Separation of Lutetium from Ytterbium for medical n.c.a Lu-177 Production

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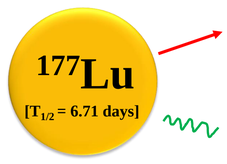
Introduction

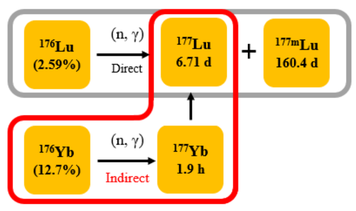
▶ Lu-177 theranostic application



beta radiation
E_β (max) = 497 keV
: Treatment of cancer
gamma radiation
E_γ = 208 keV
: Cancer diagnosis

Lu-177 is primarily applied to treat neuroendocrine tumors(NETs), prostate cancer and certain bone metastases.

▶ Production methods of Lu-177



- The "Direct" method with carrier
  : $^{176}Lu(n, \gamma)^{177}Lu$
  : $^{176}Lu(n, \gamma)^{177m}Lu$ [By-product]
- The ""Indirect" method without carrier
  : $^{176}Yb(n, \gamma)^{177}Yb \xrightarrow{\beta^-} {}^{177}Lu$

Need to separate Lu form Yb mixture

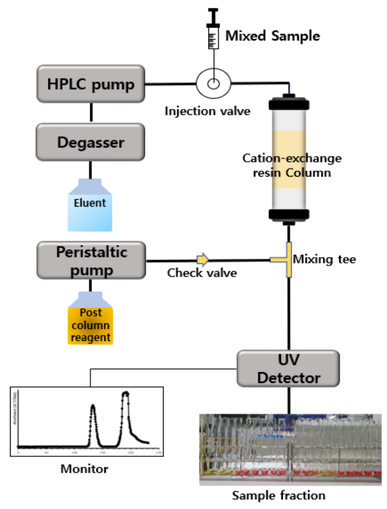
Radiation therapy requires high radioactivity, making "Indirect" production methods essential.

Lu-177 is used radiopharmaceutical in targeted cancer therapy, particularly in the treatment of neuroendocrine tumors and prostate cancer. It emits both beta particles, which are effective in destroying cancer cells, and gamma rays, which allow for imaging and tracking within the body. In this experiment, separation trials were prioritized using stable isotopes of Ytterbium and Lutetium to establish optimal conditions for production standardization through ion exchange chromatography. Based on the successful establishment of these conditions, we applied the same method to produce Lu-177 via neutron irradiation of Ytterbium-176. We effectively separated Lu-177 from the irradiated target using ion exchange chromatography, confirming its high purity and suitability for medical applications. Additionally, we are developing a remote-controlled automated system to minimize radiation exposure and optimize production efficiency.

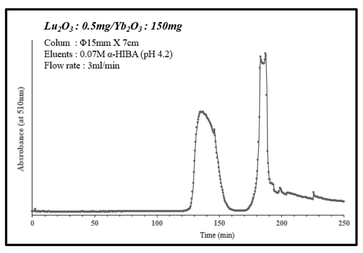
Cold-process

▶ Separation

1. **α-HIBA is passed through the column using an HPLC pump.**
2. **The baseline is checked by measuring absorbance at 510 nm using a UV detector.**
3. **PAR is mixed with α-HIBA using a connected pump and the absorbance at 510 nm is monitored to confirm the presence of PAR.**
4. **Once the absorbance stabilizes, the prepared sample is injected.**
5. **The column separates Lu, which reacts with PAR to produce a red color, allowing for the assessment of the separation process through measured absorbance.**
6. **When Lu detection is complete and Yb detection begins, the α-HIBA concentration is increased to rapidly recover large amounts of Yb.**

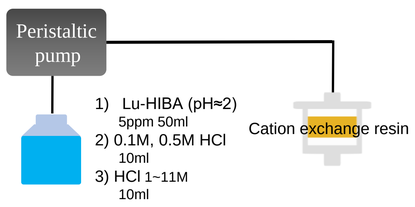


▶ Results



The separation of 0.5mg of Lu and 150mg of Yb using ion-exchange chromatography is presented in the graph. The method utilizes the principle that the smaller ionic radius of Lu allows for a stronger interaction with the α-HIBA, resulting in Lu eluting first from the column, followed by Yb. The total separation time was 250 minutes, and the resolution(Rs) was **1.85**, indicating a complete separation of Lu and Yb. Based on these results, Lu-177 can be produced by irradiation Yb-176 with neutrons and then separating the resulting Lu-177.

▶ Purification

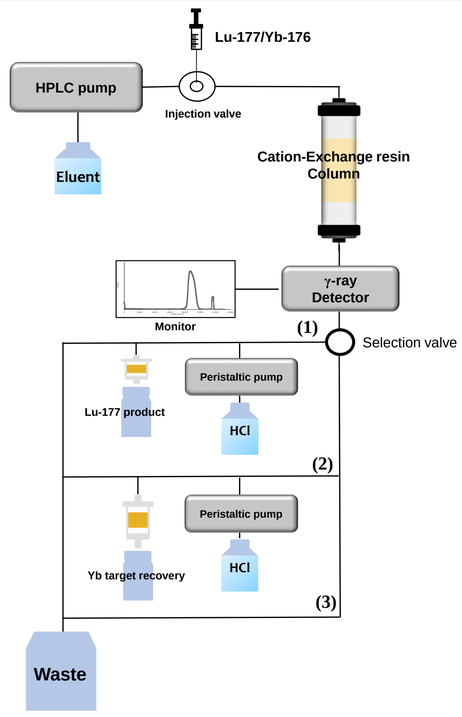


1. **Loading : Load a 5ppm Lu-HIBA solution onto a cation exchange resin using a peristaltic pump.**
2. **Washing : Sequentially wash the resin with 10ml of 0.1M and 0.5M diluted HCl to remove organic impurities.**
3. **Recovery: Desorb the Lu remaining on the resin using HCl to recover pure $LuCl_3$.**

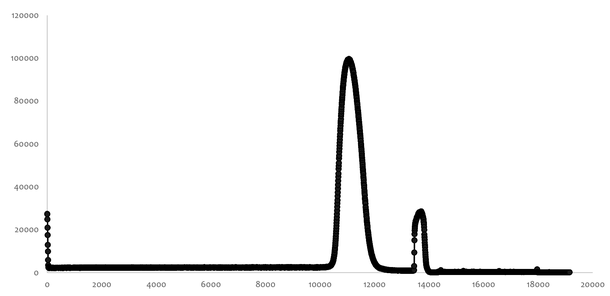
Hot-process

▶ Lu-177 Production Process

In the production process of Lu-177, the separation and purification steps are performed continuously. The progress is monitored using a gamma counter instead of colorimetric reagents. When gamma radiation is detected, the material is transferred via the selection valve to Line (1), where the purification and recovery of Lu-177 take place. Once the gamma radiation detection is complete, the process is switched to Line (2), where the concentration of the eluent is increased to rapidly and efficiently recover the Yb target.



▶ Results



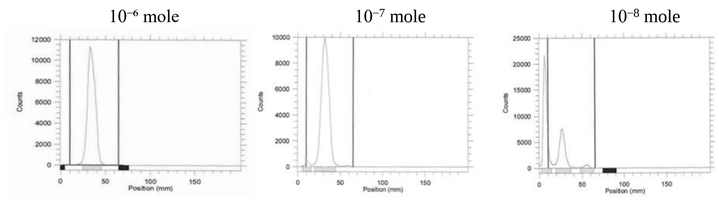
Lu-177 : 1.2Ci(10μg) / Yb target: 150mg

▶ Radiolabeling of Produced Lu-177 with DOTA

Lu-177 was radiolabeled with DOTA, a well-known chelator for radiopharmaceutical applications. The labeling was performed using 1 mCi of Lu-177 with DOTA concentrations of 10^{-6}, 10^{-7}, and 10^{-8} moles. The mixture was heated at 110° C for 30 minutes.

To confirm the labeling efficiency, TLC (Thin Layer Chromatography) analysis was conducted:

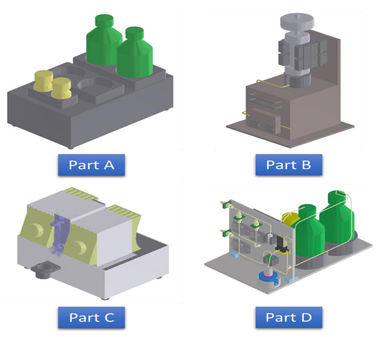
1. 10^{-6} mole: 100% labeling efficiency.
2. 10^{-7} mole: ~95% labeling efficiency.
3. 10^{-8} mole: ~30% labeling efficiency.



The results indicate that the produced Lu-177 can be effectively used for radiolabeling, demonstrating sufficient purity and performance for radiopharmaceutical applications

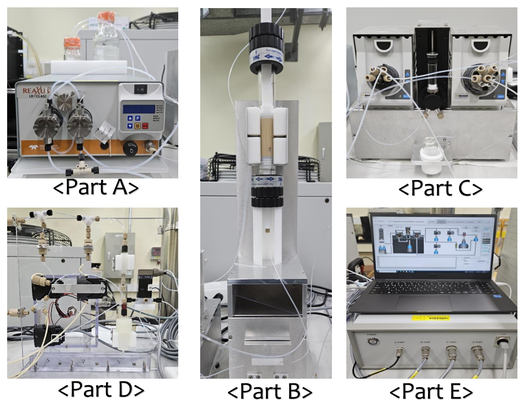
Remote Automation system

▶ Lu-177 Production Equipment 3D Modeling



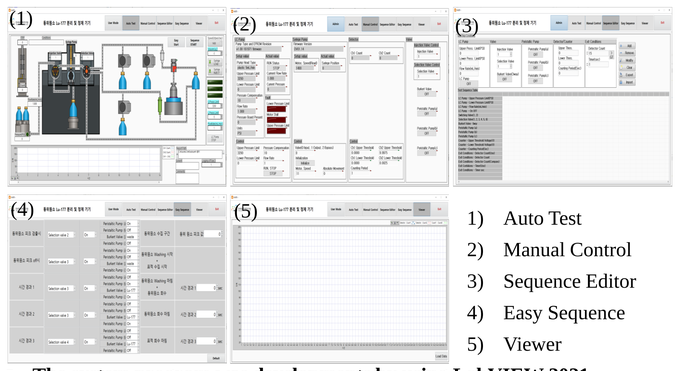
- **Part A : HPLC Pump and Eluents**
- **Part B : Column and gamma counter**
- **Part C : Injection Valve and Selection Valve**
- **Part D : Recovery Equipment(peristaltic pump and loading column)**

▶ Equipment for Actual Application



- **Part E : Integrated Control Hub and Laptop for Operation**

▶ UI(User Interface) for Program



1) Auto Test
2) Manual Control
3) Sequence Editor
4) Easy Sequence
5) Viewer

- **The system program was developments by using LabVIEW 2021**
- **The operation sequence, methods and time can be programmed and modified, and real-time monitoring is available.**

Conclusion

Using experimental data obtained from natural isotopes of lutetium and ytterbium, Lu-177 was successfully produced. The separation and purification conditions were optimized through ion-exchange chromatography, ensuring high efficiency. The radiochemical purity of the produced Lu-177 was evaluated through radiolabeling reactions with DOTA, confirming its suitability for medical applications. Furthermore, a remote-controlled automated system is being designed to optimize production and contribute to the standardization of Lu-177 production to meet high medical demand.

Reference

1. *Dash A, Pillai M R A, Knapp F F. Production of ^{177}Lu for targeted Radionuclide Therapy: Available Option. Nucl Med Mol Imaging 2015;49:85-107.*

2. *Kim AR, Choi KH. Preparative chromatographic separation of neighboring lanthanides using amines as a pH adjusting additive for producing carrier-free ^{177}Lu. Journal of Radioanalytical and Nuclear Chemistry. 2022;331:1451-1457.*