Pair selection of III - IV valence element radionuclides for novel generator types design

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The work relevance. In nuclear medicine, depending on their nuclear-physical properties, radionuclides are used for molecular imaging and therapy of oncological and cardiac diseases, etc.

Currently, III valence radionuclides are effectively and widely used in target radionuclide therapy and diagnostics, and primarily in theranostics (^{47}Sc/^{44}Sc, ^{90}Y/^{86}Y, ^{177}Lu/^{68}Ga, ^{225}Ac/^{68}Ga, etc.). A wide range of monovalent radionuclide nuclear-physical properties makes it possible to carry out and develop effective methods of diagnostics and therapy. These factors resulted in the development of a wide multiplied radiopharmaceutical (RPC) lines based on III valence elements (Me(III)–*DOTA–TOC/TATE/NOC*, Me(III)–*PSMA*, Me(III)–*DOTA–FAPI*, Me(III)–*DOTA–5G*, etc.). New effective production methods of almost any suitable III valence radionuclide immediately find a response as an available radiopharmaceutical based on it. On the one hand, this expands the set of the existing synthesis methods and the radiopharmaceutical application, on the other hand, it allows them to be optimized.

It should be emphasized that the radionuclide generators are a very effective production way of medical radionuclides due to the availability and high specific activity of the produced radiopharmaceuticals.

The degree of development of the topic. The choice of radionuclides in this study has made due to their active use in the concept of theranostics as diagnostic and therapeutic components (^{68}Ga, ^{86}Y, ^{90}Y, ^{225}Ac), as well as the need to develop their production methods.

There are a number of commercial generators ^{68}Ge→^{68}Ga, however problems remain with impermanence and a sufficiently large amount of breakthrough, as well as with activity scaling and disposal. In the case of the ^{90}Sr→^{90}Y generator, one of the main problems is the contamination of the radiochemical rooms and preparations with traces of strontium. Optimization implies the development of efficient generator schemes that are easy to operate and suitable for automation, providing a minimum number of dangerous stages (evaporation, other interfacial transformations, close contact of personnel with a radiopharmaceutical). Despite the low cost of the parent radionuclide, interest in the daughter ^{90}Y has recently been declining. In addition to the hardness of ^{90}Y beta radiation, this is due to high requirements for the safe efficient operation of the $^{90}Sr \rightarrow ^{90}Y$ generator. The use of modern approaches in therapy and diagnostics may reveal the potential of ^{90}Y. Especially considering its use in tandem with the diagnostic ^{86}Y. It should be emphasized that it is physically possible to implement the $^{86}Zr \rightarrow ^{86}Y$ generator, which has not been developed yet.

The development of production methods of ^{225}Ac both by the generators and the accelerator method is a "hot" actual topic, this is evidenced by a large number of publications published in recent years.

The development and operation of radionuclide generators ($^{68}Ge \rightarrow ^{68}Ga$, $^{86}Zr \rightarrow ^{86}Y$, $^{90}Sr \rightarrow ^{90}Y$, $^{229}Th \rightarrow ^{225}Ra \rightarrow ^{225}Ac$) as a source of medical radionuclides, as well as the isolation of target radionuclides from irradiated targets, requires studying the sorption behavior of pairs II – III, III – IV valence elements in suitable chemical systems.

The study aim is the development of production methods for medically significant III valence radionuclides from generators and from irradiated targets using the example of ^{68}Ga, ^{86}Y, ^{90}Y, and ^{225}Ac.

Based on the study aim, the following **study tasks** were set:

1. To select the pairs of genetically related radionuclides suitable for use in nuclear medicine;
2. To determine the distribution coefficients of Th(IV), Ge(IV), Zr(IV), Y(III), Ac(III), Sr(II) and Ra(II) in solutions of carboxylic acids on ion-exchange and extraction resins;
3. To develop the schemes of radionuclide generators $^{68}Ge \rightarrow ^{68}Ga$, $^{86}Zr \rightarrow ^{86}Y$, $^{90}Sr \rightarrow ^{90}Y$;

4. To develop the production and isolation methods of parent radionuclides for generators from irradiated targets Ge(IV) and Zr(IV);

5. To develop the production and isolation methods ^{225}Ac from irradiated thorium targets.

Scientific novelty.

1. A radionuclide generator $^{86}Zr \rightarrow ^{86}Y$ has been proposed. A production method of ^{86}Zr via the Y(p, 4n) reaction with protons in the energy range of 70–45 MeV has been developed.

2. A scheme of the $^{68}Ge \rightarrow ^{68}Ga$ radionuclide generator based on anion-exchange chromatography in an oxalate–hydrochloric medium with different elution modes: direct and reverse, has been proposed.

3. A chemical separation scheme of Ge(IV) isotopes from gallium targets irradiated with protons based on extraction from a liquid target with subsequent re-extraction in DGA Resin in a trichloroacetic acid medium has been developed.

4. A reverse scheme of the $^{90}Sr \rightarrow ^{90}Y$ radionuclide generator based on cation-exchange chromatography in an acetic acid-ammonium acetate medium has been proposed.

5. A dissolving method of thorium in complexing trichloroacetic acid for the purpose of chromatographic isolation of Ac(III) and Ra(II) on a cation exchanger has been developed. A scalable isolation method of Ac(III) and Ra(II) isotopes (the products of spallation reaction) from proton-irradiated thorium targets has been developed.

6. For the first time, the distribution coefficients of Ge(IV), Zr(IV) and Y(III) on cation exchanger Dowex 50×8 and anion exchanger Dowex 1×8 in mixtures of ethanedioic and hydrochloric acids; Zr(IV) and Y(III) on extraction chromatographic resin UTEVA Resin in ethanedioic acid solutions; Th(IV), Ac(III) and Ra(II), as well as Ac(III) and Ra(II) in the presence of thorium macroquantities on cation exchanger Dowex 50×8 in a trichloroacetic acid medium; Sr(II) and Y(III) on cation exchanger Dowex 50×8 and anion exchanger Dowex 1×8 in solutions of

acetic acid and a mixture of acetic acid and ammonium acetate have been determined.

Theoretical and practical significance of the work.

1. The developed radionuclide generators $^{68}Ge \rightarrow ^{68}Ga$, $^{86}Zr \rightarrow ^{86}Y$ and $^{90}Sr \rightarrow ^{90}Y$ make it possible to produce of medical radionuclides ^{68}Ga, ^{86}Y and ^{90}Y.
2. The developed isolation method of ^{225}Ac from thorium macroquantities makes it possible to increase its production through the use of massive targets, as well as the isolation of radium radioisotopes.
3. The results of evaluation of the II, III, and IV valence elements sorption behavior on the ion-exchange and extraction resins in carboxylic acid media can be used in the elements separation, as well as in evaluation of their chemical properties.

Defense provisions:

1. The sorption characteristics of Th(IV), Ge(IV), Zr(IV), Ac(III), Y(III), Ra(II), and Sr(II) on the ion-exchange and extraction resins in solutions of carboxylic acids.
2. The production methods of positron-emitting radionuclides ^{86}Y and ^{68}Ga via $^{86}Zr \rightarrow ^{86}Y$ and $^{68}Ge \rightarrow ^{68}Ga$ radionuclide generators? As well as parent radionuclides from irradiated targets.
3. The production methods of ^{90}Y via $^{90}Sr \rightarrow ^{90}Y$ radionuclide generator with the reverse scheme of elution.
4. The production methods of therapeutic radionuclide ^{225}Ac from thorium targets irradiated by protons with medium energy.