Short thesis for the degree of doctor of philosophy (PhD)

Optimizing the reaction conditions for radiolabeling with positron-emitting metal isotopes and their follow-up by liquid chromatography

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Introduction and the aim of the work

Positron emission tomography (PET) is a non-invasive functional diagnostic technique that can be used to determine the exact location of radioactive positron emitting isotopes introduced into the body. When using PET, we can create an image with 511 keV energy gamma photons, originating from the interaction of a positron and an electron. The positron-emitting isotopes of the elements, found in living organisms, such as ^{15}O, ^{13}N and ^{11}C, have short half-lives, enabling only rapid, local use. During the production of labeled small molecules, the introduction of the ^{18}F isotope with similar properties by covalent bonding is most often used, which can be produced in high yield with a cyclotron and can also be used in complex radiopharmaceutical syntheses due to its much longer half-life. One of the most common radiopharmaceuticals is 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG), which enables the evaluation of the intensity of sugar uptake in individual tissues . For peptides, proteins and antibodies, labeling with metal isotopes can often be preferable. The main advantages of radiometals are the longer half-life and the fact that radiolabeling can also be carried out in an aqueous medium at room temperature.

Among the radiometal ions, [^{44}Sc]Sc^{3+} ($t_{1/2}$=3.97 hours), [^{68}Ga]Ga^{3+} ($t_{1/2}$=67.71 minutes) and [^{52}Mn]Mn^{2+} ($t_{1/2}$=5.59 days), can also be produced with a cyclotron, stand out for their favorable properties. Their application is complicated by radionuclides, formed in side reactions during isotope production, as well as polluting metal ions from external sources. The inactive contaminant ions can originate from the raw materials used, or they can get into the solution containing the metal isotope during the preparation and processing steps of the target material, which reduce the effectiveness of the labeling reaction due to their similar coordination properties. Isotopes with

different half-lives make image quantification more difficult. *Therefore, we choose to develop methods for the qualitative- and quantitative determination of radioactive- and non-radioactive metal contaminants as one of the objectives of this thesis. Radioactive nuclides were detected by gamma spectroscopy, while inactive metal ions were determined using 4-(2-pyridylazo)-resorcinol (PAR) and xylenol orange (XO) derivatizing agents by using liquid chromatographic and colorimetric methods.*

Liquid chromatographic methods that utilize the retention of a biomolecule, conjugated with a chelator, for its separation from free metal ions, are usually used to track the labeling with radiometals. However, methods using mostly reversed-phase columns are not suitable for following the labeling of free chelators, i.e. for separating metal ions and metal complexes, since most chelators and the resulting complexes are polar, so they are not retained on the apolar column. *Therefore, another goal of my thesis was the development of new liquid chromatographic methods that enable the monitoring of the labeling of free- and biomolecule-conjugated chelators with positron emitting metal isotopes. During the development of the methods, one of the goals was to achieve the retention of the free metal isotope with reversible binding, as well as the elution of the active complex.*

We used mixed-mode chromatographic stationary phases for method development, which allow the use of more than one interaction for the separation of sample components. In addition to apolar chains, they also contain cation- and/or anion-exchange groups, so multiple chromatographic separation modes can be used during one elution. They excel in the separation of compounds with low reverse phase retention, especially polar- and charged molecules.

Methods

For the production of radiometals, calcium (99.99%), isotope-enriched ^{68}Zn (98.60%) and chromium (99.99%) were irradiated with a GE PETtrace type cyclotron, using our in-house developed target system, and then isotope-specifically DGA, Zr, TK200 and AG® 1-X8 resins. Glass microfiber thin-layer chromatography paper (iTLC-SG) impregnated with silica gel was used for quick purity checking.

The DOTA and NOTA chelators used for chromatographic method development were purchased from ChemaTech, while the other ligands were provided by the members of the Rare Earth Metals Research Group of the Department of Physical Chemistry and their students, and Zsolt Baranyai and his colleagues.

For the determination of metal ions before- and after the column with 4-(2-pyridylazo)-resorcinol (PAR) and xylenol orange (XO) derivatizers, as well as for a more accurate evaluation of the colorimetric tests, we used a liquid chromatographic system composed of the following components: metal-free Jasco PU- 2080i pump, Knauer 3800 autosampler (plastic valve, needle, and 10 μL PEEK injector loop), Hamamatsu Photonics H10493-001 radioactivity detector, and Waters 2487 dual λ absorbance detector. Chromatographic separations were performed on Dionex IonPac CS5A (2 x 250 mm) type ion chromatography and LiChrospher 100 RP-18 (75 x 4 mm, 5 μm) columns.

For the separation of radiometals and their complexes, we used a Waters Acquity UPLC I-Class chromatography system equipped with an eluent delivery unit (BSM), autosampler (with flow-through needle and 100 μL loop), a column changer, a diode array detector and a scintillation detector with photoelectron multiplier tubeand a radioactivity detector (Hamamatsu Photonics). For method development, the following columns were used:

Adsorbosphere XL SCX (Grace, 4.6 x 150 mm, 5 µm), Obelisc N (Sielc, 4.6 x 150 mm, 100 Å, 5 µm), Obelisc R (Sielc, 4.6 x 150 mm, 100 Å, 5 µm), Coresep S (HELIX chromatography, NP-SCX 4.6 x 50 mm, 90 Å, 2.7 µm), Coresep 100 (HELIX chromatography, RP-SCX 4.6 x 50 mm, 90 Å, 2.7 µm) and Kinetex XB-C18 (Phenomenex, 50 x 4.6 mm, 100 Å, 2.6 µm).. Data acquisition and chromatogram evaluation were performed with Empower 3 software for all systems.

In each case, 10 µL of the aqueous solution of the chelator was added to 80 µL of buffer solution, to which 10 µL of the respective isotope ($[^{44}Sc]Sc^{3+}$, $[^{68}Ga]Ga^{3+}$ or $[^{52}Mn]Mn^{2+}$) was added (~0.15-0.40 MBq) in hydrochloric acid soluiton. The radiolabeling reactions were carried out in 1.5 ml Eppendorf tubes, in a heating block thermostated at 95 °C, with a reaction time of 5-30 minutes. Samples were spotted to iTLC sheets and developed in 0.05 M Na_2CO_3 or pure water. Raytest miniGita Star Radio-TLC scanner (Beta Detector GMC) and GINA Star TLC software were used for the evaluation of thin-layer chromatography tests.

We have built a microfluidic system for the automated study of the effect of different reaction conditions (concentration of reagents, pH, temperature, reaction time, etc.) of radiolabeling reactions. With the help of the system, using the LabVIEW 16.0 software, we were able to inject reagents together in a pre-programmed way, thermostat- and inject the reaction mixtures on to the HPLC column immediately after the elapse of the reaction time

New scientific results

1. We optimized the production and purification processes of ^{44}Sc, ^{68}Ga and ^{52}Mn metal isotopes with a cyclotron based on gamma spectrometry tests.

The positron-emitting isotopes were identified by gamma spectrometry in the target soluiton samples. In all cases, we proved that the contaminating radionuclides were bound on the ion exchange resins and could be selectively separated from the desired metal isotopes using acidic elution. The average radiochemical purity of the purified final fractions were:

1) ^{44}Sc 98.94%, ^{47}Sc 0.08%; egyéb izotópok: ^{43}Sc, ^{48}Sc, ^{44m}Sc 0.98%;
2) ^{68}Ga 99.97%, ^{67}Ga 0.018%, ^{66}Ga 0.012%;
3) ^{52}Mn 100%.

2. We have developed three procedures for the quantitative- and qualitative determination of non-radioactive contaminatingtransition metal ions using derivatizing reagents.

In addition to the metal ions (Ca^{2+}, Zn^{2+}, Cr^{3+}) from the target material, radioactive- and additional non-radioactive ions were always formed, which reduced the achievable radiochemical yields during the subsequent complexation reactions.

We developed post-column and pre-column derivatization procedures for liquid chromatographic systems, enabling the examination of the non-radioactive metal ion contaminants in the samples within a short period of time after production. Based on the results obtained, the chromatographic separation with post-column derivatization proved to be a more selective and sensitive method for the detection of metal ions. However the complexity of the

chromatographic system and the experienced baseline instabilities, the method cannot be used for routine quality control.

As a third method, we also examined the applicability of colorimetric reagents without chromatographic separation. Commercially available- or self-developed colorimetric tests can be useful for the detection of contaminant metal ions in higher concentrations (more than a few ppm), but have not proven to be selective enough for use in the ppb range, which is the typical metal content of radioactive samples. We found that the reliability and documentation of the colorimetric test can be improved if the samples are injected into the HPLC-UV detector in the absence of a column. Furthermore, HPLC detection allows the use of much smaller sample volumes (30 μL instead of 5-20 mL), which significantly reduces the material loss of short-lived radioactive metals during the quality control tests.

3.We developed liquid chromatography methods for mixed mode phase analytical columns to follow the radiolabeling reactions of the produced metal isotope with chelators.

Metal complexes of DOTA and NOTA ligands were used as model compounds. We developed methods on three mixed mode stationary phase analytical columns, on which the components to be tested were retained. The common feature of the methods is that the metal complexes interacted weakly with the stationary phase, presumably its central metal ion, but the interaction is so weak that the complexes can also be eluted from the column with pure water. On the other hand, in an aqueous solution, the free metal ions are adsorbed on the column. By using a high concentration of salt or a chelating agent, the bound metal ions could be eluted. We studied the extent of metal ion

adsorption on the HPLC system, which was highly dependent on the quality of the inorganic salt used in the eluent.

4. We determined the charge of the free radiometals and their complexes using a self-made electrophoresis device.

The tested radiometals moved in the direction, corresponding to their charge, as a result of voltage, applied to the appropriate electrolyte solution. The method can also be used to study the charge-, adhesion- and chromatographic behavior of radioactive metal ions and their complexes. During the comparative examination of the purified ^{44}Sc samples, we did not find any difference in the electrophoretic behavior of the active component even in the case of different labeling efficiency, based on this we concluded that the change in the labeling efficiency cannot be caused by the change of the chemical form of $^{44}Sc^{3+}$ in solution.

5. We performed the optimization of the radiolabeling reactions of ^{44}Sc, ^{68}Ga and ^{52}Mn metal isotopes.

For the investigation of radiolabeling reactions, during the production of each isotope, the fractions with the highest radionuclide purity, (typically the 3-4. eluate fractions) were used. The DOTA and NOTA derivatives used in the development of chromatographic methods are favorable for scandium, their complexes are exceptionally stable and inert, while only very low radiochemical yields were obtained for derivatives with a piclene frame, which are also macrocyclic ligands. The stability achieved, is lower due to the size-, backbone-, coordination number and quality of the donor atoms. Open-chain chelators are able to form complexes with many metal ions, but their stability

is lower, while the semi-macrocyclic AAZTA compound family showed outstanding radiochemical yields for binding [^{44}Sc]Sc^{3+}.

We compared the radiochemical yields of several [^{68}Ga]Ga-complexes as a function of the corresponding ligand concentrations. During the preliminary experiments, the volume of radiometal solution in the labeling mixtures had to be increased to 50 ul due to the low activity, available from the aging isotope generator. AAZTA derivatives and the open-chain CDDADPA and HXTA gave the highest yields. Among the macrocyclic ligands, DOTA and NOTA derivatives can also be highlighted in the case of gallium, so we used these chelators for further optimization studies. In addition to the widely used ammonium acetate, we also investigated the complex formation reaction of [^{68}Ga]Ga-NOTA and [^{68}Ga]Ga-DOTA with so-called non-coordinating buffers. The highest labeling efficiencies were achieved with AmAc, MOPS and HEPES buffers. In the case of HEPES and MES buffers, the lowest recovery was obtained during the chromatographic separation, the activity eluted from the column in a lower percentage. However, during the liquid chromatographic separations, among the non-coordinating buffers, the appearance of their complexes with [^{68}Ga]Ga^{3+} was also detected in the case of MOPS, HEPES and PIPES, therefore the further experiments were performed in AmAc buffered solutions.

The complex formation tendency of the studied chelators was also investigated with an increased reaction time, using [^{52}Mn]Mn^{2+} radionuclide. With manganese, smaller than gallium, the chelator with a bispiclene framework (BP2A) showed outstanding labeling efficiency. In the case of bispiclene and DOTA, labeled with good efficiency, we examined the effect of pH on complex formation. pH 7 proved to be better for complex formation, in contrast to pH 4, experienced with other radiometals so far.

6. We have built and used a microfluidic system for the optimal application of liquid chromatography separation methods and to investigate the possibility of rapid automation of complex formation reactions.

In the case of the DOTA ligand, the effect of the MOPS buffer proved to be unfavorable in an automated microfluidic system. We tested the buffer at pH 4.0 and pH 6.7, however we only achieved radiochemical yields under 10%, in both cases. With HEPES (similarly to the manual labeling results) the complexation was already measurable at low chelator concentrations, but we rejected its long-term use due to its high tendency for adsorption on solid surface. The use of the AmAc buffer proved to be better for this system as well.

Possible utilization of the results

During my doctoral work, I developed methods for the liquid chromatographic separation of positron-emitting radiometals and their complexes with various ligands By using the developed methods, I was able to follow the rate of formation of metal complexes during labeling optimization experiments.

Liquid chromatographic- and colorimetric tests cannot replace atomic spectroscopy techniques for the determination of contaminating metal ions in radioactive samples, but they can find their role in the development of production and purification methods, as well as in the rapid routine quality control of radiometal solutions for isotopic tracers.

The liquid chromatographic separations developed for reversed stationary phases are suitable for replacing the thin-layer chromatographic methods widely used in the field of radiochemistry, speeding up and simplifying the serial measurements, reducing the radiation exposure, and increasing the reproducibility of the results.

Microfluidic equipment has accelerated and simplified labeling optimization. With its help, we determined the time- and concentration dependence of several complex formation processes without lengthy sample preparation.

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List of publications related to the dissertation

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