Pre-concentration and purification of generator-produced ^{68}Ga

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Introduction: The ^{68}Ge/^{68}Ga generator (^{68}Ge: $T_{1/2}$ = 270.8 d) provides a cyclotron-independent source of positron-emitting ^{68}Ga ($T_{1/2}$ = 68 min, β^+ branching = 89%), which can be used for labelling of biomolecules via bifunctional chelators. It is thus of great interest for clinical PET and PET/CT [1].
Commercially available ^{68}Ge/^{68}Ga generators based on TiO_2 (Cyclotron Co., Obninsk, Russia) allow to elute > 50% of ^{68}Ga in 5-7ml 0.1 M HCl solution. However, the eluate normally is contaminated with long-lived ^{68}Ge and contains small amounts of Zn(II), Ti(IV), Fe(III) and residuals of construction materials used. For labelling, ^{68}Ga must thus be treated following several principles (i) pre-concentration; (ii) purification; (iii) transfer of ^{68}Ga into a form useful for labelling (volume, pH). The aim of this work was to develop a system for pre-concentration and purification of ^{68}Ga from 0.1 M HCl solutions and to obtain ^{68}Ga in solutions of small volume and acceptable H^+ concentration. Analysis of cation exchange distribution coefficients with Bio-Rad AG 50W-X8 in hydrochloric acid / acetone media [2] showed, that Ga(III) can be eluted from the resin using low acid concentration. Furthermore, it is possible to separate Ga(III) from Ge(IV), Zn(II), Ti(IV) and Fe(III).

Experimental: A micro-chromatography column was prepared using 53 mg of Bio-Rad AG 50W-X8 cation exchanger. A 20 mCi ^{68}Ge/^{68}Ga generator (~12 months old) was used to obtain about 110 MBq of ^{68}Ga in 7 ml of 0.1 M HCl. The activity of ^{68}Ge in the eluate was 170-200 kBq (determined 48 h after generator elution using γ-spectroscopy on HPGe detector).
^{59}Fe was produced in a neutron capture reaction on natural iron. 198 mg of iron oxide Fe_2O_3 were irradiated for 50 days at the HMI neutron source BER II at $1.6\cdot10^{14}$ n cm^{-2} s^{-1}, resulting in 440 MBq ^{59}Fe. ^{54}Mn was co-obtained with an activity 0.25 MBq per 1 MBq of ^{59}Fe. ^{69}Zn was produced with specific activity of ~700 kBq/mg by irradiation of 380 µg of >98% enriched ^{68}Zn for 6 h at the TRIGA reactor Mainz at a neutron flux of $4\cdot10^{12}$ cm^{-2} s^{-1}.
^{68}Ga in 7 ml of 0.1 M HCl was loaded dynamically on the chromatography column. For purification from ^{68}Ge, Zn(II) and Fe(III) an 80% acetone / 0.15 M HCl solution was selected. ^{68}Ga itself was subsequently eluted with 400 µl of a 97.6% acetone / 0.05 M HCl solution. The chromatography column was purified with 1 ml 4 M HCl and 1 ml H_2O.
Distribution of radionuclides ^{59}Fe, ^{54}Mn and ^{69}Zn, containing 83 µg and 130 µg of Fe(III) and Zn(II), respectively, was measured in solutions, using an HPGe detector. The distribution of about 20 µg Ti(IV) was studied by an Elan 5000 ICP-MS (Perkin-Elmer).

Results: More than 97% of ^{68}Ga could be obtained finally in 400 µl of the 97.6% acetone / 0.05 M HCl solution (Tab.1) containing < 0.1% of ^{68}Ge. About 0.1% of Ti(IV) and 10% of Mn(II) were detected in the eluted solution.
The purification step using 80% acetone / 0.15 M HCl solution allows to reduce the amount of Zn(II) up to 10^{-3} % and of Fe(III) up to 11% (Tab.1).
The presented system allows to concentrate ^{68}Ga from 0.1 M HCl solutions and to obtain it with high specific activity and contamination of ^{68}Ge less than 0.1% in a small volume with low HCl amount ($2\cdot10^{-5}$ mol). Cation exchanger with hydrochloric acid-acetone media seem to be a useful tool also for the preparation of other gallium isotopes such as cyclotron-produced ^{66,67}Ga.

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References

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*Table 1. Relative distribution [%] of ^{68}Ga(III), ^{68}Ge(IV), Zn(II), Ti(IV), Fe(III) and Mn(II) on a micro-chromatography column (53mg Bio-Rad AG 50W-X8 cation exchanger) using **a)** 0.6 ml and **b)** 5 ml of 80% acetone / 0.15 M HCl solutions for purification*

Volume	***Step / concentration***	***Relative distribution [%]***					
a)		Ga(III)	Ge(IV)	Zn(II)	Ti(IV)	Fe(III)	Mn(II)
7 ml	Generator elution: 0.1 M HCl	0.16	97.08	0.77	7.30	0.13	4.41
0.6 ml	Purification: 80% acetone / 0.15 M HCl	1.43	2.92	98.15	0.68	37.86	0.49
0.4 ml	**Ga(III) elution: 97.6% acetone / 0.05 M HCl**	**97.82**	**$3\cdot10^{-2}$**	**1.08**	**$7\cdot10^{-2}$**	**49.78**	**11.10**
1 ml	Washing: 4 M HCl	0.41	$5\cdot10^{-3}$	$5\cdot10^{-3}$	72.15	11.61	69.38
1 ml	Washing: H_2O	0.18	$3\cdot10^{-3}$	$<10^{-3}$	19.80	0.62	14.62
b)							
7 ml	Generator elution: 0.1 M HCl	0.11	97.68	0.43	7.18	0.73	5.20
5 ml	Purification: 80% acetone / 0.15 M HCl	6.29	2.32	99.57	3.99	87.37	1.71
0.4 ml	**Ga(III) elution: 97.6 % acetone / 0.05 M HCl**	**92.73**	**$5\cdot10^{-3}$**	**$<10^{-3}$**	**0.11**	**11.10**	**9.79**
1 ml	Washing: 4 M HCl	0.77	$2\cdot10^{-3}$	$<10^{-3}$	86.54	0.71	83.09
1 ml	Washing: H_2O	0.10	$2\cdot10^{-3}$	$<10^{-3}$	2.18	0.09	0.21