Evaluation of modern radiopharmaceuticals' stability using nuclear spectrometric methods

The author list from the Experimental Department of Nuclear Spectroscopy and Radiochemistry of DLNP JINR:

D. V. Filosofov, E. S. Kurakina, A. I. Velichkov , D. V. Karaivanov, O. I. Kochetov, A. V. Salamatin, V. V. Timkin, J. Kh. Khushvaktov

The series of papers consists of four articles.

Metal complexes (Figure 1) are a key component in radiopharmaceuticals (RP), where they are used in the attachment of radionuclides to selective delivery systems for the treatment and/or diagnosis of tumors and metastases.

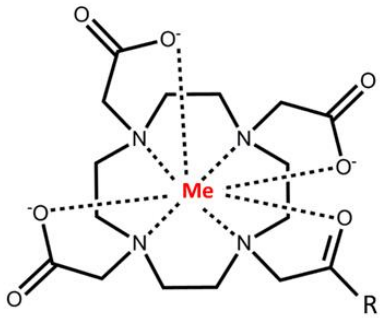
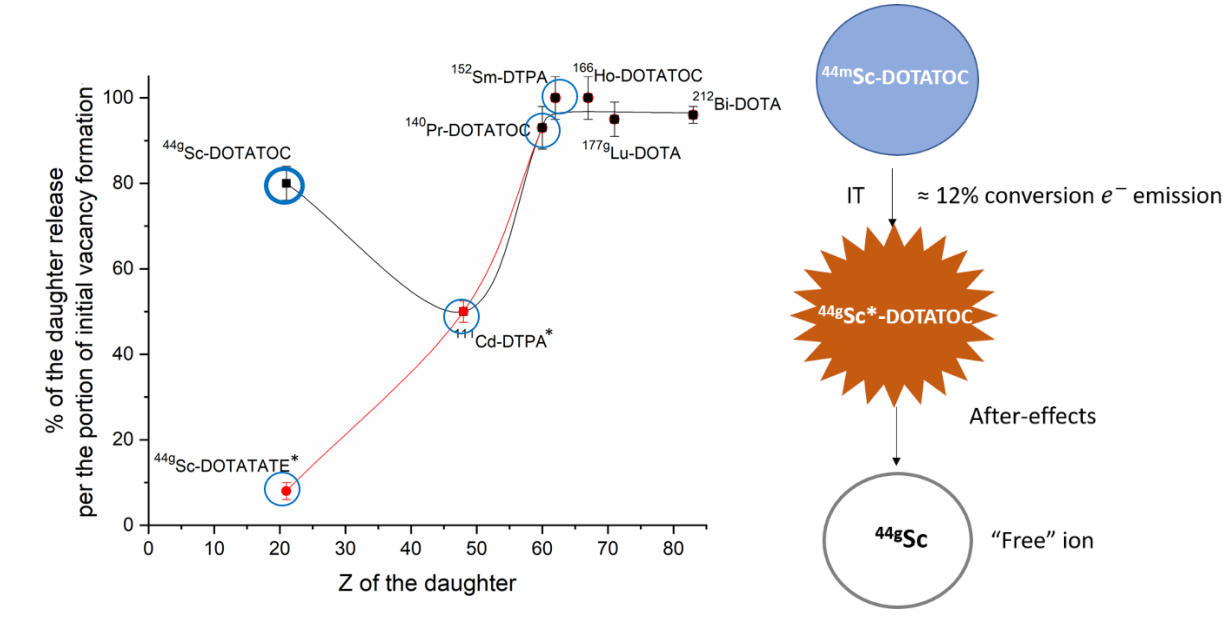


Figure 1. Metal complex with DOTA

The integrity of the radiopharmaceutical, and therefore the selective delivery to the tumor, may be compromised due to the subsequent effects of radioactive decay. Such effects are commonly called after-effects, the main mechanism of which is autoradiolysis. While after-effects can negatively affect radiopharmaceuticals based on in-vivo generators, they can also be leveraged as the basis for real in-situ radionuclide generators. Despite the attention given to such phenomena in review articles on related topics, unfortunately, experimental data are lacking. It should be noted that there exist barely any dynamic models based on detailed knowledge of autoradiolysis processes at the microscale (more precisely, the nanoscale) in the vicinity of radioactive decay for metal complexes, which occur over intervals on the order of 10^{-15} - 10^{-9} s. Usually, such processes are considered within the framework of radiolysis models.

Present studies were based on the study of metal complexes by perturbed angular correlations (γγ-PAC) and the method of radioactive tracers (in the latter case with macrocycles with very slow kinetics). Perturbed angular correlations (γγ-PAC) is a unique method in studying the behavior of complexes of a chelator and a radionuclide at ultramicroconcentrations (up to 10^{-12} M). ^{111}In and ^{111m}Cd, ^{152}Eu and ^{154}Eu pairs were measured using the PAC method.

The series of papers are the most clearly presented in Figure 2. It should be mentioned that in our results, in the case of the complexes ^{111m}Cd- DTPA (IT transition through γ-radiation) and ^{154}Eu-DTPA (β^--decay), the daughter nuclides do not leave the environment of the parent.



a) b)

Figure 2. A trend of the percent of the daughter radionuclide released (*per portion of initial vacancy formation) depending on the Z number of the daughter. Our data are circled in blue; the asterisk indicates data obtained by other authors that are in agreement with our data. In the figure, ^{111}Cd-DTPA corresponds to the case where the parent radionuclide is ^{111}In; b) - On the right, the mechanism of separation of nuclear isomers ^{44m}Sc/^{44g}Sc is shown

A number of works on the design of radionuclide generators of lanthanide pairs ^{140}Nd/^{140}Pr and isomers ^{44m}Sc/^{44g}Sc using the autoradiolysis mechanism are also presented. In both cases, it was possible to design radionuclide generators using DOTATOC as a chelator adsorbed on a Strata C-18E cartridge. It should be noted that ^{140}Pr and ^{44g}Sc can find application in nuclear medicine for positron emission tomography (PET), and are involved in preclinical studies.

Main conclusions:

- An efficient PAC spectrometer was assembled. For the first time, the PAC nuclear spectrometric method was used to determine the stability constants of metal complexes. The PAC method with ^{154}Eu and ^{111}In was shown to be a unique and sensitive tool in the nanosecond range for studying the dynamics of radiopharmaceuticals and autoradiolysis.
- For the first time, a ^{44m}Sc/^{44g}Sc generator was designed using modern radiopharmaceuticals. A yield of 80% of ^{44g}Sc per portion of conversion during the isomeric transition reveals a general picture of the dependence of autoradiolysis processes on Z. It is shown that in the region of medium Z the mechanisms of autoradiolysis can reflect Mendeleev periodic law. This generator can be used to produce medical daughter ^{44g}Sc, which is already used in preclinical studies for PET diagnostics.
- For the first time, a ^{140}Nd/^{140}Pr radionuclide generator was designed. The ^{140}Pr yield is more than 95%. ^{140}Pr has been used in preclinical studies for PET diagnostics.
- The data obtained will make it possible to identify the mechanisms of autoradiolysis, including in biological objects. These results are necessary for the evaluation of radiopharmaceuticals using in-vivo generators.

List of the series of papers:

1. Kurakina E. S., Wharton L., Khushvaktov J., Magomedbekov E. P., Radchenko V., Filosofov D. V. Separation of 44mSc/44gSc Nuclear Isomers Based on After-Effects. Inorg. Chem. 2023, https://doi.org/10.1021/acs.inorgchem.3c01495
2. Kurakina E. S., Radchenko V., Belozub A. N., Bonchev G., Bozhikov G. A., Velichkov A. I., Stachura M., Karaivanov D. V., Magomedbekov E. P., Filosofov D. V. Perturbed Angular Correlation as a Tool to Study Precursors for Radiopharmaceuticals. Inorg. Chem. 2020, 59 (17), 12209−12217. 431.
3. Zhernosekov K. P., Filosofov D. V., Qaim S. M., Rosch, F. A 140Nd/140Pr radionuclide generator based on physico-chemical transitions in 140Pr complexes after electron capture decay of 140Nd-DOTA. Radiochimica Acta, 2007, 95(6), 319–327. https://doi.org/10.1524/ract.2007.95.6.319
4. Brudanin V. B., Filosofov D. V., Kochetov 0. I., Korolev N. A., Milanov M., 0strovskiy I. V., Pavlov V. N., Salamatin A. V., Timkin V. V., Velichkov A. I., Fomicheva L. N., Tsvyaschenko A. V., Akselrod Z. Z. PAC spectrometer for condensed matter investigation. Nuclear Instruments and Methods in Physics Research A 547, 2005, 389-399.