Auger-Emitting Lanthanides for Radiobiological Studies

Brooklyn D. Green, Taylor R. Johnson, Jonathan W. Engle, Paul A. Ellison

Introduction

Recently FDA approved radiopharmaceuticals, ^{177}Lu-PSMA-617 (Pluvicto™) and ^{177}Lu-DOTATATE (Lutathera®), have attracted interest into radionuclides similar to ^{177}Lu. ^{161}Tb is similar in chemical structure but differs in its co-emission of 12-13 conversion and Auger electrons (CAEs) per decay. Radiobiological investigations into the advantages of CAEs are necessary for radiopharmaceutical consideration. However, the short half-life of primarily CAE emitting lanthanides, such as ^{165}Er ($t_{1/2}$= 10.36 h, 7-8 CAEs/decay[1]), can be a limiting factor. Separation of the radionuclide from the bulk target material may be difficult – requiring the separation of adjacent lanthanides. In order to aid these radiobiological studies, yield calculations of two nuclear reactions producing longer lived radiolathanides, ^{167}Tm ($t_{1/2}$=9.25 d, 13-14 CAEs/decay[1]) and ^{169}Yb ($t_{1/2}$=32.03 d, 29-30 CAEs/decay[1]), with a low-energy cyclotron were performed. Additionally, a lanthanide quantification method was tested on holmium solutions. The results indicate a possible application in rapidly assaying holmium concentration in fractions produced during chromatographic separation of lanthanides.

Figure 1: Region of the chart of the nuclides.

Materials and methods

Yield Calculation

A Microsoft EXCEL based calculator was created using SRIM stopping range values and TALYS-evaluated excitation functions[2] to calculate the yield of the ^{165}Ho(p,n)^{165}Er reaction and these yields were compared to the IAEA Medical Isotope Browser[3]. This calculator was then adapted to calculate the yields of the nuclear reactions, Yb(p,2n)^{167}Lu(β-)^{167}Yb(β-)^{167}Tm (with a natural Yb target and an enriched $^{168}Yb_2O_3$ target) and ^{169}Tm(p,n)^{169}Yb. The activities of the desired isotope produced from these reactions were then weighed against the activities of long-lived isotopes produced alongside them and their ratio assessed.

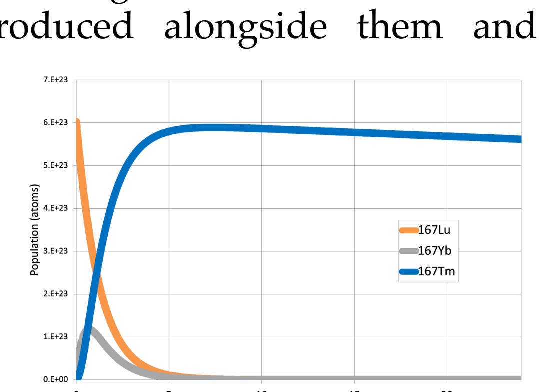

Figure 2: Decay chain of the Yb(p,2n)^{167}Lu(β-)^{167}Yb(β-)^{167}Tm reaction.

Lanthanide Quantification

Arsenazo III (ArIII) is a dye often used for spectrophotometric studies. In the past, it has shown use in its ability to complex lanthanides and allow for absorbance measurements. Various concentrations of samples of holmium in nitric acid (0.3 M, 130 µL) were prepared and aliquots of phosphate buffer (0.5 M, 1.1 mL) and ArIII dye (20 – 2000 ppm, 65 µL) in buffer solution were added. These samples were then analyzed by UV-Vis (Tecan Spark® Microplate Reader) in 96-well plates to achieve a high throughput. Different parameters including the pH of the buffer, well volume, dye concentration, and time of analysis were tested in the process of determining the best method for lanthanide quantification.

Results

Yield Calculation

Calculations of the Ho(p,n)^{165}Er reaction at 12.5 MeV and varying target thicknesses were compared to the IAEA Yield Calculator and experimental yield values[4] **(Figure 3)**. The yield from irradiating (14 MeV, 1 µA, 1 h) a natural 300 µm thick Yb target has a ratio of ^{167}Tm to ^{17x}Lu on the order of 10^{-3} whereas 90-98% enriched ^{168}Yb targets of the same thickness have ratios between 1 – 10 **(Figure 4)**. According to the Microsoft EXCEL yield calculator and using an excitation function from Nuclear Data for Selected Therapeutic Radionuclides[5], a 16 MeV proton irradiation of a thick Tm target can produce a maximum of 1.3 MBq µA^{-1} h^{-1} of ^{169}Yb **(Figure 5)**.

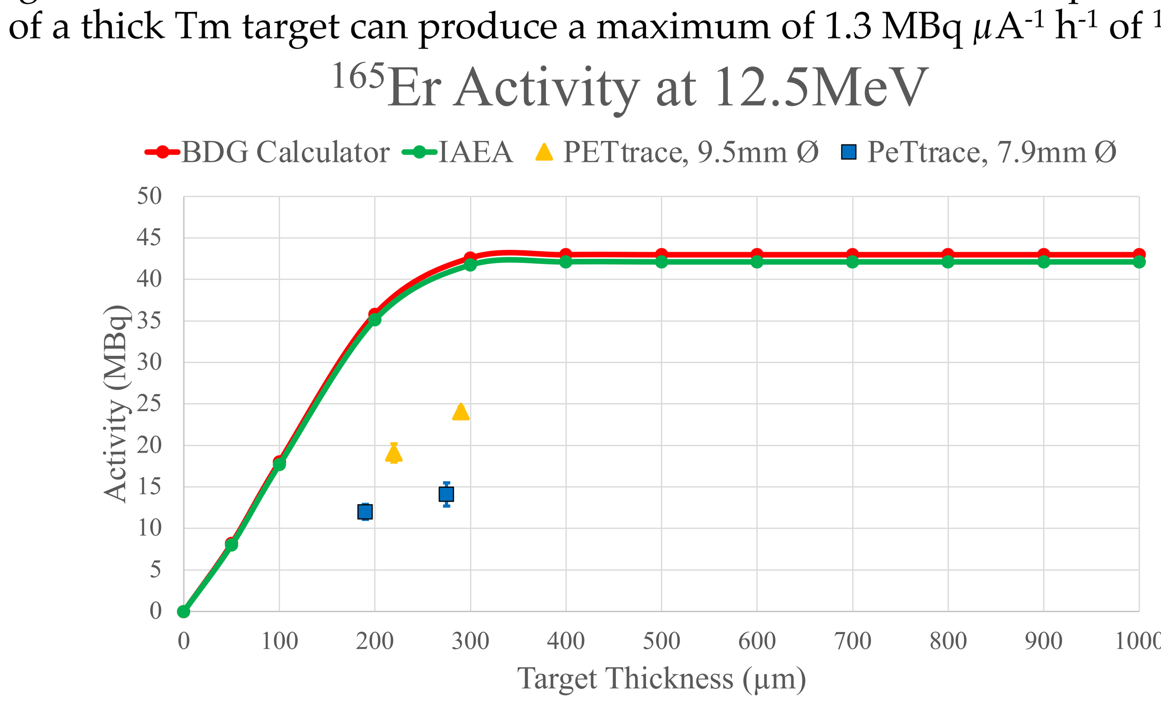

Figure 3: ^{165}Er yield production differences between the EXCEL calculator, IAEA Medical Isotope Browser, and experimental values.

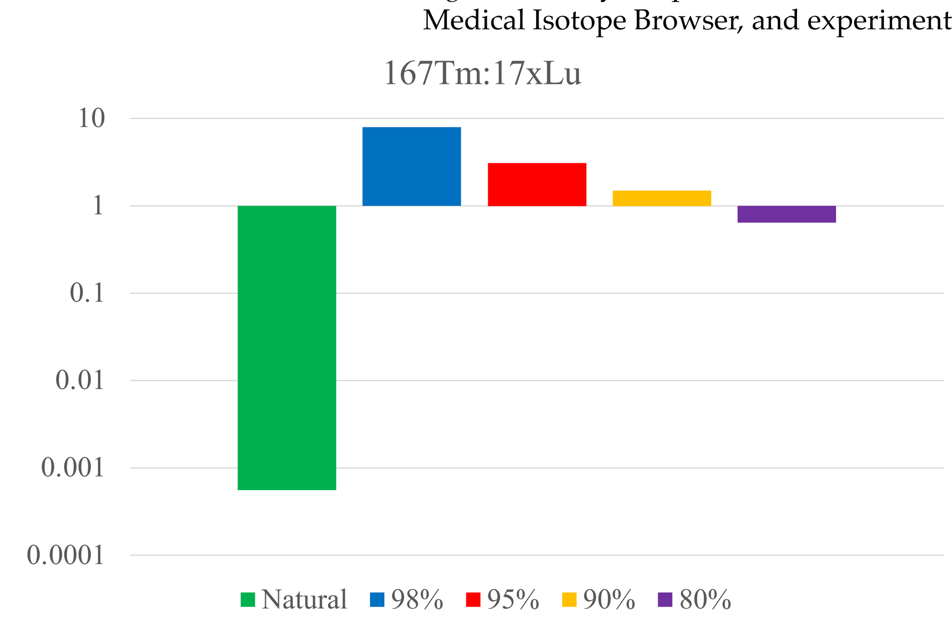

Figure 4: Ratio of ^{167}Tm to long -lived isotopes across different target enrichments.

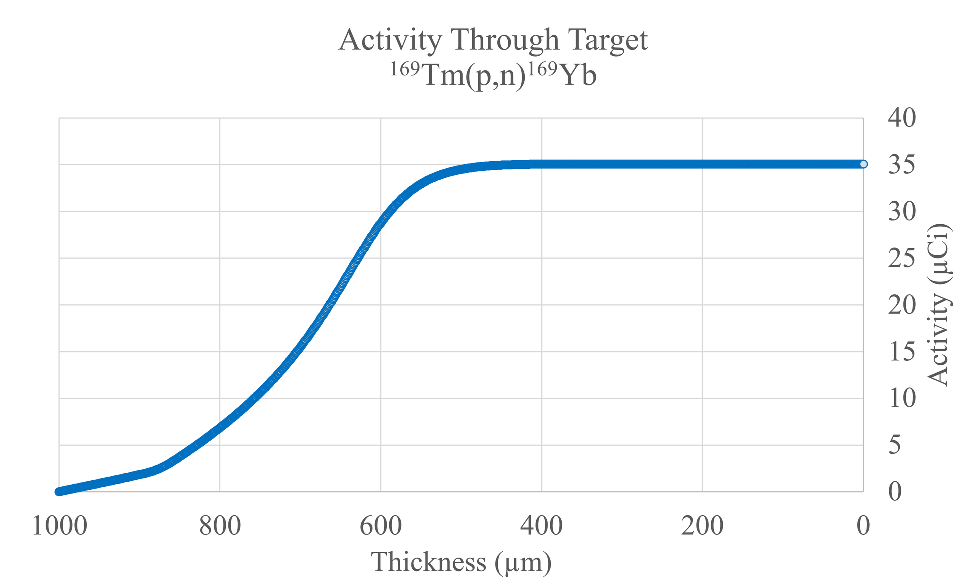

Figure 5: Activity of ^{169}Yb in the ^{169}Tm(p,n)^{169}Yb reaction through the targets' thickness.

Lanthanide Quantification

Assays containing different ArIII dye concentrations in buffer solution show that 2000 ppm dye led to higher error in lower holmium concentration assays and 20 ppm dye in the assays resulted in a slope too insignificant for accurate quantification **(Figure 6)**. Buffer solutions of different pH values show that a pH of 3.5 resulted in less deviation and a higher linear correlation of absorbance values in comparison to a buffer solution with a pH of 2.7 **(Figure 7)**. 200 µL, 350 µL, and 400 µL aliquots per well (corresponding to absorbance pathlengths of ~0.6, 1.0, and 1.1 cm) were compared. A well volume of 400 µL shows the smallest deviation and highest linear correlation compared to the other well volumes tested **(Figure 8)**. Several dyed samples were run again after initial absorbance measurement. The absorbance decreased significantly after an hour, indicating that the complex may not be stable in solution.

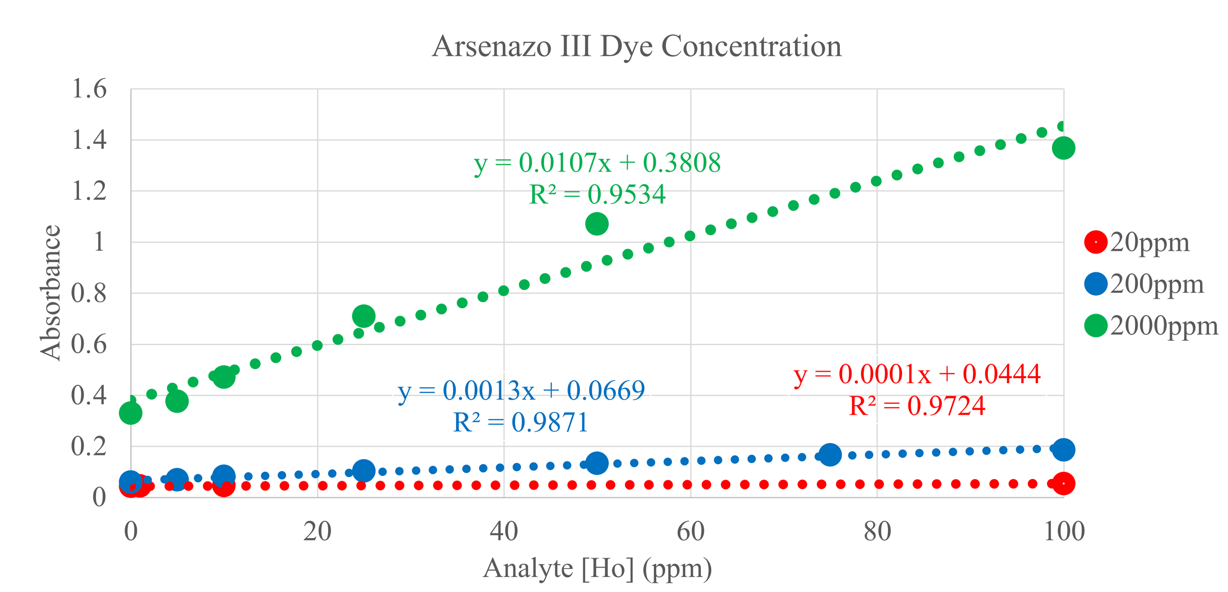

Figure 6: Absorbance values of assays with different ArIII dye concentrations.

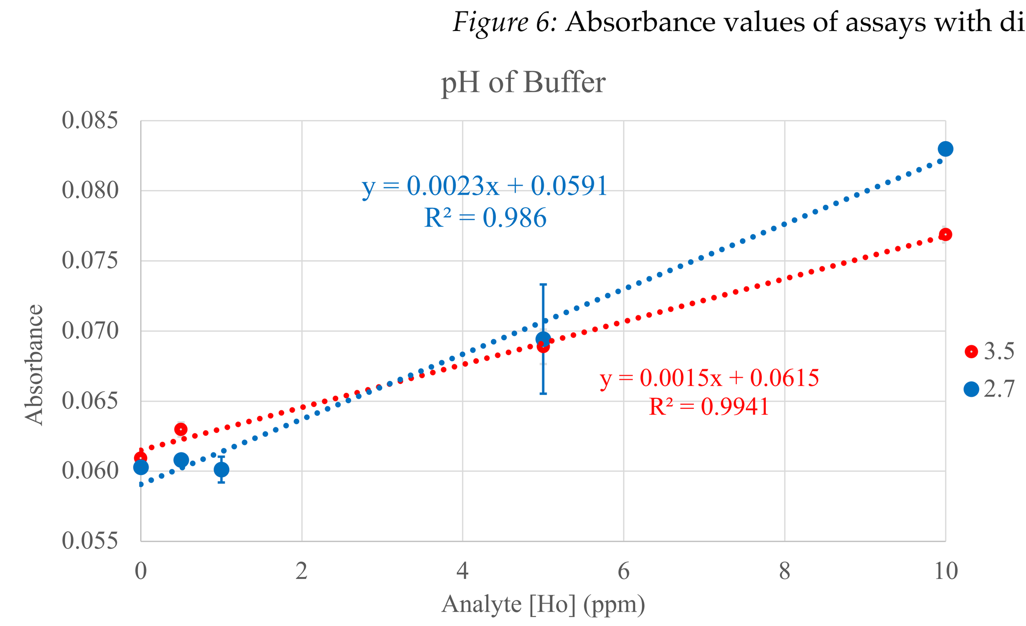

Figure 7: Absorbance values of assays with different buffer solution pHs.

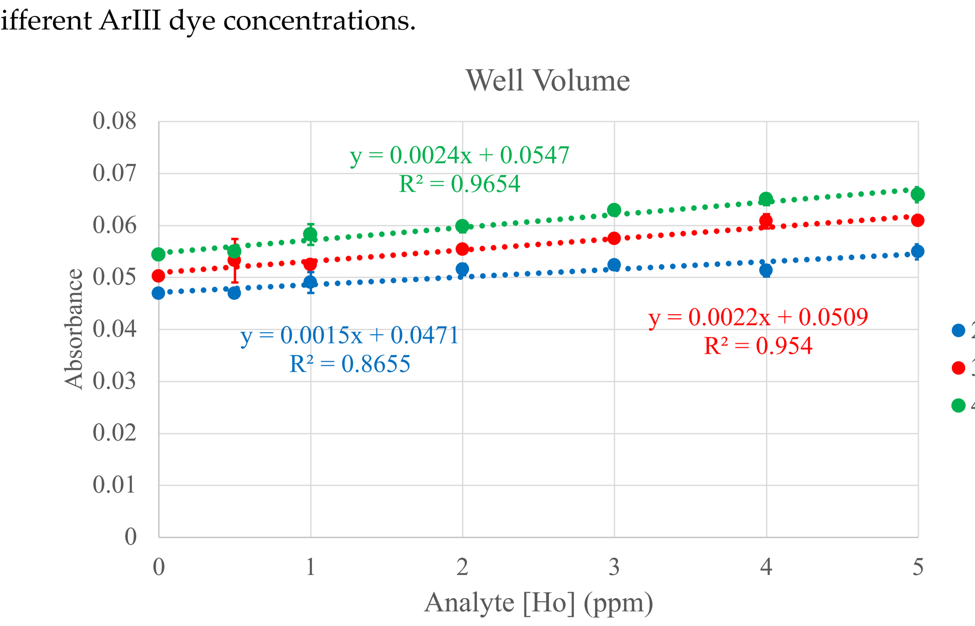

Figure 8: Absorbance values of assays with different volumes in wells.

Conclusions

Yield Calculation

The yields calculated by the Microsoft EXCEL-based calculator and the IAEA Medical Isotope Browser for the ^{165}Ho(p,n)^{165}Er reaction were within 1– 3% of each other. The experimental yields were 50% of theoretical calculated values. This may be attributed to beam diameters larger than the target. Product yield ratios of the Yb(p,2n)^{167}Lu(β-)^{167}Yb(β-)^{167}Tm reaction have a very low ^{167}Tm-to-^{17x}Lu ratio in natural Yb targets but ^{168}Yb enrichment results in much higher ratio. The ^{169}Tm(p,n)^{169}Yb reaction produces only 1.30 MBq µA^{-1} h^{-1} of activity at 16 MeV, making its production not ideal for a low-energy cyclotron.

Lanthanide Quantification

After developing ideal assay parameters, the method was based on preparing solution of holmium in 0.3 M nitric acid. 130 µL of each sample solution were added to 1100 µL of 3.5 pH 0.05 M phosphate buffer solution and 65 µL of 200 ppm Arsenazo III dye prepared in 3.5 pH 0.5 M phosphate buffer solution. 400 µL of each mixture were transferred to individual wells and analyzed by a UV-Vis microplate spectrophotometer. Applying this method to standardized holmium solutions allows for a calibration curve to be prepared and applied to holmium concentration measurement for unknown samples between 1 – 25 ppm Ho.

Literature cited

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Further Work

- A method for target fabrication and recycling of enriched Yb_2O_3 targets needs to be developed.
- A method for the radiochemical separations needs to be theorized and tested.
- Other lanthanides involved in radiochemical separations need quantification methods investigated.
- The buffer capacity of the phosphate buffer needs testing with more concentrated acidic lanthanide solutions.
- The concentrations calculated using UV-Visible absorbance values need to be cross-checked with ICP-OES or MP-AES values.

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