Production, isolation, and shipment of clinically relevant quantities of Astatine-211: A simple and efficient approach to increasing supply

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Astatine-211 (^{211}At) is a promising and elusive candidate of considerable interest for novel cancer treatment as a modality of targeted alpha therapy (TAT). In the United States, a small number of facilities are capable of accelerating α beams to produce ^{211}At [1], and it has a modestly short half-life (7.2 h). It is desirable to develop strategic methods for shipping ^{211}At in a form adaptable to advanced radiochemical reactions, or other desirable uses, so to advance biomedical applications. For this study, a 3-octanone impregnated Amberchrom® CG300M resin bed in a column cartridge was used to separate ^{211}At from the bismuth matrix at the production accelerator (Texas A&M). Aliquots of 6 M HNO_3 containing up to ~2.22 GBq of ^{211}At from the dissolved target were successfully loaded and retained on columns. Air-dried column hold times of 6.4 h and 34 h did not inhibit simple and efficient recovery of ^{211}At. Seven shipments of exempted packages (less than 370 MBq) arrived at a destination radiochemistry facility (University of Texas MD Anderson Cancer Center) in the form of an air-dried column. The eluted solution from the column was used to successfully radiolabel a model compound, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline, with ^{211}At. An HPGe gamma-ray detector was utilized to confirm the identity of ^{211}At. This method to prepare and ship ^{211}At paves the way for the distribution of ^{211}At to research institutions and clinical oncology centers in Texas and elsewhere.

Astatine-211 shows promise using alpha-emitting radionuclides connected to a targeting agent such as a monoclonal antibody or other small molecule [2]. The half-life of 7.2 h requires a cyclotron near the site of use with sufficient power to produce an alpha beam of 28.8 MeV total energy to produce the reaction ^{207}Bi(α,2n)^{211}At. There are only about thirty cyclotrons in the world that have the capacity to accelerate alpha particles sufficiently to produce ^{211}At thereby limiting the number of laboratories where studies of fundamental astatine chemistry and subsequent development of radiotherapies can be performed.

Some institutions are developing the capability to produce enough ^{211}At for clinical trials. Currently in the United States, ^{211}At is only available through the National Isotope Development Center (NIDC) from the University of Washington in Seattle [1,3]. It is shipped in liquid form as sodium astatide in 4 N NaCl solution for radiochemistry research and clinical trials. Other sites around the country (Duke University, University of California-Davis, and University of Pennsylvania) are currently producing or

developing the capability to produce ^{211}At in useful quantities. The Texas A&M University Cyclotron Institute (TAMU CI) is in the process of increasing its ^{211}At production capability, having made up to 3700 MBq, with the goal of becoming part of the University Isotope Network (UIN) of the NIDC. This will allow more clinical trials with ^{211}At -radiolabeled drugs to be performed in the United States and expand the regions in which such trials can be performed.

A vital part of the effort to increase the availability of ^{211}At includes developing processing chemistry for the target and resulting solution. Previously, we have developed a unique chemical procedure that begins by dissolving the target in HNO_3 and allows for At and Bi separation by utilizing a nitric acid dissolution solution without chemical manipulations [4-6]. In order to expand the availability of ^{211}At across the country and minimize the amount of chemical processing at the destination facility, it is advantageous to have a method that allows ^{211}At to be directly added to various desired radiochemistry reaction configurations. We have since developed and use an automated approach of dissolving the target with minimal dose to personnel [7].

By shipping the ^{211}At on an air-dried column cartridge, the ^{211}At can be washed off the column using pure ethanol (EtOH) which could expedite the use of ^{211}At for labeling and radiochemistry studies. This work describes the process of loading and stripping the column, the effects of leaving the ^{211}At on a dry column with the freestanding liquid removed for long periods of time (>24 h), as well as progress made in shipping an exempt package (less than 370 MBq at the time of shipment) from TAMU CI, College Station, TX to The University of Texas MD Anderson Cancer Center, (UTMDACC) in Houston, TX via a commercial courier service. The distance of the shipment traversed is 103 miles, door-to-door, which takes approximately two hours with normal traffic. After the shipment arrived the ^{211}At was eluted and used to label a model compound 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline, demonstrating the success of our column cartridge shipping procedure and proving the reactivity of the resultant ^{211}At.

We developed a simple method to load ^{211}At on a dried column cartridge, ship it from the production site, TAMU CI, to an external research institution, UTMDACC, and recover the ^{211}At activity from the cartridge by eluting with ethanol. Focused tests were performed before shipping ^{211}At outside our production center. The cartridge was loaded with ^{211}At solution in ~6 M HNO_3, washed, flushed, air-dried, and set aside for 6.4 h and 34 h, to mimic shipment to facilities within a day's journey and overnight shipments. Both tests resulted in a simple and efficient recovery of ^{211}At. The ^{207}Bi produced from the decay of ^{211}At accumulates on the column during shipment and can be eluted from the cartridge prior to ^{211}At stripping. The remaining sample's radiopurity and the contaminants' removal are discussed in further detail in Refs. [5,7].

Once this column cartridge was received by UTMDACC, it was stripped using EtOH. Fig. 1 shows the stripping profile of ~215 MBq of ^{211}At from the column cartridge on September 21, 2021, October 20, 2021, and November 15, 2021. For all three shipments shown, the column cartridge left the TAMU CI between 10:30–11:10AM and arrived at UTMDACC between 1:45–3:00PM. The stripping profile for the shipments was very similar, which demonstrated the reproducibility of these processing methods.

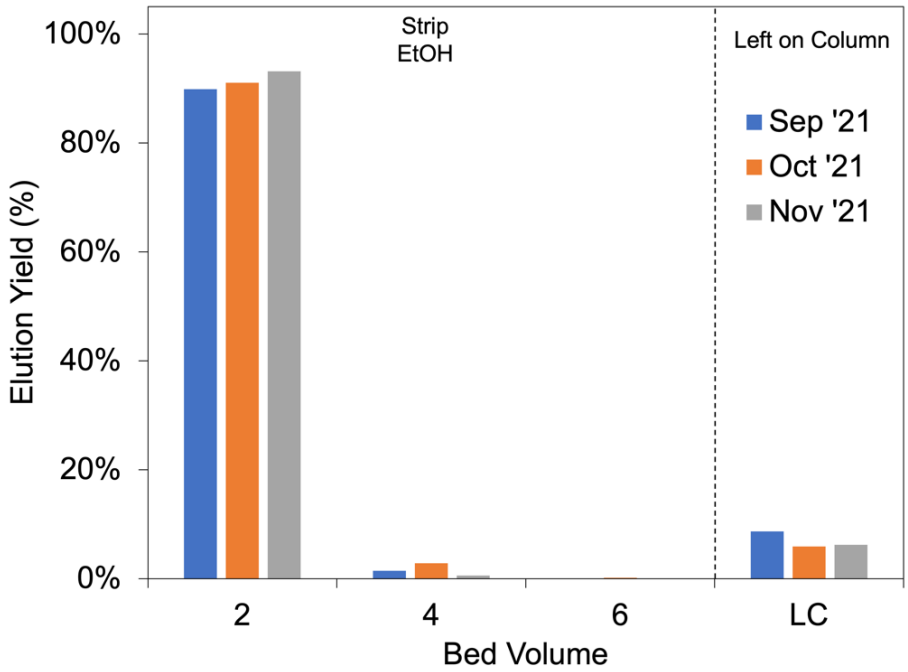

Fig. 1. Stripping profile of ~215 MBq of ^{211}At of a 3-octanone impregnated Amberchrom® CG300M resin bed housed in a column cartridge (0.5 mL BV, 8 mm ID x 10 mm height). Cartridge had been shipped from the TAMU CI at 11:00 AM and stripped by UTMDACC at 2:55 PM on September 21, 2021 (blue), and at 11:10 AM and stripped by UTMDACC at 2:32 PM on October 20, 2021 (orange) and at 10:30 AM and stripped by UTMDACC at 2:14 PM on November 15, 2021 (grey).

Shipments:

Table I details the activity and eluted activity on each column that was shipped from TAMU CI to UTMDACC in June, July, September, October, and November 2021. The percent ^{211}At eluted has been 87-94%, which demonstrates that the majority of the ^{211}At could be eluted from a shipped column.

Drying the column and leaving the ^{211}At to sit on the column for 34 h, to mimic an overnight shipment from College Station, TX did not impede the stripping of the column with EtOH. A small amount of ^{211}At remained on the column, presumably due to resin imperfections. This amount is negligible when the loading is above 37 MBq.

The amount of ^{211}At loaded onto the cartridge was also scaled up to 2.2 GBq, which has the potential to be enough radioactivity to support the synthesis of a radiopharmaceutical for a robust set of experimental animal studies. This column performed similarly to the other, smaller amounts of ^{211}At, and demonstrates the applicability of this method to larger shipment sizes.

Table I. This table details the activity and eluted activity on each column that has been shipped from TAMU CI to UTMDACC. An error of 10% was assigned to address sources of error. *In July, the lur lock cap leaked, which resulted in the loss of some activity, not due to the column or the stripping process.

Date	Activity of Column at Delivery (MBq)	Eluted Activity (MBq)	Activity left on Column (MBq)	Elution Yield	Column Residues
June 9, 2021	135±14	118±12	15.0±1.5	86.9±8.7%	11.2±1.1%
July 28, 2021*	204±20	137±14	37.7±3.8	67.5±6.8%	18.5±1.9%
September 21, 2021	218±22	192±19	18.4±1.8	88.0±8.8%	8.4±0.8%
October 20, 2021	222±22	202±20	12.8±1.3	91.0±9.1%	5.8±0.6%
November 15, 2021	126±13	114±11	7.6±0.8	93.8±9.4%	6.2±0.6%
April 6, 2022	226±23	196±20	20±2	96.7±9.7%	8.8±0.9%
April 26, 2022	233±23	176±11	44±4	75.5±7.6%	18.9±1.9%
August 2,2022	188±19	179±18	15.9±16	95±9.6%	8.5±1.2%
September 8,2022	222±22.2	209±20.9	6.8±0.7	94±13%	3.1±0.4%
October 11,2022	148±15	132±13	8.5±0.9	89±13%	5.7±0.8%
October 12,2022 ∗ ∗	22.6±2.3	20.7±2.1	1.0±0.1	92±13%	4.4±0.6%
December 14,2022	161±16	151±15	6.8±0.7	94±13%	4.2±0.6%
December 15,2022 ∗ ∗	61.6±6.2	58.4±5.8	1.4±0.1	95±13%	2.2±0.3%

[1] Y. Feng and M.R. Zalutsky, J. Nucl. Med. Bio. **100-101**, 12 (2021).

[2] J. Elgqvist *et al.*, Front. Oncol., **3**, 1 (2014), https://doi.org/10.3389/fonc.2013.00324.

[3] V. Radchenko *et al.*, J. Nucl. Med. Bio. **62**, 1495 (2021).

[4] J.D. Burns *et al.*, Chem. Commun. **56**, 9004 (2020); 10.1039/d0cc03804k.

[5] J.D. Burns *et al.*, Sep. Purif. Tech. **256**, 117794 (2021); 10.1016/j.seppur.2020.117794.

[6] E.E. Tereshatov *et al.*, Sep. Purif. Tech. **282**, 120088 (2022); 10.1016/j.seppur.2021.120088.

[7] E.E. Tereshatov *et al.*, Chem. Eng. J. **442,** 136176 (2022); 10.1016/j.cej.2022.136176.