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Cyclotron production of ^{68}Ga and "in house" preparation of positron emission tomography (PET) radiopharmaceuticals

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Abstract
Solid targets and a medical cyclotron were used for the large-scale preparation of ^{68}Ga. The target preparation, proton irradiation of a ^{68}Zn-enriched target, dissolution of the target, separation of ^{68}Ga from zinc, and labelling procedure for the [^{68}Ga]Ga-DOTATOC, [^{68}Ga]Ga-DOTANOC, and [^{68}Ga]Ga-PSMA-11 radiopharmaceutical are presented. The radiopharmaceuticals were prepared with a good manufacturing practices quality of up to 6 GBq of the final product per batch at the end of synthesis (EOS) time. A quality control of ^{68}Ga-labelled tracers showed an acceptable radiochemical purity and stable product at least five hours after the EOS. A separation procedure for the effective separation of ^{68}Ga from an iron interferent was developed.

Keywords Peptide · Cyclotron · Radiopharmaceuticals · ^{68}Ga · Solid target

Introduction

The demand for ^{68}Ga has increased considerably over the last few years due to its extensive use in positron emission tomography (PET) imaging germanium ^{68}Ge/^{68}Ga generators have been used in the field of nuclear medicine for over half a century. The production of ^{68}Ga using first-generation germanium generators began in the 1960s [1], but the first commercial use of the ^{68}Ge/^{68}Ga generators did not begin until the early twenty-first century [1].

The commercial generators usually consist of 1.85 GBq (50 mCi) ^{68}Ge. The activity elution of ^{68}Ga is limited during the operation of the generator since the activity of the parent ^{68}Ge decreases over time (half-life 271 days) and there is a potential threat of ^{68}Ge breakthrough. In the US, approved ^{68}Ge/^{68}Ga generators are currently being used, including E&Z Galliapharm and IRE Galli-Eo [2, 3].

The preparation of cyclotron ^{68}Ga can be achieved through the irradiation of liquid or solid targets. Pandey et al. and Alves et al. dealt with the preparation of these liquid targets [4, 5]. The proton irradiation of a ^{68}Zn solution may lead to the formation of ^{68}Ga [4]. The production of radioisotopes with half-lives longer than that of ^{68}Ga (T1/2 = 67.7 min) i.e. ^{66}Ga, (T1/2 = 9.5 h), and ^{67}Ga (T1/2 = 3.3 days) requires attention. As a result, the radionuclide purity of the ^{68}Ga solution will be reduced. The elimination (^{66}Ga and ^{67}Ga) requires lowering the incident beam energy and the ^{66}Ga production is determined by the presence of a ^{66}Zn target impurity. The ^{67}Ga radioisotope has an effective cross-section of 800 mb at Ep = 20 MeV [6]:

$$^{68}\mathrm{Zn}\,(\mathrm{p},2\mathrm{n})^{67}\mathrm{Ga} \tag{1}$$

while the ^{66}Ga radioisotope is formed by a nuclear reaction:

$$^{66}\mathrm{Zn}\,(\mathrm{p},\mathrm{n})^{66}\mathrm{Ga} \tag{2}$$

and has an effective cross-section of 700 mb at Ep = 13 MeV [7].

Compared with generators, liquid targets have the advantage of being able to prepare the same activity ^{68}Ga for every production. While liquid targets are simpler in terms of material handling, they still require some kind of recycling ^{68}Zn with particular care being taken to accumulate

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long-lived and stable impurities.The main advantage of using liquid targets is the low radiation load for operators during handling with a radioactive solution. The application of liquid targets using protons to irradiate ^{68}Zn is covered by a European patent [8]. When using liquid targets, the ^{68}Ga separated from the ^{68}Zn solution acts as a direct substitute for the ^{68}Ga produced by the ^{68}Ge/^{68}Ga generators. The preparation of ^{68}Ga from liquid targets is associated with a risk of damaging the cyclotron if the target fails. The risk of target failure could be eliminated by using proper beam shape and conducting regular target maintenance. Cyclotrons are usually separated from the targets by a beamline equipped with fast valves which help protect the cyclotron vacuum.

Solid targets provide much higher ^{68}Ga activities than liquid targets. Such target materials could consist of ZnO or elemental Zn [9–12].

Another method for solid target preparation is the electrolytic deposition of enriched ^{68}Zn on a platinum disk [13]. The dissolution time as well as the separation of ^{68}Ga must be minimised as much as possible. The advantage of automation is that it helps minimise the operator radiation exposure as well as the contamination of the target itself during its transport [9, 11].

Solid targets are advantageous since they can produce a high activity of ^{68}Ga. Up to 74–148 GBq of ^{68}Ga can be obtained in 1–2 h of irradiation time, which is more than what can be achieved with liquid targets or ^{68}Ge/^{68}Ga generators. [^{68}Ga]Ga-PSMA-11 has been prepared with an activity of 43 GBq using a solid target with a high activity of about 100 GBq alongside the separation of ^{68}Ga using a TK – 400 column from *TRISKEM,* synthesised in *FASTLAB* [2].

The European Pharmacopoeia has approved the use of ^{68}GaCl$_3$ prepared by cyclotron since 2021. Enriched ^{68}Zn is commonly used for the preparation of ^{68}Ga by proton irradiation. In the European Pharmacopoeia monograph for cyclotron-produced ^{68}Ga, the limit for its radionuclide purity is 98% [14]. In 2019, the Food and Drug Administration (FDA) approved the use of [^{68}Ga]Ga-DOTA-TOC for imaging gastroenteropancreatic tumours [15]. In 2020, the FDA approved the use of [^{68}Ga]Ga-PSMA-11 for the diagnosis and imaging of prostate cancer. In Europe (Austria, Germany, and France), [^{68}Ga]Ga-DOTA-TOC was approved as early as 2016 [16]. Furthermore, ^{68}Ga can be used to label [^{68}Ga]Ga-DOTA-NOC and [^{68}Ga]Ga-DOTA-TATE, which are used to diagnose and image neuroendocrine tumours.

Zinc and mainly iron can negatively impact the radiochemical yield (RCY) of radiopharmaceuticals due to their complexation reactions with peptides in competition. In its purest form without metal contaminants, ^{68}Ga requires a separation procedure. Fe(III) has similar chemistry to Ga(III). One scheme to improve the separation of iron from gallium involves a reduction process with ascorbic acid from Fe(III) to (II) while Ga(III) is not affected by ascorbic acid [17]. Ascorbic acid is routinely used as a protective agent in peptide radiolabelling [11]. The principles of reduction of Fe(III) by ascorbic acid have also been used in the analytical determination of Fe(III) by its sorption on annex resin and elution with 5% ascorbic acid in 0.5 mol dm^{-3} hydrochloric acid (HCl). This method allows the preconcentration of iron and its determination by spectrophotometry [18].

We here describe a target preparation procedure using the proton irradiation of enriched ^{68}Zn, and the dissolution, separation, and labelling procedure for [^{68}Ga]Ga-DOTATOC, [^{68}Ga]Ga-DOTANOC, and [^{68}Ga]Ga-PSMA-11 radiopharmaceuticals. A chemical reaction that was used for iron reduction with ascorbic acid to separate iron from ^{68}Ga is also presented.

Experimental

All chemicals used in this work were of pharmaceutical or supra pure quality. The corresponding PSMA-11 peptide used met good manufacturing practice (GMP) and active pharmaceutical ingredient (API) for clinical trials and was purchased from Advanced Biochemical Compounds (ABX, Germany). TK-400 ion exchange columns were purchased from TRISKEM (France) and contained octanol impregnated on an inert support. All chemicals used for the syntheses such as NaCl, ethanol, sterilised water for injection, phosphate buffer and water/ethanol (1:1), HEPES (2-[4-(2-hydroxyethyl)piperazin-1-yl]ethane-1-sulfone), and cartridges were purchased from ABX. The HCl (37% suprapur®) was purchased from Millipore Sigma (USA). Sterile FG Millex filters and sterile FG Millex ventilation filters were also obtained by Millipore Sigma.

The dissolution of the target containing enriched 98.2% ^{68}Zn metal rough powder Campro Scientific GmbH (Germany) on a niobium coin was performed at the ^{68}*Ga-DISTA* dissolution station (BIONT a.s., Bratislava, Slovakia). The target was dissolved in 7 mol dm^{-3} HCl. The ^{68}Ga separation itself took place at the ^{68}*Ga–SEPUR* separation station (BIONT a.s., Bratislava, Slovakia). The ^{68}Ga was separated from ^{68}Zn on a TK-400 column by washing with 7 mol dm^{-3} HCl and the ^{68}Ga was eluted with 0.05 mol dm^{-3} HCl. The peptide was labelled with ^{68}Ga on the appropriate commercial production cassette in the *TRACERlab MX* synthesis module made by GE-healthcare.

The radiopharmaceuticals were analysed according to European Pharmacopoeia procedures. The activity and half-life of [^{68}Ga]Ga-PSMA-11 PET radiopharmaceuticals were determined using a Curiementor PTW (Germany) dose calibrator. The radionuclide purity of the radiopharmaceutical was determined with a Canberra Packard (USA) germanium detector. The [^{68}Ga]Ga-DOTATOC, [^{68}Ga]Ga-DOTANOC, and [^{68}Ga]Ga-PSMA-11 were analysed for radiochemical and chemical purity by high-performance liquid chromatography (HPLC) on a 1260 Infinity instrument (Agilent Technologies, USA) using an Elysia s. POMO radiometric detector (Belgium) and an Agilent Technologies (USA) UV/Vis detector. An Elysia-Raytest (Belgium) MiniGita scanner was used for both thin layer chromatography (TLC) and instant TLC (iTLC) measurements. The solvent residues were measured on an Agilent 7890 B gas chromatograph (Agilent Technologies), with an Agilent 7697 A headspace sampler, on a gas chromatography (GC) column (Resteck Corporation, USA).

The metals in the radiopharmaceuticals (zinc and iron) were determined by voltammetric differential pulse polarography on a hanging mercury drop electrode (HMDE; Metrohm Ltd., Switzerland).

The voltammetric determination of iron with concentrations < 200 μg dm^{-3} was performed on a HMDE. The detection limit for this method was β (Fe) = 2 μg dm^{-3}. The limit of quantification was β (Fe) = 6 μg dm^{-3}. The sensitivity of the method could not be improved by deposition. Iron was determined using the HMDE method in an electrolyte consisting of solutions of triethanolamine at a concentration of 0.05 mol dm^{-3}, potassium bromate at a concentration of 0.1 mol dm^{-3}, and NaOH at a concentration of 0.3 mol dm^{-3}. Ultrapure water (Merck suprapur® Millipore Sigma) with a resistance of > 18 MΩ cm (25 °C), type I (ASTM D1193) was used. The method was suitable for samples with iron concentrations of up to 200 μg dm^{-3}. The required pH of the measured solution should be 12 and max. 12.4 [19].

Zinc was determined in a solution prepared from sodium acetate and potassium chloride on a HMDE using anodic stripping voltammetry. The reagents used were required to be of the purest quality and used 30% sodium hydroxide, 100% acetic acid, potassium chloride (TraceSelect® Sigma-Aldrich), a commercially available Zn standard solution with concentration 1 g dm^{-3} in ultrapure water. A standard solution of β (Zn(II)) = 10 mg dm^{-3} was prepared using c (HNO_3) = 0.014 mol. If necessary, the pH of the solution was adjusted to 4.6 ± 0.2 [20].

Target preparation and irradiation

The target was prepared by pressing zinc (^{68}Zn) powder with an enrichment of 98.2% and weighing about 25–35 mg onto a niobium coin with a purity of 99.99%. A space for zinc powder was excavated on the niobium coin, which was pressed with a hand press at a pressure of 195 MPa. The prepared target was placed in a ^{68}Ga-solid target irradiation station and irradiated with protons at 10.9 MeV. The 18 MeV cyclotron beam was degraded to 10.9 MeV with a beam intensity of 35 µA hitting the target. The target coin was water-cooled from behind by triscus cooling. Following its irradiation, the target fell into the dissolution vessel using an automated control system ^{68}*Ga-DISTA*.

Dissolution and separation

The dissolution of the irradiated target was monitored with the $^{68}Ga - DISTA$ control system. Dissolution was performed using 10 cm^3 of 7 mol dm^{-3} HCl. Subsequently, the dissolved ^{68}Ga was transferred to the separation module through the transport capillary.

The separation of ^{68}Ga from ^{68}Zn took place in a ^{68}*Ga–SEPUR* module. Initially, the *TRISKEM* sorbent TK-400 column was conditioned with 7 mol dm^{-3} HCl and the ^{68}Ga solution from the dissolved target was thereafter loaded to the separation column. Seven mol dm^{-3} HCl was used to wash off the ^{68}Zn out of the column. In the last step, ^{68}Ga was eluted with 0.05 mol dm^{-3} HCl. The ^{68}Ga was separated with 8 cm^3 0.05 M HCl and diluted with another 7 cm^3 of 0.05 HCl to achieve a total volume of 15 cm^3. No further pH adjustments were made. More experimental details are included in the experimental section.

^{68}Ga labelling of peptides

All gallium-labelled radiopharmaceuticals such as [^{68}Ga]Ga-DOTANOC (50 µg precursor), [^{68}Ga]Ga – DOTATOC (50 µg precursor), and [^{68}Ga]Ga-PSMA-11 (10 µg precursor) were prepared by the methods proposed by ABX for the *TRACERlab MX* module. DOTANOC (50 µg) and ^{68}Ga (4.1 GBq), DOTATOC (50 µg) and ^{68}Ga (2.76 GBq), and PSMA-11 (10 µg) and ^{68}Ga (6.37 GBq) for all prepared radiopharmaceuticals the ratio of precursor to ^{68}Ga was more than 250 times.

^{68}Ga was transferred from the ^{68}*Ga–SEPUR* separation unit to the *TRACERlab MX* module where it was a trapped on a PS-H$^+$ cation exchange column. The acidity of the radiopharmaceutical ^{68}Ga had to be adequate as the PS-H$^+$ column loses sorption efficiency for gallium with increasing acid concentrations. ^{68}Ga was eluted from the column with a 5 mol dm^{-3} NaCl solution and into a reactor containing the precursor dissolved in a 1.5 mol dm^{-3} HEPES buffer solution. The reaction was performed at 125 °C for 6 min. The product was separated from the impurities on a C-18 column and eluted with the aqueous-ethanol solution. Osmolality was adjusted with a phosphate buffer.

Quality control

The resulting radiopharmaceutical was subjected to several tests under the European Pharmacopoeia for quality control. A HPLC instrument equipped with a Zorbax Eclipse C-18 column (250 × 4.6 mm I.D. 5 µm) was used to determine its chemical and radiochemical purity. The composition of the mobile phase was: A) 5% ACN (V/V) + 10 mmol dm^{-3} TFA; B) CAN + 10 mmol dm^{-3} TFA. The temperature of the analytical column was set to 25 °C. The flow-rate of the mobile phase was 1 cm^3/min. For the detection of the separated complexes and free peptides, the UV/DAD was used at wavelengths of 225 nm, 240 nm, and 280 nm. The gradient profile was from 10% B in 0–2 min, linearly increasing to 75% B for 10 min, 75% B for 2 min, and equilibration for 1 min to 10% B.

The radiopharmaceutical was measured by TLC using iTLC-SG chromatographic paper with a mobile phase containing 1 mol dm^{-3} of ammonium acetate with MeOH in a ratio of 1:1. The analysis was developed on 8 cm chromatographic paper. Subsequently, the TLC plate was scanned on a MiniGita scanner and evaluated with the GINA-Star TLC software.

Results and discussion

The ^{68}Ga isotope was produced using a Cyclone IBA 18/9 cyclotron. Different types of degraders were examined and the optimal energy of 10.9 MeV was chosen to obtain the highest radionuclide purity of ^{68}Ga. Proton irradiation of a ^{68}Zn-in-niobium press powder target was performed with a ^{68}Ga solid target station. The ^{68}*Ga-DISTA* dissolving station was used to dissolve the target in 10 cm^3 of HCl for six minutes inside a cyclotron vault at room temperature. A dissolution time of six minutes was sufficient to dissolve the target material completely. An ethylene tetrafluoroethylene (ETFE) transfer capillary was used to deliver the solution with dissolved zinc powder and ^{68}Ga to a separation module in a "class-C" production room. The ^{68}*Ga-SEPUR* module was used for the separation of ^{68}Zn and ^{68}Ga. The scheme of the separation ^{68}*Ga-SEPUR* module is shown in Fig. 1.

The separation procedure consisted of conditioning the TK-400 column (the volume of the TK-400 resin was 2 cm^3 and the particle size was 50–100 µm) with 5 cm^3 of 7 mol dm^{-3} HCl. The TK-400 column was loaded with 10 cm^3 of the ^{68}Ga solution obtained from the dissolved target. The column was washed with 35 cm^3 of 7 mol dm^{-3} HCl to eluate the zinc contents. The ^{68}Ga was then eluted from the column after using 15 cm^3 of 0.05 mol dm^{-3} HCl.

As previously mentioned, the protocol described here was used for the preparation of radiopharmaceuticals labelled with ^{68}Ga, such as [^{68}Ga]Ga-DOTANOC (50 µg DOTANOC), [^{68}Ga]Ga -DOTATOC (50 µg DOTATOC), and [^{68}Ga]Ga -PSMA-11 (10 µg PSMA-11). The time from the end of the beam (EOB) to the end of the analysis was 88 min, and the decay corrected radiochemical yield of the ^{68}Ga-radiopharmaceuticals was between 50 and 60%.

The ^{68}Ga-labelled radiopharmaceuticals underwent a quality control using the procedures described in the experimental part. Their radiochemical purity was determined by TLC and HPLC (Fig. 2 and Table 1). Around 93.0% of the radiochemical purity of ^{68}Ga-PSMA11 (Fig. 2) referred only to the main peak on the chromatogram, but PSMA-11 formed two isomers with Ga, and the sum of the secondary and main peaks was included in the total radiochemical purity. In the end, a value of 99.9% was obtained.

With the exception of the sterility and LAL tests that were determined several days after the synthesis, the quality control tests were performed immediately after the synthesis

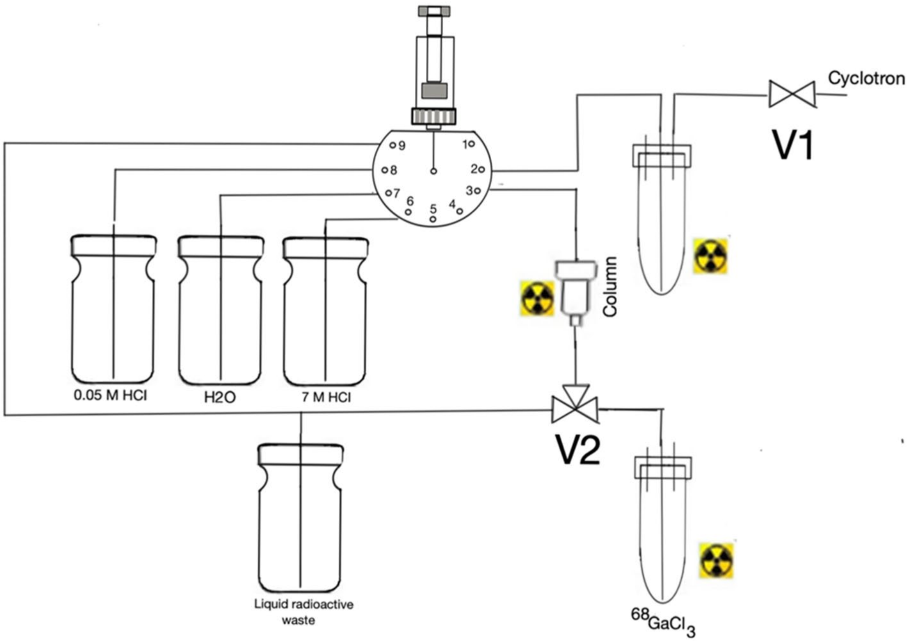
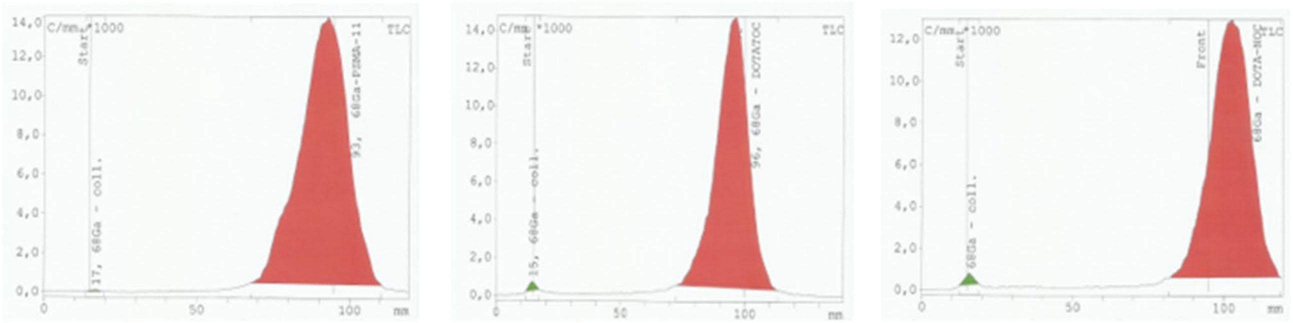
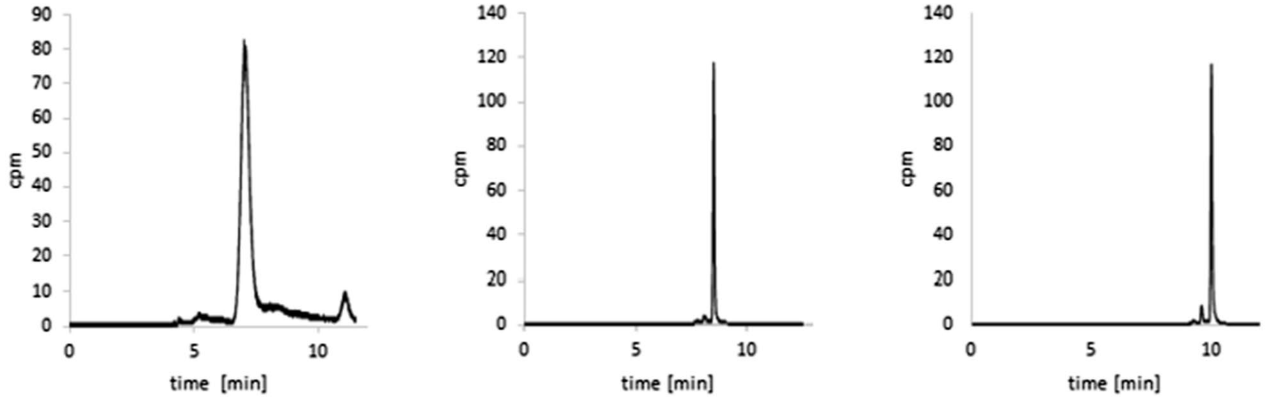


Fig. 1 Scheme of the ^{68}*Ga-SEPUR* separation module



$[^{68}\text{Ga}]$Ga-PSMA-11 99.9 % TLC $[^{68}\text{Ga}]$Ga-DOTATOC 99.4 % TLC $[^{68}\text{Ga}]$Ga-DOTANOC 99.1 % TLC



$[^{68}\text{Ga}]$Ga-PSMA-11 93.0 % HPLC $[^{68}\text{Ga}]$Ga-DOTATOC 99.7 % HPLC $[^{68}\text{Ga}]$Ga-DOTANOC 99.6 % HPLC

Fig. 2 Thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC) analyses of $[^{68}\text{Ga}]$Ga-PSMA-11, $[^{68}\text{Ga}]$Ga-DOTANOC, and $[^{68}\text{Ga}]$Ga-DOTANOC

Table 1 Production and analysis of $[^{68}\text{Ga}]$Ga-DOTATOC, $[^{68}\text{Ga}]$Ga-PSMA-11, and $[^{68}\text{Ga}]$Ga-DOTANOC

	$[^{68}\text{Ga}]$Ga-DOTATOC	$[^{68}\text{Ga}]$Ga-DOTANOC	$[^{68}\text{Ga}]$Ga-PSMA-11	Limit
Mass of target ^{68}Zn [mg]	25	27	27	n/a
Amp-hour [µA/hr]	15	25	35	n/a
Current [µA]	29.5	30.5	29.1	n/a
Time EOB to EOS [min]	86	88	89	n/a
Activity EOS [GBq]	2.76	4.1	6.37	n/a
Appearance	Clear	Clear	Clear	Clear
γ-spectrometry confirmed id by 511 & 1077 [keV]	Confirmed	Confirmed	Confirmed	Confirmed
$T_{1/2}$ [min]	65.7	67.2	67.1	62–74 min
Radiochemical purity TLC & HPLC [%]	99.4	99.11	99.9	> 91
pH	7.5	7.5	7.5	7.5
Radionuclide purity [%]	100	100	100	> 98
Concentration Fe [µg /GBq]	–	2	< 0.8	< 10
Concentration Zn [µg/GBq]	–	4.1	1.9	< 10
Pyrogen; Sterility	< 175 EU/max; Ster	< 175 EU/max; Ster	< 175 EU/max; Ster	< 175 EU/max; Ster
HEPES [µg/ml]	< 20	< 20	< 20	< 20

was completed. The data in Table 1 fulfill the criteria determined by the European Pharmacopoeia.

According to the European Pharmacopeia, the purity of a radionuclide is expected to be 98% for ^{68}Ga produced by cyclotrons. The main radionuclides causing a decrease of ^{68}Ga purity are ^{66}Ga and ^{67}Ga. These radionuclides are produced through the irradiation of ^{66}Zn and ^{68}Zn nuclear reaction ^{66}Zn(p,n)^{66}Ga and ^{68}Zn(p,2n)^{67}Ga. The quantity of ^{66}Ga depends on the purity of the enriched starting material while the activity of ^{67}Ga depends on the energy of the protons used for irradiation. According to our results, the purity stayed above 98% until seven hours after the EOB in the proton energy of 10.9 MeV (Fig. 3).

Separation scheme for iron and gallium separation

The reduction potential of Fe(III) to Fe(II) at a low pH was around + 0.8 V and that of Ga(III) to Ga(II) was around – 0.6 V [14, 21]. Ascorbic acid can selectively reduce Fe(III) because of the large difference in their potentials. The fact that TK-400 resins do not strongly bind Fe(II) means that Fe(II) could be eluted with no loss of ^{68}Ga. The ^{68}Ga was eluted from the TK-400 column with 0.05 mol dm^{-3} HCl. In this study, 50 mg of iron solutions in 0.5 dm^{3} of 7 mol dm^{-3} HCl were used for the experiments with iron. The TK-400 resins sorbed very well iron from 7 mol dm^{-3} HCl concentration (step 1, Table 2), and only a small amount of iron(III) was desorbed using 1% ascorbic acid in a strongly acidic medium (steps 2–5, Table 2).

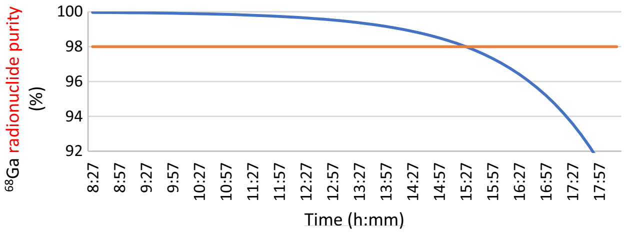


Fig. 3 Radionuclide purity at 10.9 MeV of proton irradiation (^{68}Ga ≥ 98%; 7:00 h), EOB = 8:27

By decreasing the acidity of the HCl, we were able to increase the efficacy of washing ^{68}Ga from the TK-400 column. Mixing a 1:1 solution of 4 mol dm^{-3} HCl and 1% ascorbic acid with 5 mol dm^{-3} NaCl provided a solution containing sufficient chloride for complexing ^{68}Ga, allowing the development of negative chloride complexes and sufficient protons for protonating octanol to support a positive surface on the TK-400 resin. The sorption of gallium was due to the ion exchange mechanism of the negative gallium complex with a positive surface of the TK-400. The TK-400 resin was eluted with a solution consisting of 2.5 mol dm^{-3} NaCl, 2 mol dm^{-3} HCl, and 0.5% ascorbic acid, resulting in a very effective separation of iron from gallium. The ^{68}Ga was washed out from the column with 0.05 mol dm^{-3} HCl. The acidity of the solution left in the dead volume of the resin was less acidic. The ^{68}Ga eluted solution did not require dilution to achieve an acidity compatible with the ^{68}Ga separation step of the *TRACERlab MX* synthesiser module. The determined of H^{+} proton concentration was 0.49 mol dm^{-3} and that of Cl^{-} was 0.98 mol dm^{-3} based on titration (step 5).

Step 1: Loading iron and ^{68}Ga in 7 mol dm^{-3} HCl into the TK-400 column; step 2: washing with acid in 7 mol dm^{-3} HCl; step 3: washing with 1% ascorbic acid in 7 mol dm^{-3} HCl; step 4: washing with a solution consisting of 2.5 mol dm^{-3} NaCl, 2 mol dm^{-3} HCl, and 0.5% ascorbic acid; step 5: elution with 0.05 mol dm^{-3} HCl. The volume 5 cm^{3} in the all steps.

The efficiency of the separation process was 95.3% decay corrected. The ^{68}Ga was obtained from the Galli-Eo ^{68}Ge/^{68}Ga generator. The Curiementor isotope calibrator was used to measure the ^{68}Ga activity of loading solutions No. 1 and 5, while a NaI scintillation detector was used to measure the activity of washing solutions Nos. 2–4 because their activity was too low to be determined with Curiementor. The elution profile of ^{68}Ga from Fe influenced by the mobile phase is presented in Fig. 4. The initial iron activity was 500 µg/cm^{3}. After applying the sample (step 1), 1.94% of iron flowed into the eluate. After using the reducing solution (step 4), 98% of the iron was leached. A 95.3% activity was achieved when ^{68}Ga was eluted with 0.05 M HCl.

Table 2 Sorption and elution of iron from the TK-400 using 1% ascorbic acid in 7 mol dm^{-3} HCl

Step	V [5 cm^{3}]	Sorbent TK-400 Fe [µg/cm^{3}]	Solution Fe [µg/5 cm^{3}]
1	Loading iron in 7 mol dm^{-3} HCl to column TK-400	490	9.7
2	Washing with 1% ascorbic acid in 7 mol dm^{-3} HCl	479.4	10.9
3	Washing with 1% ascorbic acid in 7 mol dm^{-3} HCl	471.1	8.4
4	Washing with 1% ascorbic acid in 7 mol dm^{-3} HCl	459.3	11.8
5	Washing with 1% ascorbic acid in 7 mol dm^{-3} HCl	448.5	10.9
6	Elution with 0.05 mol dm^{-3} HCl	< 1	448.5
	Sum	–	500.2

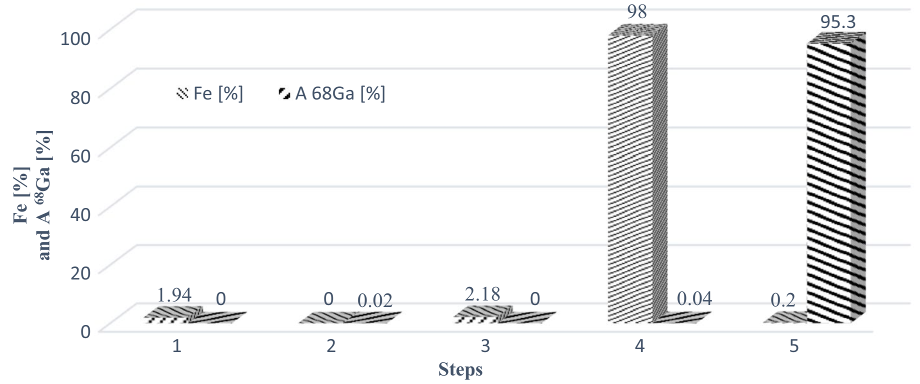


Fig. 4 Elution profiles of ^{68}Ga and Fe depending on the mobile phase composition

Conclusions

The separation of ^{68}Ga prepared by irradiating powder pressed ^{68}Zn targets and dissolving the targets in the ^{68}*Ga-DISTA* module was rapid and fully automated. A ^{68}*Ga-SEPUR* separation station was developed. The separation of gallium from transition metal interferents showed a reliable radiochemical yield. The *TRACERlab MX*, a disposable sterile cassette, and chemicals from ABX were used to label the ^{68}Ga peptides according to good manufacturing practices. The labelled product exhibited a five-fold higher activity than a ^{68}Ge/^{68}Ga generator with a starting activity of 1.85 GBq. The resulting product would allow twice the number of patients to be examined by cyclotron production ^{68}Ga compared to the generator produced ^{68}Ga. The product was manufactured in accordance with the regulations specified in the European Pharmaceutical Pharmacopoeia. The final product met the quality requirements stated in the pharmacopoeia 10.3. A separation procedure for the effective separation of iron was developed. The radiochemical yield of ^{68}Ga from such a separation process exceeded 95%. The final ^{68}Ga product was prepared up to 6 GBq at the end of synthesis.

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Declarations

Conflict of interest The authors declare no conflicts of interest.

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