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Determination of ionic ^{68}Ga impurity in radiopharmaceuticals: major revision of radio-HPLC methods

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Abstract
Determination of purity of ^{68}Ga-radiopharmaceuticals is an extremely important part of quality control in routine clinical practice as well as during R&D of ^{68}Ga-radiopharmaceuticals. HPLC results do not always match TLC results. This uncertainty most likely comes from nonspecific sorption of ionic ^{68}Ga on C18 phase. The aim of this study was to develop reliable HPLC analysis procedure. It was shown that simple replacement of trifluoroacetic acid in the eluent with citric acid results into change of the results obtained using HPLC analysis.

Keywords HPLC · TLC · ^{68}Ga · Quality control of radiopharmaceuticals · Radiochemical purity · Citric acid

Introduction

Since the commercialization of ^{68}Ge/^{68}Ga generators ^{68}Ga-radiopharmaceuticals (^{68}Ga-RPs) hold never-fading interest of scientific and medical communities [1–7]. Few ^{68}Ga-RPs are already being used in clinical practice ([^{68}Ga]Ga-DOTA-TOC/TATE/NOC, [^{68}Ga]Ga-PSMA-11/617, etc.). About a dozen of papers on new molecules labeled with ^{68}Ga are published annually.

Quality control of RPs is extremely important during routine clinical practice. Knowing exact value of content of every impurity is even more important during R&D of ^{68}Ga-RPs. Radiopharmaceutical chemistry of ^{68}Ga dictates two main radiochemical impurities in radiopharmaceutical preparations: hydrolyzed ^{68}Ga ("colloidal") and so-called "free" ^{68}Ga [8]. By "free" or "unbound" ^{68}Ga the whole set of ^{68}Ga ionic species that have not underwent complexation or hydrolysis is meant. Henceforth we will refer to these species as "ionic ^{68}Ga". Both impurities have strict limits set by European Pharmacopoeia: e.g., for ^{68}Ga Edotreotide Injection the amount of [^{68}Ga]gallium in colloidal form should not exceed 3 per cent of the total radioactivity due to gallium-68, and the amount of [^{68}Ga]gallium(III) ion should be not more than 2 per cent [9].

HPLC in its nature is not suitable for detection of colloidal particles (such as colloidal ^{68}Ga) since particles like that never reach the detector being captured on the column (or on the precolumn, preferably). Thus, in case of ^{68}Ga-RPs the only radiochemical impurity that can be detected with HPLC is ionic ^{68}Ga. However, it was previously shown that HPLC results do not always match TLC results [10]. Although there are published data [11] declaring that correlation between pharmacopeial HPLC and TLC methods is satisfactory, thorough study [10] has shown that it can be the case only when analyzing radiopharmaceutical preparations with radiochemical purity (RCP) $\geq$ 95% and/or pH $\leq$ 3. The lower RCP and the higher pH of the preparation the higher the error in the determination of the ionic ^{68}Ga content carried out by HPLC.

It is very likely that the uncertainty between HPLC and TLC methods comes from nonspecific sorption of ionic ^{68}Ga on the reversed phase of the HPLC column (C18). In pH range from 3 to 6 a significant capture (up to 80%) of ^{68}Ga ionic forms on the C18 phase is observed [10]. The nature of this phenomenon is a subject of pure radiochemistry and is still to be understood later. But in terms of practical radiopharmacy it leads to significant error in the ionic ^{68}Ga content

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evaluation and, consequently, the error in the resulting RCP value.

In order to get reliable data on the ionic ^{68}Ga content new effective TLC methods were developed and validated [12, 13]. Still in some cases HPLC analysis can be difficult to replace. The aim of the current study was to develop new HPLC analysis procedure giving truly reliable data on the content of ionic ^{68}Ga in RPs.

Experimental

Chemicals and reagents

Only deionized water 18.2 MΩ·cm (Milli-Q Millipore or TKA Smart2Pure) was used. All the chemicals were of pharma, analytical, or HPLC grade (Panreac, Spain, Sigma-Aldrich, USA). The GMP-grade RP precursors DOTA-TATE, NODAGA-RGD$_2$, PSMA-617 and Ga-DOTA-TATE reference standard were purchased from ABX Chemicals (Germany). NODAGA-Lys-(HE)$_2$-folate was synthesized in Moscow State University [14].

^{68}Ge/^{68}Ga generator

^{68}Ge/^{68}Ga generator (Cyclotron Co., Ltd, Obninsk, Russia) with the initial activity of 740 MBq was used.

Preparation of ^{68}Ga-labeled compounds

[^{68}Ga]Ga-DOTA-TATE, [^{68}Ga]Ga-NODAGA-RGD$_2$, [^{68}Ga]Ga-PSMA-617 and [^{68}Ga]Ga-NODAGA-Lys-(HE)$_2$-folate were obtained using standard procedures described elsewhere [3, 15, 16]. In short: to an Eppendorf test tube containing various amounts of precursor solution (5–20 µg), an aqueous solution of sodium acetate (0.1–0.3 M) and eluate of ^{68}Ge/^{68}Ga generator (in 0.1 M HCl) were added. The reaction mixtures were incubated at 25 or 95 °C for 1 to 15 min. The activity of each preparation was from 30 to 200 MBq, pH was in the range of 2.5–6.5, RCP was ≥ 99% in all cases.

Preparation of model samples

To obtain model samples of labeled compounds with RCP < 99% method described in [10] was used. In short: ^{68}Ga-labeled compounds were spiked with solutions containing ionic ^{68}Ga with pH equal to that of every preparation (pH level was adjusted using sodium acetate solution). For data to be reliable it is essential in these experiments that in every sample the pH of spiking solution is equal to that of original one. The concentration of sodium acetate was also kept constant. In order to keep it so the concentration of sodium acetate solution being used and its ratio with ^{68}Ge/^{68}Ga generator eluate were carefully adapted every time with pH control of every sample.

TLC

Previously developed TLC method (*method 1* [12]) was used for the control of RCP of every preparation. Other TLC methods (*methods 2–4*) were used as control and showed complete agreement with *method 1* [9, 10, 12]. The detailed description of methods used is presented in Table 1.

HPLC

HPLC measurements were performed with a Knauer Smartline HPLC system (Germany) equipped with an fLumo radiometric detector (Berthold, Germany). Various base-deactivated octadecylsilyl silica gel columns were used: 100 × 4.6 mm, Chromolith Performance (Merck, Germany), 150 × 3 mm, Luna, and 150 × 4.6 mm, Jupiter (Phenomenex Inc., USA), 150 × 4.6 mm, ACE (Advanced Chromatography Technologies Ltd., UK). All columns have 5 µm particle size and 100 Å pore size. The column thermostat temperature was 40 °C and the eluent flow rate was 0.5–2.0 mL min^{-1} in all cases. Particular isocratic or gradient mode was used for every ^{68}Ga conjugate. Some methods based on pharmacopeial HPLC method for analysis of [^{68}Ga]Ga-DOTA-TATE are presented in Table 2.

Table 1 Description of TLC methods

	Stationary phase	Mobile phase	*Rf*		
			Colloidal ^{68}Ga	^{68}Ga conjugates	Ionic ^{68}Ga
method 1	iTLC-SG*	4% TFA in water (v/v)	0.0	0.4–0.6	0.9–1.0
method 2	iTLC-SG	0.05 M citric acid water solution	0.0	0.0–0.2	0.9–1.0
method 3	iTLC-SG	1 M CH_3COONH_4 in methanol–water mixture (1:1)	0.0	0.9–1.0	0.0–0.1
method 4	Whatman 2 CHR**	0.1% TFA in acetonitrile–water mixture (1:1)	0.0	0.9–1.0	0,8–1.0

*Silica gel impregnated fiberglass strips (Varian and Thermo Fisher Scientific, USA)

**Cellulose chromatography paper (Merck KGaA, Germany)

Table 2 Modifications of pharmacopeial HPLC method for analysis of [^{68}Ga]Ga-DOTA-TATE

#	Column dimensions (mm)	Method	Retention time (min)	Reference
1	150×3.0	Gradient flow (0.6 mL min^{-1}): 0–8–9–14 min = 76–76–40–40% A (A—0.1% TFA in water, B—0.1% TFA in acetonitrile)	4.3	[9]
2	150×3.0	Gradient flow (1 mL min^{-1}): 0–10 min = 80–70% A (A—0.1% TFA in water, B—0.1% TFA in acetonitrile)	3.5	Modifications
3	150×3.0	Gradient flow (0.5 mL min^{-1}): 0–10 min = 80–70% A (A—0.1% TFA in water, B—acetonitrile)	5.0	
4	100×4.6	Gradient flow (1.0 mL min^{-1}): 0–10 min = 80–65% A (A—0.1% TFA in water, B—acetonitrile)	7.3	
5	100×4.6	Gradient flow (1.0 mL min^{-1}): 0–10 min = 80–70% A (A—0.1% TFA in water, B—acetonitrile)	4.5	
6	100×4.6	Isocratic flow (2.0 mL min^{-1}): 80% A, 20% B (A—0.1% TFA in water, B—acetonitrile)	5.3	
7	100×4.6	Isocratic flow (2.0 mL min^{-1}): 80% A, 20% B (A—0.05 M citric acid in water, B—acetonitrile)	1.7	
8	100×4.6	Isocratic flow (2.0 mL min^{-1}): 90% A, 10% B (A—0.05 M citric acid in water, B—acetonitrile)	> 10	
9	150×4.6	Isocratic flow (1.5 mL min^{-1}): 80% A, 20% B (A—0.05 M citric acid in water, B—acetonitrile)	4.1	
10	150×4.6	Gradient flow (1.2 mL min^{-1}): 0–3–6–8–9–15 min = 100–100–0–0–100–100% A (A—0.05 M citric acid in water, B—acetonitrile)	6.9	

Results and discussion

It was previously shown [10, 17] that in cases when ^{68}Ga is presented in the form of small complex (such as [^{68}Ga]Ga-DOTA or [^{68}Ga]Ga-NOTA) there is no capture of ^{68}Ga on C18 column. Thus, the idea of using a complexing agent in the course of HPLC analysis came along. DTPA, DOTA, NOTA and HBED were the first ones to think about. But DOTA, NOTA and HBED are too expensive, and DTPA has its own limitations (such as solubility and acidity considerations). There has to be an easier solution. And there is one.

It is well known that gallium tends to easily form relatively stable citrate complexes [18]. That is why not only citric acid is widely used in TLC analysis of ^{68}Ga-RPs [9, 12], but [^{68}Ga]Ga-citrate itself is also an RP [19, 20]. Citric acid is highly soluble in water and acetonitrile [21] and its 0.05 M water solution has pH 2.5 ± 0.2, which is convenient for analysis of peptide-like molecules using C18 stationary phase. Nevertheless, we did not manage to find any paper on using citric acid as a component of eluent in the HPLC analysis. This may be due to the fact that the presence of citric acid may interfere with the UV-detection. The other inconvenience arising from using citric acid may assumedly be caused by its complexation properties. In any case, when using radio-detection the quality of UV-spectrum plays no role, and in case of ionic ^{68}Ga determination the presence of complexing agent can only be helpful.

The whole idea behind the new HPLC method was simple replacement 0.1% trifluoroacetic acid (TFA) with 0.05 M citric acid. So, the main objective of the current study was to evaluate the applicability of this approach and accordingly to modify existing TFA-based methods so that they become applicable. For this purpose in the first series of experiments [^{68}Ga]Ga-DOTA-TATE conjugate was used.

We have been working with various ^{68}Ga-conjugates, including [^{68}Ga]Ga-DOTA-TATE, for a long time and created few modifications of pharmacopeial HPLC method [9] for everyday use (Table 2, ##2–6). It turned out that even isocratic flow method (Table 2, #6) can give valid and reproducible results when the ratio of the eluents is carefully adapted to one specific column being in use. In this case not only time of analysis is similar to that in pharmacopeial method [9], but there is no need to stabilize the system after every sample. So, it is very easy to carry out the analysis of big batches of samples when it is necessary.

Bearing this in mind we used method #6 (Table 2) as a starting point and tried to replace 0.1% TFA with 0.05 M citric acid. Model samples of [^{68}Ga]Ga-DOTA-TATE with RCP < 80% were analyzed using this new method (method #7). It turned out that method #7 provides results on the ionic ^{68}Ga content being in a very good correlation with data for the same sample obtained with TLC. Interestingly, the retention time of [^{68}Ga]Ga-DOTA-TATE when using method #7 is about three times lower than that obtained when using method #6. However, just like in case with methods ##1–6 and other similar to them [10, 22], in case of using method #7 slight tailing or even doubling of the first peak is observed. With the retention time of [^{68}Ga]Ga-DOTA-TATE being close to that of the ionic ^{68}Ga this tailing leads to poor resolution of the peaks (Fig. 1a). To be able to separate these peaks in order to get more calculable data at first we tried to use less acetonitrile (Table 2, method #8). But with acetonitrile content in the eluent being less than 20% the retention time of [^{68}Ga]Ga-DOTA-TATE was too long (> 12 min). So, we got back to 20%, but used a 150 mm column (Fig. 1b). So, isocratic method #9 (Table 2) was used in further experiments on the comparison of TLC and HPLC results (Figs. 2, 3).

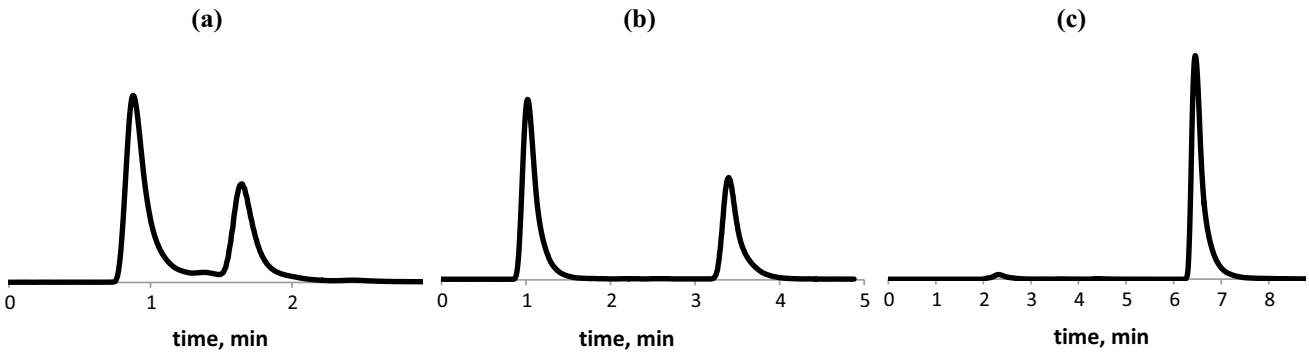
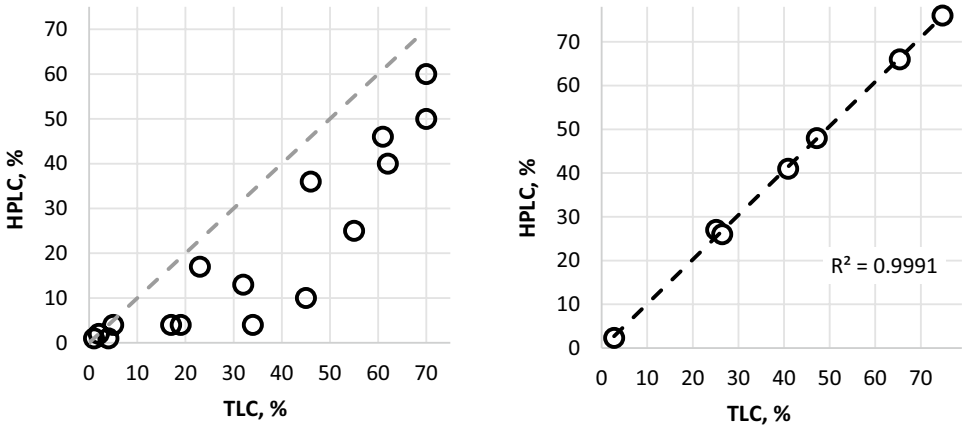


Fig. 1 Chromatograms of [^{68}Ga]Ga-DOTA-TATE samples analyzed using citric acid as a component of the eluent: **a**—method #7, **b**—method #9, **c**—method #10. First peak always corresponds to ionic ^{68}Ga, second peak is [^{68}Ga]Ga-DOTA-TATE

Fig. 2 Correlation between TLC and HPLC data on ionic ^{68}Ga content for model preparations with pH 4.5 (data obtained with method #2 on the left, data obtained with method #9 on the right)



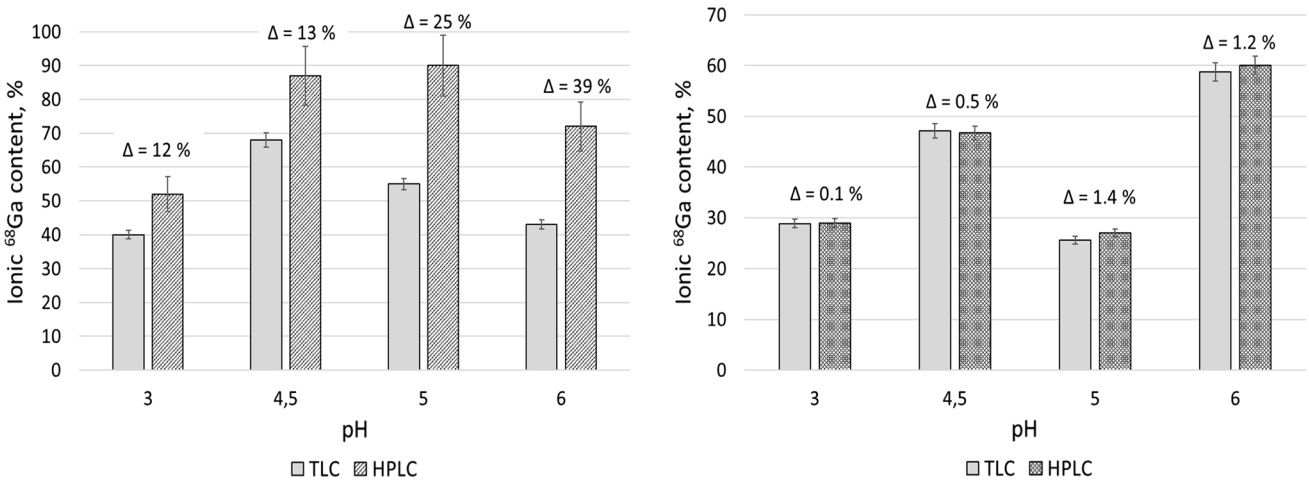


Fig. 3 Comparison of TLC and HPLC data on ionic ^{68}Ga content as functions of pH (data obtained with method #2 on the left [10], data obtained with method #9 on the right)

Results presented in Figs. 2 and 3 clearly demonstrate that the accuracy of method #9 is significantly higher than that of method #2.

In order to check the applicability of the concept of using citric acid in HPLC analysis of ^{68}Ga-preparations, in the second series of experiments we analyzed three

more conjugates: [^{68}Ga]Ga-NODAGA-RGD$_2$, [^{68}Ga]Ga-PSMA-617 and [^{68}Ga]Ga-NODAGA-Lys-(HE)$_2$-folate. No surprise that isocratic flow method used for [^{68}Ga]Ga-DOTA-TATE is applicable to no one of those three. Thus, the method had to be modified.[^{68}Ga]Ga-NODAGA-RGD$_2$ and [^{68}Ga]Ga-PSMA-617 needed the presence of more than 50% acetonitrile in the eluent to have retention time of the main peak less than 10 min.[^{68}Ga]Ga-DOTA-TATE has the retention factor close to 1 already when using 30% acetonitrile isocratic flow; and [^{68}Ga]Ga-NODAGA-Lys-(HE)$_2$-folate acts the same way unless the concentration of acetonitrile in the eluent is very low. Consequently we ended up using the following basic gradient flow: 0–3–6–8–9–15 min = 100–100–0–0–100–100% A (A—0.05 M citric acid in water, B—acetonitrile, #10 Table 2). Retention times of all ^{68}Ga-species obtained are specified in Table 3. Chromatogram of [^{68}Ga]Ga-DOTA-TATE analyzed using method #10 is presented in Fig. 1c. In this case the sample was not spiked with ionic ^{68}Ga containing solution; this is why the first peak (2.3 min) is relatively small. Still Fig. 1c clearly demonstrates decent resolution of the peaks provided using method #10.

Our data (Figs. 2, 3, Table 3) have conclusively demonstrated that replacement 0.1% TFA with 0.05 M citric acid can be effectively applied to a number of other ^{68}Ga-RPs HPLC analysis procedures. In every specific case particular isocratic or gradient flow method can be easily developed. Our study has shown that in case of using citric acid containing eluents no ^{68}Ga is captured on HPLC columns.

Table 3 Retention times of ^{68}Ga-species obtained using method #10

Ionic ^{68}Ga	2.40 ± 0.16 min
[^{68}Ga]Ga-DOTA-TATE	6.46 ± 0.06 min
[^{68}Ga]Ga-NODAGA-Lys-(HE)$_2$-folate	6.50 ± 0.19 min
[^{68}Ga]Ga-NODAGA-RGD$_2$	6.61 ± 0.06 min
[^{68}Ga]Ga-PSMA-617	6.86 ± 0.13 min

Every conjugate was analyzed at least three times

In order to evaluate the usability of citric acid based HPLC methods for precursors content evaluation preliminary validation tests were run using method #9 (Table 2). For 0.5–1.5 mg mL^{-1} DOTA-TATE solutions the peptide amount can be effectively determined using method #9 and UV-detection at 220 nm (wavelength recommended in [9]). The retention time of DOTA-TATE analyzed using this method is about 3.2 min. When analyzing more radiopharmaceutical-like preparations (25–75 µg mL^{-1} DOTA-TATE solutions) it turned out that that at 220 nm signal/noise ratio is too low, moreover, the peak is barely distinguishable which leads to relatively poor linearity. This wavelength cannot be used for proper quantitative DOTA-TATE evaluation.

According to our results the DOTA-TATE solution in citric acid has two absorption peaks in its UV–visible spectrum: 234 nm and 278 nm. At 234 nm and 250–295 nm the peak with retention time of 3.2 min can be clearly seen and quantitatively evaluated. The comparison of the DOTA-TATE peak parameters obtained with two methods is presented in Table 4. In this table parameters ##1–5 are calculated for 50 µg mL^{-1} DOTA-TATE solution. Concentration-signal function linearity parameters (R^2, #6) are calculated for 25–75 µg mL^{-1} range.

The parameters obtained for DOTA-TATE quantitative analysis demonstrate that in principle "cold" peptide-like molecules can be analyzed with citric acid based HPLC methods, although in the case of every single molecule another particular approach may be needed.

Another "cold" experiment was carried out in order to evaluate the influence of the buffer agent. For this purpose three 0.1 mg mL^{-1} solutions of Ga-DOTA-TATE reference standard (ABX Chemicals) were prepared. The first one was containing nothing but the reference standard. The second one was prepared in 0.1 M sodium acetate water solution, and the third one was prepared in 0.1 M HEPES solution. All three samples were analized using method #9 (Table 2). The only slight difference between the three chromatograms was the shape of the dead volume peak. The retention time, shape and the area of Ga-DOTA-TATE peak (measured with UV detector) remained unaffected by the presence of the

Table 4 The comparison of HPLC methods for analysis of DOTA-TATE

Parameter		Method #6 (Table 2, TFA based)	Method #9 (Table 2, citric acid based)				
UV detection wavelength		220 nm	220 nm	234 nm	254 nm	278 nm	290 nm
1	Retention factor	1.8	1.4	1.4	1.4	1.4	1.4
2	S/N (hight)	107	19	52	194	603	276
3	Peak width, 5%	0.239	0.354	0.213	0.229	0.232	0.317
4	Peak width, 50%	0.102	0.086	0.086	0.085	0.085	0.084
5	Plate number	2533	5611	5477	5474	5540	5581
6	R^2	0.999	0.973	0.996	0.999	0.998	0.995

buffers. Thus, the method is robust to the buffer change, at least with sodium acetate and HEPES buffers, which are the most widely used buffers for ^{68}Ga-RPs preparations.

Conclusions

Apart from our previously obtained data [10] there is at least one published testimony [17] on the fact that we are not the only ones observing the phenomenon of the uncertainty between HPLC and TLC methods when analyzing gallium-68 radiopharmaceutical preparations. We have also received a number of personal communications reporting that HPLC results can differ from TLC significantly. Unfortunately, data like these usually are not published. And it's easy to understand why: no one wants to have an RP with RCP < 90%, so there's no need to bother about how analysis of these "bad" preparations will go. We find this reasoning wrong not only from the fundamental point of view, but from the practical point of view too. In routine clinical practice everyone hopes, of course, that we always obtain high quality product. But the risk of something going wrong is always there. And in this one out of a million times, when the content of ionic ^{68}Ga in the preparation will be > 5% pharmacopeial HPLC method [9] will inevitably fail us indicating that there is nothing wrong [10, 17].

Reliable HPLC analysis procedure for determination of ionic ^{68}Ga in radiopharmaceutical preparations was developed and validated. It was shown that simple replacement of trifluoroacetic acid in the eluent with citric acid results into dramatic positive change of the results obtained using HPLC analysis. It was also found that amount of "cold" DOTA-TATE can be analyzed with citric acid based method as well using UV-detection (e.g., at 254 nm).

This new method can be very useful during R&D of ^{68}Ga-radiopharmaceuticals. It also can be considered as new method of choice in routine clinical practice.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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