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Poster

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Poster Category: Radiochemistry - Radiometals

P-132 | HPLC for determination of unbound gallium-68 in radiopharmaceuticals: Pitfalls and solutions

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Objectives

Determination of radiochemical purity (RCP) of ^{68}Ga-radiopharmaceuticals (RPs) is an extremely important part of QC in routine clinical practice. Knowing the exact value of content of every radiochemical impurity is very important during R&D of ^{68}Ga-RPs as well. It was previously shown that HPLC results do not always match TLC results, especially for unbound ^{68}Ga content.[1] This uncertainty comes from nonspecific sorption of unbound ^{68}Ga on C18 phase. The aim of this study was to fix the weakness of the HPLC analysis procedure, since in some cases it can be difficult to replace.

Methods

^{68}Ge/^{68}Ga generator (Cyclotron Ltd, Russia) was used. All chemicals and solvents were of high-purity or pharmaceutical grade and were purchased from Sigma-Aldrich or Panreac. Radiopharmaceutical precursors were purchased from ABX. Chelators were purchased from CheMatech, ABX and TRC Canada. iTLC-SG strips by Thermo Fisher Scientific were used. Different radio-TLC systems were used to determine all ^{68}Ga species content. PET-MiniGita (Raytest) scanner was used. For HPLC analysis Knauer Smartline chromatograph with fLumo (Berthold) radiodetection system was used. The mobile phase for HPLC consisted of 0.1% TFA solutions in water and acetonitrile in different ratios in accordance with 9th Ph. Eur. recommendations. Different HPLC C18 columns were used (Merck, Phenomenex, ACE).

Results

It was found that, in pH range from 3 to 6, there is a significant capture of the ^{68}Ga ion forms on the reversed phase of the HPLC column (e.g. 60% capture with pH 4.6). The value of the capture also depends on the nature and concentration of buffer agent in the preparation. The nature of this phenomenon is a subject of pure radiochemistry. New data shedding light on this effect will be presented. In order to avoid this capture during HPLC analysis, a new procedure of sample processing and analysis was developed. The procedure involves usage of chelators in order to prevent ^{68}Ga sorption on the column. For this purpose, DTPA, DOTA, NOTA, and HBED were evaluated. The details of their influence on the course of analysis will be presented.

Conclusions

In a number of cases, the results of HPLC analysis of ^{68}Ga-cojugates performed according to 9th Ph. Eur. recommendations did not reflect the real unbound ^{68}Ga content in radiopharmaceutical preparations. It was highly probable that the same effect can occur when analyzing other metal-based RPs (such ^{111}In, ^{177}Lu, etc.). To avoid this effect, new procedure of HPLC analysis was designed.

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Poster Category: Radiochemistry - Radiometals

P-133 | New phosphonic acids as components of bone seeking radiopharmaceuticals

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Objectives

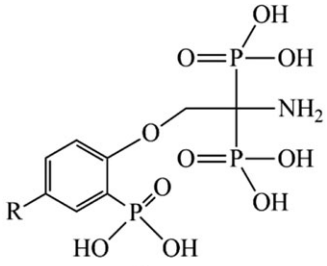
Modern radiopharmaceuticals are complexes of radiometals with organic ligands. The ligand selectively binds and stabilizes radionuclide and delivers it to the target organs and tissues. Phosphonic acids have a high affinity for the bone matrix; therefore, they are promising compounds for developing bone seeking radiopharmaceuticals. In the present work, new phosphonic acids were synthesized. Physico-chemical and biological properties of these acids and their complexes with ^{68}Ga, ^{153}Sm, and ^{188}Re were studied.

Methods

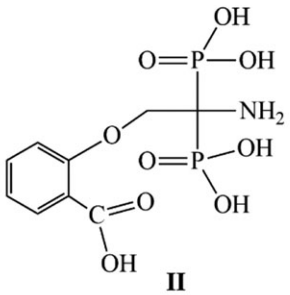
New aminobisphosphonic acids **I-V** were obtained by addition of H_3PO_3 to the corresponding nitriles. Compound **I** is a salicylic acid derivative. Compound **II** is a derivative of 2-oxyphenylphosphonic acid. Acids **III-V** are analogs of the widely used organic ligand which is a part of the [^{153}Sm]samarium oxabifore radiopharmaceutical. The known methods of synthesis of cyclen-containing phosphonic acids **VIa-d** with the side chain of different length and asymmetrically substituted with methylenepyridine fragment were improved, and new approaches were developed. Complexation of Ga^{3+} and Sm^{3+} cations with the obtained compounds was studied by ^{1}H, ^{13}C, and ^{31}P NMR and potentiometry for the first time. The yields of labeling reactions with ^{68}Ga, ^{153}Sm, and ^{188}Re were estimated using radio-TLC method. The biodistribution of labeled compounds was evaluated by direct radiometry.

Results and Discussion

Phosphonic acids **I-VI** with the well-known coordination fragments 2-oxyphenylphosphonic (**I**), salicylic (**II**), aminobisphosphonic acids (**III-V**), and cyclen (**VI**) were synthesized through a short and efficient synthesis. Protonation constants of **III, V**, and **VIa** in water were determined using potentiometry. Species distribution diagrams of the deprotonated forms of acids as a function of pH were plotted. The stability constant log K_{ML} of Ga^{3+} complex with **III** is equal to 16.2. The stability constant of the Ga^{3+} complex with the fully deprotonated ligand **VIa** log K_{ML} = 27.8 is higher than the corresponding constant of the Ga^{3+}complex with DOTA, the ligand most used in radiopharmacy (log K_{ML} = 21.3). It is also higher than the constant of the Ga^{3+} complex with plasma protein transferrin (log K_{ML} = 20.3), which makes the **VIa** a promising ligand for the use in radiopharmacy. Interaction of Ga^{3+} and Sm^{3+} cations with **III** was studied using ^{1}H, ^{13}C, and ^{31}P NMR in D_2O. The results indicate that only two α-aminophosphonic groups of **III** participate in 1:1 complex formation with Sm^{3+}. The mixture of several Ga^{3+} complexes with different protonation states and different interactions between metal cation and donor atoms was found. The effect of temperature,



I
R=H, Et



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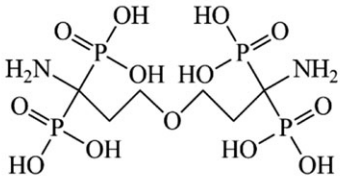
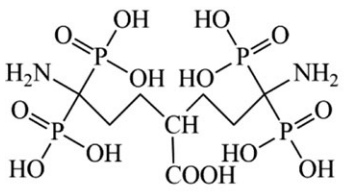
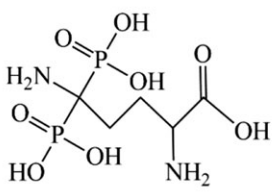


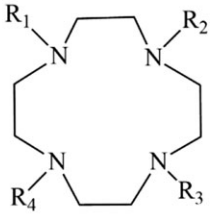
III



IV



V



VIa $R_1=R_2=R_3=R_4= CH_2P(O)(OH)_2$;

VIb $R_1=R_2=R_3=R_4= CH_2CH_2P(O)(OH)_2$;

VIc $R_1=R_2=R_3=R_4= CH_2CH_2CH_2P(O)(OH)_2$;

VId $R_1=R_2=R_3= CH_2P(O)(OH)_2$; $R_4=$ 

reaction time, pH and buffer solution on the yield of the ^{68}Ga complexes with **III, IV** and **VI** was studied. Based on preliminary evaluation of biodistribution *in vivo*, it was found that [^{153}Sm]Sm-**III,** [^{68}Ga]Ga-**III**, **[**^{68}Ga]Ga-**VIa**, **[**^{68}Ga]Ga-**VId**, and [^{188}Re]Re-**V** show moderate bone uptake and increased accumulation in bone fracture sites, which were used as models of bone metastasis.

ACKNOWLEDGMENTS

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Poster Category: Radiochemistry - Radiometals

P-134 | Zirconium-89 solutions: Preparation, formulation, analysis, and comparison of applicability for radiopharmaceutical purposes

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Objectives

The aim of this study is to develop a handy procedure for preparation of zirconium-89 in the form of an oxalate-free physiologically acceptable solution suitable for radiolabeling. Another objective was to design an adequate quality control procedure and to compare this formulation with other frequently used ones.

Methods

All chemicals and solvents were of high-purity or pharmaceutical grade and were purchased from Sigma-Aldrich or Panreac. Quality control was carried out with TLC chromatography (iTLC-SG strips, different eluents; PET-MiniGita radio-TLC scanner). Dowex1, Chelex-100 (Sigma-Aldridge), ZR (Triskem), and Chromafix-HCO_3 (Macherey-Nagel) resins were used. [^{89}Zr]$ZrCl_4$ in 5 M HCl was purchased from Cyclotron Ltd (Russia).

Results

A handy procedure of production of [^{89}Zr]zirconium oxalate isotonic (0.115 M oxalate) solution suitable for radiolabeling was developed previously.[1] Since ambiguous interpretation of oxalate toxicity and there is a possibility that it can interfere with the labeling process, we modified the procedure the following way. A new oxalate-free method using sodium citrate solution was developed. Using Chelex-100 resin allows obtaining ^{89}Zr in 0.1-1.0 M sodium citrate solutions with high yield (≥95%). The solutions are stable for at least 10 days, pH 5-7. The solutions were successfully used for obtaining ^{89}Zr-labeled DFO-conjugates with high radiochemical purity. Our data indicate that citrate anion forms a weaker complex with [^{89}Zr]zirconium than oxalate. Therefore, we assume, citrate will interfere with the labeling process less. It was found that, in some cases, the previously reported method of analysis does not reflect the true content of [^{89}Zr]zirconium in unbound 'active' form. An adequate method of analysis was designed. We suggest using the method iTLC/CH_3OH-H_2O (1:1), 4% TFA (v/v). Using this method, we carried out the comparison of oxalate-free method with frequently used ones. Experimental results will be presented in detail.

Conclusion

A handy procedure for preparation of zirconium-89 in the form of oxalate-free physiologically acceptable solution suitable for radiolabeling was developed. An adequate quality control procedure for this new formulation was designed. During this study, new features of [^{89}Zr]zirconium chromatographic behavior were observed. These new data are very important for understanding zirconium-89 radiopharmaceutical chemistry.

ACKNOWLEDGMENTS

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Poster Category: Radiochemistry - Radiometals

P-135 | Investigations on the mechanism of simultaneous photochemical conjugation and radiolabelling of proteins with modified arylazides

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