Radiation and chemical aspects of the stability of radiopharmaceutical precursors based on trivalent metals

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Relevance of the study. Nowadays radiometals are successfully used in nuclear medicine as components of modern radiopharmaceuticals (RPs). They find application in diagnostics – for instance, the γ-emitting ^{111}In for single-photon emission computed tomography (SPECT) and ^{68}Ga for positron emission tomography (PET); in therapy: alpha emitters (^{225}Ac, ^{213}Bi, ^{223}Ra, etc.), beta emitters (^{177}Lu, ^{90}Y, ^{161}Tb, etc.), and low-energy electron emitters (^{119}Sb, ^{135}La, ^{103}Pd); and in theranostics, which utilizes a combination of radionuclides for simultaneous diagnostics and therapy. Trivalent metals are ideal for designing theranostic pairs due to the high stability of the resulting complexes and their substitutability in such systems. Current study proposes production methods of several promising trivalent radiometals for RPs: ^{111}In for SPECT diagnostics, ^{44}Sc for PET diagnostics, and ^{135}La for Auger therapy.

Nuclear transformations accompanied by Auger cascades and/or the emission of converted electrons can lead to chemical and radiation consequences. This can lead to the release of the daughter from the complex contained in the RP. This phenomenon could be used to develop radionuclide generators, which are particularly valuable for separating nuclear isomers. Moreover, knowledge of these processes is necessary to evaluate the *in vivo* performance of generators, when both the parent and daughter radionuclides are involved in therapy and/or diagnostics. An important aspect of this study is the development of methods to evaluate chelate complexes of the RPs at ultra-micro concentrations in the nanosecond range using the perturbed angular correlation (PAC) technique.

The combination of developed methods for the production of radiometals for radiopharmaceuticals, their synthesis, and the analysis of their chemical and radiation stability is undoubtedly relevant.

The aim of this work is the development of methods for production of ^{111}In, ^{44}Sc, and ^{135}La from irradiated targets and evaluation of the influence of after-effects in the precursors of trivalent metal-based radiopharmaceuticals.

To achieve the aim the following problems have to be solved:

1. To develop methods for the production of a number of studied radionuclides (^{111}In, ^{44}Sc, and ^{135}La) with high specific activity and chemical purity.

2. To determine the stability constants of the ^{111}In[In]-DFO and ^{111}In[In]-DTPA, ^{111m}Cd[Cd]-DTPA, and ^{152,154}Eu[Eu]-DTPA complexes using the PAC and evaluate the influence of after-effects of radioactive decay on their stability.

3. To develop a ^{44m}Sc/^{44g}Sc radionuclide generator based on radiopharmaceutical precursors and evaluate the after-effects of radioactive decay via the yield of the daughter ^{44g}Sc[Sc^{3+}].

Scientific Novelty

1. ^{111}In was isolated from a natural antimony target irradiated with 600 MeV protons for the first time. Sb/In as well as Sb/Te separation schemes have been developed.

2. Direct-flow two-stage schemes have been developed for the first time to separate the promising Auger emitter ^{135}La and medical ^{44g}Sc from natural Ba and Ca targets, respectively, irradiated with 12.8 MeV protons.

3. A ^{44m}Sc/^{44g}Sc generator based on the after-effects of radioactive decay using [^{44m,g}Sc]Sc-DOTATOC radiopharmaceutical has been developed for the first time.

4. A protocol for measuring and processing PAC data for radiopharmaceutical precursors using ^{111}In, ^{111m}Cd, and ^{152,154}Eu has been developed.

The **theoretical and practical significance** of this work is as follows:

1. A scheme for the isolation of several radionuclides from an irradiated antimony target has been developed enabling the production of ^{111}In a radiopreparation used in diagnostics and nuclear physics studies, as well as ^{119m}Te for a ^{119m}Te/^{119}Sb generator to produce ^{119}Sb Auger emitter.

2. A scheme for the isolation of ^{44}Sc from an irradiated natural calcium target has been developed to enable a quick and cost-effective production of medical ^{44}Sc

for application in preclinical studies. The advantage of this scheme is that the medium of the final fraction (0.1 M NH_4-α-HIB) is suitable for subsequent radiolabeling.

3. A scheme for the isolation of ^{135}La from an irradiated barium target has been developed to enable the production of a therapeutic ^{135}La Auger emitter for preclinical studies.

4. The design of the ^{44m}Sc/^{44g}Sc radionuclide generator will enable the production of relatively short-lived medical ^{44g}Sc away from nuclear facilities.

5. The proposed parameter for processing PAC data demonstrates the effectiveness of this method for determining the stability constants of radiopharmaceutical precursors. It can be applied to study of new chelators.

6. Experimental data on the release of daughter nuclides from complexes as a result of the after-effects of radioactive decay over a wide range of element Z values demonstrate a new trend in the dependence of the formation of initial vacancies in the inner shell of an atom at low Z.

The provisions to be defended:

– Production method of ^{111}In from natural antimony targets irradiated with 600 MeV protons via spallation reaction using a three-stage radiochemical separation on ion-exchange resins;

– Production method of medical ^{44}Sc from natural calcium targets irradiated with 12.8 MeV protons;

– Production method of ^{135}La from barium targets irradiated with 12.8 MeV protons;

– Methodology for determining the stability constants of [^{111}In]In-DFO, [^{111}In]In-DTPA, [^{111m}Cd]Cd-DTPA, and [^{152,154}Eu]Eu-DTPA complexes and assessing the after-effects of radioactive decay in [^{111}In]In-DTPA and [^{152}Eu]Eu-DTPA complexes using PAC technique;

– The development of the ^{44m}Sc/^{44g}Sc radionuclide generator based on the after-effects of radioactive decay and assessment of the after-effects of radioactive decay in this pair.