Calculated astatine-211 production yields for radioimmunotherapy

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Abstract. As an alpha particle emitter, astatine-211 (211At) has been suggested as a candidate for radioimmunotherapy; thus better understanding of optimum irradiation parameters, radioactivity yields and possible impurities during its production is of paramount importance. In this work, theoretical calculations of bismuth-209 (209Bi) target thickness were performed using the SRIM 2013 codes whereas radioactivity yields of 211At were calculated based on the TENDL 2015, TENDL 2017 and EXFOR nuclear cross-section data. The calculated yields were also compared with available experimental results published elsewhere. According to the calculated results, while 211At was readily produced at alpha particle energy of just over 20.7 MeV, the maximum expected end-of-bombardment (EOB) yield was as much as 136.84 MBq/µAh when 209Bi target was bombarded using 35-MeV alpha particles. However, at this alpha particle energy, safety concern should be raised due to possibly high level of Polonium-210 (210Po) radioactivity generated via 209Bi(α,3n)210At → 210Po nuclear reaction as an indirect impurity. Production of 211At was therefore recommended using alpha particles ranging from 25 to 28 MeV.

1. Introduction
Cancers have been one of the deadliest diseases worldwide with increasing number of cases each year and have become the global burden [1-2]. In some cases, cancers do not successfully respond to chemotherapy, radiotherapy and/or surgery; thus nuclear-based method called radioimmunotherapy could be of great interest due to its effectiveness in destroying cancer cells without any significant damages to the surrounding healthy cells. One of typical targeted radiotherapy employs alpha particles emitted by a radioactive isotope to kill the abnormal cells after being labeled to a chemical substance such as peptides [3] and antibodies [4]. Recent progress in nuclear medicine indicates that astatine-211 (211At) has been suggested as a promising radioisotope for radioimmunotherapy [5-7].

As a relatively short half-life of just over 7.2 hours, 211At is readily produced using cyclotron-accelerated alpha particles via 209Bi(α,2n)211At nuclear reaction. Previous research suggested that production of 211At could be performed by bombarding 209Bi target using high energy alpha particles. Alfaro and co-workers irradiated a 0.25 mm 209Bi target using alpha incident energy ranging from 15.5 to 34.5 MeV [8]. In their experimental results they found that 211At yield could reach over 120 MBq/µAh, which is high enough to be used in radioimmunotherapy of several patients. Another study by Nagatsu et al [9] highlighted that with alpha particle energy of 28.5 MeV, the 211At yield could reach 22 MBq/µAh. Furthermore, free carrier 211At has been successfully separated in recent experimental study [10].
While $^{211}$At-labeled chemical compounds have been widely studied elsewhere [5-7], calculated nuclear data on $^{211}$At production including optimum target thickness, alpha energy, excitation function, end-of-bombardment (EOB) yield as well as radionuclidic impurities are not readily available. In this paper, such nuclear data are, therefore, comprehensively discussed.

2. Materials and Methods
Stopping and Range of Ions in Matters (SRIM 2013) code, which can be found on www.srim.com was employed to calculate the ranges of energetic alpha particles in pure bismuth (Bi) and bismuth oxide ($\text{Bi}_2\text{O}_3$) targets in which the optimum target thicknesses were then determined from the alpha ranges. The SRIM 2013 codes have been widely used to calculate target thickness for production of $^{18}$F [11], $^{99m}\text{Tc}$ [12] and some other radionuclides [13], including for ion beam analysis [14-15].

Nuclear cross-sections for $^{209}\text{Bi}(\alpha,2n)^{211}\text{At}$ and $^{209}\text{Bi}(\alpha,3n)^{210}\text{At}$ nuclear reactions were derived and compared from 3 different sources, namely the TALYS-Evaluated Nuclear Data Library 2015 (TENDL 2015) [16], TALYS-Evaluated Nuclear Data Library 2017 (TENDL 2017) [16] and EXFOR (available online on https://www-nds.iaea.org/exfor/endf.htm). TENDL 2015 has been previously used to study radioactive by-products in $^{18}$F production [17], whereas TENDL 2017 has not been used elsewhere.

The end-of-bombardment (EOB) yields of $^{209}\text{Bi}(\alpha,2n)^{211}\text{At}$ and $^{209}\text{Bi}(\alpha,3n)^{210}\text{At}$ nuclear reactions were calculated based on the yield formulae discussed elsewhere [11-12]. The calculated results were then compared with available experimental data.

3. Results and Discussion

3.1 Proposed target thickness
Since alpha particle is a relatively heavy particle, its range is also expectedly short when penetrating through a target. The SRIM calculated range of energetic alpha particle in pure bismuth (Bi) and bismuth oxide ($\text{Bi}_2\text{O}_3$), ranging from 10 MeV to 60 MeV is shown in Figure 1. According to the data, the range gradually increases with increasing alpha particle energy. In general, at the same kinetic energy, alpha particle can go deeper in $\text{Bi}_2\text{O}_3$ target compared to that of pure Bi target. For a 27 MeV incident alpha particle, the proposed Bi and $\text{Bi}_2\text{O}_3$ target thicknesses are 192 µm and 337 µm respectively. Furthermore, when the incoming alpha particle energy is increased to 40 MeV, the range increases to 686 µm in Bi target and 1240 µm in $\text{Bi}_2\text{O}_3$ target.

![Figure 1. SRIM calculated range of 10 – 60 MeV alpha particles ($R_\alpha$) in Bi and $\text{Bi}_2\text{O}_3$ targets](image)

Based on the SRIM calculated range data, one can recommend Bi and $\text{Bi}_2\text{O}_3$ target thicknesses for various alpha particle energies as given in Table 1. For a 27 MeV-incident alpha particle, the proposed Bi and $\text{Bi}_2\text{O}_3$ target thicknesses are 192 µm and 337 µm respectively. In addition, when the incoming alpha particle energy is accelerated to 40 MeV, the target thicknesses should be increased by nearly
1.9 times to 355 µm for Bi target and 633 µm for Bi$_2$O$_3$ target. These predicted target thicknesses are of paramount importance prior to $^{211}$At radioisotope production.

**Table 1.** Recommended target thickness for Bi and Bi$_2$O$_3$ targets for $^{211}$At production

| Target       | Proposed target thickness at various E$\alpha$ (µm) |
|--------------|---------------------------------------------------|
|              | 27 MeV | 28 MeV | 29 MeV | 30 MeV | 32 MeV | 35 MeV | 40 MeV |
| Bi foil      | 192    | 203    | 214    | 226    | 250    | 287    | 355    |
| Bi$_2$O$_3$  | 337    | 357    | 377    | 398    | 441    | 510    | 633    |

3.2 Nuclear Cross-sections and EOB yields

According to the calculated data derived from TENDL 2015, TENDL 2017 and EXFOR, the threshold energy for $^{211}$At production via $^{209}$Bi($\alpha$,2$n$)$^{211}$At nuclear reaction is 20.7 MeV. The maximum nuclear cross-section occurs at alpha energy of 30 MeV as seen in Figure 2. At alpha particle energy of lower than 25 MeV, there is no significant difference in the calculated excitation functions. However, for alpha energy between 25 and 40 MeV, the TENDL 2015 calculated data undermines the ones derived from TENDL 2017 and EXFOR data. In general, EXFOR calculated nuclear cross-section is greater than those of TENDL 2015 and TENDL 2017 when alpha energy is over 30 MeV.

**Figure 2.** Comparison of nuclear cross-sections evaluated from TENDL 2015, TENDL 2017 and EXFOR data.

**Figure 3.** EOB yields of $^{211}$At calculated using evaluated nuclear cross-section data of TENDL 2015, TENDL 2017 and EXFOR.

Using evaluated nuclear cross-section data (TENDL 2015, TENDL 2017 and EXFOR), the three calculated EOB yields very well agree with each other when alpha particle energy is below 30 MeV, though significant difference in the yields are more apparent for alpha energy greater than 30 MeV (Figure 3). The maximum calculated EOB yields are between 100 and 140 MBq/µAh and the yields start to decrease when the incident alpha energy is increased to more than 35 MeV. The calculated results are in good agreement with some experimental data published elsewhere [8] as shown in Table 2 with a maximum difference of 3.4%.
Table 2. Comparison of calculated and experimental $^{211}$At yield

| $E_\alpha$ | Yields (MBq/µAh) | This calculated work | experiment [8] |
|------------|------------------|----------------------|----------------|
| 22.1       | 0.22             |                      | 0.243          |
| 24.15      | 7.46             |                      | 8.37           |
| 26.25      | 24.88            |                      | 24.62          |
| 27.9       | 46.34            |                      | 44.02          |
| 30.45      | 80.11            |                      | 82.01          |
| 32.55      | 109.91           |                      | 111.18         |
| 34.55      | 136.24           |                      | 141.047        |

3.3 Indirect Production of $^{210}$Po

While EOB yield is maximum at alpha energy of greater than 30 MeV as shown in Figure 3, one should note that there is a great possibility of indirect production of $^{210}$Po by-product via $^{209}$Bi($\alpha$,3n)$^{210}$At $\rightarrow$ $^{210}$Po nuclear reaction. As a parent radionuclide, $^{210}$At decays into $^{210}$Po with a half life of 8.1 hours, whereas $^{210}$Po decays into stable $^{206}$Pb with a half life of 138.4 days. As widely known, $^{210}$Po is very toxic inside human body since it decays by emitting alpha particles which could damage healthy cells.

![Figure 4. EOB yields of $^{210}$At calculated using evaluated nuclear cross-section data of TENDL 2015, TENDL 2017 and EXFOR.](image)

Based on the EOB yields calculated using evaluated nuclear cross-section data of TENDL 2015, TENDL 2017 and EXFOR, $^{210}$At radionuclide is significantly produced when alpha particle is incident at greater than 28.6 MeV (Figure 4). The calculated EOB yields increase with increasing alpha particle energy with a maximum yield of 177 MBq/µAh at alpha particle energy of 40 MeV. In general, as can be seen in Table 3, the calculated $^{210}$At yield is greater than that of $^{211}$At yield for alpha particle energy of greater than 37 MeV (calculated using TENDL 2015 and TENDL 2017 data) and 39 MeV (calculated using EXFOR). It should also be noted that the yield ratio between $^{210}$At and $^{211}$At is greater than 1% even for alpha energy of 29 MeV (calculated using TENDL 2015 and TENDL 2017 data) and 30 MeV (calculated using EXFOR). Thus safety concern should be raised when producing $^{211}$At using alpha particle energy of greater than 29 MeV. It is therefore recommended that $^{211}$At production should be performed with alpha particle energy between 25 and 28 MeV.

Compared to recent experimental data [8], the calculated ratio obtained from this work is higher. Thus further experiments are required for better results.
Table 3. Calculated yield ratio of $^{210}$At and $^{211}$At

| E (MeV) | Yield ratio of $^{210}$At/$^{211}$At |
|---------|-----------------------------------|
|         | TENDL 2015 | TENDL 2017 | EXFOR |
| 28      | 0.00       | 0.00       | 0.00   |
| 29      | 0.03       | 0.02       | 0.00   |
| 30      | 0.05       | 0.04       | 0.01   |
| 31      | 0.15       | 0.13       | 0.04   |
| 32      | 0.27       | 0.24       | 0.10   |
| 33      | 0.42       | 0.38       | 0.19   |
| 34      | 0.59       | 0.53       | 0.32   |
| 35      | 0.78       | 0.70       | 0.46   |
| 36      | 0.97       | 0.88       | 0.61   |
| 37      | 1.16       | 1.06       | 0.77   |
| 38      | 1.35       | 1.26       | 0.93   |
| 39      | 1.55       | 1.46       | 1.08   |
| 40      | 1.76       | 1.67       | 1.21   |

4. Conclusion
Theoretical calculations of optimum target thickness for $^{211}$At radionuclide production has been performed using the SRIM 2013 codes, whereas $^{209}$Bi($\alpha$,2n)$^{211}$At nuclear cross-sections derived from TENDL 2015, TENDL 2017 and EXFOR have been compared. According to the calculated EOB yields, as much as 136.84 MBq/µA.hr when $^{209}$Bi target was bombarded using 35-MeV alpha particles, though at this alpha particle energy, toxic impurity $^{210}$Po radionuclide could present in the post-irradiated $^{209}$Bi target at high radioactivity. Theoretical calculation indicates that $^{210}$Po level of greater than 1% could be detected in the post-irradiated $^{209}$Bi target when the target is bombarded with 29-MeV alpha beams. Therefore, in order to avoid excess of $^{210}$Po radionuclide the safest and optimum alpha energy should be between 25 and 28 MeV.

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