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journal homepage: [www.elsevier.com/locate/apradiso](http://www.elsevier.com/locate/apradiso)Improved column-based radiochemical processing of the generator produced  $^{68}\text{Ga}$ N.S. Loktionova<sup>a</sup>, A.N. Belozub<sup>b</sup>, D.V. Filosofov<sup>b</sup>, K.P. Zhernosekov<sup>c,d,e</sup>, T. Wagner<sup>c</sup>, A. Türler<sup>c,e,f</sup>, F. Rösch<sup>a,\*</sup><sup>a</sup> Institute of Nuclear Chemistry, University of Mainz, 55128 Mainz, Germany<sup>b</sup> Joint Institute of Nuclear Research, DLNP, 141980 Dubna, Russian Federation<sup>c</sup> Chair of Radiochemistry, Technical University of Munich, 85748 Garching, Germany<sup>d</sup> Center for Radiopharmaceutical Science, Paul Scherrer Institute, 5232 Villigen, PSI, Switzerland<sup>e</sup> Laboratory of Radiochemistry and Environmental Chemistry, Paul Scherrer Institute, 5232 Villigen, PSI, Switzerland<sup>f</sup> Labor für Radio- und Umweltchemie Departement Chemie und Biochemie Universität Bern, 3012 Bern, Switzerland

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## ABSTRACT

An improved chemical strategy for processing of the generator produced  $^{68}\text{Ga}$  was developed based on processing of the original  $^{68}\text{Ge}/^{68}\text{Ga}$  generator eluate on a micro-column. Direct pre-concentration and purification of the eluted  $^{68}\text{Ga}$  is performed on a cation-exchange resin in hydrochloric acid/acetone media. A supplementary step based on a second micro-column filled with a second resin allows direct re-adsorption of  $^{68}\text{Ga}$  eluted from the cation exchanger.  $^{68}\text{Ga}$  is finally stripped from the second resin with a small volume of pure water. For this purpose a strong anion exchanger and a novel extraction chromatographic resin based on tetraalkyldiglycolamides are characterized. The strategy allows online pre-concentration and purification of  $^{68}\text{Ga}$  from the original generator eluate. The supplementary column allows transferring  $^{68}\text{Ga}$  with high radionuclide and chemical quality in the aqueous solution with small volume and low acidity useful for direct radiolabeling reactions.

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## 1. Introduction

The  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generator provides an excellent source of positron emitting  $^{68}\text{Ga}$  for the application of  $^{68}\text{Ga}$ -labeled compounds using PET. However, currently available “ionic”  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generators are not necessarily optimized for the routine synthesis of  $^{68}\text{Ga}$ -labeled radiopharmaceuticals in a clinical environment. The eluates have rather large volumes (up to 5–10 ml for a complete generator elution), a high acidity (0.1–1.0 N, depending on the generator type), an initial breakthrough of  $^{68}\text{Ge}$  in the range  $10^{-3}$ – $10^{-2}\%$ , increasing with time or usage frequency, and metallic impurities such as stable  $\text{Zn}^{\text{II}}$  (generated by the on-generator decay of  $^{68}\text{Ga}$ ),  $\text{Ti}^{\text{IV}}$ ,  $\text{Sn}^{\text{IV}}$  or other metals as a consequence of use of the metal oxide based generator matrixes.

Recently, we have introduced a generator associated post-processing approach to adsorb  $^{68}\text{Ga}$  online from generator eluates on a micro cation-exchange column, to purify it using a HCl/acetone mixture of 0.15 M HCl/80% acetone. Subsequently

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the radionuclide is desorbed from the resin quantitatively with 0.4 ml of a 0.05 M HCl/98% acetone solution. The process takes 3 min only and allows obtaining 96% of  $^{68}\text{Ga}$  with the highest radionuclide and chemical purity in the form useful for the radiolabeling reaction (Zhernosekov et al., 2007). Thus the technique is successfully applied for the preparation of  $^{68}\text{Ga}$ -labeled peptides for clinical studies (Asti et al., 2008). Contents of the acetone in the reaction mixture are low and non-toxic. They might be, however, avoided for direct *in vivo* applications or for the radiolabeling reactions performed under high temperature.

Alternatively,  $^{68}\text{Ga}$  can be pre-concentrated on an anion exchanger because of high distribution coefficients of  $\text{Ga}(\text{III})$  (Hofmann et al., 2001; Meyer et al., 2004; Schumacher and Maier-Borst, 1981). This technique does not allow, however, direct pre-concentration from the original generator eluate and adjustment of the hydrochloric acid concentration must be done. Finally  $^{68}\text{Ga}$  is eluted with small volumes of pure water.

The aim of the present study is to develop an improved column-based chemical strategy combining aspects of both methods. Direct pre-concentration of  $^{68}\text{Ga}$  from the original eluate and its purification is supposed to be performed on the cation exchanger (Zhernosekov et al., 2007). The  $^{68}\text{Ga}$  can be eluted with hydrochloric acid solutions at high concentration

> 2–3 M. For an effective transfer of the purified  $^{68}\text{Ga}$  into the aqueous phase of low acidity and small volume a secondary micro-column is introduced into the process, which allows direct re-adsorption of gallium eluted from the cation exchanger and can be finally stripped with a small volume of pure water. For this propose anion exchanger and a novel extraction chromatographic resin based on tetraalkyldiglycolamides (DGA) is characterized in details.

## 2. Materials and methods

### 2.1. Chemicals and reagents

Only analytic reagent grade chemicals and Milli-Q water (18.2 M $\Omega$  cm; Millipore) were used. The ion exchange resins AG 50W-X4 (–400 mesh, H<sup>+</sup>-form) and AG 1-X8 (200–400 mesh, Cl<sup>–</sup>-form) were purchased at Bio-Rad Laboratories (Richmond, CA, USA). The extraction chromatographic resins based on N,N,N',N'-tetra-n-octyldiglycolamide (TODGA) and N,N,N',N'-tetrakis-2-ethylhexyldiglycolamide (TEHDGA) 50–100  $\mu\text{m}$  particle size were provided by Eichrom Technologies. 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) conjugated with D-Phe<sup>1</sup>-Tyr<sup>3</sup>-octreotide (DOTATOC), GMP-grade, was obtained from piChem R&D (Graz, Austria).

### 2.2. $^{68}\text{Ge}/^{68}\text{Ga}$ radionuclide generator

A generator based on a modified TiO<sub>2</sub> phase adsorbing  $^{68}\text{Ge}^{\text{IV}}$  was obtained from Cyclotron Co. Ltd., Obninsk, Russian Federation. In the present study, a 250 MBq, 2 years old device was used. The  $^{68}\text{Ge}$  content in the eluate was  $10 \pm 2$  kBq.

### 2.3. Determination of $\text{Ga}^{\text{III}}$ and $\text{Ge}^{\text{IV}}$ distribution on DGA

5 ml of 0.1 M HCl generator eluate were mixed with 12 M HCl solution to obtain  $^{68}\text{Ga}^{\text{III}}$ ,  $^{68}\text{Ge}^{\text{IV}}$  solutions with hydrochloric acid concentrations in the range 0.1–8 M. The uptake of  $\text{Ga}^{\text{III}}$  and  $\text{Ge}^{\text{IV}}$  ions by the DGA resins was measured by combining 2.5 ml of the solution with about 50 mg of the resin in a glass vial. The samples were shaken well for 1 h. After equilibration with the resin, the aqueous phase was filtered through 20  $\mu\text{m}$  PTFE syringe filter. All experiments were performed at room temperature between 20 and 23 °C. Weight distribution ratios  $D_w$  were calculated using the following equation:

$$D_w = (A_0 - A_s)V / A_s m \quad (1)$$

where  $A_0$  and  $A_s$  are the aqueous phase activity before and after equilibration,  $V$  is the volume of the aqueous phase in milliliters and  $w$  is the weight of the resin in grams.  $D_w$  values were then converted to  $k'$  (the resin capacity factor) as described elsewhere (Horwitz et al., 2005a)

$$k' = 0.57D_w \quad (2)$$

### 2.4. Micro-columns

For the preparation of micro-columns, as described previously (Zhernosekov et al., 2007), 50 mg of wet cation exchangers AG 50W-X8 (–400 mesh in H<sup>+</sup>-form), 50 mg of wet anion exchanger AG 1-X8 (200–400 mesh, Cl<sup>–</sup>-form) and 100 mg DGA resin (Eichrom Technologies, 50–100  $\mu\text{m}$  particle size) were used.

### 2.5. Pre-concentration and purification of $^{68}\text{Ga}$ on cation exchanger

The first step of concentration and purification of the initial  $^{68}\text{Ge}/^{68}\text{Ga}$  generator eluate was performed on a micro cation-

exchange column. The generator was eluted with 7 ml of 0.1 M HCl online through the chromatographic column. Next, the column was eluted with a 1 ml solution of 80% acetone/0.15 M HCl (N1) to remove the main parts of the chemical and radiochemical impurities of the generator eluate (Zhernosekov et al., 2007).

To desorb the purified  $^{68}\text{Ga}$  from the cation exchanger, the column was stripped with hydrochloric acid solutions. HCl concentrations of 1–8 M and of 0.5, 1.0 and 2.0 ml volumes have been tested.

### 2.6. Processing of $^{68}\text{Ga}$ on anion exchanger and DGA resin

Adsorption of  $^{68}\text{Ga}$  on the anion exchanger and DGA resin was investigated by dynamic loading of the activity on the columns with hydrochloric acid solutions of 1–8 M concentrations and of 0.5, 1.0 and 2.0 ml volume.

### 2.7. Combining cation exchange with anion exchange

A closed system was assembled by connecting the micro-column and the generator using standart capillary and 3-way valves (Fig. 3a). The system could be operated using single-use syringes. The generator was eluted directly through the cation-exchange column (direction 1 on Fig. 3a). 3 ml of the 5 or 4 M HCl solution was used to strip the cation-exchange column online through the anion-exchange or DGA column (direction 3 on Fig. 3a). Finally,  $^{68}\text{Ga}$  was desorbed from anion exchanger or DGA resin with pure water (direction 4 on Fig. 3a).

### 2.8. Measurement of radioactivities

Measurement of  $^{68}\text{Ga}$  was accomplished in a dose calibrator M2316 (Messelektronik, Dresden GmbH). The absolute activity of  $^{68}\text{Ge}$  was analyzed by  $\gamma$ -spectrometry using an HPGe-detector at least 2 days after the corresponding radionuclide generator elution.

### 2.9. Radiolabeling of DOTATOC

For labeling reactions, 2 mL tubes (Eppendorf) were used. Heating was performed in ThermoMixer MHR13 from HLC BioTech. For labeling of octreotide derivatives, DOTA-D-Phe<sup>1</sup>-Tyr<sup>3</sup>-conjugated octreotide (DOTATOC) was used.

### 2.10. Analyses of contents of acetone

The acetone content in the processed fractions was analyzed by gas chromatography (HP 6890 series GC system).

## 3. Results and discussion

### 3.1. Direct pre-concentration of $^{68}\text{Ga}$

Direct pre-concentration of the generator produced  $^{68}\text{Ga}$  can be effectively performed on a miniaturized cation-exchange column. Application of HCl/acetone media allows purification of the activity from traces of  $^{68}\text{Ge}$ , Zn(II), Ti(IV) and even Fe(III) (Zhernosekov et al., 2007). In contrast to our previous work, elution of  $^{68}\text{Ga}$  from cation exchanger is performed in concentrated HCl solutions. As these are not applicable, however, for direct radiolabelling reaction, a transfer of  $^{68}\text{Ga}$  into an aqueous phase of low acidity and small volume is introduced based on a second micro-column. For this propose strong anion exchanger and extraction chromatographic resin DGA were characterized.

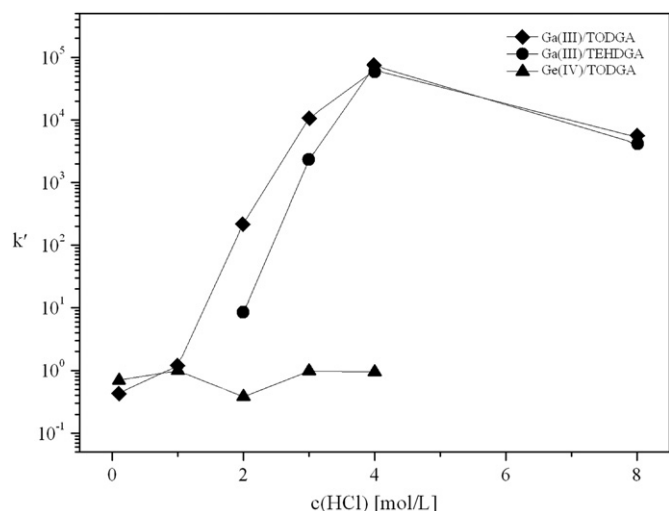


Fig. 1.  $k'$  for Ga(III) and Ge(IV) on DGA resin (50–100  $\mu\text{m}$ ) versus HCl concentration, 1 h equilibration time, room temperature.

### 3.2. $^{68}\text{Ga}(\text{III})$ behavior on DGA resin

Commercially available DGA resins have recently been proposed as very promising for processing of radionuclides such as  $^{90}\text{Y}(\text{III})$  or  $^{177}\text{Lu}(\text{III})$  for medical use (Horwitz et al., 2005a, 2005b). Fig. 1 shows the dependency of Ga(III) and Ge(IV) uptake on hydrochloric acid concentration on DGA. The DGA resins show negligible gallium adsorption at low acid concentration up to 1 M. The retention on the resin, however, increases rapidly with increasing hydrochloric acid concentration. Thus, in contrast to strong anion exchanger such as AG 1-X8 (Nelson, 1963), the DGA resins show increased adsorption to trivalent gallium at lower HCl concentration, but TODGA resin has a little bit higher coefficients than TEHDGA. Ge(IV) has only negligible retention on the TODGA resin in a wide range of the HCl concentration. For further investigation TODGA resin was chosen.

### 3.3. Pre-concentration and purification of $^{68}\text{Ga}$ on cation exchanger

$^{68}\text{Ga}$  is quantitatively adsorbed from the original generator eluate on the cation-exchange column and effectively purified using 80% acetone/0.15 M HCl solution (Zhernosekov et al., 2007). Optimum desorption of  $^{68}\text{Ga}$  from the cation-exchange column was achieved with 2 ml of 2–4 M HCl solutions (Fig. 2a), which corresponds to known characteristics of distribution coefficients of Ga(III) on strong cation exchangers (Nelson et al., 1963).

### 3.4. Characterization of anion exchanger and TODGA resin columns

Adsorption efficiency of  $^{68}\text{Ga}$  on the anion-exchange and TODGA column from HCl solutions at different acid concentrations is given in Fig. 2b and c. An effective retention of  $^{68}\text{Ga}$  on the TODGA resin could be achieved at > 3–4 M HCl, whereas not less than 5–6 M HCl concentration was needed for nearly complete adsorption of  $^{68}\text{Ga}$  on AG 1-X8. Elution of the activity could be quantitatively performed in pure water for both resins. However, 300  $\mu\text{l}$  of  $\text{H}_2\text{O}$  was used to strip  $^{68}\text{Ga}$  from the anion-exchange column and up to 1000  $\mu\text{l}$  was needed for its elution from the TODGA column.

### 3.5. Improved column-based $^{68}\text{Ga}$ processing using column combinations

Quantitative desorption of  $^{68}\text{Ga}$  from cation-exchange column is achieved at 2–4 M HCl, which corresponds to known

distribution characteristics of Ga(III) on strong cation exchangers (Nelson et al., 1963). However, 2–4 M HCl solutions of Ga(III) are not adequate to adsorb Ga(III) on the strong anion exchangers such as AG 1-X8. Thus HCl concentrations of 6–8 M are needed. The extraction chromatographic resin TODGA shows, in contrast, a higher adsorption profile to trivalent gallium at lower acid concentration. Thus, an effective  $^{68}\text{Ga}$  adsorption can be performed at 4 M HCl concentration. In this context, 5 and 4 M HCl

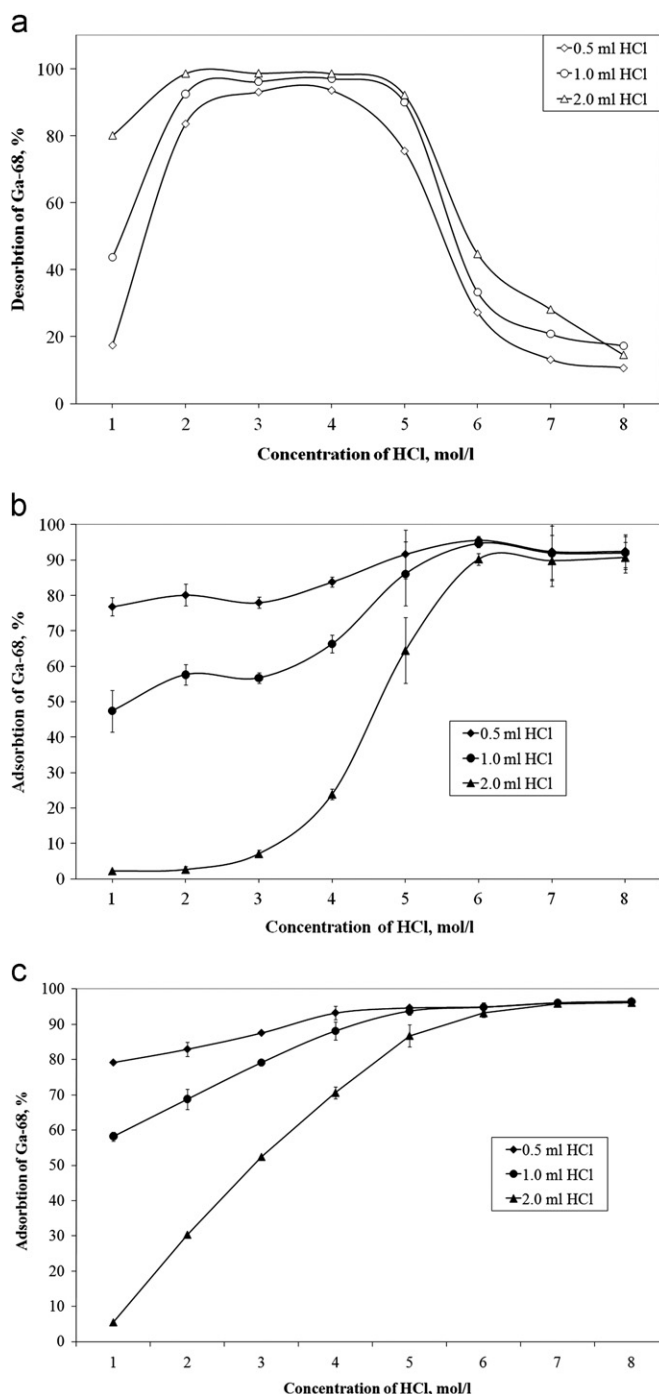
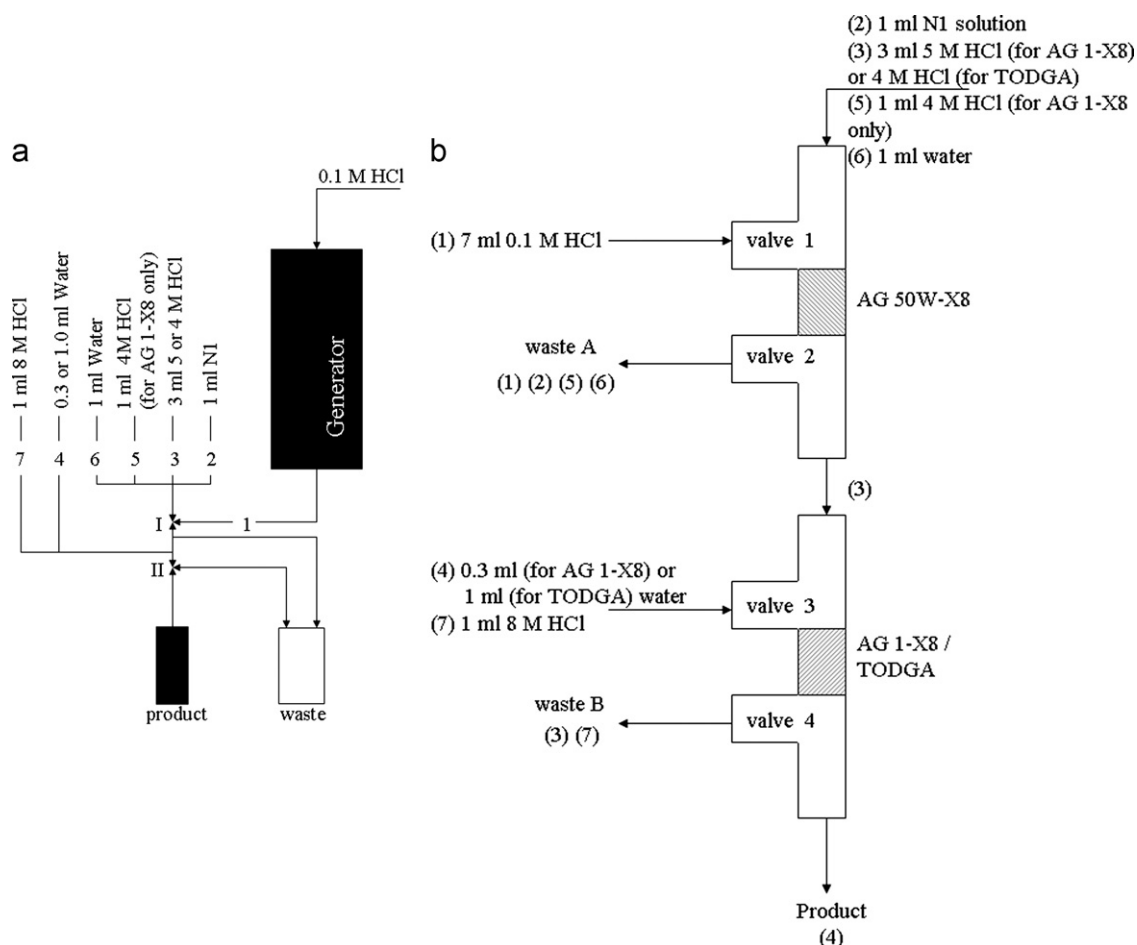


Fig. 2. (a) Yields of  $^{68}\text{Ga}$ , eluted from the cation-exchange resin with 0.5, 1.0 and 2.0 ml of various concentrations of HCl. (b) Yields of  $^{68}\text{Ga}$ , adsorbed at the AG 1-X8 resin (50 mg) with 0.5, 1.0 and 2.0 ml of various concentrations of HCl used to desorb  $^{68}\text{Ga}$  from the AG 50W-X8. (c) Yields of  $^{68}\text{Ga}$ , adsorbed at the TODGA resin (100 mg) with 0.5, 1.0 and 2.0 ml of various concentrations of HCl used to desorb  $^{68}\text{Ga}$  from the AG 50W-X8.



**Fig. 3.** Sketch of  $^{68}\text{Ge}/^{68}\text{Ga}$  generator elution with cation and anion-exchange columns in tandem (a) and indication of detailed flows (b). (a) I—50 mg AG 50W-X8, II—50 mg AG 1-X8 or 100 mg TODGA.

solutions were applied for desorption of  $^{68}\text{Ga}$  from cation exchanger and re-adsorption of the activity on anion-exchange and DGA columns, respectively.

A conceptual flowsheet of the system, including combination of cation-exchange and anion-exchange or TODGA columns is presented in Fig. 3b. The columns are connected consecutively via 3-way valves. In the first step (1) 7 ml 0.1 M HCl passes through the generator and the cation-exchange resin into the waste A. Step (2) involves eluting the cation exchanger with 1 ml of hydrochloric acid/acetone solution N1 into waste B. The third step (3) is the nearly quantitative transfer of  $^{68}\text{Ga}$  from the cation-exchange column onto the anion exchanger or TODGA resin with 3 ml of 5 or 4 M HCl. While  $^{68}\text{Ga}$  is quantitatively adsorbed on both resins, the 3 ml of HCl continues to the waste vial B. From the supplementary anion-exchange or TODGA columns,  $^{68}\text{Ga}$  is eluted using 0.3 or 1.0 ml of water, respectively, (4) into the product vial. With 98% effectivity for the cation exchange part, the 92% and 98% yields obtained for desorbing  $^{68}\text{Ga}$  from the anion exchange and chromatographic TODGA columns, respectively, the overall yield in the final 0.3–1.0 ml water fraction is  $87 \pm 5\%$  (for AG 1-X8) and 96% (for TODGA resin) related to the initial generator eluate (Table 1).

For recondition of the columns the cation-exchange resin should be washed with 1 ml 4 M HCl (5) and 1 ml of water (6), consecutively, into the waste A. The anion-exchange resin should be washed with 1 ml of 8 M HCl (7) into the waste B.

**Table 1**

Distribution of  $^{68}\text{Ga}$  and  $^{68}\text{Ge}$  for every eluted fraction. I—AG 50W-X8, II—AG 1-X8 or TODGA.

N	Solution	Via	Volume (ml)	Yield (%)	
				$^{68}\text{Ga}$	$^{68}\text{Ge}$
<i>AG 50W-X8 (50 mg) only<sup>a</sup></i>					
1	0.1 M HCl	I	7	$0.16 \pm 0.05$	$97.08 \pm 1.99$
2	N1	I	1	$1.43 \pm 0.18$	$2.92 \pm 0.46$
3	N2	I	0.4	<b><math>97.82 \pm 2.01</math></b>	<b><math>3 \times 10^{-2} \pm 2 \cdot 10^{-3}</math></b>
4	4 M HCl	I	1	$0.41 \pm 0.09$	$5 \times 10^{-3} \pm 1 \times 10^{-4}$
5	Water	I	1	$0.18 \pm 0.02$	$3 \times 10^{-3} \pm 2 \times 10^{-4}$
<i>AG 50W-X8 (50 mg)+AG 1-X8 (50 mg)<sup>b</sup></i>					
1	0.1 M HCl	I	7	$0.41 \pm 0.57$	$94.36 \pm 2.44$
2	N1	I	1	$4.50 \pm 1.87$	$3.87 \pm 1.52$
3	5 M HCl	I+II	3	$5.54 \pm 6.98$	$1.23 \pm 0.98$
4	Water	II	0.3	<b><math>86.55 \pm 4.82</math></b>	<b><math>1 \times 10^{-2} \pm 1 \times 10^{-2}</math></b>
5	4 M HCl	I	1	$2.67 \pm 2.08$	$0.42 \pm 0.15$
6	Water	I	1	$0.33 \pm 0.35$	$0.11 \pm 0.05$
<i>AG 50W-X8 (50 mg)+TODGA (100 mg)<sup>b</sup></i>					
1	0.1 M HCl	I	7	$0.58 \pm 0.06$	$91.53 \pm 1.2$
2	N1	I	1	$2.20 \pm 0.09$	$6.75 \pm 1.19$
3	4 M HCl	I+II	3	$1.35 \pm 0.16$	$1.47 \pm 0.30$
4	Water	II	1.0	<b><math>95.63 \pm 0.21</math></b>	<b><math>1 \times 10^{-2} \pm 2 \times 10^{-2}</math></b>
5	Water	I	1	$0.24 \pm 0.05$	$0.25 \pm 0.06$

<sup>a</sup> Data from work of Zheronosekov et al., 2007, total breakthrough of  $^{68}\text{Ge}$  is 170 Bq.

<sup>b</sup> Experimental data, total breakthrough of  $^{68}\text{Ge}$  is 10 Bq.

The complete processing takes about 5 min only. Final  $^{68}\text{Ge}$  contents were below  $10^{-2}\%$ , indicating additionally purification of  $^{68}\text{Ga}$  generator eluates from the initial breakthrough of  $^{68}\text{Ge}$  by a factor  $10^5$ . The pH of the final  $^{68}\text{Ga}$  fraction was  $0.3 \pm 0.1$  according to the hydrochloric acid residues on the columns. This pH can be shifted towards pH 2 using diluted sodium hydroxide solution instead of pure water.

The final  $^{68}\text{Ga}$  fraction was used for preparation of  $^{68}\text{Ga}$ -DOTATOC. For this propose 0.5 M NaAc buffer solution was used to adjust the pH of the reaction mixture to 2.5–3. The radiolabeling was performed utilizing 14 nmol of the peptide providing  $98 \pm 2\%$  labeling yield.

#### 4. Conclusions

A combined protocol of processing  $^{68}\text{Ge}/^{68}\text{Ga}$  generator eluate has been developed. It utilizes the significant advantages of cation-exchanger based processing of  $^{68}\text{Ga}$ . To avoid any presence of acetone in radiolabelling mixtures processing,  $^{68}\text{Ga}$  was transferred from the cation exchanger to the supplementary micro-column filled with strong anion exchanger or a novel extraction chromatographic TODGA resin. An effective processing of generator produced  $^{68}\text{Ga}^{\text{III}}$  could be performed within 5 min only. The  $^{68}\text{Ga}^{\text{III}}$  preparation could be obtained in a reduced volume with high chemical and radiochemical purity in a form useful for radiolabelling reactions. Overall yields of  $^{68}\text{Ga}$  for anion exchanger and TODGA resins are 87% and 96%, respectively.

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