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Thermal diffusion of ^{67}Ga from irradiated Zn targets

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HIGHLIGHTS

- Gallium-67 was separated from Zn targets based on thermal diffusion in concentrated acetic acid.
- Purification of gallium-67 was performed by cation exchange in ammonium medium.
- The final gallium-67 solution was obtained in HCl medium and with high purity ready to prepare radiopharmaceuticals.

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ABSTRACT

Gallium-67 is a cyclotron produced radionuclide and ^{67}Ga-citrate complex scans are performed in a variety of applications in Nuclear Medicine. The aim of this study was to evaluate a new method for the chemical separation of ^{67}Ga from Zn targets. The method has 2 steps, first the thermal diffusion of ^{67}Ga with concentrated acetic acid and then purification by cation exchange in ammonium medium. The final ^{67}Ga solution was obtained in 0.1 mol L^{-1} HCl with the desirable high purity.

1. Introduction

The physical properties, the availability and the coordination chemistry of ^{67}Ga complexes make it an interesting nuclide for radiopharmaceutical research (Bandoli et al., 2009). ^{67}Ga-citrate is well-known for detection of soft tissue tumors and abscess, bone tumors, inflammatory/infectious lesions, for the determination of treatment strategy and prognosis in Hodgkin's disease or non-Hodgkin's lymphoma (Tsan, 1985, 1986; Ben-Haim et al., 1996; Re et al., 2008; Yavari et al., 2009; Jalilian et al., 2009a, 2009b, 2009c).

In recent years, many new complexes with ^{67}Ga have been prepared such as ^{67}Ga-activated charcoal for colonic transit study (Cheng et al., 2003); ^{67}Ga-Matolate for treatment of hepatocellular carcinoma (Chua et al., 2006); ^{67}Ga-DTPA-hCG for colon, ovarian, endometrial and uterine cervix malignancies (Jalilian et al., 2009a, 2009b, 2009c); ^{67}Ga-AATS for tumor imaging agent (Jalilian et al., 2009a, 2009b, 2009c); ^{67}Ga-DOTA-Bz-folate for folate receptor-positive cancer and inflammatory diseases (Muller et al., 2011) and ^{67}Ga-DOTA-Bn-SCN-HBP for bone scintigraphy (Ogawa et al., 2011).

The most common modes for the production of ^{67}Ga are proton, deuteron or alpha particle bombardment on thick targets such as zinc, copper, germanium or cobalt in a cyclotron (Nayak and Lahiri, 2001; Naidoo and Van der Walt, 2001). Gallium-67 decays by electron capture to stable ^{67}Zn and its emissions include γ-rays of 93.3 keV (37%), 184.6 keV (20.4%) and 300.2 keV (16.6%).

After irradiation, two general methods for ^{67}Ga chemical separation from solid targets have been employed: ion exchange chromatography and liquid extraction (IAEA, 2009).

One limitation of these 2 methods is the total dissolution of the irradiated target in strong acids to obtain ^{67}Ga. To achieve a better production yield, with high radionuclidic purity, the targets used for producing radionuclides are isotopically enriched, which makes them expensive. With the dissolution of the irradiated target, losses may occur with the isotopically enriched material and the recovery is mandatory.

One method for the separation of radioisotopes from solid targets is thermal diffusion, which is also known as dry distillation. The temperature of extraction is close to the melting point of the target when the diffusion coefficients in solid state are in the same order as in liquid.

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A produced radionuclide can be considered to be dissolved in the target material. In this technique, a solid target is heated to a temperature at which the radioisotope can be concentrated on the target surface without evaporation and losing target material making it possible to remove the produced nuclide (Tolmachev et al., 1997). This is especially important when enriched target material is used.

This technique allowed a separation of ^{110}In or ^{111}In from an enriched Cd-target with a radiochemical yield of 60% or better. The irradiated target foils were heated to 306 °C and the indium isotopes were diffused out to the surface of the foils and stirred with concentrated acetic acid (Lundqvist et al., 1995). The irradiated targets consisting of natural Cd electroplated onto Cu/Ni backings were heated to 300 °C and the extraction of ^{110}In from the surface of target was higher than 80% (Lion, 2002).

Tolmachev and Lundqvist (1996) irradiated foils of natural zinc with protons to produce ^{66}Ga and ^{68}Ga. After irradiation, the targets were heated at 400 °C for 30 min and then vigorously stirred in 0.05 mol L^{-1} HCl. The separation efficiency of the ^{66}Ga and ^{68}Ga of the target material was 60%.

The aim of this study was to report a new method for the chemical separation of ^{67}Ga from ^{nat}Zn targets with chemical and radionuclidic purities, suitable for use in the labeling of molecules for use in radiodiagnostics.

The method has 2 steps, first the thermal diffusion of ^{67}Ga with extraction in concentrated acetic acid (HAc), without the need for complete dissolution of the target, and then a purification step by cation exchange.

2. Experimental

2.1. Target preparation

In order to develop the thermal diffusion technology, the targets used were made of natural zinc throughout the whole work.

Targets used in the ^{67}Ga production were prepared by the electrodeposition of the natural zinc onto Cu/Ni backings. The zinc target electrolyte consisted of a 0.45 mol L^{-1} $ZnSO_4 \cdot 7H_2O$ (Analytical Reagent Grade, Merck, Germany) solution. The current was kept at 30 mA and the voltage applied was approximately 4–6 V. After 2 h a thin deposit of zinc was obtained.

The evaluation of the deposit obtained was performed by the following:

1. Visual analysis in order to verify appearance and adherence of deposits.
2. Weighing the plate to evaluate the mass of the deposit.
3. Thickness and homogeneity measurements of the deposit done with a micrometer in 6 positions distributed along the area of electrodeposition. A standard deviation of ±5% in the average thickness is acceptable.

2.2. Target irradiation

The zinc targets were irradiated at the Cyclone-30 cyclotron (IBA, Belgium). In order to have a better heat dissipation, the target was irradiated at a 6° angle relative to the external proton beam direction. Cooling of the target was carried with cold water running on into the back of the target and the proton beam intensity was measured by a Faraday cup.

The nuclear reactions most widely used to produce ^{67}Ga are ^{68}Zn (p,2n) ^{67}Ga and ^{67}Zn (p,n) ^{67}Ga, that present different energy thresholds. The best energy range for (p,n) reaction is between 10 and 20 MeV and for the (p,2n) reaction between 15 and 30 MeV. The (p,2n) route was employed in the work (IAEA, 2009).

The incident proton energy was 26 MeV in order to maximize the (p,2n) reaction and minimize the (p,3n) reaction. The irradiation time was 1 h at a beam current of 10 μA. After 3 days, the irradiated material was subjected to the chemical separation of ^{67}Ga.

2.3. ^{67}Ga separation procedure

After irradiation, the irradiated targets were weighed and then heated to 300 °C for 2 h in a hotplate. After cooling, the targets were put in contact with 15 mL of concentrated acetic acid (HAc) (Analytical Reagent Grade, Merck, Germany) to extract ^{67}Ga.

Evaluation of ^{67}Ga extraction yield was checked by total dissolution of the zinc target in 15 mL of concentrated HCl (Analytical Reagent Grade, Merck, Germany).

Assays of radionuclidic purity for original HAc solution and HCl solution were performed by γ-spectroscopy using a HPGe detector (GX1518, Canberra Inc., U.S.A.).

The energy calibration of the detector was performed using a source of ^{60}Co (1173.23 and 1332.50 keV) and ^{137}Cs (661.66 keV) with 5.6328 kBq activity and 4.2568 kBq activity, respectively. The source is homogeneously distributed in 1 mL of HCl medium in a 25 mL glass flask.

The efficiency calibration of the detector was performed using a source of ^{152}Eu with 24.5408 kBq activity. The source is distributed in 1 mL of HCl medium in a 25 mL glass flask.

The extraction yield was calculated according to Eq. (1).

$$^{67}Ga_{HAc}\text{Yield }(\%) = [\text{Activity}_{HAc}/(\text{Activity}_{HAc} + \text{Activity}_{HCl})] \times 100 \quad (1)$$

2.4. ^{67}Ga purification procedure

Purification of radiogallium from the HAc solution was carried out using a cation exchange resin, Dowex 50 W × 8, 100–200 mesh, H^+ form, packed in a 60 × 20 mm column (Sigma-Aldrich, U.S.A) conditioned in 0.5 mol L^{-1} NH_4OH medium (Analytical Reagent Grade, Merck, Germany).

The solution obtained in HAc was evaporated to dryness and the residue was taken up in 3 mL of 0.5 mol L^{-1} NH_4OH. This solution was loaded onto the column. The column was washed with 30 mL of 0.5 mol L^{-1} NH_4OH and 10 mL of 0.1 mol L^{-1} HCl.

Samples were collected every 3 mL for the loading and every 10 mL for the washing step. Assays of radioactivity determinations were performed in a dose calibrator (CRC-15C, Capintec Inc., U.S.A.) to verify ^{67}Ga elution.

The dose calibrator is an efficient device for the direct measurement of radioactivity in a sample. The electrometer parameters for the calibrator used were as follows: *accuracy*=better than ±2%; *linearity*=within ±2%; *response time*=2 s and *resolution*=0.001 MBq (0.01 μCi). The calibration of the dose calibrator was performed by the direct method using a source of ^{137}Cs with 4.070 MBq activity. The ^{137}Cs source was homogeneously incorporated into approximately 4 mL of resin in a 25 mL glass flask. The verification of the repeatability of the equipment was performed from the sequence of 10 measurements with the standard source of ^{137}Cs for comparison with the data source reference stored internally on the equipment. The coefficient of variation was less than 5%.

After elution, the solution containing ^{67}Ga was evaporated to dryness and taken up in 2 mL of 0.1 mol L^{-1} HCl.

2.5. Quality control tests

Physical–chemical tests were carried out to check the purity of ^{67}Ga in the HAc solution and in the final product.

Gamma spectra of produced solutions were measured in order to estimate radionuclidic impurities. Assays of radionuclidic purity were performed by γ-spectroscopy using HPGe detector. The γ-ray energies analyzed were 1039 keV (^{66}Ga), 184 and 300 keV (^{67}Ga) and 1115 keV (^{65}Zn).

The chemical purity was assayed by ICP-OES (Inductively Coupled Plasma Optical Emission Spectroscopy, Vista-MPX, Varian Inc., Australia) to evaluate the presence of chemical impurities such as Ni, Cu, Fe and Zn, originate from target or chemical reagents.

Purified water used to prepare the standard solutions was obtained from the Ellix-10 water system (Millipore, U.S.A). The calibration and blank solutions were stabilized in 3% v/v concentrated HNO_3 (Analytical Reagent Grade, Merck, Germany).

The Cu, Fe, Ni and Zn standard solutions for the working calibration curves were prepared by diluting the single element ICP grade standard solution (100 μg mL^{-1}, Merck, Germany). The range of the calibration curve was from 0.2 to 1.0 μg mL^{-1}.

Radiochemical purity was evaluated by paper chromatography using Whatman 3MM paper (Whatman International Ltd., United Kingdom) and a Pyridine Ethanol Water (1:2:4) solution as mobile phase (Merck, Germany) (Kulprathipanja and Hnatowich, 1977).

In this system, the Rf value for the $^{67}GaCl_3$ and Complex-^{67}Ga were about 0.0 and 0.8, respectively. The radioactivity distribution was determined by cutting the paper strips into 7 pieces and each piece was separately measured in a gamma-detector (Cobra II, Packard Bioscience Company, United Kingdom) during 0.20 min in the energy range of 200–500 keV.

3. Results and discussion

3.1. Target preparation

The ideal deposit for irradiation should be strongly adherent and uniformly distributed along the surface of the support. The thickness of the electroplated layer of Zn was 0.13 ± 0.01 mm (n=6).

The deposits obtained were adherent to the substrate and slightly shiny. The electroplated zinc mass was 0.49 ± 0.02 g (n=6).

3.2. Target irradiation

The production yield of ^{67}Ga at the end of bombardment was (40 ± 18) MBq/μAh (n=6). The high deviations of the results were probably due to the irregular irradiation conditions or beam sweep of the target. The loss of zinc mass from the target was less than 0.02 g.

3.3. ^{67}Ga separation procedure

After irradiation, the targets were heated at 300 °C for 2 h and placed in contact with concentrated acetic acid for 1 h. After heating and etching with HAc the extraction yield of ^{67}Ga was (72 ± 10)% (n=6).

In normal production of ^{67}Ga, the irradiation process during 10–15 h and the targets were heated. This heating is sufficient to surface concentration of gallium isotopes without additional heating of the targets (Tolmachev and Lundqvist, 1996).

An irradiated zinc target represents a binary system, zinc and gallium, with different melting points: 420 °C and 30 °C, respectively. When the target is heated above 30 °C, gallium isotopes diffuse and concentrate at the surface of the target.

This is especially important when enriched target material is used. The use of acetic acid as eluent has the advantage that it simplifies the process because it is not corrosive for the hot cell components.

3.4. ^{67}Ga purification procedure

The acetic ^{67}Ga solution obtained was evaporated and the residue was taken up in 0.5 mol L^{-1} NH_4OH.

^{67}Ga was readily and quantitatively eluted by the Dowex 50WX8 resin in 23 mL of 0.5 mol L^{-1} NH_4OH. The ^{67}Ga recovery was (98 ± 2)%. The measurements were performed in the dose calibrator described above. A typical elution curve of this process is shown in Fig. 1.

According to Abrão (1972) in an alkaline medium gallium could be separated from nickel, copper and zinc using a cation resin with polystyrene matrix. Amino-complexes of copper, nickel and zinc have a positive charge and remain retained on the resin. Gallium presents an amphoteric character and is eluted in the form of gallate ion, $^{67}Ga(OH)_4^-$.

3.5. Quality control tests

The ^{67}Ga solution in NH_4OH medium was evaporated and taken up in 0.1 mol L^{-1} HCl.

The radionuclidic purity was higher than (99.9%). The spectrum of original HAc solutions and HCl solutions showed that the only gamma-rays detectable were ^{67}Ga (184 and 300 keV) and ^{65}Zn (1115 keV) and no ^{66}Ga was found. Fig. 2 represents the spectrum of final ^{67}Ga solution in HCl medium.

The chemical purity of the final ^{67}Ga solution was evaluated by ICP-OES and the radiochemical purity of the ^{67}Ga final solution was evaluated by paper chromatography to verify $^{67}GaCl_3$ form. Table 1 illustrates the results obtained for chemical and radiochemical analysis.

The chemical impurities can originate from the target material or reagents used and can interfere with the labeling of biomolecules with radioisotopes.

USP 36 NF-29 (2012) and EP (2011) do not refer to values for chemical purity of the final ^{67}Ga citrate solution. USP 36 NF-29 (2012) recommends that the total concentration of metals should be less than 1 μg mL^{-1} for an ^{111}In solution. In "General Chapter on Inorganic Impurities" the *USP Parenteral Limit* for Cu, Fe, Ni and Zn are 5, 150, 10 and 150 μg g^{-1}, respectively.

According to the "Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents" (2008) the limits for Cu, Fe, Ni and Zn are 25, 130, 2.5 and 130 mg mL^{-1}, respectively. The objective of this guideline is to recommend the maximum acceptable concentration limits for the residues of metal catalysts or metal reagents that may be present in pharmaceutical substances or in drug products.

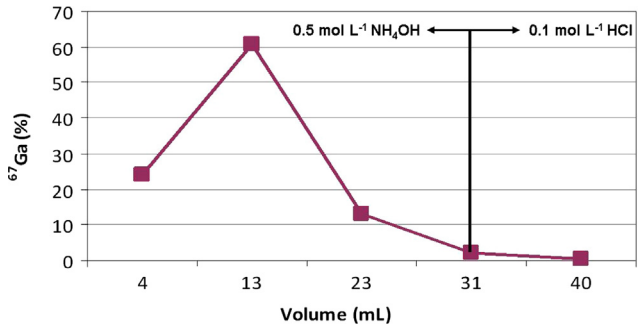

Fig. 1. Elution curve for ^{67}Ga from cation exchange resin in 0.5 mol L^{-1} NH_4OH (n=6).

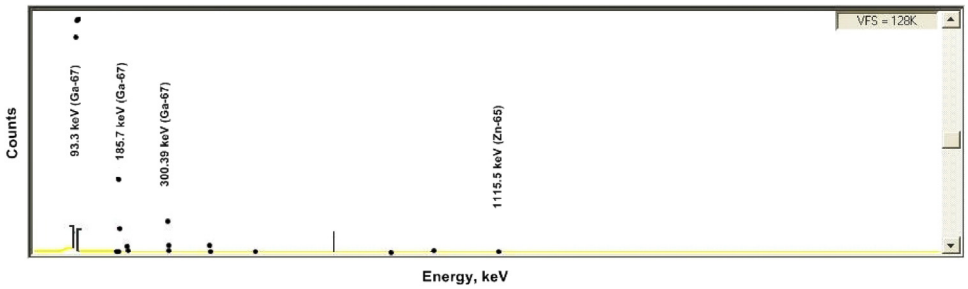

Fig. 2. Gamma spectrum of final ^{67}Ga solution in HCl medium (after 3 days of irradiation).

Table 1
Chemical and radiochemical results for final ^{67}Ga solution ($n=6$).

[Zn] (μg mL^{-1})	[Fe] (μg mL^{-1})	[Cu] (μg mL^{-1})	[Ni] (μg mL^{-1})	RP (%)
1.81 ± 0.80	0.24 ± 0.08	0.11 ± 0.07	0.27 ± 0.10	97 ± 2

4. Conclusion

The present work showed a new method suitable to obtain high purity ^{67}Ga to prepare radiopharmaceuticals. Purification of ^{67}Ga from the ^{nat}Zn targets has been easily achieved by a method based in thermal diffusion.

Thermal diffusion is an efficient and nondestructive method to separate gallium radioisotopes from Zn targets. This method allows the reutilization of the targets.

The heating process facilitates the diffusion and concentration of gallium to the surface of the target. The use of acetic acid as eluent has a further advantage because it is not corrosive.

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