Preparation of [^{211}At]-labeled sodium astatide (NaAt) by reducing with ascorbic acid for the treatment of thyroid cancer†

Y. Shirakami,[*1] K. Kaneda,[*1] A. Toyoshima,[*1,*2] T. Watabe,[*3] K. Ooe,[*1,*3] A. Shinohara,[*4] and J. Hatazawa[*4]

Iodine-131 (^{131}I)-labeled sodium iodide, [^{131}I]-NaI, has been used in clinics as the standard medication for patients with thyroid cancer. NaI can be transferred into cancer cells via sodium-iodide symporters (NIS), resulting in cell death owing to β^- particles emitted from the ^{131}I atoms. The agent has some limitations: i) [^{131}I]-NaI does not work in some patients, even though the agent accumulates in tumor lesions, and ii) the patients treated with the drug require isolated hospitalization within a week.

[^{211}At]-NaAt is expected to be a novel therapeutic agent for patients with thyroid cancer as an alternative to [^{131}I]-NaI because the linear energy transfer (LET) of ^{211}At is much higher than that of ^{131}I. Several papers have proven the efficacy of the drug in animals and humans.[1,2] The drug, however, has not been well evaluated in humans yet. One of the major problems of the agent is the difficulty in the chemical identification of NaAt due to the lack of a stable isotope of astatine. The aim of our study is to develop methods for the quality control of the drug.

Bismuth-209 was irradiated with helium-4 (α) at 29 MeV, and ^{211}At was produced through the ^{209}Bi($\alpha, 2n$)^{211}At reaction. The target was placed in a quartz tube and heated up to 850°C under a mixture of helium and oxygen gas flow (30 mL/min and 10 mL/min, respectively). Dry-distillated ^{211}At was collected in a teflon tube cooled in an ice-water bath. Through the tube, 100 μL of distillated water was passed, and an aqueous solution of ^{211}At (bulk solution) was collected in a micro PFA vial.

An aqueous solution of [^{211}At]-NaAt was prepared using the following procedures. An aliquot of the bulk solution was transferred to a glass vial containing an aqueous solution of 7 w/v% sodium hydrogen carbonate. Subsequently, an aqueous solution of 3 w/v% ascorbic acid was added to the vial. The mixture solution was kept for 1 h at room temperature. The radioactivity of the solution was adjusted to 10 MBq/mL.

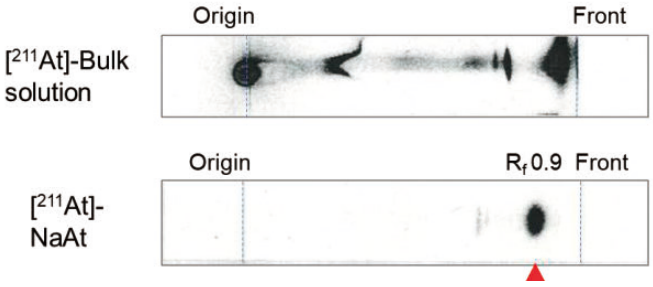

Fig. 1. TLC profiles of the [^{211}At] bulk solution and [^{211}At]-NaAt. Plate: Silica gel, Solvent: acetonitrile/water (2/1).

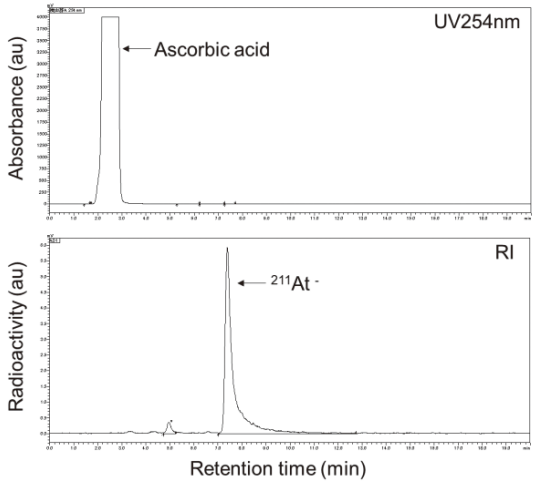

Fig. 2. HPLC profiles of [^{211}At]-NaAt. Column: reversed phase C-18 (Nakarai Tesque, Kyoto). Solvent: 20 mmoL/L tetrabutylammonium chloride/acetonitrile (7 : 3). Upper: UV trace, Bottom: RI trace.

Representative TLC profiles of the [^{211}At] bulk solution and [^{211}At]-NaAt are shown in Fig. 1. The [^{211}At] bulk solution was comprised of several radioactive spots having irregular shapes (Fig. 1, upper). This result indicated that the bulk solution is a mixture of several chemical species of ^{211}At, including the higher oxidation states of astatine (At^+ and/or At^{3+}) as well as astatide ion (At^-). The radioactive species were converged on a single component (relative to front (Rf) = 0.9, radiochemical purity (RCP) > 90%) after the addition of ascorbic acid (Fig. 1, bottom). The component was also presented as the major radioactive peak (retention time (Rt) = 7.42 min, RCP > 90%) by high-performance liquid chromatography (HPLC) analysis, as shown in Fig. 2. The component was estimated to be [^{211}At]-NaAt.

In thyroid cancer cells, the solution of [^{211}At]-NaAt was accumulated in cells specifically via NIS. The solution also inhibited tumor growth in mice with thyroid cancer.

These results suggest that ascorbic acid is efficient for the preparation of [^{211}At]-NaAt having high radiochemical purity. In conclusion, it is proved that [^{211}At]-NaAt is a promising agent for the treatment of patients with thyroid cancer.

† Condensed from the article in J. Nucl. Med. **60**, 1301 (2019)
*1 Institute for Radiation Sciences, Osaka University
*2 RIKEN Nishina Center
*3 Graduate School of Medicine, Tracer Kinetics and Nuclear Medicine, Osaka University
*4 Research Center for Nuclear Physics, Osaka University

References

1) J. G. Hamilton *et al.*, Exp. Biol. Med. **86**, 366 (1954).
2) S. Carlin *et al.*, J. Nucl. Med. **44**, 1827 (2003).