120,121] Additionally, various chelating agents, such as diethylenetriamine pentaacetate (DTPA) and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), can be used to elute ^{213}Bi.[107]

However, the use of a single column in the separation process poses high requirements on the adsorbents with regard to their high affinity for ^{225}Ac and a low sorption capacity for ^{213}Bi complexes to ensure the production of ^{213}Bi with a high yield and purity. As most of the adsorbents are prone to radiolytic damage, a safe and sustainable operation to obtain high-activity ^{213}Bi for medical applications is compromised.[48,109,132–134]

4.3.2 Two-column direct ^{225}Ac/^{213}Bi generators. A two-column direct ^{225}Ac/^{213}Bi generator system is used to increase the purity and concentration of ^{213}Bi eluates.[39,45,107,129] The separation process of the first column is similar to that of a single-column direct ^{225}Ac/^{213}Bi generator. The ^{213}Bi eluate from the first column is passed into the second column (Fig. 10a), also called the guard column or concentrated column, where the adsorbent has a higher affinity for ^{225}Ac than for ^{213}Bi-halide complexes. In such separation systems, the ^{213}Bi-halide complexes with low volume and suitable conditions for ^{225}Ac sorption onto the second column can be directly passed through the second column. However, when the volume of ^{213}Bi eluates from the first column is high (*e.g.*, >5 mL), both ^{213}Bi and ^{225}Ac need to be adapted for adsorption on the second column, and subsequently ^{213}Bi can be selectively eluted, which can further increase the ^{213}Bi concentration and purification.

Wu *et al.* designed a two-column direct ^{225}Ac/^{213}Bi generator (Fig. 10b) by employing the actinide resin (AC resin, silica gel impregnated with di-2-ethylhexyl-methane-bis-phosphonic acid) in the first column and MP-50 as the adsorbents in the second columns, respectively.[39] The first column was filled with AC resin and equilibrated with 0.5 M HNO_3. Two-thirds of the AC resin sorbed the ^{225}Ac in the 0.5 M HNO_3 solution for 30 min under gentle agitation at room temperature before packing it to the generator column. Thereafter, the AC resin was equilibrated with 1.0 M HCl. Moreover, 1.0 M HCl could eluate ^{213}Bi from the AC resin. The breakthrough of the ^{225}Ac for the first column was less than 0.05%. Subsequently, the ^{213}Bi eluate from the first column was diluted using water, and the ^{213}Bi was adsorbed onto the second column containing MP 50. Finally, the ^{213}Bi that adsorbed on MP-50 was eluted using 0.1 M HI. No ^{225}Ac was detected in the ^{213}Bi eluate after the MP-50 column.[39]

Recently, a new type of two-column direct ^{225}Ac/^{213}Bi generator was developed at the Institute for Nuclear Research of

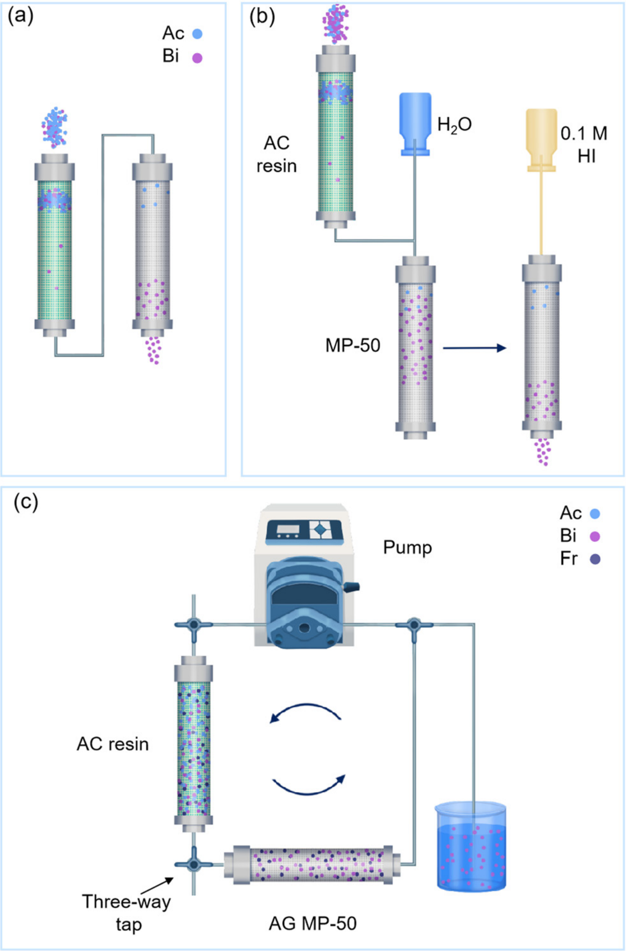

Fig. 10 Separation process of two-column direct ^{225}Ac/^{213}Bi generator, highlighting the functions of second column in further purification (a), both purification and concentration (b), and purification (automatic) (c).

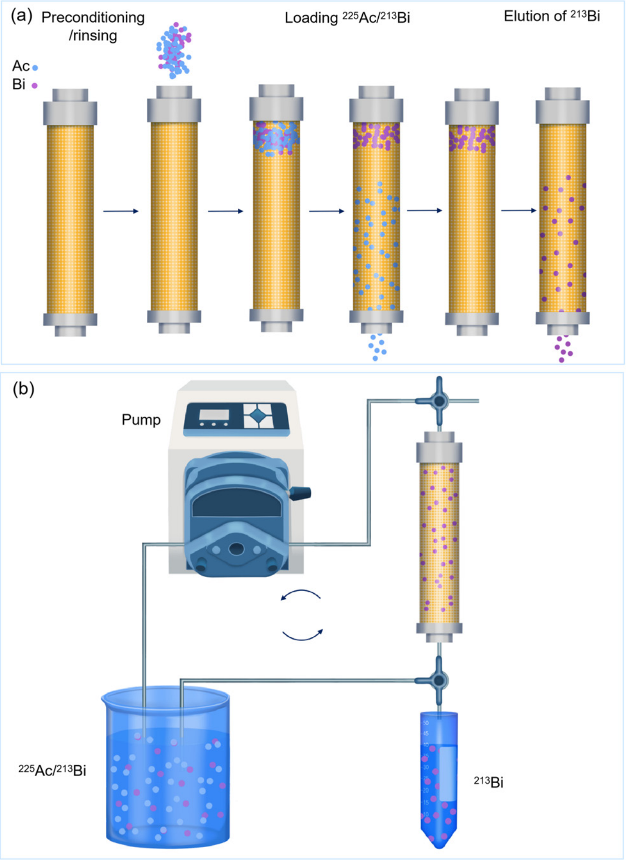

Fig. 11 Simple separation process of the inverse ^{225}Ac/^{213}Bi generator (a) and an automatic separation scheme (b).

the Russian Academy of Sciences (INR RAS) (Fig. 10c).[107,129] The parent ^{225}Ac is adsorbed onto the first column containing AC resin, while the ^{221}Fr can be selectively and continuously washed with HNO_3 and NH_4Cl, which can be called a ^{225}Ac/^{221}Fr generator. Next, ^{221}Fr is adsorbed onto the second column using the AG MP-50 resin and decays to ^{213}Bi. After a certain period, ^{213}Bi can be milked from the second column by using 0.1 M HCl/0.1 M KI, DOTA or DTPA.

Two-column generator aims to ensure the high purity and concentration of ^{213}Bi. The requirements for the sorbents used in the first column are less strict in terms of ^{225}Ac breakthrough. In other words, the ^{213}Bi purity from the first column may not satisfy the requirements in medical applications, but adsorbents must operate for a long time when loading high-activity ^{225}Ac. The AG MP-50 and AC resins are well-known materials used in the second column because of their high affinity for ^{225}Ac, which can improve the purity of ^{213}Bi. It should be noted that the two-column direct ^{225}Ac/^{213}Bi generator is slightly more complex than the single-column direct ^{225}Ac/^{213}Bi generator. However, this generator remains useful in cases where an ideal sorbent for a single-column direct ^{225}Ac/^{213}Bi generator is unavailable.

4.3.3 Single-column inverse ^{225}Ac/^{213}Bi generators. Another approach to achieve selectivity is the inverse generator, where the sorbent must have a high affinity towards Bi^{3+}/Bi-complexes over ^{225}Ac.[38,40,44] Inverse generator systems typically comprise the following steps (Fig. 11a): (1) preconditioning the column, (2) rinsing the column, (3) loading the ^{225}Ac/^{213}Bi stock solution, (4) stocking ^{225}Ac in a vial, (5) eluting ^{213}Bi, and (6) regenerating the column. During the ^{225}Ac/^{213}Bi loading step, ^{213}Bi can be selectively adsorbed onto the column when the ^{225}Ac/^{213}Bi stock solution passes through the column, but no ^{225}Ac is adsorbed onto the sorbent (ideal condition). Subsequently, the ^{213}Bi can be eluted with various elutes, such as HNO_3, NaOAc, HCl, halide ions, and DTPA.[38,40] Typically, this generator produces a higher ^{213}Bi yield in a smaller eluate volume than direct generators. However, compared to direct generators, ^{213}Bi eluates from inverse generators usually have a higher ^{225}Ac impurity because of the small amount of ^{225}Ac adsorbed onto the column.[38,40,44,48] It is challenging to find a suitable sorbent for the inverse generators to produce ^{213}Bi with a high purity that is suitable for radiopharmaceuticals. However, the sorbents used in inverse generators receive a relatively lower radiation dose than those used in direct generators. This is because stocking ^{225}Ac in a vial shortens the contact time between the sorbents and the radionuclides. One example of an inverse generator is the Bi-generator from the Pacific Northwest National Laboratory (PNNL), which uses organic anion-absorbing resins incorporated into a cartridge.[38] This generator also possibly provides additional ^{213}Bi purification to avoid the influence of ^{225}Ra, ^{221}Fr, ^{229}Th, and ^{227}Ac. One drawback of the inverse generators is the more complex separation process and the longer time for handling and manipulating radionuclides. This can be overcome to some extent by implementing automation in the separation equipment.[38] Vasiliev *et al.* reported an automatic separation scheme (Fig. 11b) that can minimize the irradiation exposure for the personnel handling radionuclides.[44] Analogous to the some direct generators, a second column (guard column) is required for the further purification of the ^{213}Bi eluate to satisfy the radiochemical requirements.[49]

4.3.4 Multicolumn selectivity inversion generators. The multicolumn selectivity inversion generators (MSIGs) system typically comprises a primary separation column and a guard column (Fig. 12a).[49,75,135–137] The primary separation column also refers to an inverse column with a strong affinity for ^{213}Bi or ^{213}Bi-halide complexes and a weak/no adsorption affinity for ^{225}Ac. The guard column is usually used to improve the purity of ^{213}Bi originating from the primary separation column (inverse generator) while maintaining a minimal influence on the ^{213}Bi yield. Here, ^{213}Bi from the inverse generator can pass through the guard column, which adsorbs the possible ^{225}Ac impurity. Apart from the production of high-purity ^{213}Bi, this separation technique minimizes the irradiation of radionuclides onto the sorbents. Additionally, it is possible to selectively adsorb ^{213}Bi onto a small column, resulting in a high ^{213}Bi concentration. Generally, the AG MP-50 and its analogs with a low radiation stability can be utilized as the guard column owing to the decreased irradiation time.[49] The UTEVA-AG MP-50 generator is a representative MSIG used for the ^{225}Ac/^{213}Bi separation.[49] The UTEVA resin used in the primary separation column has a high affinity for ^{213}Bi–chloride complexes while exhibiting a low affinity for ^{225}Ac. Subsequently, the ^{213}Bi eluate is passed through the AG MP-50 column to improve its purity. At INR RAS, an automatic MSIG was developed by employing inorganic materials in the primary column, as shown in Fig. 12b.[75] The commercial MSIG system has been approved by the US Food and Drug Administration for use in the ^{99m}Tc generator in NorthStar.[138]

4.3.5 Millifluidics-controlled electrodeposition-based ^{225}Ac/^{213}Bi generators. The different generators described above are all based on adsorption. Alternatively, electrochemistry is also a useful separation technology. This new type of radionuclide generator can selectively separate the target isotope onto an electrode owing to the electroplating mechanism.[34,46] Following that, recovery of the target isotope from this electrode can be achieved by applying an external potential. The radionuclide deposited on the metal substrate can show high radiolytic stability. Fig. 13 shows a schematic diagram of the electrochemical radionuclide generator.[139] Recently, researchers at the Los Alamos National Laboratory (Los Alamos, United States) developed a millifluidics-controlled electrodeposition-based ^{225}Ac/^{213}Bi generator using nickel and titanium electrodes.[46] After 15 min reaction duration, 70%–98% of ^{213}Bi was deposited on the nickel plates. By applying an outside potential (2.0 V for 10 min at pH 4.0–5.5), 60%–94% of ^{213}Bi (Bi/Bi^{3+}, +0.317 *vs.* SHE) could be recovered.[140] This new generator exhibits high durability and reliability, which are necessary for separating high-activity ^{225}Ac and ^{213}Bi radionuclides. However, such generators may have limitations. The separation process requires electrochemical and radiochemical skills. Additionally, strict adher-

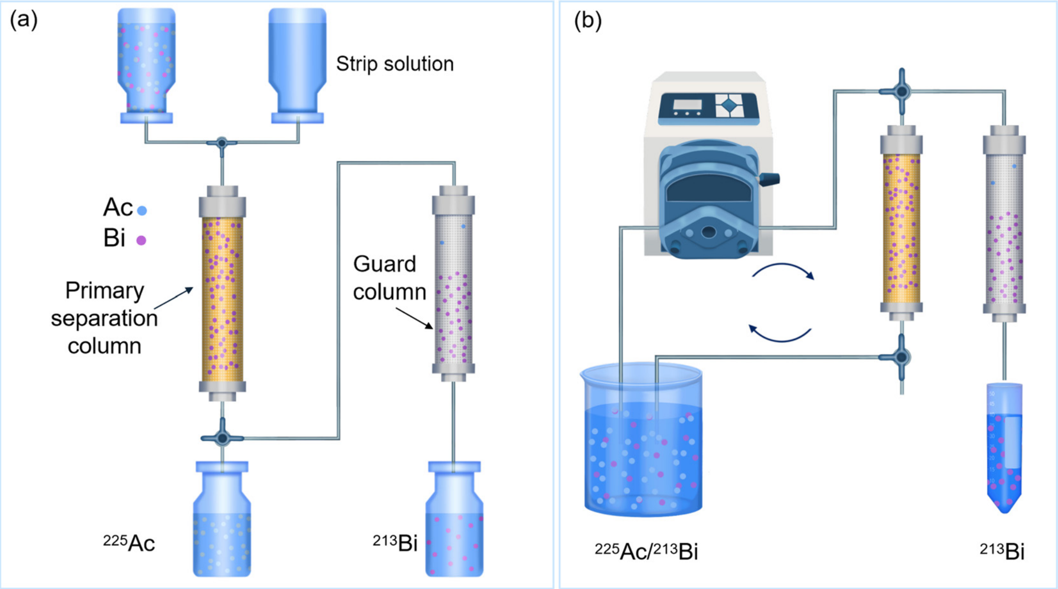

Fig. 12 Simple separation process of MSIG (a) and an automatic separation scheme (b).

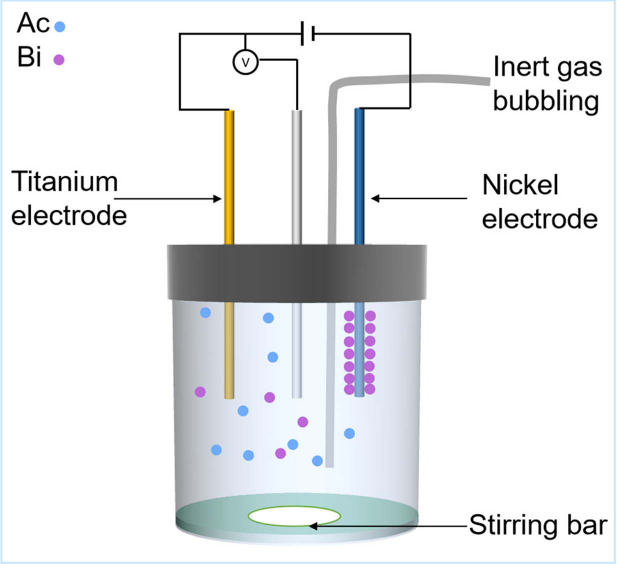

Fig. 13 Schematic diagram of the electrochemical radionuclide generator setup.

ence to operating procedures (*e.g.*, concentration of reactants or electrolytes, voltage and current, temperature, impurities, electrode surface, pH levels, and mass transfer) is essential because of the sensitivity of the electrochemical process.[34] Further optimization of the process and the related set up will be required to assess the potential of this approach as radiopharmaceutical generators.

4.4. ^{213}Bi elution

The conditions for the ^{213}Bi elution are determined by the nature of the adsorbent materials, but also by the ^{213}Bi labeling conditions. Table 1 provides an overview of conditions for ^{213}Bi eluates and their corresponding labeling conditions from previous research.[39–41,69,107,120–125] While the elution occurs at acid pH (pH < 2), labeling is performed at higher pH values (pH 4.0–8.4). To bridge this pH gap, a buffer solution (often citrate or acetate) is added, providing the additional benefit of preventing ^{213}Bi hydrolysis due to weak complexation.[1,37] In case I^- ions to eluate ^{213}Bi, demetallized L-ascorbic acid is added to decolorize the eluate.[41] The labeling process generally lasts about 1–10 min. Considering the short half-life of ^{213}Bi, achieving a high ^{213}Bi yield in the eluate is crucial and should be a requirement for ^{225}Ac/^{213}Bi radionuclide generators. Adjusting the pH values enables elution with a high-acidic concentration, such as 2 M HCl, to be suitable for the labeling conditions. The influence of salt concentrations on ^{213}Bi labeling may be minimal. Chelators are also used as eluents to elute ^{213}Bi from the radionuclide generators. This is believed to reduce the loss of ^{213}Bi during the labeling process.[107] However, it should be carefully examined whether other chelators can form selective complexes with ^{213}Bi rather than ^{225}Ac. The ^{213}Bi eluates shown in Table 1 can be adjusted to a standard labeling condition from the previous research. Therefore, the choice of such or similar elution is expected to have a minimal effect on the labeling process.[39–41,69,107,120–125]

5. Sorbents

Various adsorbents have been explored for use in the ^{225}Ac/^{213}Bi radionuclide generators. These adsorbents have been categorized into six types in this review. Before explaining in more detail these classes, a short section will be devoted to explain in general the different types of adsorption mechanisms.

5.1 Cation exchange sorbents with sulfonic acid groups

Cation exchange resins with sulfonic acid groups (Fig. 14a) are the commonly used adsorbents in direct ^{225}Ac/^{213}Bi genera-

Table 1 A representative summary of the ^{213}Bi eluates and their corresponding labeling conditions

	Labelling conditions		
^{213}Bi elution	Chelators/molecules	Standard labelling conditions	Ref.
0.1 M HCl/0.1 M NaI	CHX-A-DTPA-HuM195	~0.23 M NH_4OAc, pH 4–5, RT, 10 min	41
	CHX-A″-DTPA-chelated anti-EGFR-mAb	0.4 M NH_4OAc, pH 5.5, RT, 7 min	69 and 122
	DOTATATE	0.15 M Tris buffer, 2.6 mM ascorbic acid, pH 8.4, 95 °C, 5 min	123
0.1 M HI	Anti-Tac-CHX-A-DTPA	NH_4OAc, pH 5.0–5.5, RT, 6 min	39
	CHX-A″-DTPA conjugated scFv or diabody	NH_4OAc, pH 5.0, RT, 10 min	124
0.5 M HCl	BSA-DOTA	Saturated Na_2CO_3 solution, pH 5.5–7, RT, 10 min	121
1 HCl	Picolinate containing acyclic ligand	Phosphate-buffered saline (PBS, $c(PO_4^{3-})$ = 0.01 M) and morpholino ethane sulfonic acid, pH 5.5–6.5, RT, 1–2 min	120
	Picolinate containing macrocyclic ligand		
2 M HCl	2D11-DTPA	0.1 M citrate buffer, pH 5.5, RT, 15 min	125
	MOPC-DTPA		
0.05 M NH_4OAc (pH 4.4)	Cyclohexyl-DTPA-derivatives	RT, 10 min	40
DTPA, acetate buffer, pH 2–5.3, RT	—	—	107

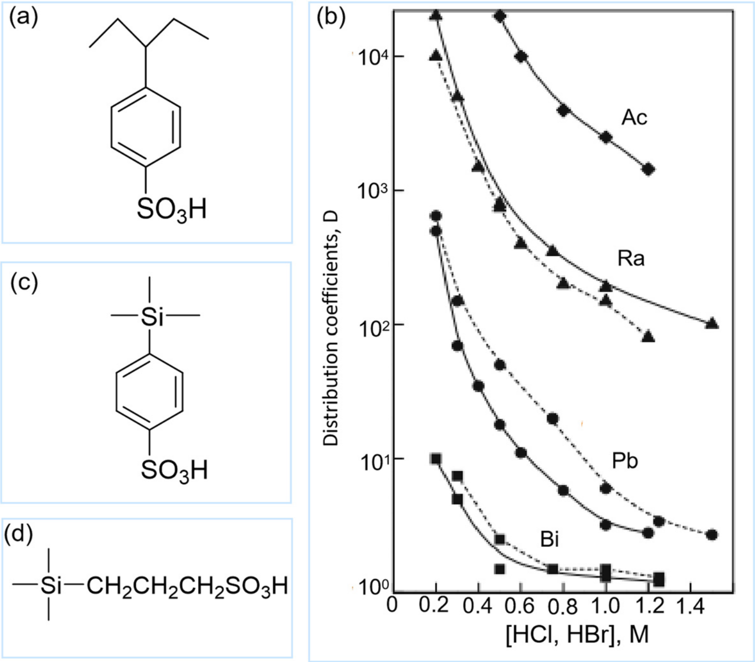

Fig. 14 Schematic structure of cation exchange resin (a); distributing coefficients of Dowex 50-X8 as a function of HCl (dashed lines) and HBr (solid lines) concentrations (b) (reproduced (adapted) from ref. 126 with permission from Springer Nature, copyright 2010); and schematic structures of Isolute SCX (c) and SCX-2 (d).

tors, due to the strong affinity of the sulfonic acid groups towards ^{225}Ac and a weak affinity for ^{213}Bi complexes, such as Bi-halide and Bi-DTPA complexes.[39,107,110,126] The adsorption mechanisms can be attributed to a combination of electrostatic attractions between the negatively charged sulfonic acid groups and the positively charged of ^{225}Ac species, and *via* the ion exchange between ^{225}Ac and hydrogen or salt ions (*e.g.*, Na^+) attached to the sulfonic acid groups. These resins typically comprise sulfonic acid groups bonded to styrene-divinylbenzene copolymer backbone, such as, AG 50X4 (4% cross-linkages),[131] AG 50X8 (8% cross-linkages),[127] Dowex 50W-X8 (8% cross-linkages),[26] and AG MP-50 (macroporous).[41] The crosslinking degree of the resin determines the rigidity and pore size of the resin bead. A resin with a lower cross-linkage (2%–8%) has a more open structure permeable to higher molecular weight substances than a highly cross-linked, and more rigid resin (8%–16%). It also has a lower physical resistance to shrinking and swelling, so that it absorbs more water and swells to a larger wet diameter than a highly cross-linked resin of equivalent dry diameter. Other important characteristics of the resin are the porosity and bead size, which will have an impact on the kinetics of the sorption process. In dry conditions, the resin matrix is compact. When contacted with water, the channels and the pores of the resin will be filled with water, and the beads will swell. Macroporous resins, with additional pore sizes (mesoporous) in the range of 100 nm, offer transport channels that will facilitate the transport and fasten the gel diffusion. Another consideration to take into account when selecting a resin material, if its resistance towards irradiation. High crosslinking degrees typically have a better stability towards radiation.[36,48,134]

Dowex 50W-X8, a spherical-shaped strong cation exchange resin used in direct generators, has been reported by Samad *et al.* and Geerlings *et al.*[26,118] In these studies, ^{225}Ac (in a 1 M HNO_3 or 2 M HCl solution) was adsorbed onto the Dowex 50W-X8 column, while ^{213}Bi was eluted as $BiCi_4^-$ or $Bi_2Cl_8^{2-}$ by using a 0.5–2 M HCl solution as the eluent.[26,118] However, they did not provide any information regarding the yield and purity of ^{213}Bi. Guseva and Dogadkin used the same column materials and showed a large difference in adsorption capacity between Ac^{3+} and Bi^{3+} (in 0.25 M HCl), due to the formation of Bi-halide complexes (Fig. 14b).[126] HBr and HCl (1–2 mL of 0.25–0.3 M) were used as eluates, resulting in a ^{213}Bi yield of over 90%.[126] The ^{213}Bi yield could be further maximized to 95% by using 1 mL of 10^{-3}–10^{-2} DTPA at pH 1.8–2.2.[126] Moore *et al.* reported that the ^{213}Bi yield achieved using AG-50X8 column could reach 85% ± 6% by using 0.1 M KI/HCl as the eluent, with a ^{225}Ac breakthrough of 0.01% ± 0.02%.[127] A resin with lower crosslinking degree (AG 50X4) was investigated by Boll *et al.*[131] ^{225}Ac adsorption was performed in 1 M HNO_3 stock solution, while desorption was performed in a 0.15 M HI, leading to ^{213}Bi yield between 91%–98% with an ^{225}Ac to ^{213}Bi ratio of 10^{-5}–10^{-4} and a ^{225}Ra to ^{213}Bi ratio of 10^{-3}.[36,100,131]

However, cross-linkages typically determine the radiation stability of cation exchange resins. The limited resistance of such resins to radiolysis hindered their applicability due to their relatively lower cross-linking degree. Macroporous AG

MP-50 is currently the most widely used resin, owing to its enhanced thermal stability and high radiation stability compared to similar resins.[48] In medical applications, an ^{225}Ac/^{213}Bi radionuclide generator should load high activity of ^{225}Ac (4 GBq). However, under this condition, columns that contain 200 mg of AG MP-50 cannot operate for more than one day.[48] Although the radiolytic stability of AG MP-50 is higher than that of its counterparts with a lower degree of cross-linking, it cannot separate ^{225}Ac/^{213}Bi contents sufficiently in terms of radiolytic stability for medical applications. This is because a high amount (*e.g.*, 4 GBq) of acidic ^{225}Ac solution is efficiently sorbed to a tiny layer at the top of the AG MP-50 resin.[48] Although the AG MP-50 resin provided a high yield (*e.g.*, 76%) and purity (*e.g.*, ^{225}Ac impurity less than 10^{-4}%) of ^{213}Bi, it failed to function after a few days when ~0.74 GBq (20 mCi) ^{225}Ac was sorbed on the resin.[39,48,100] Various approaches have been employed to reduce the impact of radiation on adsorbents.[41,141] Based on the unit of radiation dose (J kg^{-1}), increasing the mass of adsorbents for ^{225}Ac can decrease the absorbed dose.[41] McDevitt *et al.* introduced a technique to evenly distribute the ^{225}Ac over large parts of the AG MP-50.[41] An ^{225}Ac solution is first contacted with the AG MP-50 slurry for 30 min under gentle agitation to ensure uniform adsorption. Subsequently, the AG MP-50 slurry with ^{225}Ac is poured inside a column comprising a small amount of washed AG MP-50 which did not come into contact with ^{225}Ac and which can act as a catch plug to reduce the ^{225}Ac breakthrough during milking.[41] This technique reduces the radiation dose applied to AG MP-50 resin. The ^{225}Ac/^{213}Bi radionuclide generator, which has been developed by the Institute for Transuranium Elements (ITU), Karlsruhe, Germany, also employs this method and is capable of reliable operation when loaded with activities up to 4 GBq of ^{225}Ac.[25,28] The ^{213}Bi yield can reach 76% ± 3% in a 0.6 mL of 0.1 M NaI/0.1 M HCl solution with an ^{225}Ac breakthrough activity of less than 2×10^{-5}%.[37] Additionally, in a 4 M HNO_3 solution, the ^{225}Ac content can be distributed across approximately 60% of the resin. This distribution is ascribed to the competitive adsorption of the H^+ ions to the resin (due to the low pH), leading to a decrease of the ^{225}Ac adsorption capacity.[69] However, highly acidic solutions should be avoided as all of the ^{225}Ac from the cation exchange resins with sulfonic acid groups might be eluted; for example, 6 M HNO_3 and 8 M HNO_3 should be used for Dowex 50-X8 and AG MP-50, respectively.[141,142] An alternative strategy to obtain a more even distribution is the increase of the ionic strength by adding salts, as demonstrated by the decreased adsorption capacity of AG MP-50 towards La^{3+} (as a surrogate of Ac^{3+}).[47]

Cation exchange resins with sulfonic acid groups have also been employed in guard columns for further purification of the ^{213}Bi eluate, which can significantly reduce the radiolytic damage to such adsorbents owing to a limited contact time. As explained above, a system combining an AC resin column and an AG MP-50 column has been reported, aiming to further purify and concentrate ^{213}Bi.[39] Additionally, AG MP-50 resin can also be used in a ^{221}Fr/^{213}Bi generator. The ^{221}Fr content is eluted from the first column, such as the T-5 (100) column (explained below) and AC column.[45,107]

Apart from a polymeric backbone, also inorganic materials have been used as a matrix to graft sulfonic acids, mainly aiming to improve the irradiation stability. Moore *et al.* reported the use of Isolute SCX (benzenesulfonic acid bonded silica) and SCX-2 (propylsulfonic acid bonded silica) in direct ^{225}Ac/^{213}Bi radionuclide generators (Fig. 14c and d).[127] The Isolute SCX and SCX-2 resins are initially equilibrated with 1 M acetic acid. The ^{225}Ac content in a 0.1 M HNO_3 solution is adsorbed onto the Isolute SCX or SCX-2 resins, and then the resin with ^{225}Ac is packed to the generator column containing a 0.15 mL catch plug. The ^{213}Bi content is milked using 0.1 M KI/HCl for a 1-bed volume. The ^{213}Bi yield reached 67% ± 9% and 72% ± 1% when using the SCX-2 column and SCX column, respectively.[127] Compared to the reference AG-50 X8 column with a yield of 85% ± 6%, the ^{213}Bi recovery from Isolute SCX and SCX-2 is relatively lower. However, the ^{225}Ac breakthrough from SCX-2 (0.002% ± 0.002%) and SCX (0.002% ± 0.002%) is relatively lower than AG-50 X8 (0.01% ± 0.02%). Additionally, these columns filled with Isolute SCX and SCX-2 might surfer less damage. However, compared to the AG MP-50 resin in the ITU system, there is at least a hundred fold increase in the ^{225}Ac breakthrough of Isolute SCX and SCX-2.[37] Furthermore, the ^{213}Bi eluate from the Isolute SCX and SCX-2 must be purified using a guard column for medical applications, which can be achieved using a two-column direct ^{225}Ac/^{213}Bi generator.

Despite the promising sorption performance of such inorganic materials with grafted sulfonic acids, further research is required to have a good view on their potential in ^{225}Ac/^{213}Bi radionuclide generators. Although inorganic materials themselves are highly stable against radiolytic damage, the use of organic linkers (*e.g.*, benzenesulfonic acid and propylsulfonic acids) might lead to issues by irradiation. Also the leaching of the metal oxides at (very) low pH (*e.g.*, pH < 1) is a reason for caution.[143] One option to overcome the drawbacks mentioned, is to graft sulfonic acid groups directly onto an inorganic material surface without an organic linker. However, few synthesis strategies have been described so far, without a full investigation of their separation performance. Their separation performance should be investigated in detail as the chemical properties of such functional groups might be altered, thereby resulting in poor separation performance. Testa and Parola conducted a minireview on sulfonic acid-functionalized inorganic materials and provided detailed information regarding the grafting of sulfonic acid groups onto silica, titania, zirconia, and alumina.[144]

5.2 Extraction chromatographic resins

Extraction chromatographic resins comprise extractants that are dispersed in the pores of inert solid supports (*e.g.*, porous polymer and silica). The extractant is mainly responsible for selectively binding the target analyte(s) during chromatographic separation.[145,146] Such resins have been widely utilized for separating radioactive isotopes, such as actinides and

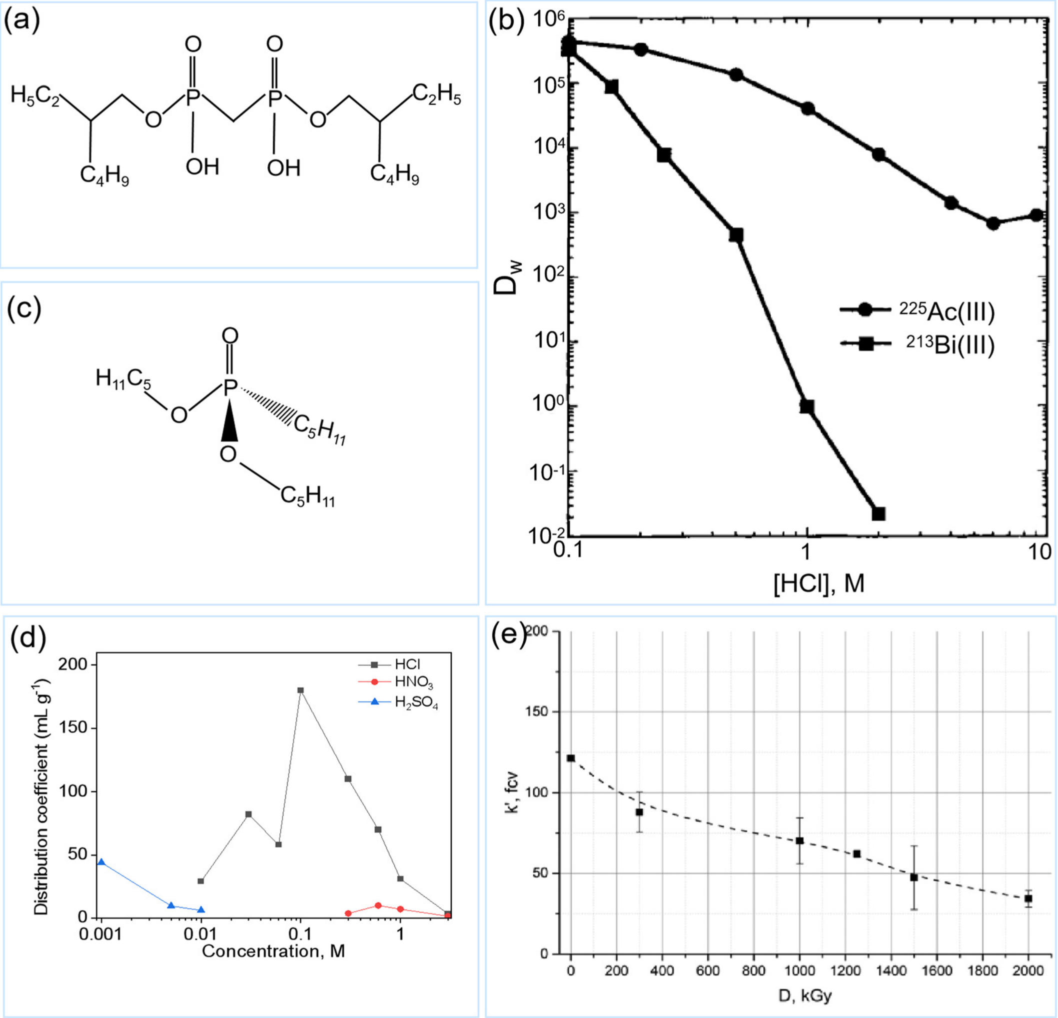

Fig. 15 Schematic structure of H_2DEH[MDP] (a); distributing coefficients of AC resin for $^{225}Ac^{3+}$ and $^{213}Bi^{3+}$ (b) (reproduced (adapted) from ref. 39 with permission from De Gruyter, copyright 1997); schematic structure of DAAP (c); adsorption capacity of ^{207}Bi onto UTEVA as a function of acid concentrations (data from the Tables 5–7 of ref. 150) (d) and adsorption capacity of ^{213}Bi onto UTEVA resin as a function of absorbed dose (e) (reproduced (adapted) from ref. 48 with permission from Taylor & Francis, copyright 2021).

lanthanides, owing to their high selectivity, excellent capacity, and easy handling.[107,120,145–147] Several commercial examples of extraction chromatographic resins include actinide, TRU, DGA, LN and UTEVA resins.[145]

Extracting agents with diphosphonic acid groups typically exhibit remarkable complexing properties towards actinide ions.[147] Actinide resin (AC resin), also referred to as DIPEX™ resin in literature, is an extraction chromatographic extraction resin based on P,P′-di(2-ethylhexyl)methanediphosphonic acid (H_2DEH[MDP]) (Fig. 15a) and an inert support.[39,107,120,148] Compared to the polymeric support, the extract impregnated into silica exhibited substantially low metal sorption kinetics and was more susceptible to radiolytic degradation in an aqueous solution.[149] Therefore, polymeric supports are preferred over silica for H_2DEH[MDP]. AC resin has been used in different separation systems.[39] Owing to its high affinity towards ^{225}Ac (as shown in Fig. 15b), the AC resin can be used in a single-column direct ^{225}Ac/^{213}Bi generator under a low ^{225}Ac activity.[120] In a small column (bead volume (BV) = 0.35), the ^{213}Bi yield can reach 85%, and the ^{225}Ac breakthrough is less than 0.0001% for the first 1.5 mL of eluate when using the 1 M HCl as the eluent. In a large column, at least 6 mL of 1 M HCl is needed to elute a high proportion of ^{213}Bi, which results in a low concentration of ^{213}Bi eluate.[120] This is why the second column with MP-50 has been typically used to concentrate ^{213}Bi.[39] Chen *et al.* reported that 0.32 mL of 2 M HCl can milk 90% of ^{213}Bi in a 0.35 mL column with DIPEX resins, whereas 1.2 mL of 1 M HCl can only milk 80% of ^{213}Bi.[130] However, the radiopurity of ^{213}Bi was not reported quantitatively. Although the ^{225}Ac breakthrough increased with a rise in HCl concentration, this can result in a higher ^{213}Bi concentration. Meanwhile, they also used an AC resin in a two-column direct ^{225}Ac/^{213}Bi generator or ^{225}Ac/^{221}Fr generator, as explained above.[39,129] However, if 200 mCi ^{225}Ac or more is used to fill the first two-thirds of a 1 mL AC resin column, the column cannot be operated for more than two days.[48] To reduce the radiolytic damage to the AC resins, a new separation technique was developed using an AC resin and AG MP-50 resin by distributing ^{225}Ac content over a large mass of the resins, as explained in the generator section.[39] However, another disadvantage is the relatively slow sorption kinetics; thus, batch sorption of high-activity of ^{225}Ac onto AC resins is necessitated before column chromatography to reduce the column volume.[120] Additionally, AC resins can also be used in guard columns to purify the ^{213}Bi eluate from the first inverse generator (such as Termoxide adsorbents, UTEVA, and surface-modified carbon columns). Horwitz *et al.* reported that DIPEX resin extractant loss remains below 4% for every 100 units of free column volume (FCV), in which about 60% of them occur during the initial rinsing when the FCY is 25 unites.[148] Although the extractant loss is expected to have little effect on the separation performance of resins if the working part does not exceed 20% of the total resin capacity, the interference of such extractants in the ^{213}Bi labeling process should be noted. The low radiation stability and leaching of extractants might hinder the applicability of these resins for the separation of high-activity ^{225}Ac and ^{213}Bi.[48,149]

The uranium and TEtraValent actinides (UTEVA) resin is formed by impregnating diamyl amylphosphonate (DAAP) (Fig. 15c) into a polymeric acrylic resin.[145] The Bi^{3+} adsorption on UTEVA resin is the function of nature and concentration of the acid in solution, as shown in Fig. 15d.[150] It can be seen that the Bi^{3+} in HCl media has a stronger adsorption affinity onto UTEVA resin than in HNO_3 and H_2SO_4 media. This increased adsorption is due to the formation of Bi-chloride complexes. Maximum K_d values for ^{213}Bi are obtained when a 0.1 M HCl feed comprising ^{225}Ac/^{213}Bi is passed through the UTEVA column, while no ^{225}Ac sorption is observed under these conditions.[49] Then, the ^{213}Bi is eluted using a NaCl/NaOAc buffer (pH = 4) with a ^{225}Ac impurity of less than 0.01%. Owing to the limited purification of the ^{213}Bi eluate from the UTEVA column, a guard column with AG MP-50 has been used for further purification of ^{213}Bi, with a ^{225}Ac impurity of less than $<10^{-7}$%.[49] However, UTEVA is highly sensitive to radiolytic damage. With an increase in the absorbed dose, the sorption performance for ^{213}Bi decreased quickly, as shown in Fig. 15e.[48] Even though such materials used in the inverse generators are expected to absorb relatively low radiation doses, the choice of high radiation stability materials is crucial in preventing the contamination that could arise from the degradation of the decomposed parts.

5.3 Zirconium-based materials with phosphate/phosphonate groups

Zirconium-based materials with phosphate ($-PO_4H$) and/or phosphonate ($-PO_3H$) groups exhibit high applicability to the direct ^{225}Ac/^{213}Bi generators.[108,109,112,113] Their general formula is as follows: $Zr(phosphonate)_x(HPO_4)_{2-x}\cdot nH_2O$, where x ranges between of 0–2; n is the number of water molecules; and the example of a phosphonate is the *N*-(phosphonomethyl)iminodiacetic acid.[112] Inorganic zirconium phosphate powders are typically dispersed into polymer matrices (*e.g.*, polyacrylonitrile (PAN)) to increase mechanical and chemical stabilities and avoid particle agglomeration. $Zr(HPO_4)_2$-PAN has been reported in a patent for use in ^{225}Ac/^{213}Bi generators.[109,112] The ^{225}Ac and ^{213}Bi can bind to the phosphate/phosphonate present on the adsorbent surface *via* electrostatic and coordination interactions, thereby leading to the formation of a stable complex. After adsorption, ^{213}Bi can be eluted by using the DTPA and NaI solutions.[109,112] The ^{213}Bi yield exceeds 80%, and the ^{225}Ac impurity remains below 0.01% when using the 0.01 M DTPA/0.005 M HNO_3 eluent. A further column filled with the same adsorbents can be used for further purification, which leads to an ^{225}Ac impurity of less than 0.0001%.[109] These promising preliminary results have sparked interest in zirconium-based adsorbent materials and their potential applications in ^{225}Ac/^{213}Bi radionuclides.[108] However, there is a lack of publications providing comprehensive information on the separation performance of these materials towards Ac^{3+} and Bi^{3+}. This knowledge gap poses a challenge for researchers and industry professionals to fully understand and optimize the use of such adsorbents in separation processes. Furthermore, investigating suitable eluents and their effect on ^{213}Bi yield is crucial.

5.4 Anion exchange resins

Anion exchange resins (*e.g.*, Anex, Dowex-1, and 3M anion exchange discs) have also been used to separate ^{225}Ac and ^{213}Bi in an inverse generator (also known as PNNL Bi-generator) *via* selective adsorption of ^{213}Bi instead of ^{225}Ac by using a suitable concentration of halide ions and hydrogen ions (*e.g.*, 0.25–1.0 M HCl).[38,111] Such anion exchange resins typically have quaternary amine (*e.g.*, $-CH_2N(CH_3)_3^+$ and $-CH_2CH_2N(CH_2CH_3)_3^+$) and amine (*e.g.*, $-NH_3^+$ and $-CH_2CH_2NH(CH_2CH_3)_2^+$) functional groups. The formation of negatively charged Bi chloro-complexed (*e.g.*, in 0.5 M HCl) enables the adsorption to the resin by electrostatic attraction, while other interfering cations such as rare earth, radium, francium, and actinium ions cannot be extracted.[40,111] The ^{213}Bi is typically eluted using a striping solution (*e.g.*, sodium acetate and DTPA) with high pH values (*e.g.*, pH = 4–4.5), and the ^{213}Bi yield can reach 85%–93%.[38,40,111] The ^{213}Bi eluate can be directly used for radiolabeling.[40] A PNNL automated generator with anion exchange resins has also been designed and evaluated.[38] For each operation, 2%–3% of ^{225}Ac is adsorbed onto the interstitial space. The activity ratio of ^{225}Ac to ^{213}Bi is about 0.07% in the ^{213}Bi eluate. This generator cannot detect other cation impurities except for Na^+ sourced from sodium acetate.[38] Regarding high ^{225}Ac impurity, ^{213}Bi eluate from the anion exchange resin must be further purified to meet the requirements of radiopharmaceutical applications.

5.5 Inorganic hydroxide sorbents

Inorganic hydroxide materials have attracted considerable attention for use in the separation of ^{225}Ac and ^{213}Bi, owing to their high radiation stability. Betenekov *et al.* and Vasiliev *et al.*

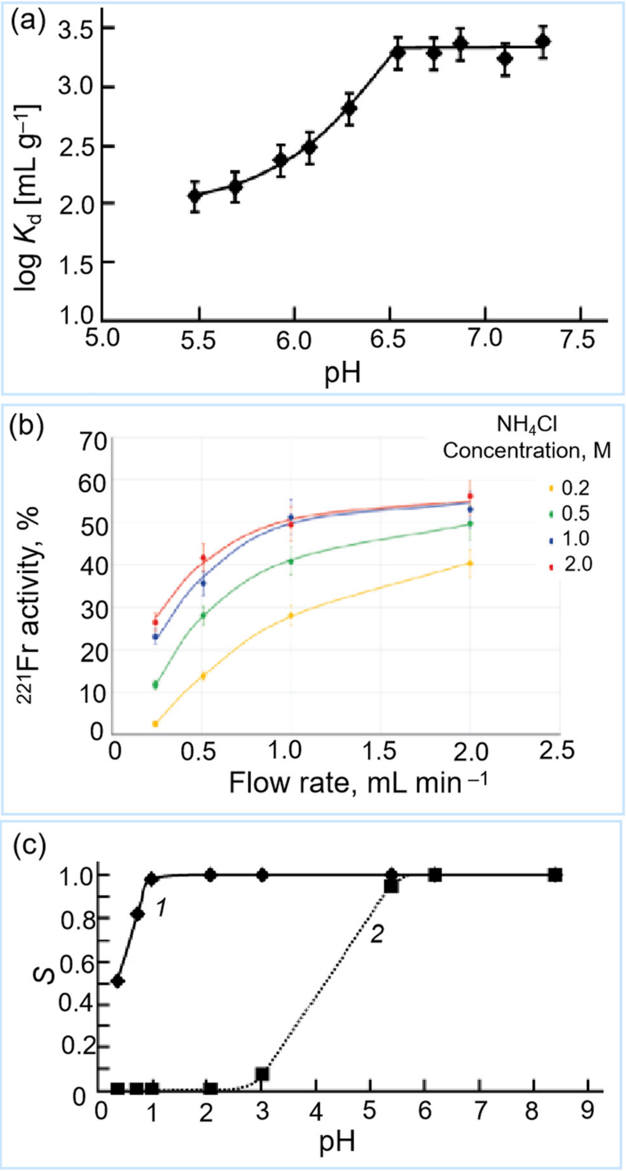

Fig. 16 Separation performance of T-5(450) for ^{225}Ac in aqueous with ~1 M NH_3/NH_4Cl buffer (a) (reproduced (adapted) from ref. 128 with permission from Springer Nature, copyright 2019); (b) the ^{221}Fr activity desorbed from the T-5(100) column as a function of flow rate of NH_4Cl (reproduced (adapted) from ref. 45 with permission from Springer Nature, copyright 2020); (c) ^{207}Bi sorption onto T-39(950) sorbent from (1) 0.1 M $NaNO_3$ and (2) 0.1 M NaCl +0.1 M KI (reproduced (adapted) from ref. 128 with permission from Springer Nature, copyright 2019).

investigated the performance of mixed oxides of titania/zirconia and zirconia/yttria annealed Termoxid-5 (T-5) and Termoxid-39 (T-39), respectively.[44,45,128] Here, T-5 has been used in a direct ^{225}Ac/^{221}Fr generators. The operational pH range for T-5 column is 5.5–7.3, which ensures the high affinity of adsorbents for ^{225}Ac (Fig. 16a), while 1 M NH_4Cl was used to elute about 50% of ^{221}Fr (Fig. 16b), implying that approximately 50% of ^{221}Fr decays into ^{213}Bi within the column, where it remains.[45] The ^{221}Fr was then be adsorbed onto the second column (^{221}Fr/^{213}Bi column) with ferrocyanide-based sorbents. Such as T-35 (hydrated zirconium oxide modified with nickel–potassium ferrocyanide).[45] The accumulated ^{213}Bi in the second column, which results from the decay of ^{221}Fr, was eluted using 1 M HCl. However, the ^{225}Ac impurity in the ^{213}Bi eluate is relatively high (~0.02%–0.11% of its initial activity).[45] Therefore, the authors recommend using a small guard column with AC resin for further purification of the ^{213}Bi eluate.[45]

T-39 cannot be employed as a sorbent in a direct ^{225}Ac/^{213}Bi generator due to the lack of suitable eluents. However, Betenekov *et al.* believed that the use of T-39 should exhibit better performance in an inverse ^{225}Ac/^{213}Bi generator owing to its selective adsorption performance for ^{213}Bi at low pH values (pH < ~2).[128] Further research has been conducted by the same group to enhance the understanding and performance of the materials and processes involved. Vasiliev *et al.* have tested the separation performance of T-39 for ^{225}Ac and ^{213}Bi by conducting batch and dynamic experiments.[44] The ^{213}Bi, in a 0.1 M HNO_3 solution, can be adsorbed on the T-39 (Fig. 16c), and then desorbed by 1 M HCl. Subsequently, they developed a new generator with a circulation mode system to regenerate the column for subsequent use. A high ^{213}Bi yield of 45%–98% can be obtained by increasing the adsorbent mass in the column. Additionally, 90% of ^{213}Bi can be eluted using 0.3 mL eluate in a 200 mg column. The ^{225}Ac impurity can be reduced to 0.01% by increasing the salt concentrations. Due to the low purity of ^{213}Bi in the eluate, a guard column was used to further purify the ^{213}Bi eluate from T-39 column.[75] These results demonstrated that T-39 has the potential for producing clinical ^{225}Ac quantities (up to 6 GBq) in an inverse ^{225}Ac/^{213}Bi generator, due to its high radiolytic stability and good sorption/desorption performance.[44] Although leaching does not have a profound impact on the ^{213}Bi yield, high leaching of Y and Zr under the acidic solutions (*e.g.*, 1 M HCl, 1 M HNO_3, and 0.1 M HNO_3) is of most concern, as it can contaminate the ^{213}Bi eluate.[44]

5.6 Surface-modified carbon materials

Carbon materials are becoming increasingly popular for their application in the separation of high-activity radionuclides, owing to their specific surface area, chemical stability, resistance to harsh conditions, thermal stability, tailorable surface chemistry, mechanical strength, and environmental friendliness.[151] However, carbon materials typically exhibit low sorption capacities because they comprise insufficient functional groups, which are decomposed under high pyrolysis temperatures. To address this limitation, the use of grafting and the addition of impregnated functional groups on the surface of carbon materials have been proposed as effective strategies.[151] Although direct grafting of appropriate functional groups on the carbon structures is an ideal strategy, interference from other functional groups must be considered.[117,152] Impregnating extractants into the porous carbon structures can produce one suitable active group; however, the leaching

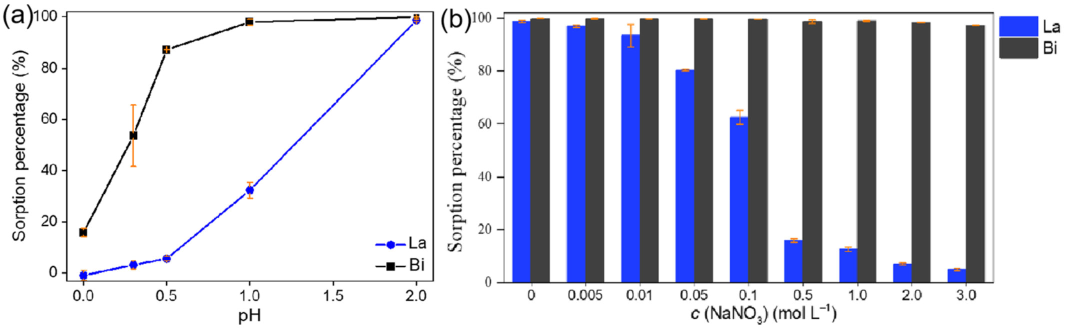

Fig. 17 Sorption percentage of surface-modified activated carbon for La^{3+} and Bi^{3+} as a function of pH (a) or $NaNO_3$ concentration (b).[47]

of the extractants from the carbon structures should be taken into account.[153]

Zhu *et al.* investigated surface-modified activated carbon materials for use in the separation of La^{3+} (which is certified as a surrogate for Ac^{3+}) and Bi^{3+}.[47] These materials with oxygen-containing groups can selectively adsorb Bi^{3+} rather than La^{3+}/Ac^{3+} by adjusting the adsorption conditions, such as pH (Fig. 17a) and salt concentration (Fig. 17b).[47] A preliminary column test shows that a 3 M HCl solution could be used to elute ^{213}Bi from the surface-modified carbon materials.[47] By adjusting the carbon structures, a 1 M HCl solution was used for ^{213}Bi eluting from the inverse generator using surface-modified carbon materials.[114] The ^{213}Bi yield can exceed 90% with a ^{225}Ac impurity of less than 0.04% in small volume (0.6–1 mL). Furthermore, AG MP-50 resin can be used in a guard column to purify ^{213}Bi eluate from this inverse generator.[114] Although it has been established that surface-modified carbon materials can be utilized in inverse ^{225}Ac/^{213}Bi radionuclide generators, they exist as irregular powders, which may limit their applicability in columns. Further efforts are still needed to optimize the morphology of carbon structures for separating ^{225}Ac and ^{213}Bi. Surface-modified carbon materials exhibit a high sorption affinity for La^{3+}/Ac^{3+} and Bi^{3+} ions at relatively high pH values, which allows them to satisfy the adsorption requirements in direct generators. However, choosing suitable eluents for the selective desorption of ^{213}Bi is a problem that has not been solved.[47]

Carbon structures can be used as supports for extractants to improve the irradiation stability compared to that achieved using polymeric supports. It should be noted that oxygen-containing groups are expected to be grafted onto the surface of carbon materials due to the high irradiation that results in the formation of free radicals under acidic conditions. The interference of such functional groups in the separation process should be examined. However, for the inverse generator, this issue seems to have a low impact on the ^{213}Bi separation. Extractions such as H_2DEH[MDP] and DAAP are expected to be impregnated into carbon structures for evaluating the separation performance of ^{225}Ac/^{213}Bi radionuclide generators.[49,147,148,153]

6. Discussion and outlook

Using ^{213}Bi for targeted alpha therapy is a promising approach for cancer treatment because of its appropriate physical and chemical properties. However, several existing limitations, such as the limited supply of its parent isotope ^{225}Ac and the development of appropriate adsorbents for ^{225}Ac/^{213}Bi radionuclide generators, must be overcome to widely use ^{213}Bi at the clinical level. The primary source of ^{225}Ac is the decay of ^{229}Th, which is isolated from the limited ^{233}U stockpile. However, the limited availability of ^{229}Th and ^{233}U hinders the application of ^{225}Ac and ^{213}Bi. As briefly discussed in this review, various other nuclear reactions have been explored and assessed to produce substantial amounts of ^{225}Ac in reactors, accelerators, and cyclotrons. Such methods offer the possibility

Table 2 The characteristics of the representative adsorbents in ^{225}Ac/^{213}Bi radionuclide generators[48]

Adsorbents	Generator type	Eluents	^{213}Bi yield (%)	Volume (mL)	^{225}Ac break-through (%)	Chemical/radiolytic stability	Ref.
AG MP-50	Direct	0.1 M NaI/0.1 M HCl	76 ± 3	0.6	$<2 \times 10^{-5}$	High/low	37
Ac resin	Direct	1 M HCl	85	1.5	$<10^{-4}$	Low/low	120
Isolute SCX-2	Direct	0.1 M KI/HCl	67 ± 9	—	<0.004	Low/medium	127
Isolute SCX	Direct	0.1 M KI/HCl	72 ± 1	—	<0.004	Low/medium	127
Ac resin + AG MP-50	Direct	1 M HCl/0.1 M HI	>85	—	—	Low/low	39
UTEVA resin + AG 50 W-X8	Inverse	0.75 M NaCl/0.5 M sodium acetate, pH = 4.0	87 ± 3	2	$<10^{-7}$	Low/low	49
Termoxide-39	Inverse	1 M HCl	80	0.5	<0.01	Low/high	44 and 48
Sulfonated carbon	Inverse	1 M HCl	94 ± 3	0.6–1	<0.04	High/high	114
An-exchanger	Inverse	Sodium acetate, pH 4–5.5	85–93	1	0.07	High/low	38

of supplying high amounts of ^{225}Ac and ^{213}Bi radionuclides in the near future.

This review highlights the need for continuous research and development in the separation of ^{213}Bi from ^{225}Ac by using the radionuclide generators. Different radionuclide generator systems, based on adsorption or electrochemistry, have been examined for the ^{213}Bi separation. Single-column direct ^{225}Ac/^{213}Bi generators should be the primary research objective because they are more convenient for hospital operators even though they have a strict set of requirements for the adsorbent materials. Table 2 illustrates representative sorbents that have been used or investigated in the ^{225}Ac/^{213}Bi radionuclide generators.[48] Different loading methods have been developed to distribute ^{225}Ac across a large mass of adsorbents in order to minimize radiation damage to the adsorbents. Although such techniques can increase the radiation stability of the adsorbents to some extent, they might impact the ^{213}Bi yield, concentration, and purity. A MSIG generator with automated equipment is also a promising technology for separating high-activity ^{213}Bi from ^{225}Ac, given the limited radiation stability of the current adsorbents used in direct generators. Adsorbents in inverse generators receive a reduced irradiation dose by allowing the ingrowth of ^{213}Bi to occur in the stored solution stored in a vial instead of on the adsorbents. Additionally, a guard column must be used to further purify the ^{213}Bi eluate from residual ^{225}Ac impurity. This process ensures that the obtained ^{213}Bi eluate meets the required chemical purity for the labeling procedure. Since radionuclide generators should produce a high ^{213}Bi eluate concentration, the ^{213}Bi eluate from the first column can occasionally be concentrated by the guard column. Typically, the adsorbents used in the direct generators are also employed in the guard column. The operation process of such generators should be further studied, and the equipment should be designed according to the number of manual interventions required by the operator, making it user-friendly. This review introduces almost all of the separation systems, which can be chosen based on the separation properties of the adsorbents.

Adsorbents are a crucial component of radionuclide generators. Therefore, in order to select the appropriate adsorbents, it is essential to thoroughly understand their separation properties for ^{225}Ac and ^{213}Bi. This can be achieved through batch adsorption experiments and column tests. Appropriate separation systems for ^{225}Ac and ^{213}Bi can be readily determined by considering the separation properties of adsorbents. If the adsorbents exhibit a stronger affinity for ^{225}Ac than for ^{213}Bi complexes, they can be employed in the direct column. The need for a guard column depends on the breakthrough of ^{225}Ac. Conversely, if ^{213}Bi is referentially adsorbed over ^{225}Ac, the adsorbent materials can be used in the inverse generator. A guard column is commonly used to enhance the purification of the ^{213}Bi eluate obtained from the inverse generator. However, there is insufficient data on the adsorption and desorption of the previously used adsorbents.

Previous studies have primarily focused on examining the sorption performance of Ac^{3+}/Bi^{3+} in relation to various acid concentrations. However, other important parameters for the adsorption performance, such as such as salt concentration, adsorption time, and halide ions, have been less studied. The impact of such factors on the adsorption process should be considered in order to provide comprehensive information on the separation mechanism. Typically, sulfonic and phosphonic acid groups exhibit a strong affinity for ^{225}Ac in highly acidic solutions, whereas the phosphate and carboxylic groups exhibit weak affinity, typically at pH levels below 2. Therefore, materials containing sulfonic and phosphonic acid groups are primarily used in direct and guard columns because they have a stronger adsorption affinity for ^{225}Ac than for Bi complexes. However, the interference of other functional groups should also be examined to ensure that they do not significantly affect the separation process. Phosphate groups may be a viable option for use in the direct generator because they are present in the structures of inorganic materials, zirconium hydrogen phosphate. However, halide ions do not appear to be ideal for ^{213}Bi elution due to the limited ^{213}Bi yield based on the batch experiments. Further studies are required to investigate the use of halide ions as eluents for eluting ^{213}Bi from materials that contain phosphate groups. Chelators, such as DTPA, are usually used to elute ^{213}Bi from the zirconium hydrogen phosphate. The possibility of other chelators preferentially forming complexes with ^{213}Bi over ^{225}Ac should also be considered and examined. Owing to the limited eluent options, it has been challenging to use materials that contain carboxylic groups in direct generators. Therefore, suitable alternative eluents for ^{213}Bi elution should be investigated to achieve ^{225}Ac/^{213}Bi separation in direct generators.

Anion functional groups can be used for the selective adsorption of ^{213}Bi over ^{225}Ac, making them suitable for inverse generators. Moreover, the materials containing cation exchange groups can also be used in inverse ^{225}Ac/^{213}Bi generators by adjusting the sorption conditions, such as pH and salt concentrations. However, it should be noted that the same functional groups usually exhibited slightly different properties in different structures. Thus, evaluating new alternative adsorbents at the laboratory level is necessary. Future studies should also thoroughly investigate the separation mechanisms of potential adsorbents.

Radiation stability is an important factor to consider when selecting adsorbents and separation systems. Typically, the radiolytic degradation of adsorbents has the following negative impacts: (1) it contaminates the ^{213}Bi elute owing to the decay of the adsorbent structures and functional groups; (2) it increases the ^{225}Ac breakthrough; (3) it decreases the ^{213}Bi yield owing to the alpha-recoil damage to the adsorbent structure; (4) it decreases the flow rates in the column owing to the formation of small fragments.[154] Such erratic performance can limit the applications of such materials. Adsorbents that cannot withstand prolonged radiation exposure are unsuitable for use in direct generators over extended periods (*e.g.*, 2–4 weeks) because of the radiolytic damage caused by ^{225}Ac (*e.g.*, 4 GBq) and its descendants on the adsorbents. However, such materials may be used in guard columns owing to the reduced irradiation time. Although the adsorbents used in inverse generators have relatively lower radiolytic stability requirements than those used in direct generators, it is still crucial to consider this aspect. Adsorbent material must remain radiation-resistant and stable throughout the process to prevent degradation or breakdown. Furthermore, the adsorbents may receive increased radiation doses in automatic systems due to prolonged cycling times. Therefore, it is imperative to aim for adsorbents with high radiation stability.

Future research should prioritize exploring and designing new sorbents with enhanced properties, in terms of sorption capacity, temperature, separation selectivity, radiation stability, and regeneration to address the limitations of previously used adsorbents. In addition, the interference radionuclides (*e.g.* ^{227}Ac) from the production of ^{225}Ac should be investigated during the separation process to obtain the high-purity ^{213}Bi. Also, the ^{225}Ac/^{213}Bi generator is a more complex system than it sounds as some descendants (*e.g.* ^{221}Fr) need to be taken into account when designing the separation system. Thus, investigating the separation performance of adsorbents for such descendants should be undertaken.

To identify the most suitable materials, it is essential to thoroughly understand the fundamental mechanisms that govern the separation process comprehensively. Collaboration between radiochemists, materials scientists, and medical professionals is critical for developing ^{225}Ac/^{213}Bi radionuclide generators and ensuring their safe and effective implementation in clinical practice. Ongoing research and collaborative efforts will lead to significant progress in this field, ultimately benefiting patients who require novel and effective therapeutic options.

Conflicts of interest

There are no conflicts to declare.

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