Labelling of DOTA-DPhe^1-Tyr^3-octreotide with generator-produced ^{68}Ga

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Introduction: Bifunctional chelators labelled with ^{68}Ga ($T_{1/2}$ = 68 min, β^+ branching = 89%) are of great interest for clinical PET. In particular the somatostatin analogue [^{68}Ga]DOTA-DPhe^1-Tyr^3-octreotide ([^{68}Ga]DOTATOC) shows great potential for diagnosis of somatostatin receptor expressing tumours [1].
Commercially available ^{68}Ge/^{68}Ga generators based on TiO_2 (Cyclotron Co., Obninsk, Russia) provide a cyclotron-independent source of ^{68}Ga. More than 50% of the activity can be eluted with 5-7 ml 0.1 M HCl. However, the eluate contains the long-lived ^{68}Ge and small amounts of Zn(II), Ti(IV), Fe(III) and cannot be used directly for labelling of DOTATOC.
Pre-concentration and purification of ^{68}Ga from the eluate can be performed on a cation exchanger in HCl / acetone media [2]. The ^{68}Ga activity can be obtained in a small volume with low HCl concentration.
The aim of this work was to develop a system for simple and efficient handling of the ^{68}Ge/^{68}Ga generator eluate for labelling of nanomolar amounts of DOTATOC. The main component of the system is a micro-chromatography column (Fig.1) filled with 53 mg of Bio-Rad AG 50W-X8 resin.

Experimental: The generator is connected to the column with tube (1) (Fig.1). PEEK capillary tubing (4) is directed to reagents vials. The column can be also eluted using a standard single-used syringe (3) and is connected to the waste vials with tube (2).
For pre-concentration and purification of ^{68}Ga the following protocol is used: (i) elution of the generator (1-2) and separation of more than 99% of ^{68}Ga from the eluate; (ii) purification of ^{68}Ga (3-2) using 1 ml 80% acetone / 0.15 M HCl solution (loss of activity < 5%); (iii) elution of ^{68}Ga directly into the reaction vial (3-4) with 400 µl of 98% acetone / 0.05 M HCl solution. The procedure takes 4 minutes. Finally, the column is purified with 1 ml 4 M HCl and 1ml H_2O (3-2).
With its relatively small ionic radius of 0.62 Å, trivalent gallium evidently hydrolyses over pH 2–3 [3] and has a high tendency to adsorbe on surfaces (glass, plastic), especially in no-carrier-added form. Ga^{3+} precipitates easily as insoluble $Ga(OH)_3$(am) with $lgK_s \cong -37$. Thus, 500 MBq of ^{68}Ga precipitate already at pH = 4.4 (Fig. 2).
For labelling of biomolecules via bifunctional chelators such as DOTATOC, due to the slow kinetics of complexation and due to the complex aqua chemistry of the cation, selecting of optimum reaction conditions is essential.

For labelling, the ^{68}Ga eluate (400 µl 98% acetone /0.05 M HCl) is added to 4 ml of heated water solution (~ 98C°), which contains 20 µg (14 nmol) of DOTATOC. $2 \cdot 10^{-5}$ mol of acid provide a pH value of 2.30±0.05. This condition

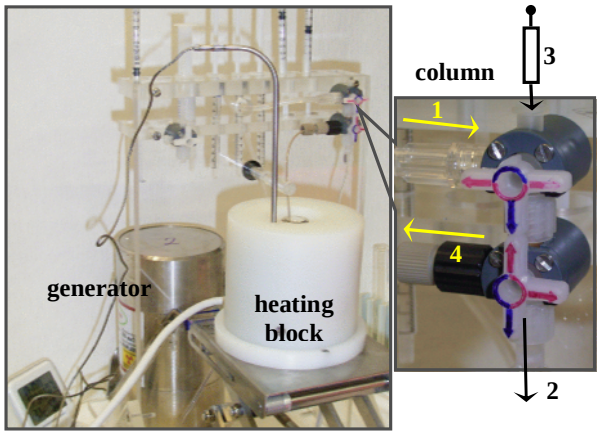

Fig. 1. Equipment for labelling of DOTATOC with generator-produced ^{68}Ga;
to the right the micro-chromatography column.

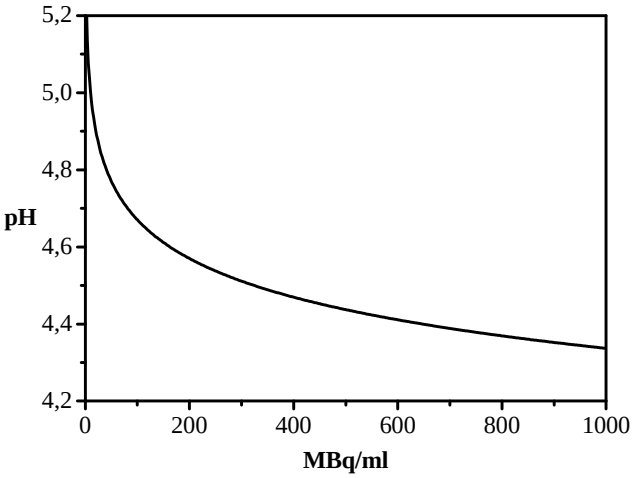

Figure 2. Solubility curve of ^{68}Ga

suppresses the hydrolysis and allows complexation in about 10 min. Finally, ^{68}Ga-DOTATOC is purified on a C-18 cartridge and can be obtained in 0.2-0.4 ml ethanol with a final specific activity of ~18 MBq per µg peptide.
The developed system represents a simple and efficient way for labelling of DOTATOC with ^{68}Ga and preparation of an injectable radiopharmaceutical within 20-25 min.

References

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