Evaluation of an Internal Cyclotron Target for the Production of $^{211}$At via the $^{209}$Bi ($\alpha$,2n)$^{211}$At Reaction

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Astatine-211 is a 7.2 h half-life $\alpha$-emitting radionuclide which has shown great promise for targeted radiotherapy. It is generally produced by cyclotron bombardment of bismuth metal targets with 28 MeV $\alpha$-particles via the $^{209}$Bi($\alpha$,2n)$^{211}$At reaction. In order to provide $^{211}$At activity levels anticipated for clinical investigations, an internal target system has been designed and evaluated. The system has a grazing-angle configuration and leading- and trailing-edge monitors. Both aluminum and copper target backings were evaluated. With approx. 28 MeV $\alpha$-particles, the $^{211}$At production efficiency was 41 ± 7 MBq/μA·h, compared with 10.6 ± 1.2 MBq/μA·h for an external target. Radionuclidic purity of $^{211}$At was high with no evidence of $^{210}$At.

Introduction

The radionuclide $^{211}$At decays by the emission of $\alpha$-particles which are of short range and high linear energy transfer. These characteristics offer the possibility of selectively delivering high radiation dose to tumor cells by means of cell-specific molecules. Dosimetry calculations have been performed which suggest that in certain settings, $^{211}$At-labeled compounds may be more effective than those labeled with $\beta$-emitters such as $^{131}$I and $^{90}$Y (Humm, 1987; Roeske et al., 1990; Roeske and Chen, 1993). The exquisite cytotoxicity of $^{211}$At-labeled compounds has been demonstrated in vitro and in animal models (Harrison and Royle, 1987; Link and Carpenter, 1992; Larsen et al., 1994a,b; Brown et al., 1994; Strickland et al., 1994; Zalutsky et al., 1994). Based on these results, a number of laboratories including our own have concluded that $^{211}$At-labeled compounds should be evaluated clinically.

Astatine-211 has a 7.2 h half-life and its production is generally accomplished by the cyclotron bombardment of natural bismuth metal with 28 MeV $\alpha$-particles via the $^{209}$Bi($\alpha$,2n)$^{211}$At reaction. Production yields of 200–400 MBq/h of irradiation have been reported (Lambrecht and Mirzadeh, 1985; Larsen et al., 1993; Zalutsky and Narula, 1988). Although higher $^{211}$At yields could be obtained by increasing the $\alpha$-particle beam energy, this would result in the production of $^{210}$At, a radionuclidic impurity which is unacceptable because of its 138 day $\alpha$-emitting daughter, $^{210}$Po. To be able to utilize the beam for maximum production of $^{211}$At, it has been calculated that the minimum thickness of the Bi target should be 200 μm if the beam hits perpendicular to the target surface (Lambrecht and Mirzadeh, 1985). The production of $^{211}$At has been limited partly due to problems with melting of the target due to the low thermal conductivity of bismuth. If the beam hits perpendicular to the target surface and the target backing is sufficiently cooled, beam currents in the range of 10–20 μA can be put on target (assuming an effective target diameter of approx. 20 mm) before melting occurs.

The lack of convenient methods for production of high activity levels of $^{211}$At is a major impediment to the clinical investigation of $^{211}$At-labeled radiotherapeutic agents. Since $\alpha$-emitting radiopharmaceuticals have not been investigated clinically for cancer treatment, there is some uncertainty with regard to the activity of $^{211}$At which will be required for cancer treatment. With $^{211}$At-labeled monoclonal antibodies (MAbs), extrapolation from animal models and dosimetric models suggest that activities of 0.37–2.59 GBq may be required (Roeske et al., 1990; Zalutsky et al., 1994; Larsen et al., 1995). Since only approx. 25% of the end of bombardment (EOB) $^{211}$At activity is recovered as $^{211}$At-labeled MAb (Larsen et al., 1994c), it may be necessary to produce at least 2 GBq of $^{211}$At.

Production of one patient dose of $^{211}$At-labeled MAb using external targets such as those in current
use would not be practical because the limits imposed on beam current due to the bismuth target material would result in prohibitively long irradiation times, particularly for cyclotrons which are also utilized for clinical purposes. Utilization of higher beam currents should be possible if the beam is spread over a target area large enough to provide sufficient dispersion of the heat. One approach to achieve this goal is to use a grazing-angle target. In this paper we present preliminary data on the evaluation of a grazing-angle internal target system designed for production of potential clinically useful amounts of $^{211}$At. Our results suggest that this system is capable of producing $^{211}$At at an activity level and purity suitable for this purpose.

Materials and Methods

Description of the MIT-I internal target system

The MIT-I internal target system (Cyclotron Inc., Napa, CA) was specifically designed for $^{211}$At production at the Duke University CS-30 cyclotron. Figure 1 shows the floor plan of the cyclotron vault with the internal target, the relocated beam probe, and the seven external beam lines used for production of various radionuclides. Installation of the MIT-I system required locating the internal target in the position previously occupied by the standard CS-30 diagnostic beam probe. This was necessary to accommodate the length of the internal target ram within the vault boundaries, and to take advantage of the favorable mid-valley beam optics. The internal target system consists of a 305 cm long motor-driven ram with the target face on the inner end, a vacuum lock for target loading and unloading, and a vault equipment cabinet.

The cabinet serves as a mechanical support for the ram table, provides space to mount a roughing pump and various valves and electrical components. The cabinet also contains a local control panel for operating the cyclotron isolation gate valve, the target recovery gate valve, the target water cooling and blow-down, the vent and vacuum pump ram positioning mechanism. The radial and angle drive operation of the target ram is accurate and repeatable to within 0.5 mm, and can be accomplished both in the vault and remotely from the CS-30 console. Digital positioning readouts are displayed at the cyclotron console operating panel adjacent to the push-buttons used to control the ram drives.

The target face shown in Fig. 2 has several unique design attributes not previously available on internal target systems. These features were included in an attempt to provide a capability of high performance combined with the safety of continuous monitoring and control of beam distribution on the target material. A curved target with a radius of 71 cm (instead of a flat 10 cm face) was used to improve distribution of the beam over the full length of the target by using small grazing angles (1.5°-4.5°). Monitoring currents in electrically isolated graphite leading- and trailing-edge monitors (in addition to the target) provides a means to continuously monitor beam current distribution during cyclotron runs. The back of the target face is water-cooled during target irradiations, and cooling efficiency is optimized by machining fins into the back of the target.

Preparation of targets

The configuration of the target backing plate used for most of the experiments is illustrated in Fig 3. The target face consists of a curved depression of approx. 10.2 x 2.1 cm, the surface of which was coated with bismuth. Target backing plates fabricated of aluminum and copper were evaluated. The bismuth was either electroplated on to a backing of copper or melted onto a backing of aluminum.

Aluminum-backed targets were prepared by heating the aluminum on a hot plate and adding bismuth metal powder (99.9% purity, 4-30 mesh; Aldrich, Milwaukee, WI). After melting, the bismuth was distributed as evenly as possible with a porcelain spatula. The thickness of the bismuth layer was measured with a micrometer at eight different points on the target and the total weight of the bismuth was estimated from the difference of weight of the target before and after plating. Due to surface tension, the bismuth tended to distribute quite evenly for thin layers (15 μm), while thicker layers (25-50 μm) were more difficult to prepare with an even thickness. The copper-backed bismuth targets were prepared by electro-deposition of bismuth using a SIFCO SPL-30 electroplating apparatus (SIFCO, Cleveland, OH). The electroplating solution contained 70 g/L bismuth as tartrate in strongly basic NaOH. After cleaning and etching, plating was accomplished at 3.5 V for 0.45 Ah to give a thickness of 50 μm bismuth. This gave a uniform distribution of the bismuth and could be used to prepare targets of different thicknesses. Further details about target design and preparation will be published separately.

Preparation of targets

A few experiments were performed using a two-piece target with reduced vertical target material height (1.0 vs 2.1 cm; see Fig. 4) and reduced bismuth surface area (9.5 vs 21.2 cm²). This target backing configuration was investigated because of the much smaller volume distillation apparatus that could be used, a factor which could improve $^{211}$At distillation yields. The target face was covered with bismuth in the same way as the one-piece, larger target.

Cyclotron irradiations

The $^{209}$Bi(α,2n)$^{211}$At reaction was used for production. The orbit corresponding to an energy of approx. 28 MeV was intercepted so that the incident α-particles had a small angle relative to the target surface. Efficient water cooling of the target backing, spread of the beam over a large target surface, and use of a thin layer of bismuth metal allowed high beam currents to be utilized without melting the
Internal target for $^{211}$At production

Fig. 1. Plan view of the Duke CS 30 cyclotron with the MIT-1 internal target, beam probe and seven external beam lines. The internal target system is located in the lower right.

targets. For the yield measurements, 60-min irradiations at beam currents of 20-40 μA were used with the internal target. For comparison, production yields using an external target consisting of a disk of aluminum into which bismuth metal had been melted were also determined. Details of this target system can be found in previous publications (Zalutsky and Narula, 1988; Zalutsky et al., 1989).

Beam currents were measured first by inserting the beam probe into the cyclotron tank to intercept the helium-ion orbit and reading the electrical current on the probe tip. The probe was then withdrawn and the
target, together with the leading- and trailing-edge monitors, was inserted into the same orbit. Currents in the two monitors and the target were determined. The target position was fine tuned to minimize current readings on the leading- and trailing-edge monitors and to maximize beam on the target. Typically, 5–10% of the beam current was deposited on the two edge monitors.

**Quantification of the radioactivity of 211At-samples**

The 211At activity levels were determined using a Ge(Li) detector by determining the counting rates for the three most abundant γ-rays emitted in the decay of 211At and its daughter, 211Po. Gamma-ray energies and abundances were taken from Lambrecht and Mirzadeh (1985) and are summarized in Table 1. Energy-dependent efficiency curves for the Ge(Li) detector were determined at three fixed positions. An automated γ-counter (LKB 1282, Sweden) and a dose calibrator (Capintec CRC-7, U.S.A.) were cross calibrated to the Ge(Li) detector to permit the evaluation of sources with a wide range of count rates. The counting efficiency for these two detectors was corrected, if necessary, for vial type and sample size to account for self-shielding and absorption in the vial of the 77–92 keV polonium x-rays used for detection.

**Radionuclidic purity**

The radionuclidic purity of the 211At produced was determined by half-life measurements and by analyses of γ-ray spectra obtained with the Ge(Li) detector. Quantification of 211At was based on counting of its associated 569.7, 687.8 and 897.8 keV γ-rays. Corrections for the presence of 569.7 keV γ-rays originating from 210Bi were applied for samples counted 24–72 h post EOB. The isotopic impurity expected to be most abundant, 210At, was sought for by analyzing the γ-spectra for its most abundant γ-rays, which are emitted at 245.3 and 1181.4 keV. The energies and relative intensities of the γ-emissions associated with the decay of 210At and its 210Po daughter are summarized in Table 2.

**Measurement of target activity after cyclotron irradiation**

Target activity was measured with the Capintec dose calibrator at the 125Xe setting 30–60 min after the end of bombardment. The activity measured in this manner were considered to only be rough estimates of 211At levels since activation of the copper or aluminum target backing material produced radio-nuclides which could interfere with 211At quantification. Exact quantification of 211At in irradiated targets was obtained from γ-ray spectra acquired...
Internal target for $^{211}\text{At}$ production

Fig. 3. Schematic of the full size internal target for production of $^{211}\text{At}$. Front view with the bismuth layer (lower left). Target backings were either copper or aluminum and bismuth thicknesses of 25–50 µm were used. Dimensions of the target backing: $4.8 \times 10.1 \times 1.2$ cm ($w \times l \times d$); dimensions of the target face: $2.1 \times 10.1$ cm; depth of the target face, 0.1 cm on the edges, 0.3 cm in the center. Rear view (upper left) shows the cavity ($2.1 \times 9.5 \times 0.6$ cm) for cooling water and the machined fins (0.2 cm deep) to increase the surface between the cooling water and the target backing. The side view of the target (lower right) is shown to illustrate the curved target surface. The two holes were used to bolt the target to the target support on the ram.

with the sample located in a fixed geometry with respect to the Ge(Li) detector. To minimize dose to personnel and dead time losses in the detector, heavily irradiated targets were analyzed 1–3 days after irradiation.

Apparatus for distillation of $^{211}\text{At}$ from the internal target

Separation of the $^{211}\text{At}$ from the internal targets could not be performed in the distillation apparatus used previously with external target disks (Zalutsky and Narula, 1988; Zalutsky et al., 1989) because of differences in target geometry. For use with internal

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Half-life</th>
<th>Decay mode</th>
<th>Intensity from $^{211}\text{At}$ decay (%)</th>
<th>Energy (keV)</th>
<th>Abundance (%)</th>
<th>Absolute intensity from $^{211}\text{At}$ decay (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{211}\text{At}$</td>
<td>7.214 h</td>
<td>EC</td>
<td>58.3</td>
<td>687.8</td>
<td>0.247</td>
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<td></td>
<td></td>
<td>x</td>
<td>41.7</td>
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<td>0.00347</td>
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<td></td>
<td>742.7</td>
<td>0.00094</td>
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<td></td>
<td>569.7</td>
<td>0.509</td>
<td>0.297</td>
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<td></td>
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<td></td>
<td></td>
<td>897.8</td>
<td>0.531</td>
<td>0.310</td>
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<tr>
<td>$^{211}\text{Po}$</td>
<td>0.516 s</td>
<td>x</td>
<td>58.3</td>
<td>328.2</td>
<td>0.0032</td>
<td>0.0019</td>
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<td></td>
<td>569.7</td>
<td>0.509</td>
<td>0.297</td>
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<td>897.8</td>
<td>0.531</td>
<td>0.310</td>
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<td></td>
<td></td>
<td>41.7</td>
<td>0.00032</td>
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<td>$^{207}\text{Bi}$</td>
<td>32.2 yr</td>
<td>EC</td>
<td>41.7</td>
<td>569.7</td>
<td>97.8</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td>1063.7</td>
<td>74.08</td>
<td></td>
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<td></td>
<td></td>
<td>1770.2</td>
<td>6.87</td>
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</tr>
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</table>

Table 1. Decay modes and associated γ-rays of $^{211}\text{At}$ and its daughters

γ-Rays

*Only the three most abundant γ-rays are listed for each nuclide.
*Data were obtained from Lambrecht and Mirzadeh (1985).
*With ingrowth of $^{207}\text{Bi}$, the intensities of these γ-rays will approach asymptotic maximum levels of 0.001043, 0.000790 and 0.000073%, respectively, relative to the EOB $^{211}\text{At}$ decay rate.
Table 2. Decay modes and associated $\gamma$-rays of $^{210}$At and its daughter$^b$

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Half-life</th>
<th>Decay mode</th>
<th>Intensities from $^{210}$At decays</th>
<th>Energy (keV)</th>
<th>Abundance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{210}$At</td>
<td>8.1 h</td>
<td>EC</td>
<td>99.82%</td>
<td>245.3</td>
<td>79.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1181.4</td>
<td>99.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1483.3</td>
<td>46.5</td>
</tr>
<tr>
<td>$^{210}$Po</td>
<td>138,376 days</td>
<td>$\alpha$</td>
<td></td>
<td>803.0</td>
<td>0.00121</td>
</tr>
</tbody>
</table>

$^a$Only the three most abundant $\gamma$-rays are listed for each nuclide.

$^b$Data were obtained from Ekström and Spanier (1989).

With ingrowth of $^{210}$Po, the $\alpha$-decay intensity of this nuclide approaches an asymptotic maximum level of 0.243% relative to the EOB $^{210}$At decay rate.

Prior to distillation, the back side of the target, which had been exposed to cooling water, was washed with 2 mL of acetone to remove any droplets of water. The oven temperature was increased to 650°C and the gas velocity of the argon carrier gas was adjusted to approx. 0.2 mL/s. Approximately 20 min were required for the oven to reach the desired distillation temperature. Calibrations made with a thermocouple inside the still indicated that the temperature was 20–30°C lower than indicated by the furnace thermocouple. The distillation time varied between 35 and 60 min but was kept at 45 min for most of the experiments.

### Results

**Cyclotron irradiation**

Internal targets composed of both copper and aluminum backing plates were irradiated with $\alpha$-particles of approx. 28 MeV and yields for the production of $^{211}$At were determined. Ten runs were performed at beam currents between 20–40 $\mu$A for each backing material (Table 3). Except for one 30 min run at 40 $\mu$A, the targets were irradiated for 1 h. With copper backing plates, $37 \pm 6$ MBq/$\mu$A.h of $^{211}$At were produced compared with $41 \pm 7$ MBq/$\mu$A.h for aluminum. To permit comparison of $^{211}$At production efficiency with the internal target to that obtainable using an external target, five irradiations were performed with copper backing plates, $37 \pm 6$ MBq/$\mu$A.h of $^{211}$At were produced compared with $41 \pm 7$ MBq/$\mu$A.h for backing plates fabricated from aluminum. To permit comparison of $^{211}$At production efficiency with the internal target to that obtainable using an external target, five irradiations were performed with copper backing plates, $37 \pm 6$ MBq/$\mu$A.h of $^{211}$At were produced compared with $41 \pm 7$ MBq/$\mu$A.h for backing plates fabricated from aluminum.

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<table>
<thead>
<tr>
<th>Backing material</th>
<th>Production efficacy (MBq/$\mu$A.h)</th>
</tr>
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<tbody>
<tr>
<td>Cu</td>
<td>$37 \pm 6^a$</td>
</tr>
<tr>
<td>Al</td>
<td>$41 \pm 7^a$</td>
</tr>
</tbody>
</table>

$^a$Standard deviation, $n = 10$ for each of the two types of backing material.

<table>
<thead>
<tr>
<th>Backing material</th>
<th>26 cm still (%) yield</th>
<th>22 cm still (%) yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu</td>
<td>$29 \pm 6^b$</td>
<td>$40 \pm 7^b$</td>
</tr>
<tr>
<td>Al</td>
<td>$47 \pm 15^b$</td>
<td>$46 \pm 9^b$</td>
</tr>
</tbody>
</table>


Table 3. Yields for the production of $^{211}$At using internal targets

Table 4. Yields for the distillation of $^{211}$At from internal targets
Three irradiations also were done using two copper and one aluminum target with reduced size. The EOB yields for these runs, 33 ± 4 MBq/μA·h, were slightly lower than those observed for the larger size targets. The reduced yield with the smaller target is consistent with the fact that higher accuracy in positioning the target was required. As a result, more of the beam tended to hit the target backing at the leading edge instead of the bismuth layer, or spill onto the lower clamping block surface.

An additional factor in the selection of the backing material for the bismuth internal targets is the nature of the byproducts produced as a result of its activation. Activation of the aluminum backings gave mainly 68P (t½ = 2.50 min), while activation of the copper backings gave mainly 66Ga (t½ = 9.5 h) and 64Ga (t½ = 1.13 h). These three radionuclides all disintegrate through β- and electron capture decay with associated high-energy γ-rays which potentially could cause problems both with the 211At detection and quantification as well as in the handling of the target after 211At production.

Distillation yield

The percentage of the total 211At activity recovered from the two bubbler traps was considered to represent the distillation yield. The distillation yields indicated considerable variation from experiment to experiment. Table 3 presents the distillation yields obtained using the 26 and 22 cm length quartz tube. Experiments with the 22 cm still indicated a higher distillation efficiency (47 ± 15%) with aluminum target backing than with copper (29 ± 6%) but the experimental reproducibility was too low to show a statistical difference between the two materials. The 22 cm still gave more reproducible yields and similar distillation efficiencies for aluminum and copper target backing materials.

The first still had a relatively large outlet joint (24/40 mm) between the still outlet and the bubbler traps. To avoid condensation of 211At on the still itself, a larger gas-velocity had to be used to carry the 211At into the collection vessels. A significant fraction (up to 50%) of the 211At trapped was poorly dissolved in organic solvents but could be readily dissolved in 0.1 M NaOH. The second still had a smaller outlet joint (14/20 mm) which allowed a lower gas velocity to be used. The 211At in the bubbler traps was easily dissolved in both organic and aqueous solvents. Typically, 5–15% of the 211At was trapped on the entry end of the quartz distillation tube.

Radiochemical and isotopic purity of 211At

The radioactivity produced by irradiation of the bismuth internal target with approx. 28 MeV α-particles decayed with a half-life of 7.2 ± 0.1 h. Gamma spectroscopy was performed on aliquots of the distillate obtained from five experiments using the Ge(Li) detector. Of principal concern was the determination of the levels of 210At which were present in the distillate. Five samples of astatine were analyzed for 210At contents. The 569.7, 687.9 and 897.8 keV peaks were used for 210At detection and the 245.3 and 1181.4 keV peaks were used for determination of 210At. Samples were analyzed 48 h after bombardment in order to enhance the contribution of small levels of longer-lived, 8.3 h 210At in the spectrum. At this time, according to the relative γ-ray abundances and variation in detector efficiency, a 0.125% contamination of 210At would give similar count rate on the Ge(Li) for the most abundant γ-ray associated with each radionuclide. No peaks corresponding to 210At could be detected in any of the samples counted at 48 h EOB. Based on the limits of detection of the Ge(Li) detector, the upper limit of 210At in the 211At samples was estimated to be less than 0.02% at EOB.

Discussion

Astatine-211 is perhaps the most promising α-emitter for endoradiotherapeutic applications. Although 211At was produced for the first time more than half a century ago (Corson et al., 1940), its clinical potential has yet to be demonstrated. A major impediment has been the lack of methodology for producing large quantities of 211At with sufficient purity to permit the evaluation of 211At-labeled tumor-specific molecules in patients and there are still problems to solve before the nuclide can be applied clinically. Production of large quantities of 211At has been reported (Berei et al., 1985); however, significant levels of 210At were also produced. An exception is the use of a target with 4π water-cooling. 6–8 h irradiations with 20 μA of 28 MeV α-particles yielded 3.5 GBq (~100 mCi) of 211At, presumably with low levels of 210At contamination (Berei et al., 1985). However, the incident α-particle energies utilized to achieve 4 π water-cooling (~100 MeV) and the long irradiation times are compatible with only a few cyclotron facilities.

Using the newly developed MIT-1 internal target system, it was possible to irradiate bismuth targets with a beam-current of 40 μA for 30 min without visible melting of the target. These beam currents and irradiation times were the maximum tested and we anticipate that longer duration runs at higher beam currents will be possible in the future. Even at 40 μA, the internal target was able to withstand about twice the beam current used previously for the irradiation of external bismuth metal targets with 28 MeV α-particles (Berei et al., 1985). The higher beam current capability of the MIT-1 target probably reflects the fact that its grazing angle configuration spreads the beam over a large target surface area. In addition, the use of thin layers of bismuth (<50 μm) supported by effectively cooled target backings also contributes to the ability of this target to withstand high beam currents.

The MIT-1 internal target also increases the maximum capacity of α-particle beam-current compared...
with external target irradiation because the septum of the deflector assembly used in the extraction process is limited by its ability to dissipate heat. For 30 MeV \( \alpha \)-particles, this limitation permits a maximum of 30 \( \mu \text{A} \) extracted, based on about 50% extraction efficiency from a 60 \( \mu \text{A} \) internal beam requiring a 21 kV dee voltage. Above 21 kV, the extraction efficiency drops precipitously due to radial and axial defocusing of the beam. However, if the beam is intercepted internally, dee voltage can be increased to 24 kV, producing a beam of approx. 100 \( \mu \text{A} \), which could be used for \(^{211}\)At production provided sufficient target cooling can be accomplished. In preliminary experiments, 4 h cyclotron irradiations with up to 95 \( \mu \text{A} \) of \( \alpha \)-particles were performed on a bare aluminum target face, confirming the potential of the internal target system for achieving high beam currents. However, since procedures for target manufacturing and beam distribution control are still being optimized, safety considerations dictated that more moderate beam currents (maximum 40 \( \mu \text{A} \)) were selected for the current study. Increasing beam current escalation for \(^{211}\)At production will be emphasized in future studies with the internal target system.

Because of its higher heat transfer capabilities, copper should be a better backing material than aluminum for applications where heat dissipation is a critical concern. An additional potential advantage of copper is that unlike aluminum, this backing material permits the use of electro-deposition to fabricate bismuth targets with only a few micrometers thickness. Nonetheless, we found that both aluminum and copper were useful as backing materials for the bismuth targets. An additional consideration dictating the selection of target backing material is the nature of the radionuclides produced either as a result of transmission of the \( \alpha \)-particle beam through the bismuth layer or deflection of \( \alpha \)-particles from the bismuth surface into the backing material. From this perspective, aluminum offers a significant advantage since the principal byproduct, \(^{30}\)P (\( t_1 \) 2.5 min), can be allowed to decay before target handling is initiated. In contrast, activation of the copper produces \(^{68}\)Ga (\( t_1 \) 9.5 h) and \(^{68}\)Ga (\( t_1 \) 1.13 h) which made these targets more difficult to handle safely.

An encouraging result of this study is that \(^{211}\)At could be produced with yields in excess of 40 MBq/\( \mu \text{A.h} \) using the internal target system and isolated in high radiochemical purity. Yields were about four times greater than obtained at similar \( \alpha \)-particle beam energies with our external target system and by other investigators using similar external targets (Lambrecht and Mirzadeh, 1985; Zalutsky et al., 1988; Larsen et al., 1993). The thick target saturation yield for \(^{211}\)At production calculated from our results was about 400 MBq/\( \mu \text{A} \), a value 1.5 times the theoretical thick target saturation yield calculated from cross section data (Lambrecht and Mirzadeh, 1985).

Since the yield for the \(^{209}\)Bi(\( \alpha \),\( 2n \))\(^{211}\)At reaction rises steeply with increasing energy near 28 MeV, one factor which could contribute to higher yields is if the energy of the \( \alpha \)-particle beam striking the internal target was higher than 28 MeV. (It is difficult to determine exactly the energy distribution of the \( \alpha \)-particle beam irradiating an internal target.) Minor fluctuations in the average \( \alpha \)-particle energy may occur and since no degrader is used, the energy distribution of the particles within the beam may differ from an external target beam which passes through a degrader and a collimator.

From the cross-section data for the \(^{209}\)Bi(\( \alpha \),\( 2n \))\(^{211}\)At reaction, increasing the \( \alpha \)-particle beam energy from 28 to 29 MeV would increase \(^{211}\)At production by only about 33% (Rambler et al., 1959; Lambrecht and Mirzadeh, 1985). In addition, if the \( \alpha \)-particle beam energy had been 29.2 MeV, then it would be expected that \(^{211}\)At/\(^{209}\)At production ratio would have been 4000:1. In this study, the \(^{211}\)At/\(^{209}\)At ratio was determined by \( \gamma \)-ray spectroscopy to be greater than 5000:1, an observation consistent with an \( \alpha \)-particle energy less than 29 MeV. Thus, uncertainty in the energy of the incident \( \alpha \)-particle energy is probably only a minor factor in accounting for the higher production yields obtained with our internal target system. A more likely explanation is that the grazing angle configuration and a thin bismuth target with a large surface area minimized losses of \(^{211}\)At from the target due to diffusion and volatilization.

Since the geometrical configuration and size of the internal target is considerably different from that of our external target, a new apparatus had to be designed for \(^{211}\)At distillation. Internal targets weighed 118 and 374 g with aluminum and copper backing plates, respectively, compared with 8 g for the external aluminum target. The larger size and mass of the internal target and backing plate could result in lower distillation efficiencies due to less efficient heating and increased adsorption of \(^{211}\)At on both metal and quartz surfaces. With copper-backed targets, decreasing the quartz still volume and reducing the size of the outlet joint increased distillation yields from 29 ± 6% to 40 ± 7%; no such effect was seen with the aluminum-backed targets.

The distillation yields obtained with aluminum-backed targets were 46 ± 9% for the smaller still. Somewhat higher \(^{211}\)At recovery efficiencies have been obtained from smaller, aluminum-backed, bismuth targets (Lambrecht and Mirzadeh, 1985; Larsen et al., 1993); for example, we have previously reported a distillation efficiency of 63 ± 7% (Zalutsky and Narula, 1988). Even higher \(^{211}\)At distillation efficiencies (70–75%) have been obtained by distillation at 700°C under a vacuum (Wilbur et al., 1993). However, our experience has been that performing the distillation at 650°C minimizes contamination of the distillate with bismuth, an impurity which should be avoided because it can interfere with \(^{211}\)At-labeling reactions.
Improving distillation yields was one of the motivations for designing a smaller internal target. With the reduced size target, a quartz still could be used with an i.d. reduced to 26 mm compared with 56 mm for the original still. A smaller i.d. quartz distillation tube may prevent back-diffusion of $^{211}$At in the still since the gas flow per unit area would be higher in a smaller still compared with a larger still for a given carrier gas flow rate. Preliminary results obtained in the distillation of reduced-size targets using a considerably smaller still but otherwise the same conditions as for the larger stills, have given distillation yields of $74 \pm 14\%$ for three experiments and with very low absorption of $^{211}$At on the still itself. It must be noted that $^{211}$At production yields with the smaller targets were about 20% lower than observed with the larger targets. This decrease is probably related to the greater accuracy needed in positioning the smaller target. As experience is gained with this system, it is anticipated that yields should improve.

In summary, we have demonstrated that the MIT-1 internal target system can be used to produce high levels of $^{211}$At in relatively short irradiation times on a medium-energy cyclotron. Yields are approximately four times higher than those obtained with external targets. Beam currents of up to 40 $\mu$A could be applied to the target without melting the bismuth, and it is anticipated that even higher beam currents will be possible. These results suggest that this system will permit the production of $^{211}$At in sufficient yield and purity to permit the initiation of clinical investigations with $^{211}$At-labeled radiotherapeutic agents. Future studies will investigate the suitability of the internal target system for use with higher beam currents and longer irradiation times.

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**References**


