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Study on the production of ^{177}Lu for medical purposes at the Dalat Research Reactor

Part 1. Study on production of ^{177}Lu at the Dalat Research Reactor

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Abstract: Lutetium-177 (^{177}Lu) radioisotope used for medical purposes has been produced at the Dalat Nuclear Research Reactor during 2012-2014. The product was synthezed by the activation reaction ^{176}Lu (n,γ) ^{177}Lu. The target was Lutetium oxide with an abundance of ^{176}Lu being 2.59% and the irradiation was conducted with a neutron flux of 2.10^{13} n cm^{-2} s^{-1}. The activity of the ^{177}Lu product was 39,59 Ci g^{-1} after 108 hous of the irradiation. The yield of this method was much higher compared to those of the reaction ^{176}Yb(n, γ)^{177}Yb → ^{177}Lu + β$^-$ which for the same time could be 15mCi/50mg only. Because of low specific radioactivity the preparation of ^{177}Lu made from the activation of ^{176}Yb cannot be applied for the medical purposes. Additionally, the separation yield of ^{177}Lu from ^{177}Yb is rather low, it is usualy of approximately 70%.

Keywords: *Activation reaction, neutron flux, lutetium, abundance separation yield*

I. INTRODUCTION

Radioisotope Lutetium-177 (^{177}Lu) is applied effectively in the targeted radio-therapy due to its short half-life (6.7 days) and its beta energy suitable for curing tumors [1, 2]. Lutetium-177 is produced, worldwide, through two methods. The first method is the activation reaction ^{176} Lu (n,γ) ^{177}Lu, and the second method is the reaction ^{176}Yb(n,γ) ^{177}Yb → ^{177}Lu + β$^-$. For the former reaction, the target used is $^{176}Lu_2O_3$ with natural abundance of ^{176}Lu being 2.59%; and the neutron capture cross section is 2050 barn. For the later reaction the neutron capture cross section is 5.5 barn. The two activation reactions used to produce ^{177}Lu for medical uses, are conducted in nuclear reactors with high neutron flux (≥10^{14} cm^{-2} s^{-1}).

The isotope ^{177}Lu emits beta radiation with its maximum energy of 497 keV accounted for 78.8% and average energy of 149keV. This isotope also emits gamma radiation with the peaks of 113, 208, 250 and 321 keV, in which the peak of 208 keV has the highest emission efficiency of 11% [1, 2].

Although the product of ^{177}Lu obtained from the second method does not contain any carrier, which is very suitable for tracing application. However, due to the small neutron capture cross section of ^{176}Yb the specific radioactivity of the product is lower than those of the first method under the same irradiation condition [2, 3].

In this article, we present the results of our study on the production of ^{177}Lu at the

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Dalat research reactor which has low nominal power and low neutron flux.

II. APPARATUS, TOOLS AND CHEMICALS

A. Apparatus:

- Dalat research reactor with a nominal power of 500 kW and neutron flux $\Phi = 2.10^{13}$ n $cm^{-2}.s^{-1}$ at the irradiation trap.

- High dose calibrator with a range from 0.001 to 80 000 mCi, Capintec, USA

- Dose calibarator, CR- 127, Capintec and ISOMED 2000, USA

- ORTEC multichannel gamma spectrometer system, USA.

- Magnetic stirring stove, Germany.

- High-performance liquid chromatography, Shimadzu , Japan

B. Tools:

- Aluminium cylindar container with a length of 23.6cm, inner diameter of 2.2cm and outer diameter of 2.6cm.

- Quartz ampules with a length of 2.5cm, inner diameter of 0.6cm, outer diameter of 0.8cm.

- Beakers of 50mL, 100mL, 250mL capacity; flasks of 50mL, 100mL capacity; pipettes, micropipettes, Germany.

- Glass ion-exchange column with inner diameter of 1cm, 30cm length and C18 column.

C. Chemicals:

- Lu_2O_3 with of 2.59% ^{176}Lu abundance , chemical purity of 99.99%, Sigma-Aldrich, USA.

- Yb_2O_3 enriched by ^{176}Y to 97.1%, chemical purity of 99.99%, Sigma-Aldrich, USA.

- Dowex-50x8 ion-exchange resin (200-400 mesh), Dow chemical company, USA

- Hydrochloric acid (37%), Merck, Germany.

(- Other chemicals and solvents used for the separation of Lu from irradiated Yb target).

III. THEORETICAL CALCULATION OF ^{177}LU ACTIVITY AFTER THE IRRADIATION OF ^{176}LU VÀ ^{176}YB TARGETS AT THE DALAT RESEARCH REACTOR

A. Estimation of ^{177}Lu activity after the irradiation of ^{176}Lu target

The activity of ^{177}Lu from the activation reaction of ^{176}Lu will be calculated as follows:

$$A_1(\tau) = \frac{6.023.10^{23}.\phi.\sigma_{ac}.G.g}{100.M}\left[1 - e^{-\frac{0.693}{T_1}\tau}\right] \quad (1)$$

Where:

- $A_1(\tau)$: The activity of ^{177}Lu to be determined at time τ

- Φ: neutron flux at sample irradiation position: 2.10^{13} $ncm^{-2}s^{-1}$

- σ_{ac}: activation cross section of ^{176}Lu : 2050 barn

- G: isotopic abundance of ^{176}Lu (%): 2,59%

- g: amount of sample to be irradiated *(g) $1\mu g=10^{-6}gram$*

- M: atomic mass of the isotope to be produced *(g): 177g $Mole^{-1}$*

- T_1: half-life of the isotope produced (*sec*): 6,7h x 3600s

- t: irradiation time in seconds

- 6,023x10^{23}: The Avogadro number

B. Estimation of ^{177}Lu activity after the irradiation of ^{176}Yb target

During irradiation, the following reaction occurs : ^{176}Yb(n,γ)^{177}Yb (T1 ½=1,911h)→^{177}Lu + β^-(T2 ½=6,7d); After irradiation for a period of time τ, radioactivity of ^{177}Lu can be calculated as follows (1):

$$A_2(\tau) = \frac{6.023.10^{23}.\varphi.\sigma_{ac}.G.g}{100.M} \times \left[K(1-e^{-\frac{0.693}{T1}\tau})e^{-\frac{0.693}{T1}t} + F(1-e^{-\frac{0.693}{T2}\tau})e^{-\frac{0.693}{T2}t} \right]$$

$$K = x\frac{T_1}{T_1 - T_2}$$

$$F = x\left(1 - \frac{T_1}{T_1 - T_2}\right)$$

Where:

Φ: neutron flux Φ = 2x10^{13} n.cm^{-2}.s^{-1} (for the Dalat reserach reactor);

σ_{ac}: activation cross section of ^{176}Yb for the ^{176}Yb(n, γ)^{177}Yb reaction, 5,5 barn

G: isotopic abundance of ^{176}Yb;

g: amount of sample to be irradiated; ;

M: atomic mass of ^{176}Yb: 176 g Mole^{-1};

T_1: half-life of ^{177}Yb, 6876s

T_2: half-life of ^{177}Lu, 5,788x10^{5}s;

τ : neutron activation time in seconds

t : cooling time. In this case, t=0 because the activity is calculated immediately after the reactor was shut down. Therefore, the above equation is simplified due to e^0=1.

x: 100% (branching ratio of the daughter radioisotope formation) .

Based on the two above-mentioned equation and parameters of ^{176}Lu và ^{176}Yb targets, we can easily calculate the activity of ^{177}Lu produced after a time period τ of irradiation. In theory, when 1 gram of ^{176} Lu with abundance of 2.59% and its neutron capture cross section of 2050barn is irradiated at the neutron trap with neutron flux of 2.10^{13}n/cm^2.sec for 108 hours, the radioactivity of ^{177}Lu obtained will be 42Ci/g.

When 1 gram of ^{176} Yb enriched to 12.76% and its neutron capture cross section of 5.5 barn is irradiated at the neutron trap with neutron flux of 2.10^{13}n/cm^2.sec for 108 hours, the activity of ^{177}Lu obtained will be 216mCi/g.

When 1 gram of ^{176} Yb enriched to 95% and neutron capture cross section of 5.5barn is irradiated at the neutron trap with neutron flux of 2.10^{13}n/cm^2.sec until the saturation point, the activity of ^{177}Lu obtained will be 1628mCi/g.

The above-mentioned results indicates that when ^{176}Yb enriched to 12,76% is irradiated at Dalat research reactor (of low nominal power), the activity of ^{177}Lu obtained is too low for medical application. Therefore, we focused on the irradiation of ^{176} Lu with abundance of 2,59% and ^{176}Yb enriched to 97,1 % in our subsequent studies.

IV. PRODUCTION OF ^{177}LU THROUGH THE IRRADIATION OF ^{176} LU WITH ABUNDANCE OF 2.59% AND ^{176}YB ENRICHED TO 97.1 %.

A. Production of ^{177}Lu through the irradiation of ^{176} Lu target with the abundance of 2.59% at Dalat research reactor.

0,3950g of Lu_2O_3 was put into a quartz glass ampule. The ampule was sealed off then put into an aluminium container. The target was irradiated at the Dalat research reactor for 108 hours. Afterwards, the target was cooled for 30 hours to allow other than ^{177}Lu radionuclides with short half-life such as ^{176m}Lu ($T_{1/2}$ = 3,7h) to decay completely. After the cooling time, the irradiated target was transfer into a fume hood with air filter, ventilation sytem, and lead brick and lead glass shielding for its processing.

The irradiated targets was dissolved by 8mL of 8M HCl and 5mL of 30% H_2O_2 in a three-neck flask connected with reflux distillation system and heated on a magnetic stirring stove for 2 to 4 hours. After the target was dissolved completely, it was evaporated

until there was only a white residue and then cooled. After that, the residue was dissolved by 5ml of 0.05 M HCl and $^{177}LuCl_3$ solution was obtained. This solution was filtered through a 0.22µm millipour filter and used as a stock solution for subsequent experiments [1, 2].

One hundred microliters (100µl) of the stock solution was taken off by a micropipette and diltued by distilled water to 10ml (solution I). After that, 100µl of solution I was taken out and diluted to 10ml by distilled water (solution II). Three microliters (3µl) of solution II was taken, absorbed in a piece of filter paper that was then dried at room temperature. After that, the radioactivity of the sample was measured by using DSPEC ORTEC multichannel gamma spectrometer with a HPGE detector that has the relative counting efficiency of 58% and energy resolution of 1,9keV at 1.332 keV of ^{60}Co**.** Figure 1 shows the obtained results .

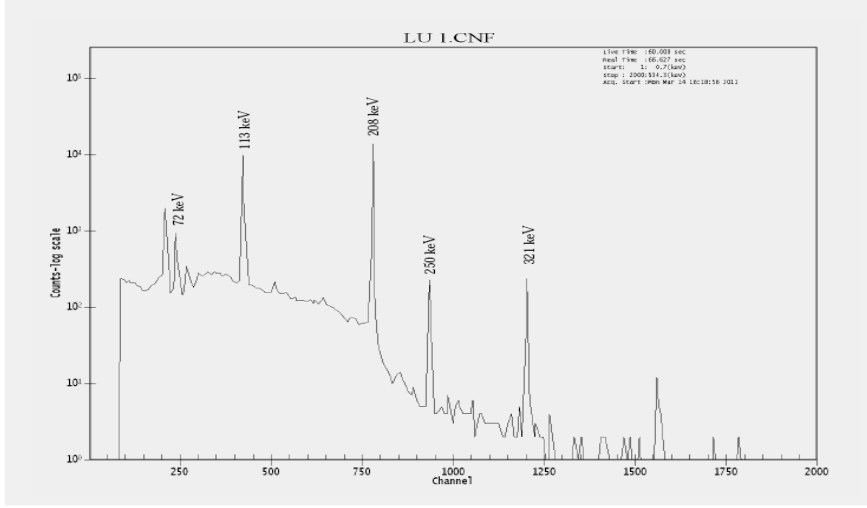

Fig.1: Spectrum of ^{177}Lu in the sample recorded on a gamma spectrometer with HPGe detector (DSPEC ORTEC)

Table I shows the results of measuring three samples.

Table I. Radioactivity of ^{177}Lu measured

Lu-177 sample (1)	**Measuring time of 1min= 60sec**
Counts	36480 (113keV)
Activity at the measuring time	2194979 = 2,19E+06 Bq
Counts	53921 (208 keV)
Activity at the measuring time	2440948 =2,44E+06 Bq
Lu-177 sample (2)	**Measuring time of 1min = 60sec**
Counts	37968 (113keV)
Activity at the measuring time	2284511 = 2,28E+06 Bq
Counts	56297 (208keV)
Activity at the measuring time	2548507= 2,55E+06 Bq
Lu-177 sample (3)	**Measuring time of 1min = 60sec**
Counts	41949 (113keV)
Activity at the measuring time	2524045 = 2,52E+06 Bq
Counts	61929 (208 keV)
Activity at the measuring time	2803462 = 2,80E+06 Bq

Radioactivity calculated at the highest peak of 208 keV as follows:

- Average activity = 2,5966x10^6 Bq

- Amount of sample: 3µl of stock solution was diluted to 100 times

- Cooling hours was 67 hours

- Deacy factor of ^{177}Lu after 67 hours is 0,7481

Based on the above measuring data, the radioactivity of ^{177}Lu in the sample was calculated to be 39.56 Ci g^{-1} as follows:

$$R = \frac{2.5966*10^6*10^2*5*10^3}{3*0.7481*3.7*10^{10}} = 39.56 Cig^{-1}$$

The result in table 1 shows that the radioactivity obtained in experiment is lower than that calculated theoretically. That is reasonable because the results in theory was obtained from an ideal condition. Meanwhile, a real production depends on many experiemental parameters such as aluminum containers, glass ampule, target density, temperature..., especially burn-up effect of the target that reduces the number of atoms participating in the neutron activation reaction.

B. Production of ^{177}Lu through the irradiation of ^{176} Yb enriched to 97,1% at the Dalat research reactor

+ Sample preparation and irradiation

After the sample of Yb_2O_3 was dried, about 50 mg of Yb_2O_3 (97,1% ^{176}Yb) was put in a quartz ampoule, sealed off, then put in an aluminum container, and irradiated at the reactor.

- Irradiation position was in neutron trap
- Neutron flux: 2.10^{13}n/cm^2.s
- Irradiation time: 108 hours
- Cooling time: 30 hours

+ Sample treatment [3, 5, 6]

After the Yb_2O_3 target was cooled, it was transferred to a fume hood. The ampoule was broken and put in a beaker, dissolved with 8ml of 8M HCl, poured the solution into a 250ml three-neck flask that was connected with reflux distillation system and put on a magnetic stirring stove. The beaker containing the sample was rinsed with 2 ml of 8M HCl (glass fragments still remained in the beaker). The stove was turned on. 5ml of 30% H_2O_2 was added to the beaker slowly and heated until the target was dissolved completely. The sample was then evaporated until there was only a white residue. Then the stove was turned off and the residue was cooled. The cooled residue was dissolved with 5ml of 0.005M HCl and the solution of $^{177}YbCl_3$ was obtained as a stock for further dilution as necessary. In order to load the sample to an ion exchange column, the concentration of Yb must be greater than 1µg/µl.

+ Separation of ^{177}Lu from the target [3, 5, 6]

The column of C18 was rinsed and connected with HPLC system. Make sure that all the parameters must be set properly in accordance with the procedure being applied. Before the sample was loaded into the column of C18, the column was rinsed with acetonitrile. Then 10µl of sample solution was injected into the column.

Mobile phase was a mixture of the complex and ion pair forming agents: 0,25M 2-HIBA and 0,01M 1-OS.

The experiement was conducted using different volume ratios between 2-HIBA 0,25M and 1-OS 0,01M: 1:2; 2:1 và 1:1 with pH ranging from 2.2 to 2.4 in the mobile phase.

The mobile phase was let move through the column with a flow rate of 0.5ml/min. The pressure in the column C18 ranged from 6-10 bar.

Because there is no radiation detector on HPLC, at the exit of mobile phase on the column, a sample changer tray with plastic tubes was used to take each mililiter of sample that had moved through the column. Each sample taken was measured on CAPRAC radiation counter. Each sample was numbered and stored for conducting further experiments. The mobile phase moved continuously and the samples were taken until the total counts of all samples measured was approximately equal to the total counts of 10µl solution injected into the column. ^{177}Lu in the mobile phase was taken separately, adjusted with 6M HCl to less than 1. After that, this solution was let to move through a glass column (inner diameter of 1,0cm and height of 30cm) had loaded with Dowex-50x8 resin. The column was pretreated by rinsing with 50 ml solution of 3M NH_4Cl, 3M HCl and distilled water twice. After that, the sample was let to move through the column. The column was then rinsed with 200 ml of 0.1M HCl to remove 2-HIBA and 1-OS .

Pure ^{177}Lu in the column was eluted with 6M HCl. The solution obtained was poured in a three-neck flask, prepared and treated as mentioned aboved, diluted with 0.05M HCl to 5ml, filtered in a pasteurized way, and measured radioactively.

- The results of separation of ^{177}Lu using the mobile phase of 0.25M 2-HIBA và 0.1M 1-OS with the ratio of 2:1

Counts 10k/µl;

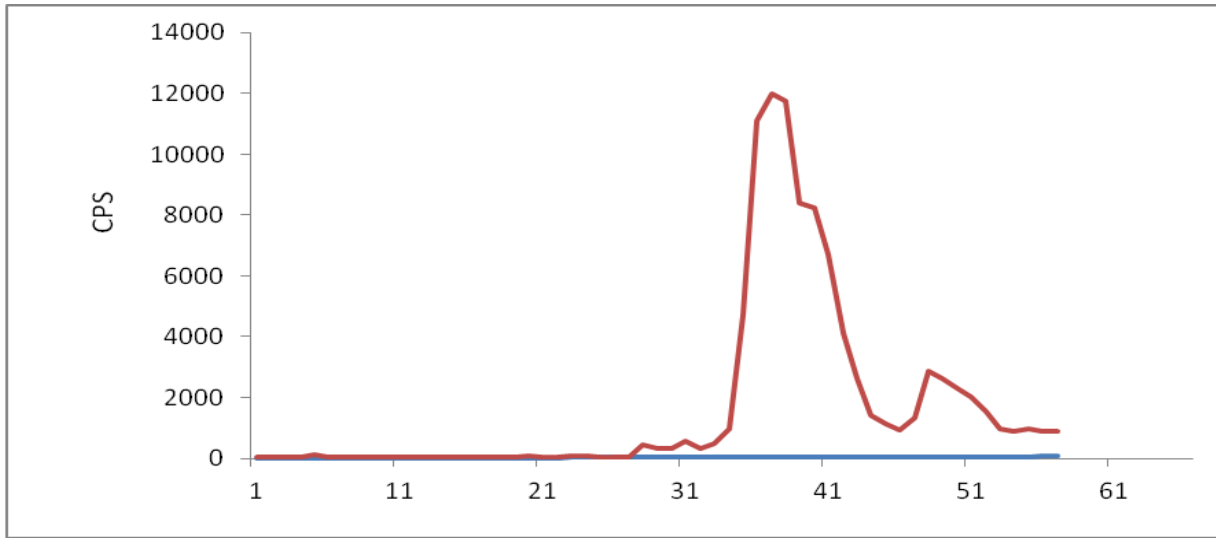

Fig 1. Diagram of separation of ^{177}Lu using the mobile phase of 0.25M 2-HIBA and 0.1M 1-OS with the ratio of 2:1.

The vertical axis represents the counts in each segment of sample while the horizontal axis represents the number of segments obtained from the mobile phase. ^{177}Lu was detected from segment 26 to 43 and ^{176}Yb was detected in the next segment.

Note: According to the result of the quality assessment of the separated isotope, separation yield was greater than 70% when use the ratio mentioned above for the mobile phase. However, the specific activity was not high enough for medical applications (~15mCi/50mg).

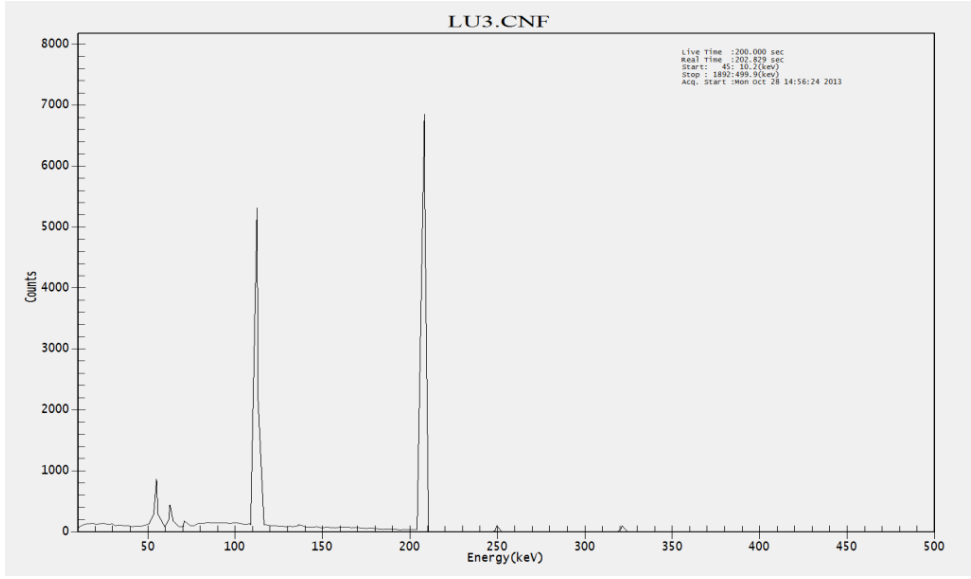

Fig. 2. Spectrum of ^{177}Lu obtained after separation of ^{177}Lu from the target

Before separation, it was impossible to obtain the above spectrum because different Yb isotopes emit beta interfering the gamma energy peaks ^{177}Lu. After separation, the gamma energy peaks ^{177}Lu appeared clearly. It shows that ^{177}Lu was separated from the Yb target. Obviously, the separation of ^{177}Lu using the mobile phase of 0.25M 2-HIBA and 0.1M 1-OS with different ratios has a lower yield and the separation is incomplete.

V. CONCLUSION

- From the results of the separation of ^{177}Lu from irradiated Yb target it was obvious that, although the specific activity of the preparation was rather low, the mobile phase of 0.25M 2-HIBA and 0.1M 1-OS with the ratio of 2:1 can be chosen to separate^{177}Lu from Yb_2O_3 target without using any carrier.

- The power and neutron flux at the Dalat research reactor are not suitable to produce ^{177}Lu by using Yb_2O_3 even if the target is enriched up to 97,1% ^{176}Yb. To be able to get ^{177}Lu by using Yb target nuclear reactor must possess a neutron flux of greater than 10^{14} n/cm^2.sec.

- It is possible to use ^{177}Lu produced by irradiating ^{176}Lu target at the Dalat research reactor for further study on the labeling of EDTMP and investigate the distribution of this radiopharmaceutical in animals for the purpose of applying it to treat relieving pain of bone cancer metastasis in human body.

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