KAERI

Separation of Lutetium from Ytterbium for carrier-free Lu-177 Large-Scale Production Processes

2024. 05. 09.

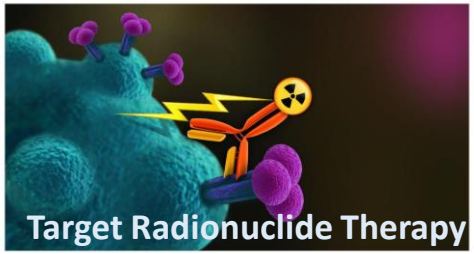
이강민

Introduction

Introduction

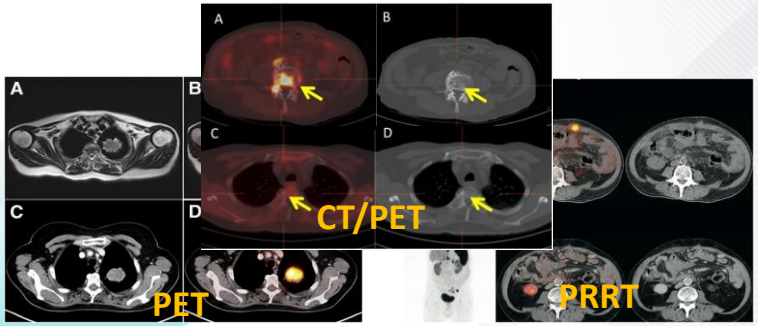
Radioisotope in Medicine

Therapy



Target Alpha-emitter Therapy(TAT)-the wave of the future in nuclear oncology/PRRT? Ronny Allan NET

Diagnosis



DiscoverMI.org for patents. Procedures homepage

Theragnosis

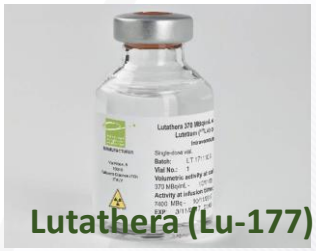
FDA NEWS RELEASE

FDA approves new treatment for certain digestive tract cancers

For Immediate Release:
January 26, 2018

The U.S. Food and Drug Administration today approved Lutathera (lutetium Lu 177 dotatate) for the treatment of a type of cancer that affects the pancreas or gastrointestinal tract called gastroenteropancreatic neuroendocrine tumors (GEP-NETs). This is the first time a radioactive drug, or radiopharmaceutical, has been approved for the treatment of GEP-NETs. Lutathera is indicated for adult patients with somatostatin receptor-positive GEP-NETs.

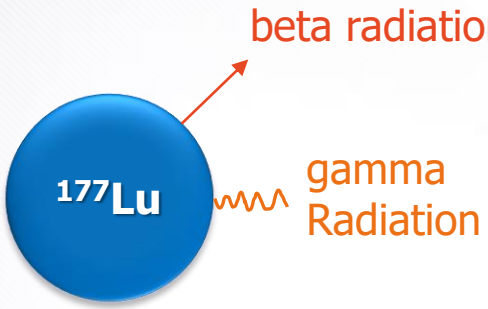
"GEP-NETs are a rare group of cancers with limited treatment options after initial therapy fails to keep the cancer from growing," said Richard Pazdur, M.D., director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "This approval provides another treatment choice for patients with these rare cancers. It also demonstrates how the FDA may consider data from therapies that are used in an expanded access (/expanded-access-compassionate-use) program to support approval for a new treatment."



Clinical Trials Arena Premium Insights 2018. 2. 5

Introduction

Lutetium-177

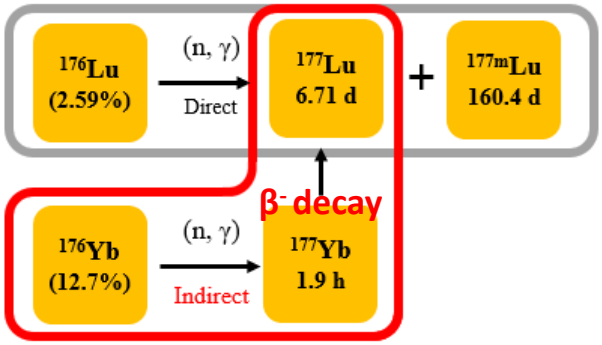


^{177}Lu [$T_{1/2}$ = 6.71 days]

E_β (max) = 497 keV: Treatment of cancer

E_γ = 208 keV (11.0%) and 113 keV (6.4%) : Diagnosis

Production methods available



- The "Direct" method with carrier

: ^{176}Lu(n, γ)^{177}Lu [By-product ^{177m}Lu ($t_{1/2}$=160.4d)]

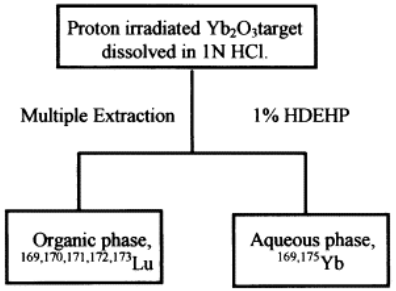
- The "Indirect" method without carrier

: ^{176}Yb(n, γ)^{177}Yb $\xrightarrow{\beta^-}$ ^{177}Lu Need to separate Lu form Yb mixture

Introduction

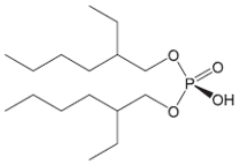
Separation methods

Solvent extraction method



S.Lahiri et al. Appl. Radiat. Isot. 911-913 (1998)

LN



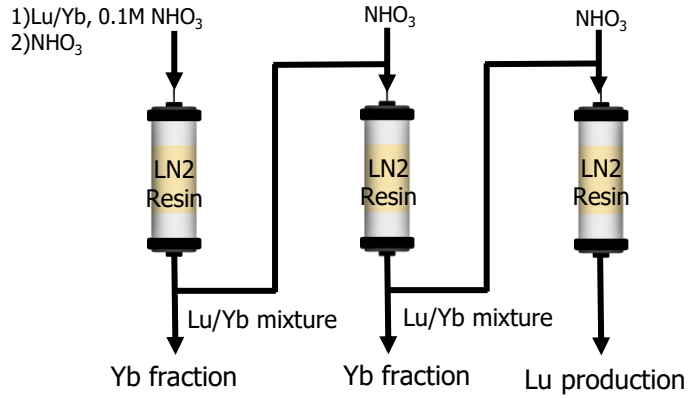
Di-2-(ethylhexyl)phosphoric acid (HDEHP, DEHPA, D2EHPA)

M. Van de Voorde *et al.* Coord. Chem. Rev. 382, 103 (2019)

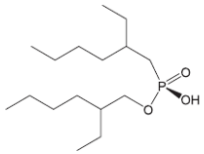
- Lanthanide form $[Ln(H_2O)_x]^{3+}$ in aqua state
- LN dissolve metals in organic phase (Lu>Yb)
- Multistage process

  (single-step about 30% extracted)

Extraction chromatographic method



LN2



2-ethylhexyl 2-ethylhexylphosphonic acid (HEH[EHP])

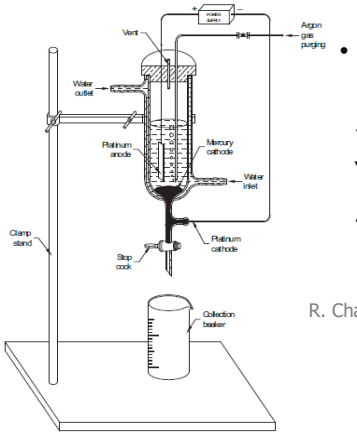
M. Van de Voorde *et al.* Coord. Chem. Rev. 382, 103 (2019)

- Chromatography-based method using LN2 resin
- Yb separates out before Lu
- Multistage process

Introduction

Separation methods

Electrochemical method



- Electrolytic reduction of Yb^{3+} in acidic pH

$$Yb^{3+} + e^- \rightarrow Yb^{2+}$$
$$Yb^{2+} + 2e^- \rightarrow Yb^0$$

The overall potential
$E^0 = -2.27$ V

R. Chakravarty *et al.* Nucl. Med. Biol. 37, 811 (2010)

- Selective reduction of Yb^{3+} to Yb^{2+}
- Yb^{2+} is known to form an amalgam, while Lu cannot
- Hg with Yb drain after electrolysis
  (difficult Yb target recovery)

Ion-exchange chromatographic method

- Lu^{3+}/Yb^{3+}
- Cation exchange resin

Eluent

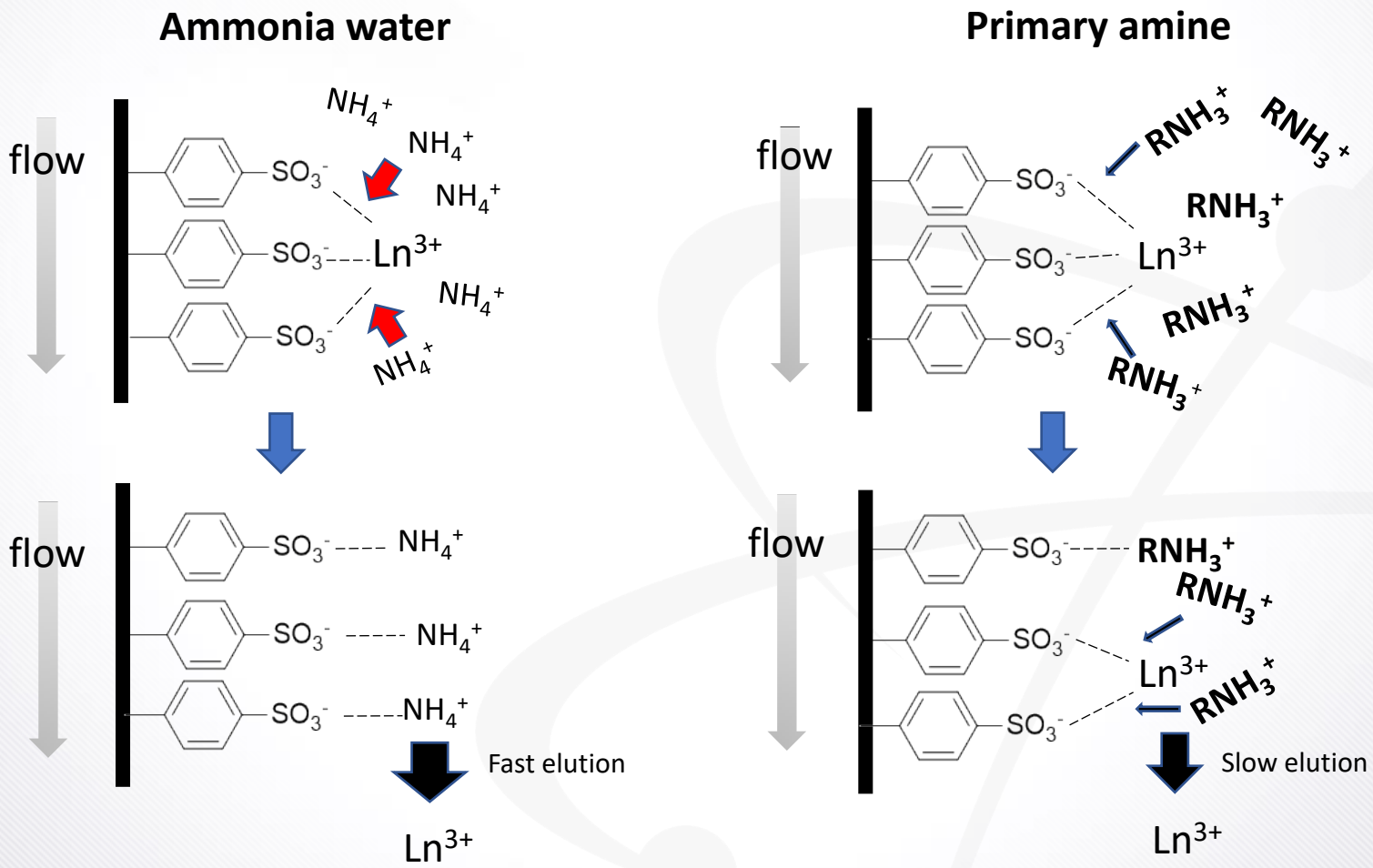
- **α-HIBA (α-hydroxyisobutyric acid)**
- EDTA (Ethylene-diamine-tetra-acetate acid)
- Diamino-cyclohexane-tetra-acetate acid

► Requires purification after separation

- Lu elutes before Yb
- Recoverable Yb target
- Low separation factor (peak tailing)

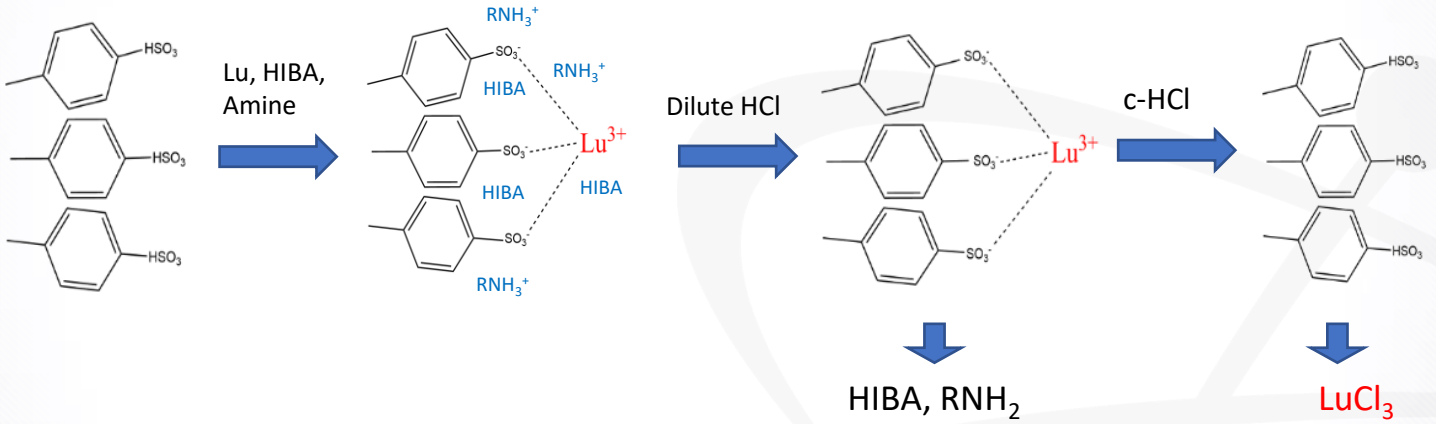
Introduction

Control the rate of exchange reactions with cations



Introduction

Purification



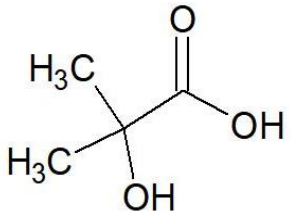
- Remove the eluents for used separation
- HIBA and amine can be removed by cation exchanger and dilute HCl
- Desorb the lutetium with HCl to produce pure $LuCl_3$

Experiments

Experiments

Ion-exchange chromatography

Mobile phase

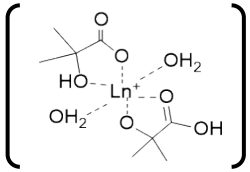


α-HIBA (α-hydroxyisobutyric acid)

- MW : 104.11
- pK_a : 4.01
- Lu/Yb separation factor(α) : 1.55

M. Van de Voorde *et al.* Coord. Chem. Rev. 382, 103 (2019)

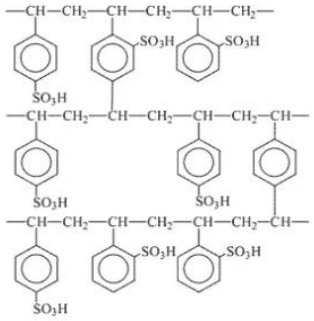
- Lu^{3+} are smaller than Yb^{3+} to form more stable complexes



Lanthanide complex

- Lower eluent concentration and pH increase separation efficiency
- The highest separation efficiency was shown at a concentration of 0.07M and pH 4.2

Stationary phase



Cation exchanger

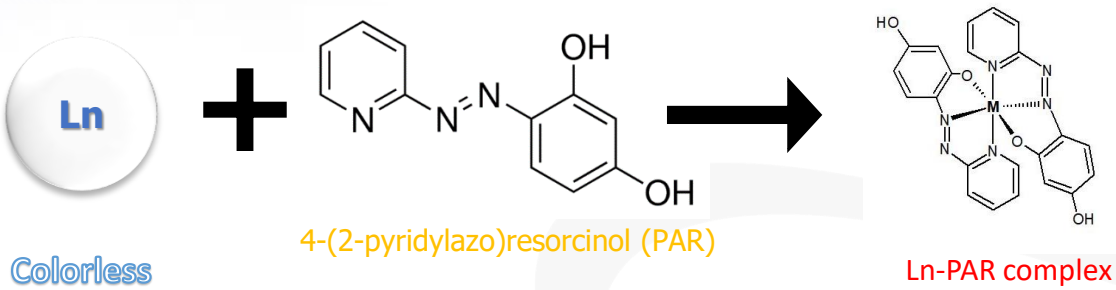
- PS-DVB co-polymer
- Substituted with a sulfonyl group
- cross-linked

https://bensonpolymeric.com/index.php/cross-link-comparison/

- H^+ in the sulfonated resin exchange with metal complex
- For the same atomic valence, the higher atomic number, the greater the selectivity (Elution order : Lu > Yb)

Experiments

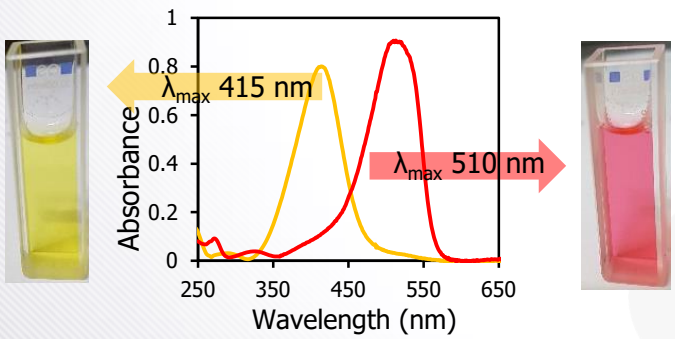
Color reagents for real-time identification of lanthanide



Colorless

4-(2-pyridylazo)resorcinol (PAR)

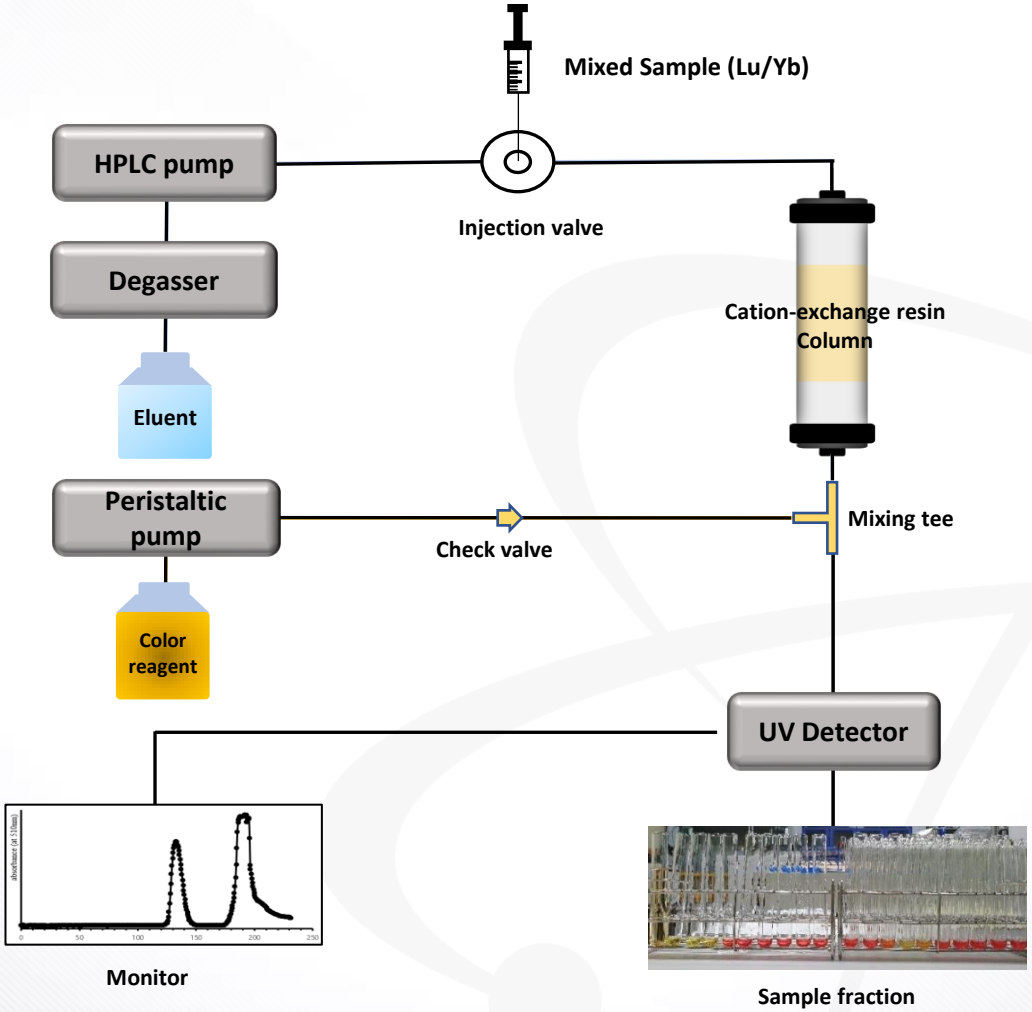
Ln-PAR complex



- ✓ Require identification of post-separation
- ✓ ICP-OES and AAS are long process time and high cost
- ✓ Color reagents can visual inspect
- ✓ Real-time absorbance measurement with UV detector

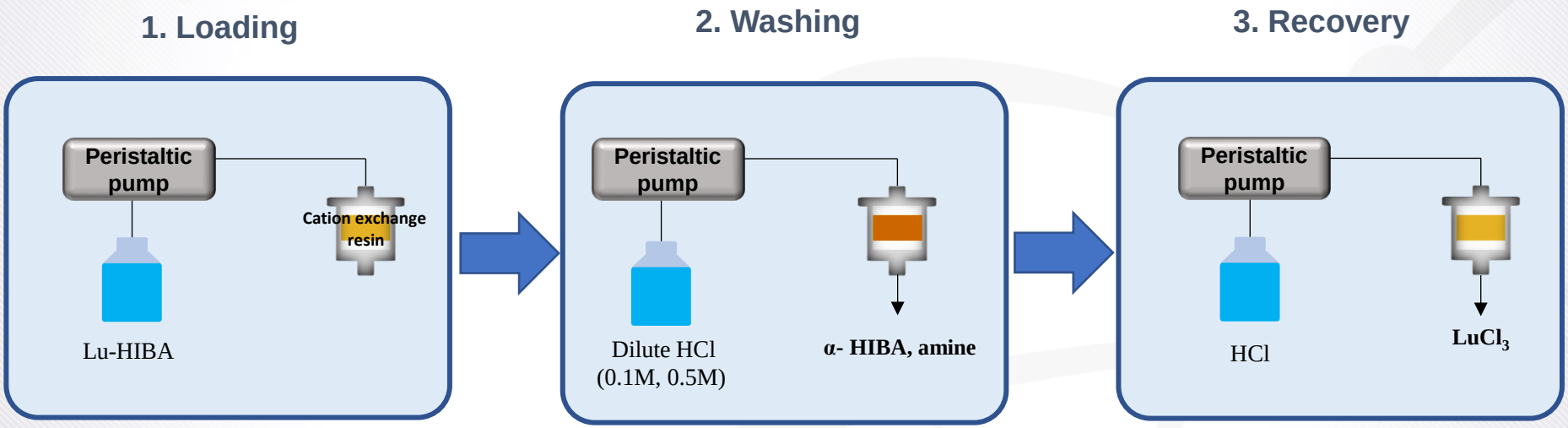
Experiments

Separation



Experiments

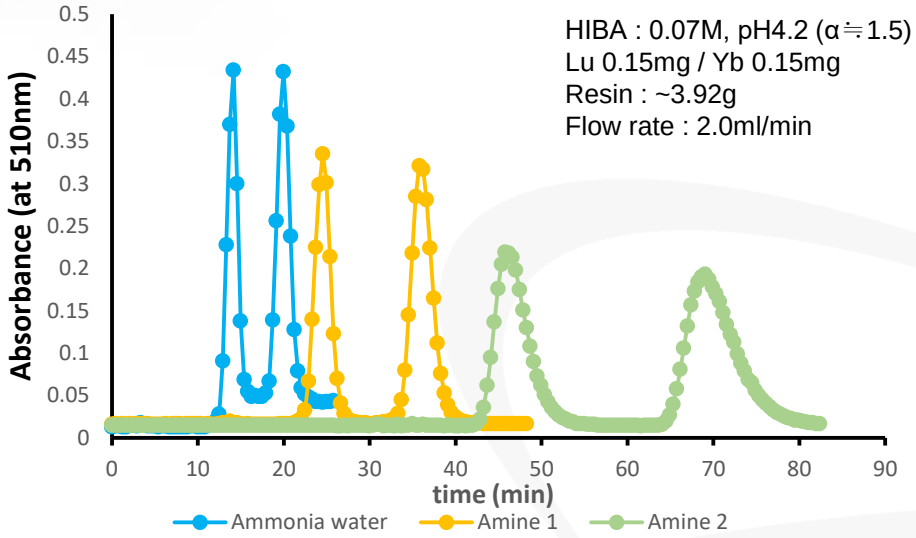
Purification



Results

Results

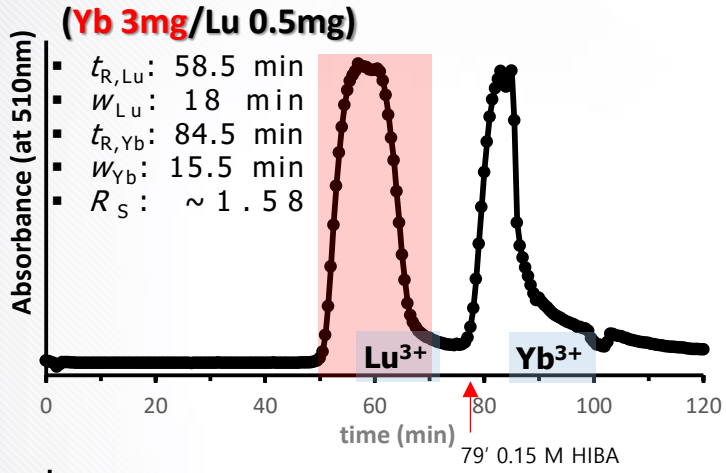
Effects of the types of ammonium ion on the separation efficiency

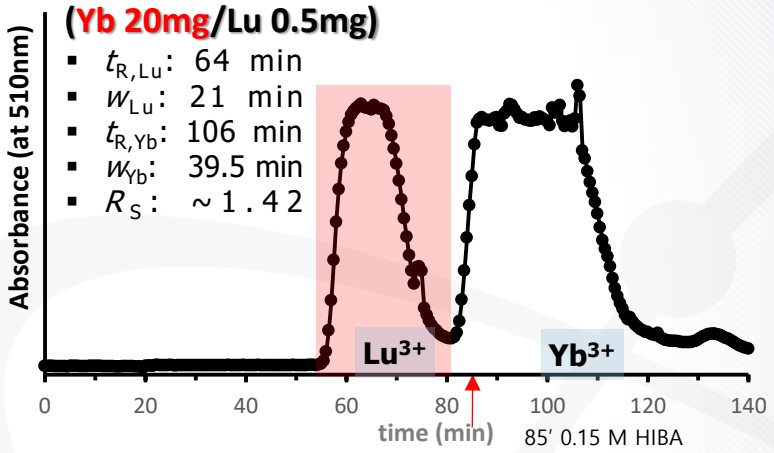


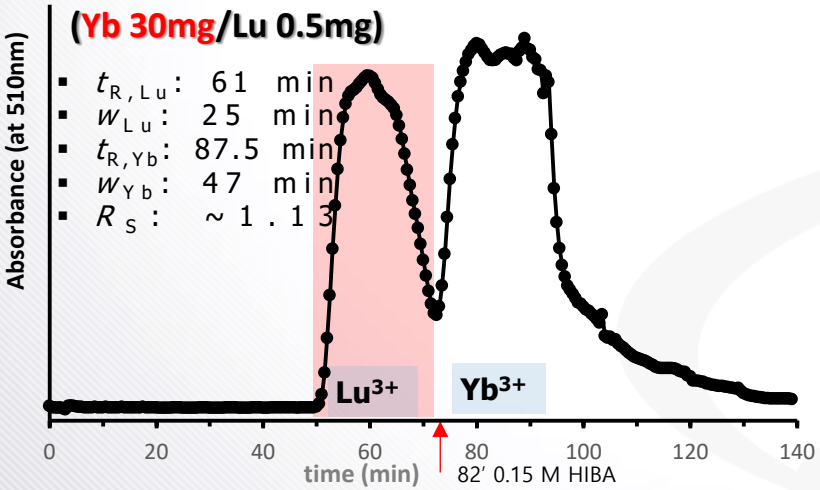
Eluent	W_{Lu}	W_{Yb}	Δt	Rs	N
Ammonia water	4.5min	5min	6.3min	1.32	157.08
Amine 1	5min	6min	11.5min	2.09	384.16
Amine 2	9.5min	12.5min	23.2min	2.11	391.62

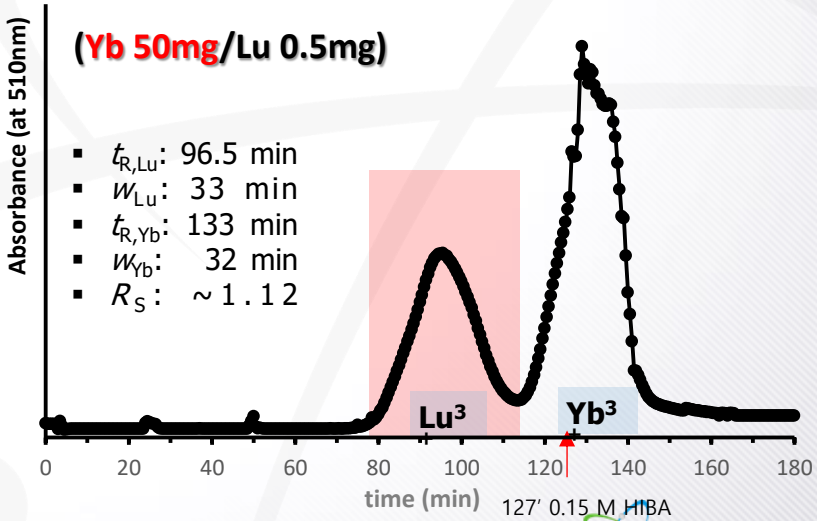
Results

Separation ability of α-HIBA with amine 1







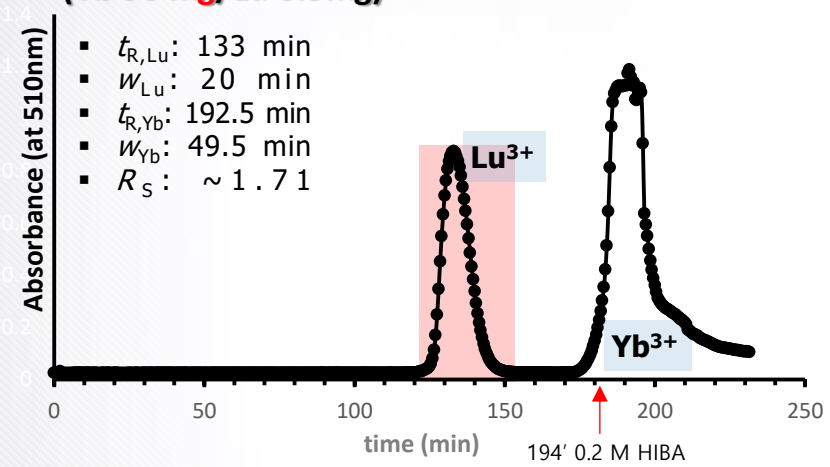


Results

Separation ability of α-HIBA with amine 2

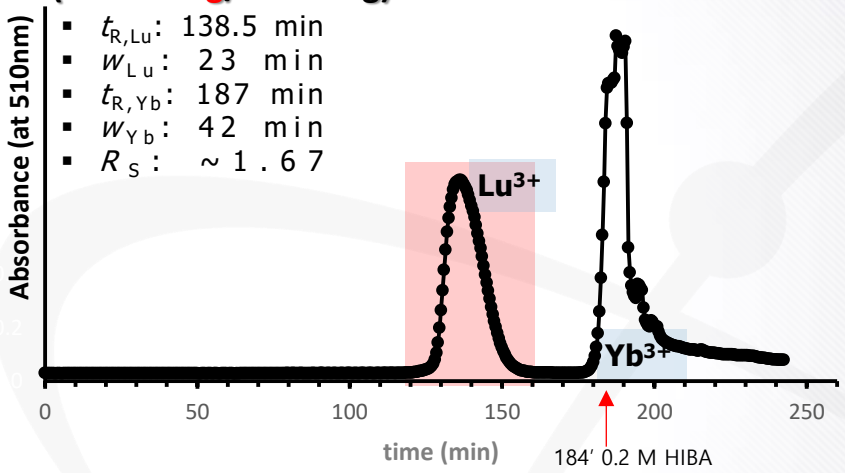
(Yb 50 mg/Lu 0.5mg)

- $t_{R,Lu}$: 133 min
- w_{Lu}: 20 min
- $t_{R,Yb}$: 192.5 min
- w_{Yb}: 49.5 min
- R_S: ~1.71



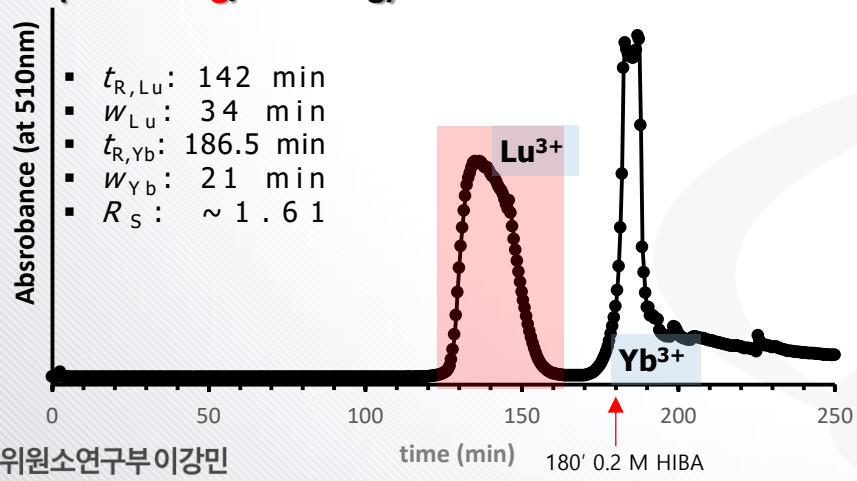
(Yb 100 mg/Lu 0.5mg)

- $t_{R,Lu}$: 138.5 min
- w_{Lu}: 23 min
- $t_{R,Yb}$: 187 min
- w_{Yb}: 42 min
- R_S: ~1.67



(Yb 150 mg/Lu 0.5mg)

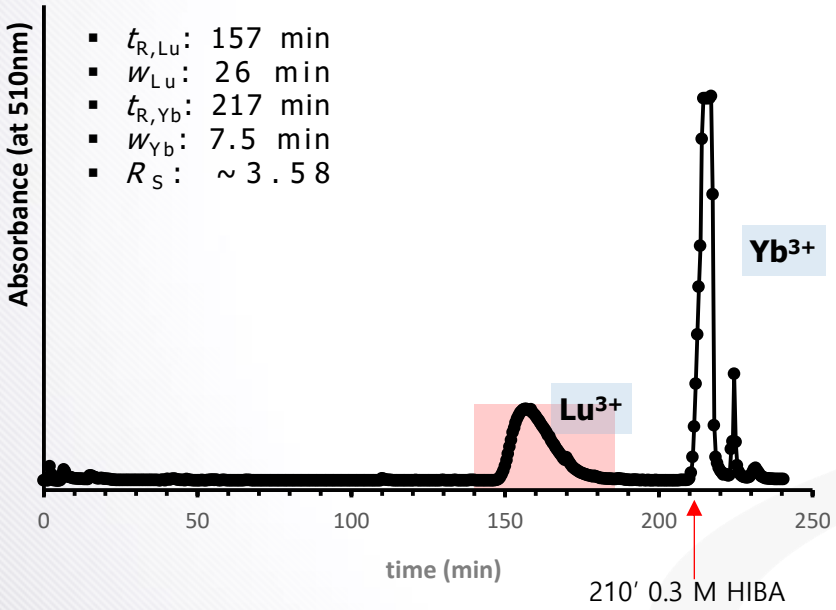
- $t_{R,Lu}$: 142 min
- w_{Lu}: 34 min
- $t_{R,Yb}$: 186.5 min
- w_{Yb}: 21 min
- R_S: ~1.61



Results

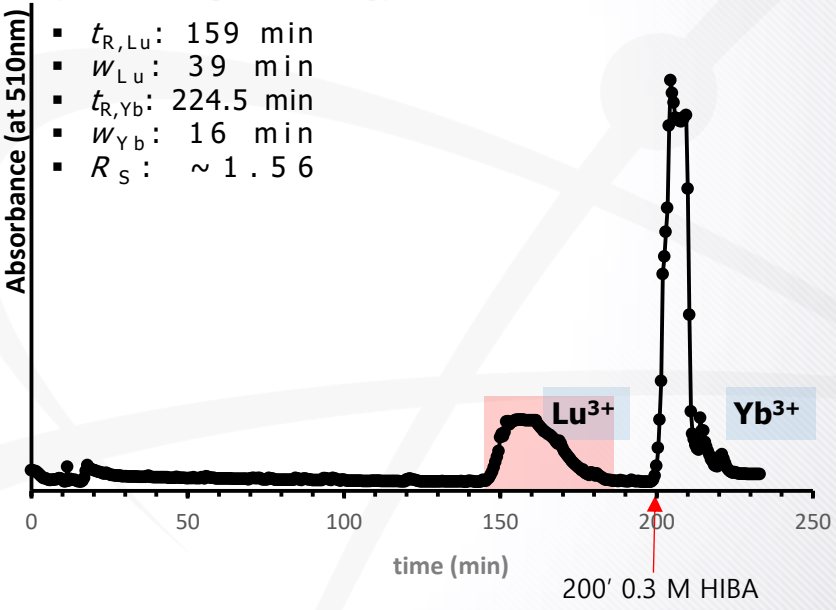
(Yb 200 mg/Lu 0.5mg)

- $t_{R,Lu}$: 157 min
- w_{Lu}: 26 min
- $t_{R,Yb}$: 217 min
- w_{Yb}: 7.5 min
- R_S: ~3.58

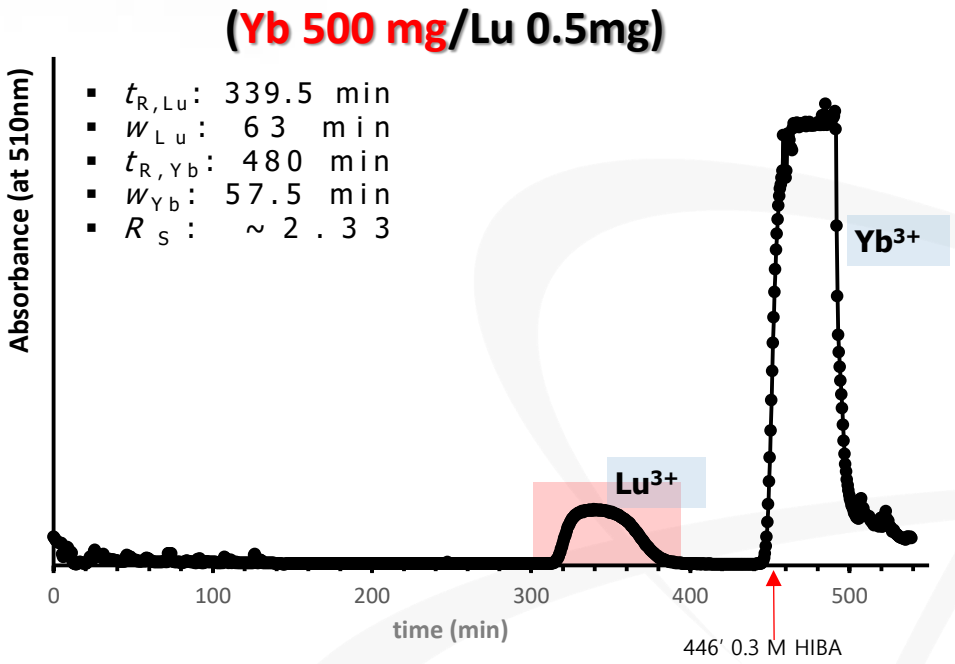


(Yb 400 mg/Lu 0.5mg)

- $t_{R,Lu}$: 159 min
- w_{Lu}: 39 min
- $t_{R,Yb}$: 224.5 min
- w_{Yb}: 16 min
- R_S: ~1.56



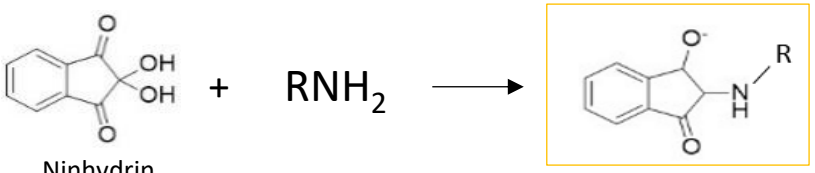
Results


(Yb 500 mg/Lu 0.5mg)
$t_{R,Lu}$: 339.5 min
w_{Lu}: 63 min
$t_{R,Yb}$: 480 min
w_{Yb}: 57.5 min
R_S: ~2.33
Absorbance (at 510nm)
Lu3+
Yb3+
0
100
200
300
400
500
time (min)
446' 0.3 M HIBA

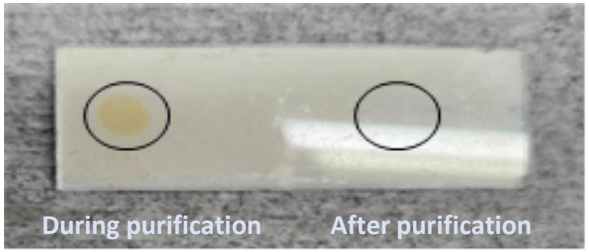
Results

Purification

Confirm purification ability



Ninhydrin



Post purification loss

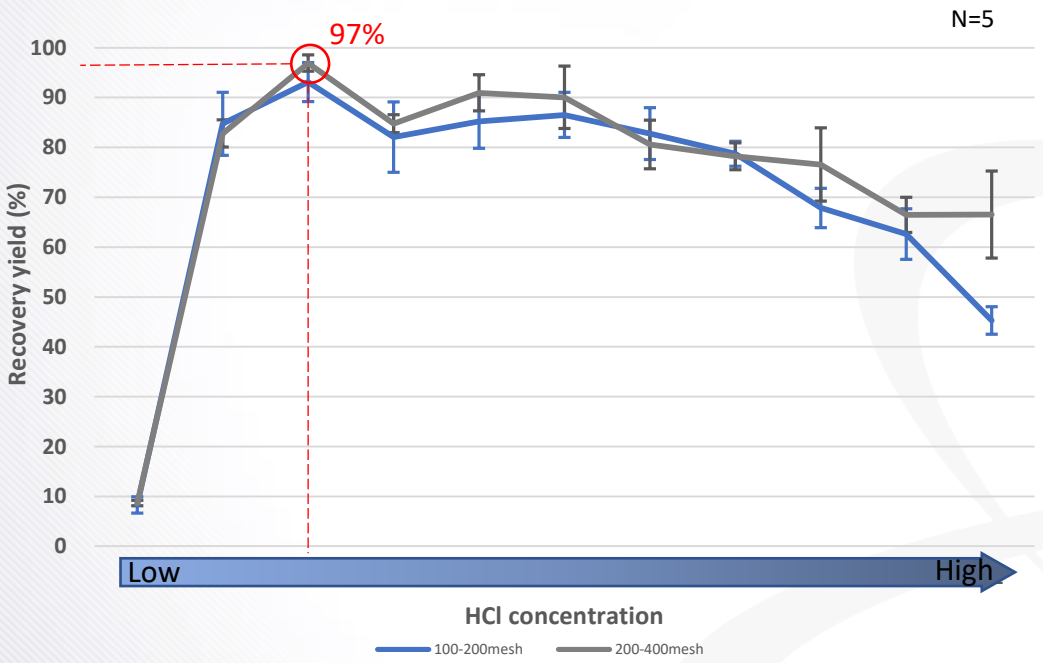
N=5

Purification	100-200mesh		200-400mesh	
HCl concentration	0.1M	0.5M	0.1M	0.5M
Loss rate(%)	0.027	0.07	0.03	0.11

- Washing dilute HCl 10ml (0.1, 0.5)
- Mix with PAR and measure absorbance to calculate concentration
- Purification with dilute HCl results in very few loss

Results

Recovery



Low concentration

HCl

High concentration

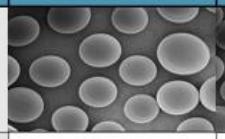
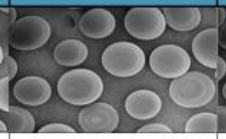
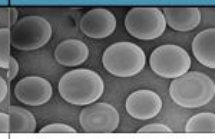
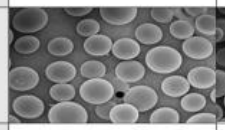
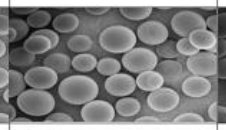
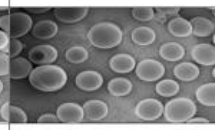
Recovery yield (%) 100-200 mesh	Recovery yield (%) 200-400mesh
8.29	8.65
84.74	82.80
93.12	96.93
82.07	84.74
85.24	90.95
86.53	90.06
82.77	80.58
78.73	78.24
67.85	76.58
62.59	66.48
45.28	66.53

Results

The resin shrinks in acidic conditions

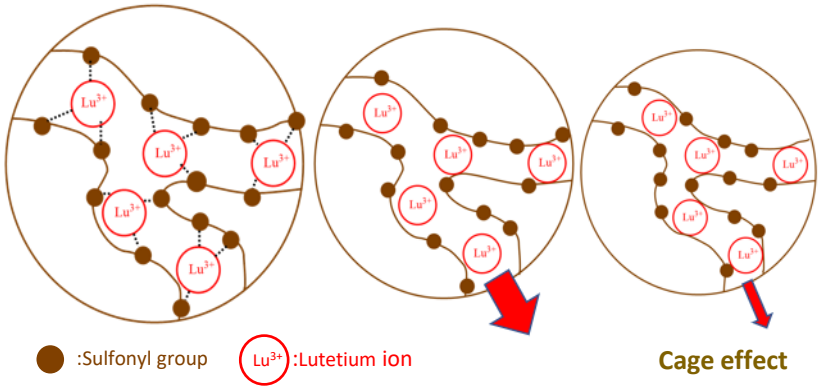
Resin shrinkage by HCl concentration

Concentration ↑ → Beads size ↓

Condition	3M HCl	6M HCl	9M HCl
100-200 Mesh resin (X250)			
Diameter average	91.91㎛	91.07㎛	87.85㎛
200-400 Mesh resin (X250)			
Diameter average	67.48㎛	65.29㎛	63.4㎛

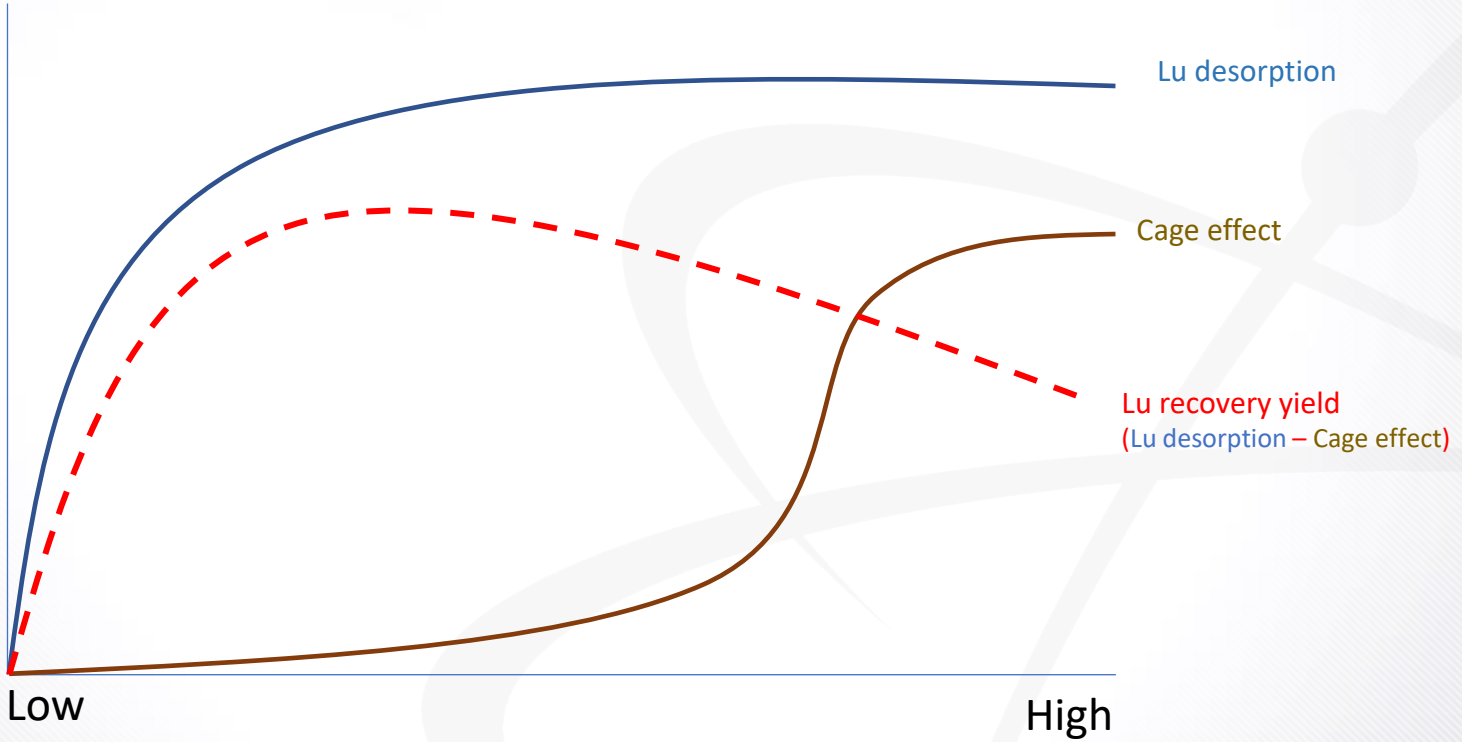
FE-SEM

Ion desorption by shrinkage



- Shrinkage cause gaps to close
- Increased resin interaction
- Recovery decrease as the concentration of acid increases

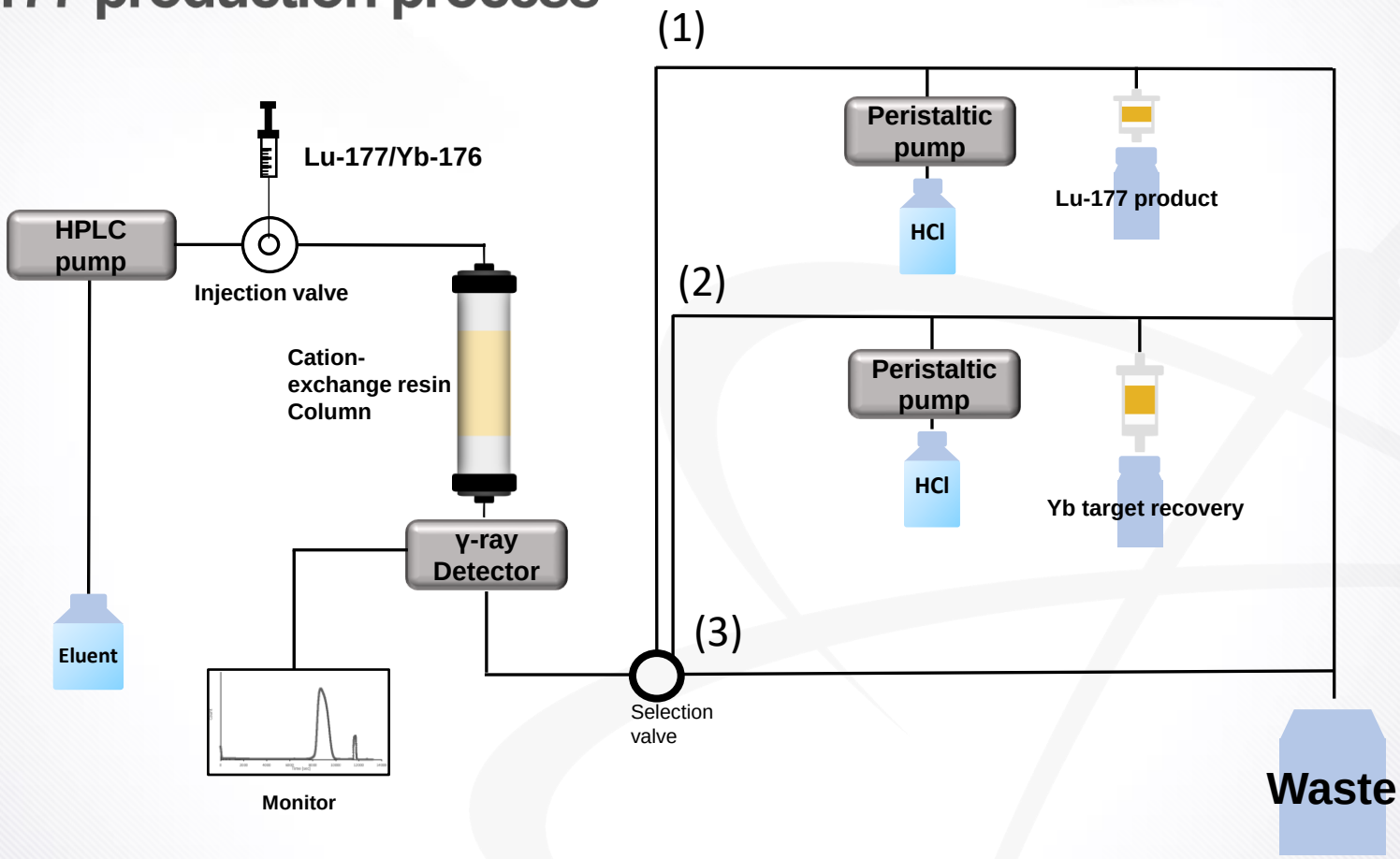
Results


Lu desorption
Cage effect
Lu recovery yield
(Lu desorption – Cage effect)
Low
High

Hot Process

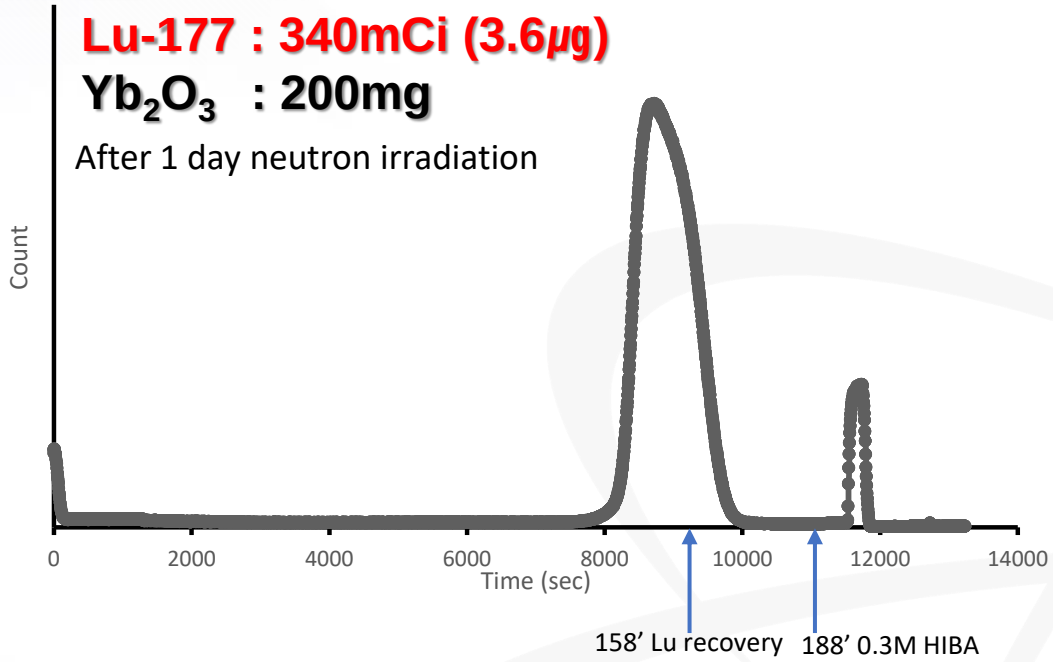
Hot Process

Lu-177 production process



Hot Process

Results



	Initial State	Separate	Recovery
Activity	**340mCi**	**270mCi**	**250mCi**
Rate	**100%**	**79.4%**	**73.5%**

Recovery yield (92.5%)

- Loaded sep-pak : 270mCi
- Recovery solvent (HCl 10ml) : 250mCi
- Post recovery Sep-pak : 14mCi

Hot Process

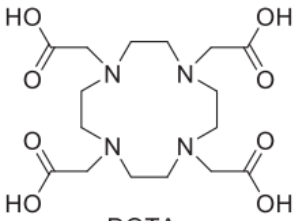
Radio labeling with DOTA(1, 4, 7, 10-Tetraazacyclodecane-1, 4, 7,10-tetraacetic Acid)

Labeling of DOTA-^{177}Lu

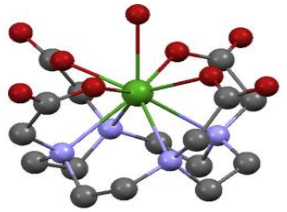
- Mixed 0.05M Na-acetate buffer, DOTA 1X10^{-7}mol and Lu-177
- Lu-177 1mCi, DOTA 1mM(0.1ml), Na-acetate buffer 1ml
- Reacted at 90 C for 20minutes

Radio TLC(Thin Layer Chromatography)

- Solvent in chromatography : Water: EtOH :0.1M HCl = 1:1:0.1

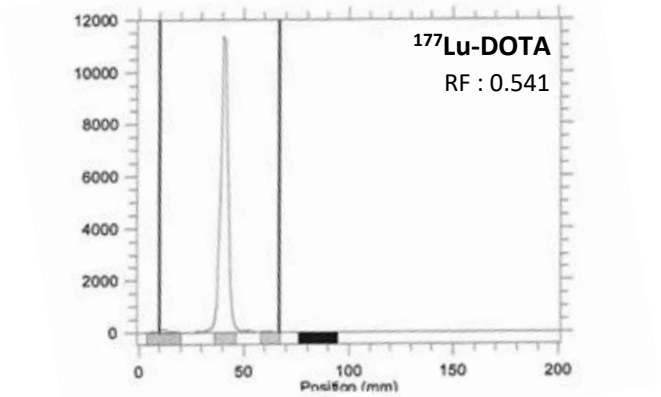


DOTA

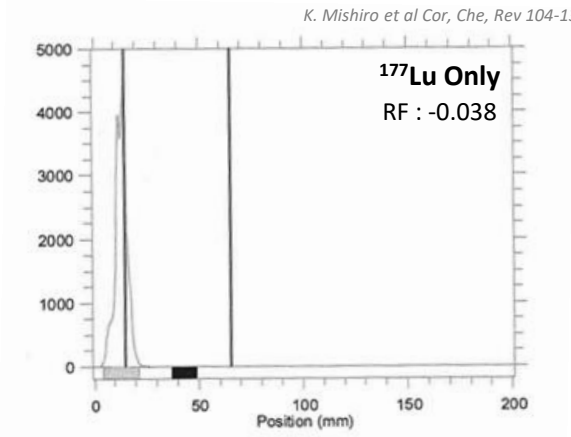


[Lu-DOTA(H_2O)]$^-$

K. Mishiro et al Cor, Che, Rev 104-131 (2019)



Reg	(mm) Start	(mm) Stop	(mm) Centroid	RF	Region Counts	Region CPM	% of Total	% of ROI
Rgn 1	4.2	20.3	12.2	0.039	896.0	896.0	1.54	1.59
Rgn 2	36.3	46.4	40.8	0.541	55212.0	55212.0	94.66	97.90
Rgn 3	58.3	67.5	61.7	0.907	290.0	290.0	0.50	0.51
Bkg 1	76.0	94.5	85.4	1.323				
3 Peaks					56398.0	56398.0	96.69	100.00



Reg	(mm) Start	(mm) Stop	(mm) Centroid	RF	Region Counts	Region CPM	% of Total	% of ROI
Rgn 1	4.2	21.1	13.1	-0.038	32776.0	32776.0	99.05	100.00
Bkg 1	37.1	49.0	42.1	0.543				
1 Peaks					32776.0	32776.0	99.05	100.00

Conclusion

Separation and purification experiments carried out to develop the technology for large scale production of carrier-free Lu-177.

Cation exchange chromatography was utilized to separated Lu from 500mg of Yb, which is sufficient to produce Lu-177 5Ci.

Cation exchange resin and HCl can be used to simply purify recover Lu without loss.

Thank you