AUTOMATED PRODUCTION OF NO CARRIER ADDED HOLMIUM-166

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ABSTRACT

Holmium-166 (^{166}Ho) is used in radiotherapeutic applications such as radio-immunospecific pharmaceuticals, bone marrow ablation and radiation synovectomy and can be produced with moderate specific activity by the ^{165}Ho[n,γ]^{166}Ho reaction. Higher specific activity carrier-free ^{166}Ho can be obtained from the decay of dysprosium-166 (^{166}Dy), produced by the double neutron capture reaction ^{164}Dy[n,γ]^{165}Dy[n,γ]^{166}Dy. ^{166}Ho can be separated from ^{166}Dy by reverse phase ion exchange chromatography in high radionuclidic purity. An automated system has been developed to process the irradiated dysprosium oxide (Dy_2O_3) targets, carry out HPLC separation and deliver ^{166}Ho in a form suitable for radiolabelling proteins and pharmaceuticals.

INTRODUCTION

Holmium-166 (^{166}Ho) has been used in radio-therapeutic applications because of its favourable physical and chemical properties. It has high energy β radiation ($E_{\beta 1}$ = 1855 keV (51%), $E_{\beta 2}$ = 1776 keV (48%) and E_{av} = 666 keV), it also emits a low intensity, low energy γ ray (80.5 keV,6%) suitable for imaging. It has a 26.4 h half-life and decays to a stable daughter. Additionally its chemical properties permit labelling of biologically active molecules such as monoclonal antibodies and peptides via bifunctional chelating agents. The absence of higher energy γ rays allow its use in outpatient therapy without the risk of significant external radiation.

Non carrier-free, low specific activity ^{166}Ho can be produced directly by neutron activation of ^{165}Ho via the ^{165}Ho[n,γ] reaction. However for the effectual labelling of proteins high specific activity is essential. An alternative production method that yields carrier free ^{166}Ho is via the decay of its radionuclidic parent ^{166}Dy, produced by double neutron capture of ^{164}Dy.

PRODUCTION AND SEPARATION METHODS

Separation methods for many lanthanides have been well documented. However the uniformity of the chemistry of members of the lanthanide series impedes the separation of micro amounts (≤ 1 μg) of one member from macro amounts(≥ 1 mg) of an adjacent member and most publications report separations on the micro scale only (Tang and Wai, 1986, Kuroda et al., 1993).

Separation of micro amounts of Tb (< 1 μg) from macro amounts of Er (> 22.6 mg) using reversed phase partition chromatography has been reported by Sochacka and Siekierski (1964). Yasumi et al (1982) reported the separation of carrier-free ^{163}Ho, produced with the ^{164}Dy(p,2n) reaction, on a cation exchange column in α-HIBA. Knight et al (1984) have reported on the use of dynamic ion exchange chromatography to separate ^{139}La from irradiated fuel. Further work using this technique has been reported by Cassidy et al (1986) who described an automated in-cell HPLC separation system. The dynamic ion exchange method

was used by Barkley and Blanchette (1986) to separate nanogram amounts of lanthanides in α-HIBA on a reversed phase column.

The successful separation of carrier-free ^{166}Ho from mg amounts of neutron activated Dy_2O_3, by reverse phase ion exchange chromatography, has been reported by Dadachova (Dadachova et al., 1994). A separation factor of about 10^3 between Ho and Dy was achieved using a metal-free system, an Aminex-A5 cation exchange column and α-HIBA as the mobile phase. This author has also reported the labelling of monoclonal antibodies with ^{166}Ho at specific activities of 3-4 mCi mg^{-1} (Dadachova et al., 1997).

AUTOMATED PRODUCTION

Automation is now widely implemented in all phases of the production of radiopharmaceuticals and radionuclides using both dedicated systems (Ruth et al., 1991, Moerlein et al., 1993, Van den Winkel et al., 1993) and multi-purpose robotic systems (Brodack & Welch 1989) particularly for the shorter lived cyclotron produced isotopes (Suzuki et al., 1995).

There are a number of advantages to be gained from automating these production systems. Production errors are minimised as hands on operations are reduced to a few well defined straightforward tasks, such as weighing out reagents or filling vials with stock solutions. Radiation exposure to personnel is minimised, as the automated system may be operated in a hot cell, or if used in a non shielded area, those parts with significant residence times can be individually shielded. Product reproducibility is maintained as parameters such as temperature, heating periods, pH, reaction time etc. are pre-set and only changed by some deliberate action on the part of the operator during initialisation. Controllers for automated systems range from simple cam sequencers, complex PLCs to computer control with full adaptive and decision making abilities. A computer controlled automated ^{166}Ho production system based on the method of Dadachova (Dadachova et al., 1994) has been developed at ANSTO to process solid $^{164}Dy_2O_3$ targets, perform HPLC separation and produce a solution of carrier-free ^{166}Ho ready for use in radiolabelling.

DESCRIPTION OF THE AUTOMATED SYSTEM

The main part of the module, comprising the HPLC separation system, is similar to those previously described for the production of iodinated radiopharmaceuticals (Izard et al., 1996). It comprises a peristaltic pump, teflon solenoid valves, a metal free auto-injector and sample loop and an ion exchange HPLC column. However the original design has been modified to include a target preparation section and a different product preparation procedure.

The target preparation part of the system consists of two sections. The first is an irradiation can opener comprising; a motorised grab to remove the can from the transport container, an air actuated vice and a motorised screwdriver. The second section is the target dissolution unit and consists of a motorised arm carrying acid delivery tubes, a diaphragm pump, an acid digestion flask heater and a cold trap.

The post HPLC product collection and preparation section consists of two heater blocks containing conical flasks and a system to deliver heated nitrogen.

Flow from the HPLC column is monitored by a sodium iodide scintillation probe and ratemeter. Output from the ratemeter goes to a chart recorder and to a voltage sensing relay adjusted to actuate a collection valve only during the product peak. The system is controlled by a PC via a 24 channel relay card and 24 channel programmable digital input/output card. The control programme is written in Quickbasic 4.5.

HOLMIUM PRODUCTION TARGET

The target consists of isotopically enriched $^{164}Dy_2O_3$ (97%) powder, sealed in a standard screw cap titanium irradiation can. It is typically irradiated in the Australian Nuclear Science and Technology

Organisation's reactor (HIFAR) at 3.5 x 10^{13} $n.s^{-1}.cm^{-2}$ for 120 h. After cooling for 2 days, the lead transport pot containing the irradiation can is transferred to the automated production module located in a hot-cell in the Radiopharmaceuticals Division Research laboratory.

PRODUCTION SEQUENCE

The irradiation can is opened and the diaphragm pump delivers 9 M HCl via a teflon tube to dissolve the $^{164/166}Dy_2O_3$ target. A second tube transfers the dissolved target via the peristaltic pump to a heated glass vial where it is evaporated to dryness under a flow of N_2. A cold trap on the N_2 outlet prevents release of HCl fumes into the cell.

The peristaltic pump dispenses HNO_3 into the evaporation vial after cooling, to re-dissolve the digest which is then transferred through a hollow fibre filter and the auto injector onto the HPLC column for separation. ^{166}Ho is separated from $^{164/166}Dy$ in 0.085 M α-HIBA mobile phase into the first product collection flask and is heated to 400 C to ensure complete decomposition of the mobile phase prior to its use for labelling (Dadachova et al., 1997). The $^{164/166}Dy$ is collected into a second decomposition flask and evaporated to dryness.

As the half life of ^{166}Dy (3.4 days) is considerably longer than that of ^{166}Ho (1.1 days) the $^{164/166}Dy$ isolate can be recycled through the separation process after reaching equilibrium with ^{166}Ho.

After 2 to 2.5 days ingrowth of ^{166}Ho, the peristaltic pump dispenses HNO_3 into the second collection flask to dissolve the $^{164/166}Dy/^{166}Ho$ fraction, which is then re-injected onto the column. ^{166}Ho is separated into another decomposition flask and heated to 400 C as before, then dissolved in buffer as required for labelling studies. The $^{164/166}Dy$ is collected for further processing if required. Repetition of this reprocessing step depends on starting activity of the $^{164/166}Dy_2O_3$ target.

RESULTS

It has been shown that the ^{166}Ho collected after the first pass through the column typically contains a significant amount of ^{165}Ho due to decay of the short lived intermediate ^{165}Dy ($t_{1/2}$ 2.4h, β^-) and so is not used for labelling studies. Following the in-growth period, the second separation run of the first $^{164/166}Dy/^{166}Ho$ fraction yielded carrier free ^{166}Ho with a specific activity of about 10^2 Ci mg^{-1} (Dadachova et al., 1997).

Production by the automated system has been evaluated against manual production for 2.5 mg targets irradiated in HIFAR for 120 h at 3.5 x 10^{13} ns^{-1} cm^{-2} (Table 1). Production run 1 was performed 2 days after irradiation and subsequent runs performed at 2.5 day intervals to allow in-growth of ^{166}Ho.

Table 1 Evaluation of the yields of carrier-free ^{166}Ho by manual and automated production methods.

Production run	^{166}Ho yield produced manually (mCi)	^{166}Ho yield produced automatically (mCi)
1	11.0	10.6
2	3.9	3.7
3	2.9	2.8
4	1.9	1.7

DISCUSSION

An automated system has been developed for the production of carrier-free ^{166}Ho from neutron activated Dy_2O_3 targets It is based on a successful manual separation method (Dadachova et al., 1994) and has been designed for use in a hot cell to permit routine production of high activity ^{166}Ho. This system is similar to the automated chemistry modules produced at ANSTO for production of ^{123}I labelled radiopharmaceuticals. It was assembled from commercially available components with a minimum of custom manufacturing and designed for ease of operation and maintenance. Its efficiency has proved to be comparable to that of the manual method and, although developed for ^{166}Ho production, it could be used for the production of other radio-lanthanides with only minor modifications to the production parameters.

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KEY WORDS

Automation, Holmium-166, Automated production, HPLC separation, radionuclide production, radio-lanthanides.