(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 288 284 A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 88303603.0

(22) Date of filing: 21.04.88

(51) Int. Cl.4: G 21 G 1/10

(30) Priority: 24.04.87 US 42129

(43) Date of publication of application: 26.10.88 Bulletin 88/43

(84) Designated Contracting States: CH DE FR GB IT LI NL

(71) Applicant: KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE
P.O. Box 3354
Riyadh 11211 (SA)

(72) Inventor: Qureshi, Muhammad A.
King Faisal Specialist Hospital Research Centre
P.O box 3354 Riyadh 11211 (SA)

Sajjad Munawwar
King Faisal Specialist Hospital Research Centre
P.O box 3354 Riyadh 11211 (SA)

Lambrecht, Richard M.
King Faisal Specialist Hospital Research Centre
P.O Box 3354 Riyadh 11211 (SA)

(74) Representative: Heath, Derek James et al
Bromhead & Co. 30 Cursitor Street Chancery Lane
London EC4A 1LT (GB)

(54) **Method of producing iodine 124 and meta-iodobenzylguanidine containing iodine 124.**

(57) This invention relates to a method for synthesising ^{124}I and ^{124}I-m-IBG comprising an innovative technique for preparing an irradiation target, irradiating the prepared target, and finally collecting ^{124}I created by the irradiation. In one embodiment of this invention, the method is further characterized by the synthesis of ^{124}I-m-IBG.

EP 0 288 284 A2

Description

METHOD OF PRODUCING IODINE^{124} AND META-IODOBENZYLGUANIDINE CONTAINING IODINE^{124}

Field of The Invention

This invention relates generally to a method for synthesising ^{124}I and ^{124}I-m-IBG. More specifically, this method comprises an innovative technique for preparing an irradiation target, irradiating the prepared target, and finally collecting the resulting ^{124}I; in one embodiment of the invention, the method is further characterized by the synthesis of ^{124}I-m-IBG.

Background of the Invention

Iodine^{123} and Iodine^{131} radioisotopes are presently used in medical diagnosis and radiation therapy. Meta-Iodobenzylguanidine sulfate (m-IBG) labelled with ^{123}I and ^{131}I has been used clinically in the diagnosis and treatment of pheochromocytomas, neuroblastomas and other paragagliomas.

Although perhaps less popular, Iodine^{124} is another iodine isotope which is useful in nuclear medicine. Iodin^{124} decays by positron emission (25%) and can therefore be used in positron emission tomography for non-invasive quantitative physiological studies. When m-IBG is labelled with ^{124}I-iodide (^{124}I-m-IBG), it is useful in obtaining quantitative images of the brain, adrenal, and myocardium.

However, Iodine^{124} and ^{124}I-m-IBG are not commonly available substances. A known method of producing Iodine^{124} is by the ^{124}Te(p,n)^{124}I reaction disclosed in Kondo K., Lambrecht, R.M., Norton E.F. and Wolf A.P., 28 Int. J. App. Rad. and Isotopes 765 (1977). However, this reaction is not efficient and typically results in low yields.

Consequently, it is an object of this invention to provide an efficient and commercially feasible method for synthesizing Iodine^{124}.

A further object of this invention is to provide an efficient and commercially feasible method for synthesizing ^{124}I-m-IBG.

A further object of this invention is to provide a method of synthesizing Iodine^{124} which is safe and reliable.

A further object of this invention is to provide a method of synthesizing ^{124}I-m-IBG which is safe and reliable.

Other objects and features of this invention will become apparent to those skilled in the art from the following specification when read in the light of the annexed drawings.

Summary of the Invention

This invention relates to a method for synthesising ^{124}I and ^{124}I-m-IBG comprising an innovative technique for preparing an irradiation target, irradiating the prepared target, and finally collecting the resulting ^{124}I. In one embodiment of this invention, the method is further characterized by the synthesis of ^{124}I-m-IBG which is useful in nuclear medicine applications.

DISCLOSURE OF THE PREFERRED EMBODIMENT

I. SYNTHESIS OF ^{124}I

A. Preparation of Tellurium^{124} Targets

In synthesising ^{124}I, a copper metal plate is first milled and uniformly lapped to the dimensional specifications required for ultimately placing the target matrix in the accelerated subatomic particle path of a nuclear accelerator apparatus. The surface of the copper plate is sanded, washed with distilled water, and dried. The copper plate is then placed in a nickel plating solution prepared from a salt, such as nickel sulfate hexahydrate, and is then electroplated using a platinum electrode as the anode.

The copper plate is then placed in a tellurium plating solution comprising isotopically enriched Tellurium^{124} dioxide dissolved in a solution of potassium hydroxide. The tellurium is electroplated onto the copper plate using a platinum electrode. The target thickness of the Tellurium^{124} is typically 10-14 milligrams per square centimeter for routine production targets.

B. Processing the Iodine^{124}

After irradiating the Terrurium^{124} by means of the the internal beam line of a cyclotron, such as the King Faisal Specialist Hospital and Research Centre CS-30 Cyclotron accelerator, the irradiated Tellurium^{124} is dissolved from the copper plate by means of a sodium hydroxide solution, preferably 5 molar, and about 30% hydrogen peroxide and water. The solution is transferred to a vessel containing about 250 milligrams of aluminum powder. Following dissolution by gradual heating, the solution is purged with air, then carbon dioxide gas. The solution volume may be reduced by boiling the solution. The solution is then passed through a filter to collect solid materials for subsequent recovery of the isotopically enriched Tellurium^{124} by use of methods known to those skilled in the art.

Table 2 illustrates Iodine^{124} production yields and levels of Iodine^{126} impurity 48 hours after irradiation of the Tellurium^{124} target of greater than 95% isotopic enrichment. Radioanalysis by gamma-ray spectrometry was performed to assess the radionuclidic purity and to identify the impurities. Irradiation conditions in the examples range from 25 to 80 microampere deutron beam current with irradiation doses ranging from 100 to 550 microampere hours.

The Iodine^{124} was prepared in quantities of greater than 100 mCi by 15 megavolt deuteron irradiation of enriched Tellurium^{124} by the $^{124}Te(d,2n)^{124}I$ nuclear reaction. Enriched Tellurium^{124} was plated in the quantity of about 13 mg/cm^2 on a nickel plated copper target. These targets were irradiated in the internal beam line of the King Faisal Specialist Hospital and Research Centre CS-30 Cyclotron. The current was varied from 25 to 60 micro-amperes, and the irradiation time was varied from 4-8 hours. Iodine^{124} was separated from the tellurium target using the chemical procedure already discussed.

For synthesis of labelled organic molecules, the ^{124}I-I was passed through a cation-exchange column to remove trace tellurium. The radioanalysis was done by gamma-ray spectrometry. The gamma-spectrum was obtained by using a 45-Cm^3 Ge(Li) detector (full width at half-maximum of 1.87 KeV at 1.33 MeV photopeak of ^{60}Co, peak-to-compton ratio of 32:1 and an efficiency of 7.7%) and a Canberra Series 80 pulse height analyzer.

Synthesis of ^{124}I-m-IBG

Non-radioactive m-IBG was synthesized by the method of Wieland, disclosed in Wieland, D.M., Wu, Jiann-long, Brown, L.E., Mangner,I T.J., Swanson, D.P., Beierwaltes, W.H., 21 Journal of Nulear Medicine 349 (1980). The m-IBG was characterized on a Nicolet Model 5DX FT-IR:(KBr) which showed broad peaks between 3100-3448 (NH_2,NH), 1660(C=N), 1590 (aromatic C=C), 772 &; 687 cm^{-1} (m-disubstituted phenyl). Mass spectrum analysis (direct probe insertion) was performed on a Finnegan MAT Model-311: molecular ion (M+) and a base peak (rel. intensity 100%) at m/z 276, a peak (rel. intensity 060%) at m/z 233 (M-43) representing the split of the -C group. HNMR analysis was performed on a Varian Model T-60A: (DMSO-d6); delta 7-7.8(m,4H aromatic), the benzylic CH_2 group is overmasked by the water peak at delta 3.4. Melting point: 167.3° (corr), Lit. 167.0° (uncorr).

The exchange reaction to prepare^{124}I m-IBG was adopted with a modification from the method of Van Doremalen, P. A. P. M., Janssen, A.G.M., 96 J. Radioanal. Nucl. Chem., Letters., 97 (1985). In a 10 mL borosilicate serum vial 2.7 micro-moles of "cold" meta-iodobenzylguanidine sulphate was mixed with 6.2 micro-moles of $Cu(NO_3)_2$. ^{124}I (5 to 20 mCi) was added. The total volume was brought to approximately 0.8 ml with water, and the mixture was then adjusted to pH 5. The vessel was stoppered and heated to 150° in an oil bath for 45 min. Upon cooling, I.5mL of 2.45% sodium biphosphate buffer solution was added to precipitate copper. Copper phosphate precipitate was then removed by filtering through 0.22$_{um}$millipore filter. The filtrate was passed through 100-200 mesh Bio-Rad AGI-X8 anion-exchange resin to remove the unreacted iodide.

Chromatography

Chromatographic and radiochemical procedures were applied to obtain less than 95% Iodine^{124} activity in th iodide anion form for further radiochemical syntheses. Sodium Iodide^{124} solution was analyzed by thin layer chromatography (TLC) using a model SG ITLC, available from Gelman Instrument Co., Ann Arbor, Michigan. The developing solvent was the organic phase prepared by mixing 3ml of NH_4OH in 12ml of water with 12ml of 1-butanol; R_f values: I^-: 0.8; IO_3^- and other radiochemical impurities: 0.0-0.15. ^{124}I-m-IBG was analyzed by TLC on silica gel plates with ethylacetate: ethanol: H_2O (20:20:1) as the developing solvent (R_f, I^-: 0.75; ^{124}I-m-IBG: 0.00). High pressure liquid chromatography (HPLC) analysis of m-IBG was performed on a Varian 5000 HPLC System. Column effluent was passed first through a variable UV detector (254 nm), and then through a radioactivity detector (NaI) connected in series with the UV detector (Figure 1).

Analysis was performed on an Altech C-18, 10 column. The column was eluted with an eluate composed of 60% 0.05M NH_4H_2Po4: 40% CH_3CN, at a flow rate of 2mL/min. Retention time for m-IBG was 4.68 min, while the unbound ^{124}I- and/or Cu^{+2} eluted with the solvent front.

Large quantities (150 mCi) of Iodine^{124} are routinely produced by the $^{124}Te(d,2n)^{124}I$ reaction. The production yield data is given in Table 1. Iodine^{124} can be produced in higher yields and final product purity by using this reaction rather than by the $^{124}Te(p,n)^{124}I$ reaction. The yields for the $^{124}Te(d,2n)^{124}I$ was 0.57mCi/micro-ampere, compared to 0.093 mCi/micro-ampere-h for the$^{124}Te(p,n)$ ^{124}I reaction reported in Kondo K., Lambrecht, R. M., Norton E. F. and Wolf A. P., 28 Int. J. App. Rad. and Isotopes., 765, (1977). The production yield of ^{124}I was directly proportional to the dose. The current could be increased to 60 micro-amperes without damaging the target. The TLC analysis indicated that greater than 95% of the radioactivity was present as iodide anion.

Incorporation of ^{124}I into m-IBG was accomplished in a radiochemical yield of 70-90%. HPLC analysis of the filtrate after removal of copper phosphate precipitate indicated the presence of unreacted iodide and occasionally the unprecipitated copper. However, a careful passage of the filtrate through a Bio-Rad anion exchange resin completely removed the^{124}I, rendering the filtrate greater than 95% radiochemically pure (Figure 2). Complete precipitation of copper was ensured by adjustment of the pH and concentration of the phosphate buffer. With this modification, the final preparation contained less than 1 g/ml of copper by wet chemical analysis.

Table 1: Iodine^{124} Production Yield Data

Dose	Current	mCi/micro-ampere hour	^{124}I mCi (EOB)	^{126}I mCi (EOB)	^{124}I (%) (After 48 hours)
100 micro-ampere-hours	25 micro-A	0.56	57.0	0.5	99.1
200 micro-ampere-hours	25 micro-A	0.60	119.0	0.6	99.5
240 micro-ampere-hours	40 micro-A	0.52	124.0	0.7	99.4
0 micro-ampere-hours	50 micro-A	0.57	143.0	0.5	99.6
300 micro-ampere-hours	60 micro-A	0.59	150.0	0.6	99.6

Table 2: Iodine-124 Production Yield Data

Dose, mAh	Fluence, µA	mCi/µAh	^{124}I mCi (EOB)	^{126}I mCi (EOB)	^{124}I (%) (after 48 hours)	Date of Production
100	25	0.56	57.0	0.5	99.1	02 Nov 86
200	25	0.60	119.0	0.6	99.5	09 Nov 86
240	40	0.52	124.0	0.7	99.4	23 Nov 86
250	50	0.57	143.0	0.5	99.6	07 Dec 86
300	60	0.59	150.0	0.6	99.6	25 Jan 87
500	75	0.48	260.0	<1.2	99.5	15 Mar 87
210	70	0.44	93.7	<0.65	99.3	08 Feb 87
325	65	0.62	201.0	<1.3	99.3	01 Mar 87
500	80	0.54	269.66	<1.83	99.3	29 Mar 87

Claims

1. A method of synthesizing Iodine^{124}, said method comprising:
   (a) placing a target means comprising copper in a nickel plating solution and electroplating said target means with nickel;
   (b) placing the resulting target means in a Tellurium^{124} plating solution and electroplating said target means with Tellurium^{124};
   (c) placing the resulting target means in line with the particle beam of a cyclotron, thereby irradiating the Tellurium^{124} and creating Iodine^{124} and;
   (d) separating the Iodine^{124} from the target means.

2. The method of synthesizing Iodine^{124} of claim 1 wherein:
the target means is a copper metal plate which is first milled and uniformly lapped to the dimensional specifications required for ultimately placing the target matrix in the particle path of the cyclotron, said copper metal plate being sanded, washed with distilled water, and dried prior to electroplating.

3. The method of synthesizing ^{124}I of claim 2 wherein:
the copper plate target is electroplated with nickel by means of a nickel sulfate hexahydrate salt solution and a platinum electrode anode, and the Tellurium^{124} electroplating is accomplished by means of a solution of isotopically enriched Tellurium^{124} dioxide dissolved in a solution of potassium hydroxide and by means of a platinum electrode.

4. The method of synthesizing ^{124}I of claim 3 wherein:
the target thickness is between 10 and 14 milligrams per square centimeter.

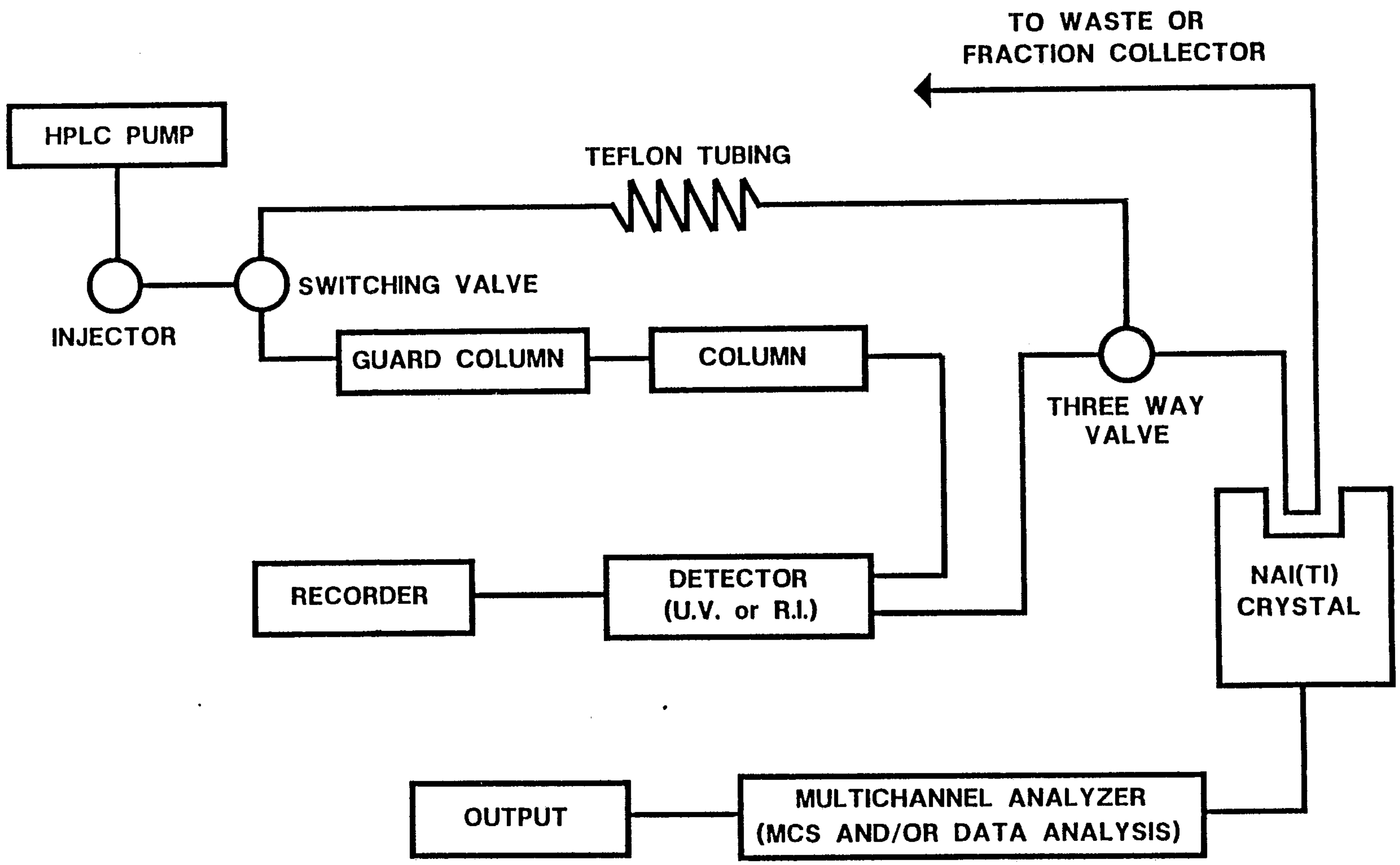
5. The method of synthesizing ^{124}I of claim 1 wherein the irradiated target is placed in a solution of sodium hydroxide solution containing hydrogen peroxide and water, subsequently, the solution is transferred to a vessel containing aluminum powder, thereafter the solution is purged with air, then carbon dioxide gas, particles in the solution are then filtered out and passed through a cation-exchange column.

6. The method of Claim 5 wherein irradiation is conducted in the range of 25 to 80 microamperes deutron beam current with irradiation doses ranging from 100 to 550 microampere hours.

7. A method of synthesizing ^{124}I-m-IBG, said method comprising:
   (a) placing a target means comprising copper in a nickel plating solution and electroplating said target means with nickel;
   (b) placing the resulting target means in a Tellurium^{124} plating solution and electroplating said target means with Tellurium^{124};
   (c) placing the resulting target means in line with the particle beam of a cyclotron, thereby irradiating the Tellurium^{124} and creating Iodine^{124};
   (d) separating the Iodine^{124} from the target means; and
   (e)combining the Iodine^{124} with m-IBG.

8. The method of Claim 7 wherein
the Iodine^{124} is combined with the m-IBG in a method comprising the mixing of meta-iodobenzylguanidene sulphate with $Cu(NO3)_2$ in a borosilicate serum vial, adjusting the pH to about 5, heating the solution to 150 degrees centigrade, cooling, adding a sodium biphosphate buffer solution, and passing the filtrate through an anion-exchange resin.

FIG. I
HPLC SYSTEM



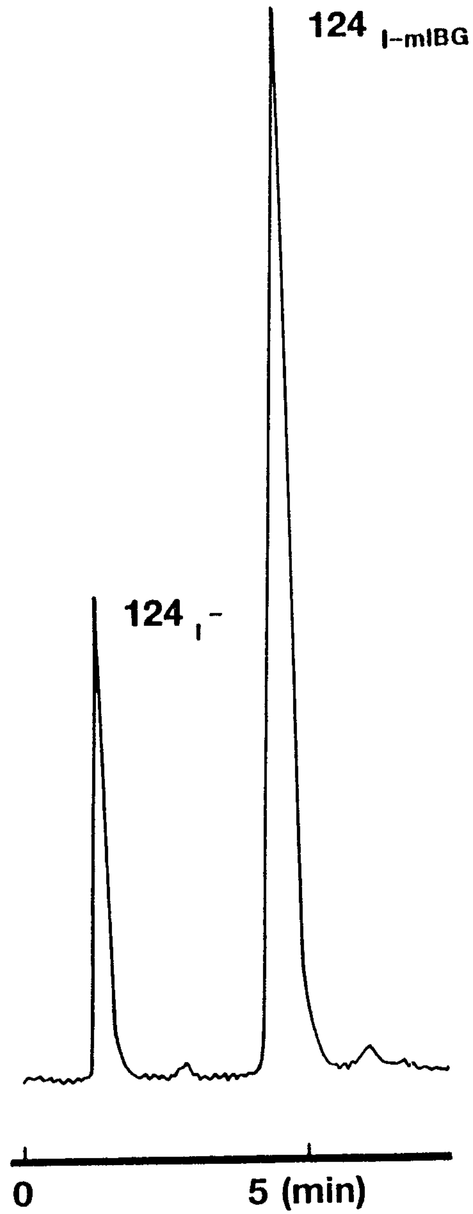


FIG. 2

HPLC CONDITIONS:
Altech C–18, 10u Column
60% 0.05M $NH_4H_2PO_4$ /
40% CH_3CN
Flow Rate: 2.0 mL/min
Radiochemical Detector (NaI)