RADIOCHEMICAL STUDIES OF ASTATINE-211 FOR PHARMACEUTICAL USES AT OSAKA UNIVERSITY

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Alpha-particle emitters are considered to be promising radionuclides for the treatment of small tumors since short range of α-particles emitted from radionuclides which are conjugated to appropriate targeting agents is suitable for efficient eradication of cancerous cells with less depositing energy on surrounding healthy ones. Among known α-emitting radionuclides, only a limited number of α-emitters exhibit nuclear characteristics potentially applicable to pharmaceutical uses. In recent decades, astatine-211 (^{211}At) has an increasing attention due to its favorable nuclear properties for targeted alpha therapy such as a moderate half-life of 7.2 h and 100% alpha-decay probability including that of its short-lived EC-decay daughter ^{211g}Po. At Osaka University, we recently started nuclear medicine studies with ^{211}At in the collaboration among Research Center of Nuclear Physics (RCNP), Graduate School of Science, and Graduate School of Medicine as well as with Graduate School of Pharmacy of Kanazawa University to perform ^{211}At production, chemical purification, labeling, and clinical trials with prepared radiopharmaceuticals [1], all of which are mandated for the development of ^{211}At pharmaceuticals. In this contribution, we report present status of our radiochemical studies of ^{211}At at Osaka University; its production at RCNP, purification by dry distillation, and resin development for one-column operation of labeling are presented.

Astatine-211 was produced in the ^{209}Bi(α, 2*n*)^{211}At reaction at RCNP. A metallic Bi target of typically 10-30 mg/cm^2 thickness was prepared on 10 μm-thick Al foil by vacuum-evaporation. Typical beam current of ^{4}He^{2+} was 0.5 particle μA. The Bi target was set at 45^o to the beam axis in an irradiation chamber. The 29-MeV α-beam delivered from the AVF cyclotron passed through a HAVAR window, He cooling gas, 10 μm-thick Al cover foil, and then entered the Bi target with incident energy of 27.3 MeV. During the irradiation, the Bi target was cooled with a circulating He-gas flow and circulating water. Irradiation time was 30 min to a few hours depending on required radioactivity of ^{211}At. After the irradiation, dry distillation was carried out to separate ^{211}At from the ^{209}Bi target material. We newly fabricated a dry-distillation apparatus [2] with simplification. In a typical procedure, He and O_2 mixed gas (3: 1 volume ratio) was used as carrier and reactive gas [3] at a flow rate of 20 mL/min. A quartz column, in which the irradiated Bi target was placed, was heated up to 840^{o}C using an electric tubular furnace. The exit of the quart column was connected to a 4-way valve and then Teflon tube (3-mm i.d.) which was cooled with liquid nitrogen to trap volatile astatine species. During accumulation of ^{211}At in the trap, an X-ray of Po attributed to ^{211}At was measured with a CdTeZn detector to monitor an amount of trapped ^{211}At. After approximately 30 min, trapped ^{211}At was stripped with 1000 μL of a desired eluent such as distilled water, saline, or methanol, at a flow rate of 250 μL/min. The effluent was fractionated into 10 aliquots to observe distribution of ^{211}At in the effluent. The radioactivity of ^{211}At was determined by γ-ray spectrometry using a Ge detector. These ^{211}At solution samples were, as required, supplied to cell experiments, pharmaceutical experiments, or animal examinations. At present, chemical yield of ^{211}At obtained in the effluents was 80 - 90% under optimum conditions. The separation time was typically 70 min.

For future automated one-column operation in ^{211}At labelling, we are newly developing a resin on which a bifunctional reagent, 3-trimethylstannylbenzoate-N-succinimidyl with trimethylstannyl group, which can be substituted with ^{211}At, and with an active ester, reactive with an antibody, is supported. In a first elution of ^{211}At solution, ^{211}At is retained on the resin via the substitution reaction, and then the ^{211}At-labeled ester is stripped from the resin by a second, antibody elution. In a batch-wise test of the resin with butylamine on behalf of antibodies, we successfully obtained a targeted ^{211}At-labeled compound with a chemical yield of 45%. At present, we perform searching for optimal conditions for improvement of chemical yield, labeling experiments with protein, and automatization of the labeling column procedure. In the symposium, present status of these radiochemical experiments will be presented.

REFERENCES

1. A. SHINOHARA, "Preparation of Radioisotopes for New Medical Use in Osaka University", *Isotope Production (#363), PACIFICHEM2015*, Honolulu, Hawaii, Dec. 16, 2015.
2. K. NAGATSU, K. MINEGISHI, M. FUKADA, H. SUZUKI, S. HASEGAWA, and M-R. ZHANG," Production of ^{211}At by a Vertical Beam Irradiation Method", *Appl. Radiat. Isot.*, **94**, 363 (2014).
3. V. M. VAKHTEL, G. V. VINEL, TS. VYLOV, I. I. GROMOVA, A. F. NOVGORODOV, YU. V. NORSEEV, V. A. KHALKIN, and V. G. CHUMIN, "Gas-Thermochromatographic Method of Isolation of Astatine", *Russ. Radiochem.* **6**, 752 (1976).