NUKLEONIKA 2006;51(2):111–117

ORIGINAL PAPER

Preparation of [^{61}Cu]DTPA complex as a possible PET tracer

**Amir R. Jalilian,
Pejman Rowshanfarzad,
Mahsheed Sabet,
Mohsen Kamalidehghan**

Abstract Copper-61 ($T_{1/2}$ = 3.33 h) produced via the ^{64}Zn(p,α)^{61}Cu nuclear reaction, using a natural zinc target, was separated from the irradiated target material by two ion exchange chromatography steps and was used for the preparation of [^{61}Cu]-diethylenetriaminepentacetate ([^{61}Cu]DTPA) using freshly-prepared DTPA cyclic dianhydride. An electroplated natural zinc layer on a gold-coated copper backing was irradiated with 22 MeV protons (22–12 MeV on the target, 180 μA irradiation, 3.2 h, final activity 220 GBq of $^{61}Cu^{2+}$, RCY > 95%, radionuclidic purity > 99%, ^{60}Cu as the only radionuclidic impurity; $T_{1/2}$ = 23.7 min). Colorimetric methods showed that traces of chemical impurities in the product were below the accepted limits. The solution of [^{61}Cu]DTPA was prepared with a radiochemical yield of more than 80% starting with ^{61}CuOAc ligand at room temperature after 30 min. RTLC showed the radiochemical purity of more than 99%. The specific activity obtained was about 9.1 TBq/mmol. The tracer was shown to be stable in the final product and in the presence of human serum at 37°C up to 3 h.

Key words copper-61 • DTPA • labeling • PET • radiopharmaceuticals

A. R. Jalilian✉, P. Rowshanfarzad, M. Kamalidehghan
Cyclotron and Nuclear Medicine Department,
Nuclear Research Center for Agriculture
and Medicine (NRCAM),
Atomic Energy Organization of Iran (AEOI),
Moazzen Blvd., Rajaee shahr, Karaj, Iran,
P. O. Box 31485-498,
Tel./Fax: +98 261 4436397,
E-mail: ajalilian@nrcam.org

M. Sabet
SSDL and Health Physics Department,
Nuclear Research Center for Agriculture
and Medicine (NRCAM),
Atomic Energy Organization of Iran (AEOI),
Moazzen Blvd., Rajaee shahr, Karaj, Iran,
P. O. Box 31485-498

Received: 25 July 2005
Accepted: 25 October 2005

Introduction

Copper offers a unique selection of radioisotopes (^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu, and ^{67}Cu) with half-lives ranging from 9.8 min to 61.9 h, suitable for imaging and/or radiotherapy [2]. Table 1 summarizes the physical properties of copper radioisotopes [3, 7].

Few production methods of copper-61 have been reported for radiolabeling of biomolecules and other applications [11, 14, 15]. Interestingly, it has been shown that the tomographic images obtained using ^{61}Cu were superior to those using ^{64}Cu, based on the larger abundance of positrons emitted by ^{61}Cu compared with ^{64}Cu (62% vs. 18%) [6].

Various nuclear reactions have been suggested for the production of ^{61}Cu, but we were interested in the ^{64}Zn(p,α)^{61}Cu reaction, due to its high yield with good radionuclidic and chemical purity of the product. However, the idea of replacing ^{64}Zn with natural zinc arose to reduce costs and to provide easily available targets.

The EDTA and DTPA complexes of copper prepared in acidic media apparently decomposed *in vivo* with the radiometal being trapped in the liver [12, 13]. That was the reason why they were not used for *in vivo* studies by direct injection into blood stream, while their *in vitro* use as cell radiolabeling tracer can be an option.

Meanwhile, there have been reports in the literature concerning the preparation and use of ^{64}Cu-DTPA for cisternography in the early 1980's [10]. At that time the positron emission tomography was not yet developed

Table 1. Nuclear characteristics of copper radionuclides

Radionuclide	$T_{1/2}$	β^- MeV (%)	β^+ MeV (%)	E.C. (%)	γ keV (%)
^{67}Cu	61.83 h	0.576 (20%) 0.4827 (22%) 0.3914 (57%) 0.1825 (1%)	–	–	184.577 (48.7%) 93.311 (16.1%) 91.266 (7.0%)
^{64}Cu	12.7 h	0.5787 (39%)	0.65308 (17.4%)	43.6	1345.77 (0.473%) 511 (34.79%)
^{62}Cu	9.74 min	–	2.927 (97.2%)	2.8	511 (194.86%) 1173.02 (0.342%)
^{61}Cu	3.333 h	–	1.2164 (51%) 1.1489 (2.3%) 0.9334 (5.5%) 0.5604 (2.6%)	38.6	656.008 (10.77%) 511 (120.87%) 373.05 (2.10%) 282.956 (12.2%) 67.412 (4.20%)
^{60}Cu	23.7 min	–	3.7719 (5%) 2.9456 (15%) 2.4784 (2.8%) 1.9805 (49%) 1.9105 (11.6%) 1.8352 (4.59%)	12.01	3124.1 (4.8%) 2158.90 (3.34%) 1861.6 (4.8%) 1791.6 (45.4%) 1332.501 (88%) 1035.2 (3.7%) 826.4 (21.7%) 511 (185.19%) 467.3 (3.52%)

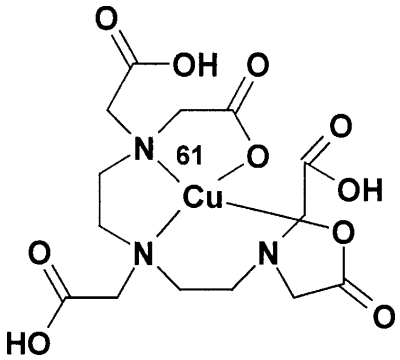

Fig. 1. Scheme of Cu-DTPA complex.

for regular clinical studies. The idea of incorporation of a PET radioisotope into a suitable chelate used in cisternographic and blood cell labeling, i.e. DTPA, came to our interest based on our recent background on the production and use of non-conventional PET tracers. Interesting imaging properties of copper-61 and the possibility of its production via the ^{64}Zn(p,α)^{61}Cu reaction using natural zinc provided a suitable source of this radionuclide for its ultimate use in radiolabeling of DTPA in alkaline media using a modified method. (Fig. 1).

Experimental

Materials

Production of ^{61}Cu was performed at the Nuclear Research Center for Agriculture and Medicine (NRCAM) 30 MeV cyclotron (Cyclone-30, IBA). Natural zinc chloride with a high purity of more than 98% was provided commercially (Merck, Darmstadt, Germany). Other chemicals were purchased from Aldrich, Germany. All exchange ion resins were provided commercially (Bio-Rad Laboratories, Canada). Radio thin-layer chromatography (RTLC) was performed on polymer-backed silica gel (F 1500/LS 254, 20 × 20 cm, TLC Ready Foil, Schleicher & Schuell®, Germany). Normal saline and sodium acetate used for labeling were of high purity and had been filtered through 0.22 μ Cativex filters (Millipore, France). Radio-chromatography was performed by counting 5 mm-slices of polymer-backed silica gel paper using a Canberra™ high purity germanium (HPGe) detector (model GC1020-7500SL). Radionuclidic purity was checked by the same detector. All calculations and RTLC counting were based on the area under curve of the 283 keV peak.

Methods

Production parameters and targetry

In this research, the ^{64}Zn(p,α)^{61}Cu reaction was selected for the production of ^{61}Cu, but natural zinc was used as the target material. Tables 2–4 show the expected nuclear reactions induced on target in the 22–12 MeV energy range for each produced element.

The optimum proton beam energy and types of possible impurities were calculated by ALICE nuclear code [1]. Target thickness corresponding to the optimum energy range was determined by SRIM nuclear code [16]. Based on these results, an 80 micron

Table 2. Zinc isotopes produced by ^{70,68,67,66,64}Zn nuclear reactions with protons, predicted by ALICE code

Isotope	Half-life	Reaction products	*Q*-value* [MeV]	Threshold* [MeV]
^{62}Zn	9.13 h	^{64}Zn(p,t)^{62}Zn	–12.49311	12.69006
		^{64}Zn(p,nd)^{62}Zn	–18.75041	19.04600
		^{64}Zn(p,2np)^{62}Zn	–20.97500	21.30566
^{63}Zn	38.1 min	^{64}Zn(p,d)^{63}Zn	–9.63707	9.78900
		^{64}Zn(p,np)^{63}Zn	–11.86166	12.04866
^{64}Zn	stable	^{66}Zn(p,t)^{64}Zn	–10.55767	10.71907
^{65}Zn	244.3 d	^{67}Zn(p,t)^{65}Zn	–9.63028	9.77530
		^{66}Zn(p,d)^{65}Zn	–8.83535	8.97041
^{66}Zn	stable	^{68}Zn(p,t)^{66}Zn	–8.76862	8.89872
		^{67}Zn(p,pn)^{66}Zn	0.00000	0.00000
		^{66}Zn(p,p)^{66}Zn	0.00000	0.00000
^{57}Zn	stable	^{67}Zn(p,p)^{67}Zn	0.00000	0.00000
^{68}Zn	stable	^{70}Zn(p,t)^{68}Zn	–7.21628	7.32029
		^{68}Zn(p,p)^{68}Zn	0.00000	0.00000
^{69}Zn	13.8 h	^{70}Zn(p,d)^{69}Zn	–6.99130	7.09206
^{70}Zn	stable	^{70}Zn(p,p)^{70}Zn	0.00000	0.00000

* Data extracted from T2-Nuclear Information Service, Los Alamos <http://t2.lanl.gov>.

Table 3. Copper isotopes produced by ^{70,68,67,66,64}Zn nuclear reactions with protons, predicted by ALICE code

Isotope	Half-life	Reaction products	*Q*-value* [MeV]	Threshold* [MeV]
^{60}Cu	23 min	^{64}Zn(p,nα)^{60}Cu	–10.86568	11.03697
^{61}Cu	3.33 h	^{64}Zn(p,α)^{61}Cu	0.84410	0.00000
		^{64}Zn(p,pt)^{61}Cu	–18.96991	19.26897
		^{64}Zn(p,n^{3}He)^{61}Cu	–19.73368	20.04478
^{62}Cu	9.74 min	^{64}Zn(p,pd)^{62}Cu	–16.34087	16.59847
		^{64}Zn(p,2pn)^{62}Cu	–18.56546	18.85814
		^{64}Zn(p,^{3}He)^{62}Cu	–10.84734	11.01834
		^{66}Zn(p,nα)^{62}Cu	–9.30912	9.45143
^{63}Cu	stable	^{64}Zn(p,2p)^{63}Cu	–7.71240	7.83398
		^{66}Zn(p,α)^{63}Cu	1.54394	0.00000
		^{67}Zn(p,nα)^{63}Cu	–5.50830	5.59125
^{64}Cu	12.7 h	^{67}Zn(p,α)^{64}Cu	2.40771	0.00000
		^{68}Zn(p,nα)^{64}Cu	–7.79056	7.90615
^{65}Cu	stable	^{67}Zn(p,^{3}He)^{65}Cu	–8.25974	8.38412
		^{68}Zn(p,α)^{65}Cu	2.11976	0.00000
^{66}Cu	5.1 min	^{70}Zn(p,nα)^{66}Cu	–6.51242	6.60628
		^{68}Zn(p,^{3}He)^{66}Cu	–11.39203	11.56106
		^{67}Zn(p,2p)^{66}Cu	–8.91188	9.04608
^{67}Cu	61.9 h	^{70}Zn(p,α)^{67}Cu	2.60481	0.00000
		^{68}Zn(p,2p)^{67}Cu	–9.99292	10.14118
^{69}Cu	3 min	^{70}Zn(p,2p)^{69}Cu	–11.10857	11.26868

* Data extracted from T2-Nuclear Information Service, Los Alamos <http://t2.lanl.gov>.

natural zinc layer was electrodeposited on a gold coated (50 μ) copper backing to avoid the interference of backing copper with the product during radiochemical separation.

Table 4. Gallium isotopes produced by ^{70,68,67,66,64}Zn nuclear reactions with protons, predicted by ALICE code

Isotope	Half-life	Reaction products	*Q*-value* [MeV]	Threshold* [MeV]
^{63}Ga	31.4 s	^{64}Zn(p,2n)^{63}Ga	–18.16406	18.45041
^{64}Ga	2.62 min	^{64}Zn(p,n)^{64}Ga	–7.94722	8.07251
^{65}Ga	15 min	^{64}Zn(p,γ)^{65}Ga	3.94238	0.00000
		^{66}Zn(p,2n)^{65}Ga	–15.09719	15.32798
^{66}Ga	9.4 h	^{66}Zn(p,n)^{66}Ga	–5.95740	6.04847
		^{67}Zn(p,2n)^{66}Ga	–13.00964	13.20554
^{67}Ga	78.3 h	^{66}Zn(p,γ)^{67}Ga	5.26939	0.00000
		^{67}Zn(p,n)^{67}Ga	–1.78285	1.80970
		^{68}Zn(p,2n)^{67}Ga	–11.98112	12.15889
^{68}Ga	67.6 min	^{68}Zn(p,n)^{68}Ga	–3.70348	3.75843
		^{70}Zn(p,3n)^{68}Ga	–19.40165	19.68129
^{69}Ga	stable	^{68}Zn(p,γ)^{69}Ga	6.60592	0.00000
		^{70}Zn(p,2n)^{69}Ga	–9.09225	9.22330
^{70}Ga	21.15 min	^{70}Zn(p,n)^{70}Ga	–1.43709	1.45780

* Data extracted from T2-Nuclear Information Service, Los Alamos <http://t2.lanl.gov>.

The plating bath was prepared by dissolution of 8.67 g of natural $ZnCl_2$ required for the deposition of four targets in 0.05 M HCl (450 ml) followed by the addition of hydrazine hydrate (2 ml, 80%) as anodic depolarizer and adjustment of pH to 2.5–3 carried out at a current density of 30.2 mA/cm^2. The cell volume was 480 ml and a current density of 3.02 mA/dm^2 was applied. Platinum was used as the anode material to give 80 μ zinc layer on the copper backing after 80 min.

[^{61}Cu]$CuCl_2$ was prepared by 22 MeV proton bombardment of the ^{nat}Zn target with a current intensity of 180 μA and a dose of 500 μAh. The resulting activity of ^{61}Cu was about 220 GBq at the end of bombardment (EOB) which corresponds to the production yield of about 440 MBq/μAh.

Radiochemical separation

After target irradiation, chemical separation of ^{61}Cu was carried out in no-carrier-added form, within two steps of ion exchange chromatography.

In the first step, gallium was separated from zinc and copper. The irradiated target was dissolved in 10 M HCl (15 ml, H_2O_2 added) and the solution was passed through a cation exchange resin (AG 50 W, H^+ form, 200–400 mesh, *h*: 7 cm, Ø: 1.1 cm) which had been pre-conditioned by passing 25 ml of 9 M HCl. The column was then washed by 25 ml of 9 M HCl with a rate of 1 ml/min to remove copper and zinc ion whereas gallium remained on the column.

In the second step, copper was separated from zinc ions. The solution obtained from the cation exchange column was evaporated almost to dryness and the residue was dissolved in 6 M HCl. An anion exchange chromatography column (AG 1×8, 100–200 mesh, Cl^- form, *h*: 13 cm, Ø: 1.6 cm) was preconditioned with 25 ml of distilled water and 100 ml of 6 M HCl in sequence. The loading rate was 2 ml/min. Copper (^{61}Cu) was washed out of the column by passing 50 ml of 2 M HCl with a rate of 2 ml/min.

After the quality control process, the resulting [^{61}Cu]$CuCl_2$ solution was ready for labeling.

Quality control of the product

1. Radionuclidic purity control. Gamma spectroscopy of the final sample was carried out by an HPGe detector coupled with a Canberra™ multi-channel analyzer, to control the radionuclidic purity of the product. The spectra were assigned during 1000 s each.
2. Chemical purity control. The presence of zinc and gold cations were checked by visible colorimetric assays. Even at 5 ppm of standard zinc concentration, the pinkish Zn-dithizonate complex is visible to the naked eye, while the test sample remains similar to the blank [9]. The amount of gold cation was checked in the final solution using color formation of acidic rhodamine B reagent reacting with gold dilutions [9].

Preparation of fresh cyclic DTPA dianhydride for radiolabeling

This compound was prepared according to the methods previously given in the literature with slight modifications [4]. Briefly, DTPA in the acidic form (0.1 mol) was heated with a 4-fold molar excess of acetic anhydride (0.4 mol), dissolved in 50 ml of pyridine and heated at 65°C for 24 h. The resulting anhydride was insoluble in pyridine and was collected by filtration, purified by repeated washing with acetic anhydride, and finally with anhydrous ether. Drying in an oven at 50–60°C removed the last traces of the solvent. The melting point was 178–180°C. ^{1}H NMR and IR spectra were consistent with those reported in the literature [4].

Preparation of [^{61}Cu]-diethylenetriaminepentacetate

The obtained [^{61}Cu]$CuCl_2$ (111 MBq), dissolved in 2 M HCl (2.5–3 ml) was transferred into a 5 ml-vial and evaporated to dryness using a flow of N_2 gas at 50–60°C. Then, 3 M sodium acetate (0.5 ml) was added to the residue to prepare a [^{61}Cu]copper acetate solution. A portion of diethylenetriaminepentacetic acid dianhydride (0.1 mg, 280 nmol) was added to the copper acetate solution and stirred at 25°C for 3–5 min. The mixture was then left at room temperature for 30 min. The vial mixture was diluted by the addition of 0.9% saline. pH was adjusted to 5–7 and the final solution was then passed through a 0.22 μm filter.

Radiochemical purity of [^{61}Cu]DTPA

Radio thin-layer chromatography was performed on polymer-backed silica gel layer chromatography sheets using 10% aqueous ammonium acetate:MeOH (1:1, v/v) as the mobile phase. The step motor was installed to count 0.4 cm-strips for 30 s through a slot of the shielded chamber. Thus, the radiochemical yields were determined by comparison of uncomplexed ^{61}Cu and the major peak.

Stability of [^{61}Cu]DTPA complex in aqueous solution

Stability tests were based on previous studies performed on radiolabeled copper complexes [8]. A sample of [^{61}Cu]DTPA (185 MBq) in the aqueous solution was kept at room temperature for 3 h while checked by RTLC every half an hour. Micro-samples (5 μl) taken from the shaken mixture, were transferred on the TLC papers and the ratio of free radiocopper to [^{61}Cu]DTPA was checked (eluent: 10% ammonium acetate:MeOH (1:1)).

Stability studies in serum

To 36.11 MBq of ^{61}Cu-DTPA (100 μl), 500 μl of freshly prepared human serum was added. The resulting mixture was incubated at 37°C for 5 h, and 1.5-ml aliquots were analyzed by RTLC after 0, 0.25, 0.5, 1, 2 and 3 h of incubation to determine the conjugate stability, TLC results were not statistically meaningful after 3 h due to radioactivity decay.

Determination of partition coefficient

Partition coefficient (log *P*) of ^{61}Cu-DTPA was calculated followed by the determination of *P* (*P* = the ratio of specific activities of the organic and aqueous phases). A mixture of 1 ml of 1-octanol and 1 ml of isotonic acetate-buffered saline (pH = 7) containing approximately 3.7 MBq of the radiolabeled copper complex at 37°C was vortexed for 1 min and left for 5 min. Following centrifugation at > 1200 g for 5 min, the octanol and aqueous phases were sampled and counted in an automatic well-type counter. A 500 μl sample of the octanol phase from this experiment was shaken again for two to three times with fresh buffer samples to ensure that traces of hydrophilic ^{61}Cu impurities did not alter the calculated *P* values. The reported log *P* values are the average of the second and third extractions from three to four independent measurements.

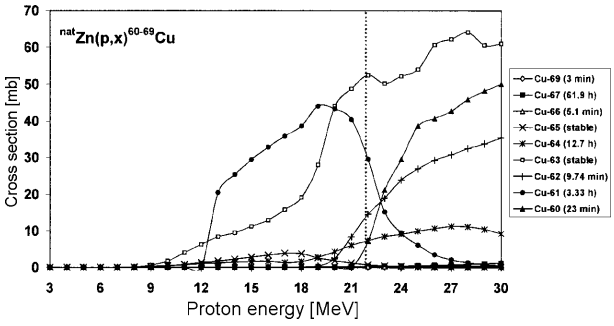

Fig. 2. Results of ALICE code for ^{nat}Zn(p,x)$^{60–69}$Cu reactions.

Results

Results of ALICE code showed that the production of ^{61}Cu via the ^{nat}Zn(p,x)^{61}Cu reaction starts to increase at 12 MeV proton energy, and the maximum production yield can be achieved with the least radioactive impurities at the energy range of 22–12 MeV (Fig. 2). It must be noted that in this energy range, the main nuclear reaction for the production of ^{61}Cu as a result of ^{nat}Zn bombardment is actually limited to ^{64}Zn(p,α)^{61}Cu [14].

According to the results of SRIM nuclear code and the characteristics of our system, an 80-micron zinc layer was electrodeposited on a gold layered copper backing.

The radiochemical separation process was based on a two step no-carrier-added ion-exchange-chromatography method with a yield of more than 95%. Other impurities such as gallium and zinc nuclides were also produced as a result of proton bombardment of natural zinc, but they could be easily removed in the radiochemical separation process. Radionuclidic control showed the presence of 67.41 (4.23%), 282.96 (12.2%), 373 (2.15%), 511 (122.9%), 656 (10.77%), 1186 (3.75%) keV gamma energies, all originating from ^{61}Cu and showed the radionuclidic purity higher than 99% (Fig. 3).

In order to check the chemical purity of the preparation, the concentrations of zinc (from target material) and gold (from target support) were determined

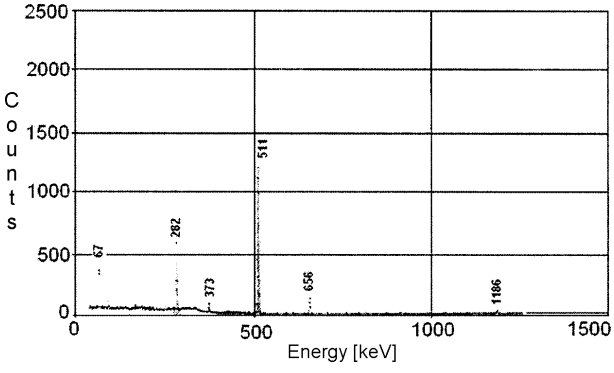

Fig. 3. Gamma spectrum of the purified final [^{61}Cu]$CuCl_2$ solution, counting time; 1000 s, in a 20 ml-vial.

using visible colorimetric assays. The colorimetric assays demonstrated that the zinc concentration was below the internationally accepted levels [5], while the gold concentration was less than 0.9 ppm.

Radiolabeling of DTPA

Because of the engagement of several polar functional groups in its structure, labeling of DTPA with copper cation greatly affects its chromatographic properties and the final complex is highly lipophilic. In TLC studies, the more polar uncomplexed DTPA and the free copper fraction, correspond to smaller R_fs (R_f = 0.1–0.2) (Fig. 4), while the DTPA complex migrates at higher R_f (R_f = 0.9) (Fig. 5). Since it has been shown that the Cu-DTPA complex has lipophillic properties, its radiolabeled forms can be used either in blood cell labeling if added directly to human blood cell fractions, or (if injected into subarachnoid space) in the imaging of cerebrospinal flow for the detection of tumors and/or pathological abnormalities in CNS.

In all radiolabeling runs (n = 9), the area under curve ratio of the radiotracer peak was constant (> 99%), showing the high radiochemical purity of the labeling method. Since the other labeling methods already reported used acidic media and the final product was finally adjusted to the pH of interest using NaOAc solution, we tried another approach using alkaline media. Interestingly, the labeling was fast in this media and no unlabeled copper species was found by RTLC, showing the radiochemical purity higher than 99%.

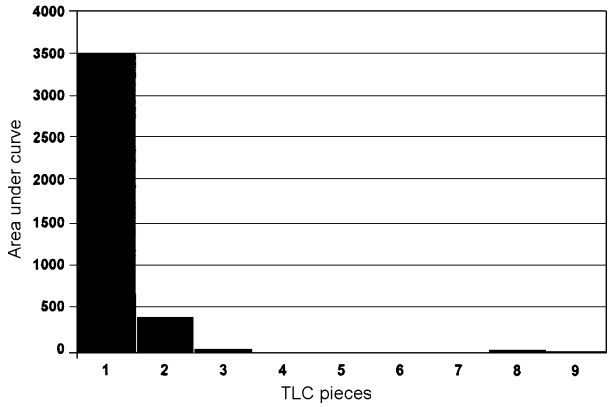

Fig. 4. RTLC of the [^{61}Cu]acetate (countings were based on the area under curve of the 283 keV peak).

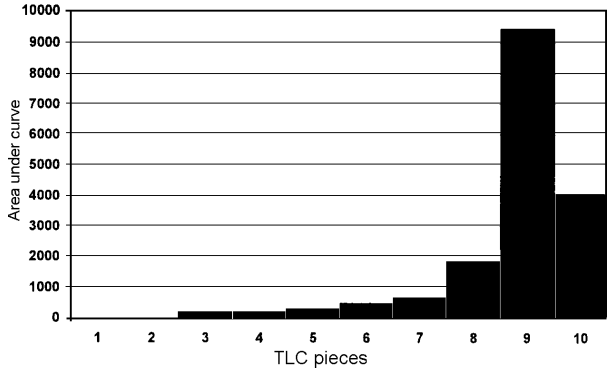

Fig. 5. RTLC of final [^{61}Cu]DTPA solution (countings were based on the area under curve of the 283 keV peak).

The final radiolabeled complex diluted with normal saline was then passed through a 0.22 micron (Cativex) filter (filtration was used to sterilize the product). Due to possible thermal instability at the autoclave temperatures, [^{61}Cu]DTPA preparation could be totally degraded giving detectable amounts of the free copper ions after autoclaving. The chemical stability of [^{61}Cu]DTPA was high enough to perform further studies. RTLC of the final product showed no change in stability and [^{61}Cu]DTPA in aqueous solutions at pH = 5.5–7 did not changed during 3 h at room temperature.

Serum stability studies

[^{61}Cu]DTPA was incubated in freshly prepared human serum for 3 h at 37°C. The aliquots of the resulting mixtures were analyzed to determine the kinetic stability of the radiolabeled conjugate. No decomposition of ^{61}Cu from the complex was observed during the course of the studies, and the radiochemical purity of the complex remained > 99% for 3 h under physiological conditions.

Partition coefficient of [^{61}Cu]DTPA

As expected, the lipophilicity of the [^{61}Cu]DTPA compound is rather high. The measured octanol/water partition coefficient, P, for the ^{61}Cu-complex was found to depend on pH of the solution. At pH 7 the $\log P > 2 \pm 0.08$ [10].

Discussion

The method used in this research for the production and chemical separation of ^{61}Cu was quite simple and cost-effective, and none of the previous studies given in the literature have reported such a high production yield [14, 15]. Total labeling and formation of [^{61}Cu]DTPA took about 40 min, with a yield higher than 99%. A significant specific activity (≈ 370–740 GBq/mmol) was obtained via insertion of the [^{61}Cu]copper(II) cation. No unlabeled and/or labeled by-products were observed upon RTLC analysis of the final preparations. The radiolabeled complex was stable in aqueous solutions as well as in human serum at 37°C for at least 3 h and no significant amount of other radioactive species were detected by RTLC. No traceable amounts of other [^{61}Cu]copper species were detected by RTLC, which showed that radiochemical purity of the [^{61}Cu]DTPA was higher than 99%. In contrast to other labeled DTPA complexes, [^{61}Cu]DTPA is a PET radiotracer with an intermediate half-life. The high chemical stability of this radiopharmaceutical makes it a very suitable candidate for cisternographic and other diagnostic applications.

References

1. Blann M, Bislinghoff J (1991) Code Alice/Livermore 91. Lawrence Livermore National Laboratory Internal Report, UCID-19614
2. Blower PJ, Lewis JS, Zweit J (1996) Copper radionuclides and radiopharmaceuticals in nuclear medicine. J Nucl Med Biol 23:957–980
3. Cutler CS, Lewis JS, Anderson CJ (1999) Utilization of metabolic, transport and receptor-mediated processes to deliver agents for cancer diagnosis. Adv Drug Deliv Rev 37:189–211
4. Eckelman WC, Karesh SM, Reba RC (1975) New compounds: fatty acid and long chain hydrocarbon derivatives containing a strong chelating agent. J Pharm Sci 64;4:704–406
5. European Directorate for the Quality of Medicines Council of Europe (2002) European Pharmacopoeia, 4th ed. Radiopharmaceutical preparations, gallium-67 citrate injection monograph, p 2319
6. Fukumura T, Okada K, Szelecsényi F, Kovács Z, Suzuki K (2004) Practical production of ^{61}Cu using natural Co target and its simple purification with a chelating resin for ^{61}Cu-ATSM. Radiochim Acta 92;4/6:209–214
7. Haynes NG, Lacy JL, Nayak N *et al*. (2000) Performance of a ^{62}Zn/^{62}Cu generator in clinical trials of PET perfusion agent ^{62}Cu-PTSM. J Nucl Med 41:309–314
8. Lewis MR, Wang M, Axworthy DB *et al*. (2003) *In vivo* evaluation of pretargeted ^{64}Cu for tumor imaging and therapy. J Nucl Med 44:1284–1292
9. Marczenko Z (1976) Spectrophotometric determination of elements. Halstead Press, New York
10. Maziere B, Stulzaft O, Verret JM, Comar D, Syrota A (1983) ([^{55}Co]- and [^{64}Cu]DTPA: New radiopharmaceuticals for quantitative tomocisternography. Int J Appl Radiat Isot 34;3:595–601
11. McCarthy DW, Bass LA, Cutler PD *et al*. (1999) High purity production and potential applications of copper-60 and copper-61. Nucl Med Biol 26;4:351–358
12. Robinson GD (1978) Cyclotron-related radiopharmaceutical development program at UCLA. Prog Nucl Med 4:80–92
13. Robinson GD, Zielinski FW, Lee AW (1980) The zinc-62/copper-62 generator: a convenient source of copper-62 for radiopharmaceuticals. Int J Appl Radiat Isot 31;2:111–116
14. Szelecsényi F, Kovács Z, Suzuki K *et al*. (2005) Production possibility of ^{61}Cu using proton induced nuclear reactions on zinc for PET studies. J Radioanal Nucl Chem 263;2:539–546
15. Tolmachev V, Lundqvist H, Einarsson L (1998) Production of ^{61}Cu from a natural nickel target. Int J Appl Radiat Isot 49;1/2:79–81
16. Ziegler JF, Biersack JP, Littmark U (2000) The code of SRIM – the stopping and range of ions in matter. January 1, Version 2000.XX