STUDY ON PREPARATION OF ^{177}Lu, LABELING WITH DOTATATE FOR USING IN DIAGNOSIS AND TREATMENT NEUROENDOCRINE TUMORS

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ABSTRACT: Due to its physical and chemical characteristics, ^{177}Lu is a very attractive radionuclide for use in nuclear medicine. Its main usage is in the treatment of neuroendocrine tumours but its applicability in the treatment of colon cancer, metastatic bone cancer, non-Hodgkin's lymphoma, lung, ovarian, and prostate cancer, has also been studied. Two alternative production routes are generally applied to obtain ^{177}Lu, namely the direct route based on neutron irradiation of lutetium targets and the indirect route based on neutron irradiation of ytterbium targets followed by radiochemical separation of ^{177}Lu from ytterbium isotopes. The comparison of theoretically calculated and experimentally determined yield for ^{176}Lu(n,γ)^{177}Lu reaction is presented.^{177}Lu could be produced with a specific activity of 42 mCi/mg by neutron activation using enriched ^{176}Lu (2.59%) target when irradiation was carried out at Dalat Nuclear Research Reactor with thermal neutron flux of 2×10^{13} n/cm^2/s for 100h. The indirect production route as an alternative production route, ^{177}Lu could be obtained as carrier-free from beta decay of ^{177}Yb produced by neutron activation of ^{176}Yb. In this way, enriched target material was used but it may be the neutron capture cross section is only 2.4 b so resulting in low activity just enough to study the separation process of ^{177}Lu from ^{177}Yb. In the other hand the study on labeling ^{177}Lu with DOTATATE is also described the optimization of the reaction conditions to obtain the complex ^{177}Lu-DOTA-TATE with a radiochemical purity > 99%, even so the studies of stability in vitro to the dilution in saline solution during 72 hours. The bio-distribution studies of this product in mice and rabbit are also investigated.

Key words: *Production of ^{177}Lu, nuclear reactor IVV-9, DOTATATE.*

INTRODUCTION

In recent years,^{177}Lu has emerged as a promising short-range β^- emitter for targeted radiotherapy. It can be employed as an alternative to ^{131}I or a complement to ^{90}Y, ^{177}Lu [$T_{1/2}$ = 6.73 d, $E_{\beta max}$ = 0.497 MeV, E_γ = 113 keV (6.4%) and 208 keV, (11%)] is being considered as another viable alternative for the development of new agents for PRRT. The use of ^{177}Lu provides an additional advantage of emission of accompanying low-energy, low-abundance gamma photons suitable for carrying out simultaneous imaging studies. While the high thermal neutron capture cross-section of ^{176}Lu (2100 b) makes it quite convenient to produce high specific activity.

^{177}Lu production could be used moderate flux reactors. The comparatively longer half-life of ^{177}Lu provides logistic advantages over the use of PRRT. Moreover, the tissue penetration range of ^{177}Lu (maximum range 2 mm) is more favourable than that of ^{90}Y (maximum range ~12 mm), especially for smaller metastases

Unlike ^{90}Y, ^{177}Lu provides an additional advantage of the possibility to perform scintigraphic and dosimetric studies with the same agent employed for therapeutic purpose.

Although ^{90}Y is obtainable in no carrier-added (NCA) from a ^{90}Sr-^{90}Y generator, but there exists the stringent requirement of purification from ^{90}Sr, a natural bone seeker with a long $T_{1/2}$ of 28.3 years. On the other hand,^{177}Lu can be easily obtained in radionuclidically pure form. The excellent radionuclidic purity of ^{177}Lu during using of enriched Lu (>60% in ^{176}Lu) target.

I. EXPERIMENTS

I.1. Equipments

The Dalat Research Reactor of 500kW; HPLC-LCMS, (Shimadzu); Calibrator ISOMED 2000 (Germany); Counter Caprac (Capintec); Heated magnetic stirrer; Micropipette; Thermostat; Bottles; Glassware…

I.2. Reagents

- DOTATATE was purchased from piCHEM R&D (Austria), (GMP-grade, >95% (HPLC); Hydrogen peroxide: concentration 35%, residue on evaporation 0.05%, heavy metals 0.0001%; Hydrochloric acid: concentration 35.0 ~ 37.0%, residue on evaporation 0.001%, heavy metals 0.000005%; Sodium acetate containing 40 mg/mL, 2,5-dihydroxybenzoic acid.

- Pure water: Purified by The PURELAB® Ultra, ultra pure water production system, conductivity ≤ 18.2 MΩ.cm

- Target specification and preparation: Lu_2O_3 99.99% (Sigma-Aldrich), Natural and enriched >60% in^{176}Lu

Impurity details:

Y_2O_3 < 5 ppm, CeO_3 < 5 ppm, Pr_2O_3 < 5 ppm, Nd_2O_3 < 5 ppm, Sm_2O_3 < 5 ppm, EuO_3 < 5 ppm, Gd_2O_3 14 ppm, Tb_2O_3 < 5 ppm, Dy_2O_3 < 5ppm, Ho_2O_3 < 5 ppm, Er_2O_3 < 5 ppm, Tm_2O_3 < 7 ppm, Yb_2O_3 22 ppm, La_2O_3 < 5 ppm, CaO < 30ppm, Fe_2O_3 < 5 ppm, SiO_2 30ppm.

II. PROCEDUCES

II.1. ^{177}Lu production

Target preparation and irradiation

Material target: Lu_2O_3 99.99%.

+ Target weight: be accurately weighed by analytical balance.

+ Irradiation container: The target is contained in quartz ampoule and placed in dedicated aluminum containers for irradiation.

- Irradiation

Based on these calculations, the neutron irradiation is established on the basis of ensuring the general requirements for radiation safety and occupational safety.

+ Irradiation position: neutron trap, thermal neutrons plux: ~ $2.10^{13}.cm^{-2}.s^{-1}$.

+ Irradiation time: 100-130 hours.

+ Cooling time: 30-48 hours

Preparation of $^{177}LuCl_3$

After cooling, the irradiated target is transferred to the box production, Where irradiated target was dissolved in 8M hydrochloric acid in 3 neck flask fitted with a reflux condenser and

heating by Heated magnetic stirrer in the presence of H_2O_2 30% within 2-4 hours, after the target have been dissolved completely, the evaporation will be carry out until appear white residue $^{177}LuCl_3$, then turn off the heater to cool. After that, cold target will be re-dissolved with 5 ml of HCl 0,05M, thus the $^{177}LuCl_3$ is obtained. The next stage is the quality control and other research applications.

Radionuclides used in nuclear medicine generally or ^{177}Lu particularly often mix some kind of similar radioactive isotopes or same group, they can join in the labeling reaction or to exist in free state. Evaluation of this impurity is called radionuclide purity. Pharmacopoeia standards define radionuclide purity must be more than 98%.

The radionuclide purity is checked by diluting the solution, then used a micropipette take 2-5 μλ (dilution estimated that the maximum activity is less than 10^7cpm/ml). The measurement samples are made simultaneously for at least 3 samples for getting the average result, The gamma spectrometer is used for recording radionuclide purity. The main gamma peaks of ^{177}Lu are 72, 113, 208, 250 and 321 keV.

II.2. ^{177}Lu-DOTATATE preparation

Radiolabelling of DOTATATE is carried out by adding 100 μL of 0.4M sodium acetate containing 40 mg/mL of 2,5-dihydroxybenzoic acid at pH 4.5 (solution A) to 10 μg of DOTATATE (0.4 mg/mL in 0.4M sodium acetate at pH 4.5) (solution B). The pH of the $^{177}LuCl_3$ solution is adjusted to 3–4, and 25 μL of this solution (containing 0.25 μg of Lu, 20 Ci/mg) (solution C) is added to the mixture of solutions A and B. The final reaction mixture (solution A + solution B + solution C) is incubated at 80–90°C for 30 min. A protocol for the preparation of ^{177}Lu-DOTATATE is presented in Table 1.

Table 1: Protocol for preparation of ^{177}Lu-DOTATATE

Reagent	Amount/volume
Solution A: CH_3COONa buffer (pH=4.5) containing of 2,5-dihydroxybenzoic acid-concentration of 40mg/ml	100μl
Solution B: CH_3COONa buffer (pH=4.5) containing of 0.4 mg/ml DOTATATE	25μl (10μg of DOTATATE)
Solution B: $^{177}LuCl_3$ solution (pH 3-4)	25μl (0.25-0.50 μg of Lu, 5mCi
Process:	Adding of solution C to a mixture of solution A and B

Labelling of ^{177}Lu with DOTATATE by optimization studies

Optimization studies of ^{177}Lu labelling of DOTATATE various parameters such as ligand concentration, incubation time and temperature, were varied extensively in order to arrive at the protocol for maximum complexation. Keeping the reaction volume at 200 μL, the amount of DOTATATE was varied from 5 to 100 μg in order to determine the optimal ligand concentration for obtaining maximum complexation. The characterization of the labelled conjugate and the complexation yield were determined by paper chromatography in 50% aqueous acetonitrile. The radiochemical purity of the labelled product was estimated by PC, TLC and HPLC analysis using the gradient elution technique described above.

Stability of the ^{177}Lu-DOTATATE

The stability of the radiolabelled peptides prepared under the conditions described above was studied. The ^{177}Lu-DOTATATE was found to be adequately stable over a period of 3 d at room temperature. The addition of free radical scavengers such as 2,5-dihydroxybenzoic acid (40 mg/ml of the final mixture) was found to be essential for the storage of high specific activity ^{177}Lu labelled DOTATATE preparations.

Quality control

- Thin layer chromatography

Thin layer chromatography studies are carried out on silica gel (aluminium sheets, Merck) in 10 cm strips as the stationary phase. Ammonium hydroxide: methanol:water (1:5:10) is used as the mobile phase. While the free activity remains at the point of origin (R_f = 0), the radiolabelled peptide migrates to an R_f of 0.4.

- Paper chromatography

The paper chromatography studies are carried out using 10 cm long Whatman 3MM chromatography papers. For these studies, 5 µl of the test solution is spotted at 1.5 cm from the lower end of the paper strips, which are developed in 10% ammonium acetate in methanol (30:70 vol./vol.). The strips are subsequently dried and cut into 1 cm segments. The radioactivity associated with each segment is measured in a well type NaI(Tl) detector. While free activity remains at the point of origin, the radiolabelled peptide migrates to an R_f of 0.7-0.8. Percent of labeling efficiency is calculated by using the formula:

$$\text{Labeling eficience (\%)} = \frac{\mathbf{A}_{177Lu}\textbf{-DOTATATE}}{\mathbf{A}_{177Lu} + \mathbf{A}_{177Lu}\textbf{-DOTATATE}} \text{x100}$$

III. RESULTS AND DISCUSSION

III.1. Preparation of ^{177}Lu

III.1.1. Theoretical calculation results

Radioactivity produced by the reaction of (n, γ) in the irradiation time τ is calculated from the formula:

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

where:

$6.023.10^{23}$: Avogadro number

Φ: neutron flux: 2.10^{13}n/cm^2.s

σ_{ac}: activation cross-section: 2050b=2050.10^{24}cm^2

G: isotopic abundance: 2.59% ^{176}Lu

g: weight of the irradiated sample gram: 1000µg

M: atomic weight: 174.97g

T_1: half-life: 160h

τ: irradiated time: 108h

The result after fill all numbers is: **42mCi/mg ^{176}Lu**

Table 2: The result consult the reference at time of 4,5 day

^{176}Lu(n, γ)^{177}Lu

$M = 174.97$ $G = 2.59\%$ $\sigma_{ac} = 2050$ barn,

^{177}Lu $T_1 = 6.7$ day

E_γ (keV) 208 113

P 0.061 0.028

Activation data for ^{177}Lu : $A_1(\tau)$, dps/μg

A_1(sat) = 1.8277/ 6

A_1(1 sec) = 2.1880/ 0

Day	0.00	0.25	0.50	0.75
0.00	0.0000/ 0	4.6655/ 4	9.2119/ 4	1.3642/ 5
1.00	1.7960/ 5	2.2167/ 5	2.6266/ 5	3.0261/ 5
2.00	3.4154/ 5	3.7948/ 5	4.1645/ 5	4.5247/ 5
3.00	4.8758/ 5	5.2179/ 5	5.5512/ 5	5.8761/ 5
4.00	6.1926/ 5	6.5011/ 5	6.8017/ 5	7.0946/ 5
5.00	7.3801/ 5	7.6582/ 5	7.9293/ 5	8.1934/ 5
6.00	8.4508/ 5	8.7016/ 5	8.9461/ 5	9.1843/ 5
7.00	9.4164/ 5	9.6425/ 5	9.8630/ 5	1.0078/ 6
8.00	1.0287/ 6	1.0491/ 6	1.0690/ 6	1.0883/ 6
9.00	1.1072/ 6	1.1256/ 6	1.1435/ 6	1.1610/ 6
10.00	1.1780/ 6	1.1946/ 6	1.2108/ 6	1.2265/ 6
11.00	1.2419/ 6	1.2568/ 6	1.2714/ 6	1.2856/ 6
12.00	1.2994/ 6	1.3129/ 6	1.3260/ 6	1.3388/ 6
13.00	1.3513/ 6	1.3635/ 6	1.3753/ 6	1.3869/ 6
14.00	1.3981/ 6	1.4091/ 6	1.4198/ 6	1.4302/ 6
15.00	1.4403/ 6	1.4502/ 6	1.4599/ 6	1.4693/ 6
16.00	1.4784/ 6	1.4873/ 6	1.4960/ 6	1.5045/ 6
17.00	1.5127/ 6	1.5208/ 6	1.5286/ 6	1.5362/ 6
18.00	1.5437/ 6	1.5509/ 6	1.5580/ 6	1.5649/ 6
19.00	1.5716/ 6	1.5781/ 6	1.5845/ 6	1.5907/ 6
20.00	1.5968/ 6	1.6026/ 6	1.6084/ 6	1.6140/ 6
21.00	1.6194/ 6	1.6248/ 6	1.6299/ 6	1.6350/ 6
22.00	1.6399/ 6	1.6447/ 6	1.6494/ 6	1.6539/ 6

Table 3: Results calculated using the Excel program

Calculated yields of Lu-177 from enriched Lu-176 (2.59%) target					
				Irradiated in DNR	
Neutron flux(cm2·sec)			**2.30E+13**		
Enrichment of Lu-176		**0.0259**		0.026	
Cross section of formation of Lu-177				**2050**	**2.05E-21**
$t_{1/2}$ (h)	Lu-177	**161.616h**			
Number of atoms of 176, in 1mg Lu			^{176}Lu	**8.86192 E+16**	=0.001x0.026/176 x6.023E+23
T(hour)		**A(Lu-177)**			
		Bq/mg			
110		**1.57151E+09**	**= 42mCi/mg**		

III.1.2. Processing of irradiated target and radioactivity measuring

After cooling, the irradiated target is transferred to the box production, Where it was dissolved in 8M hydrochloric acid in 3 neck flask fitted with a reflux condenser and heating by heated magnetic stirrer in the presence of H_2O_2 30% within 2-4 hours, after the target have been dissolved completely, the evaporation will be carry out until appear white residue $^{177}LuCl_3$, then turn off the heater to cool. After that, cold target will be re-dissolved with 5 ml of HCl 0,05M.

The stock solution is diluted into 10ml (to mark solution I), then re-dilute one time more by using 100µl solution I dilute into 10ml (to mark solution II).

Get about 1µl -5µl solution II made into 3 samples and qualitative spectrometer on gamma spectrometer (multi-channel gamma spectrometer system DSPEC ORTEC HPGe detector, the relative record efficiencies of 58%, energy resolution of 1.9 keV) the collected spectrum as shown in Figure 2.

Table 4: Measuring results achieved of 3 ^{177}Lu samples

Sample of Lu-177 (1)	Measuring time 300sec	starting measure	14h38
	208 keV	HS position 5	0.003346997
Counter	64231		
Activity at measurement time =	581534,3482		
	5.82E+05	Bq	
Sample of Lu-177 (2)	Measuring time 300sec	starting measure	14h49
	208 KeV	HS position 5	0.003346997
Counter	64801		
Activity at measurement time =	586695,0117		
	5.87E+05	Bq	
Sample of Lu-177 (3)	Measuring time 300sec	starting measure	14h57
	208 KeV	HS position 5	0.003346997
Counter	648503		
Activity at measurement time =	58363,9891		
	5.85E+05	Bq	

A measure of the average: $5.85x10^5$ Bq

- (Amount: 1 µl solution II)
- Cooling time: 136^h40, Ended after 30'
- Decay factor of ^{177}Lu at 136^h40' was 0.5548
- Experimental activity:

$\frac{5,85x10^5x10^2x5x10^3}{}$ = 14,1 Ci/0,395g Lu = **36mCi/mg Lu**

$1x0,5548x3,7x10^{10}$

Table 5: The Theoretical and experimental results

Result	*Activity* of *Theoretical calculation*	Activity of consultation	Activity calculated using the Excel program	Experimental Activity
Activity/mg	42.0mCi	42.0mCi	42.0mCi	36 mCi

III.1.3. Quality control results

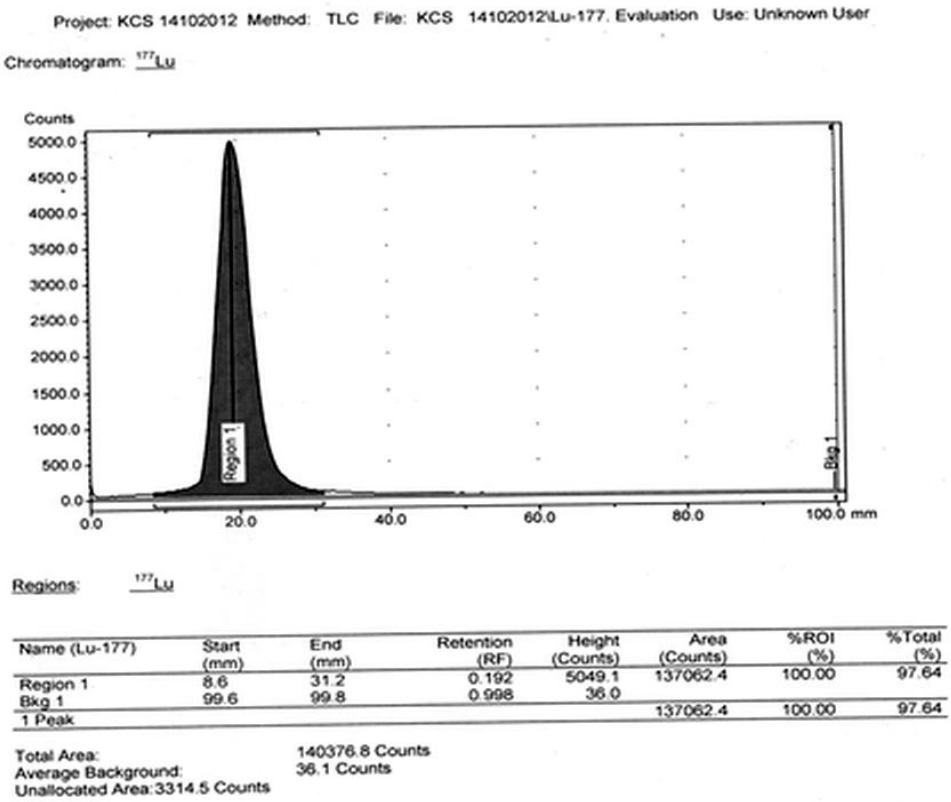


Figure 1: The result of Radiochemical purity > 97%

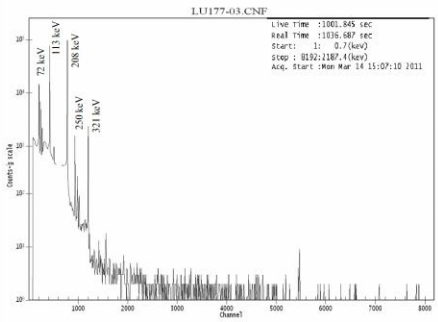


Figure 2: Gamma spectrometry results of ^{177}Lu

Figure 3: Beta spectrometry results of ^{177}Lu

Comment: The Experimental activity is always lower than the actual activity theory. This is actually considered appropriate, because theoretical results are calculated under ideal conditions, while the actual production depends very much experimental parameters. Maybe, because of the

decrease of neutron flux; and many experimental factors such samples are placed in the irradiation container as aluminum material, taget density, temperature **...**

The Quality control results: The result of Radiochemical purity > 99.9% and The result of Radionuclides purity >99%.

III.2. Preparetion of ^{177}Lu-DOTATATE

III.2.1. Radiolabelling optimization

The radiolabelling yield of ^{177}Lu-DOTATATE as a function of pH, incubation time and incubation temperature is presented in Fig. 4, 5 and 6, respectively. The results indicate that high labelling yield of ^{177}Lu-DOTATATE was obtained at pH 5 with incubation during 25-30 min at a temperature of 90^{o}C. The effect of varying the molar ratio of Lu to DOTATATE is shown in Fig.7

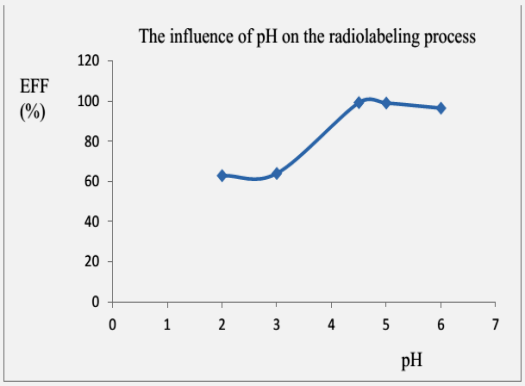


Figure 4: The influence of pH on the radiolabeling process

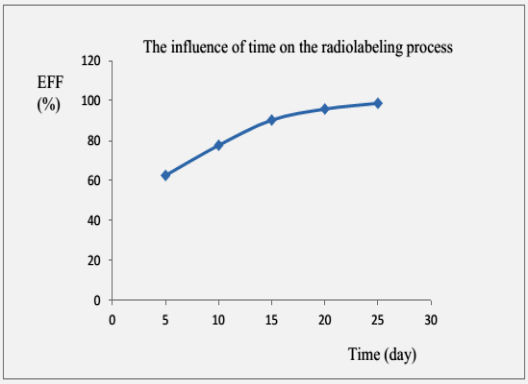


Figure 5: The influence of time on the radiolabeling process

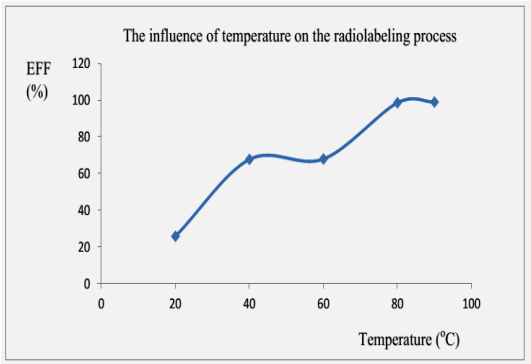


Figure 6: The influence of temperature on the radiolabeling process

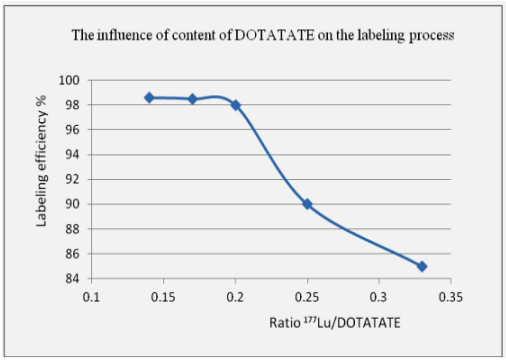


Figure 7: The influence of concentration on the radiolabeling process

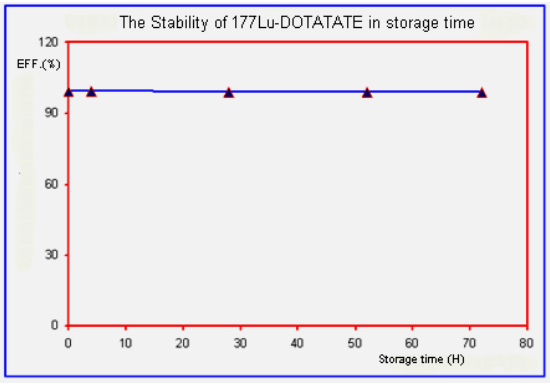


Figure 8: The influence of storage time on the radiolabeling process

III.2.2. Bio-distribution control

Rats are the animals most commonly used for testing of ^{177}Lu -DOTATATE. Using three Rats are studied at each time point.

The animals are weighed before being injected with the radiopharmaceutical and are kept in separate numbered cages. The ^{177}Lu–DOTATATE is prepared by using the lyophilized kit vial to be tested following the instructions enclosed in the kit. Generally, 0.1-0.5 ml of the preparation is injected per animal via the tail vein. The injected activity is calculated by taking the difference between the weight of the loaded syringe and that of the syringe after injection.

At the end time point, the animals are sacrificed and a blood sample is taken by heart puncture. The organs of interest are carefully dissected, rinsed in saline and placed in individual disposable plastic tubes or bags and accurately weighed. The tail, which is the site of injection, is removed and kept separately.

The activity in the organs, tail and carcass is measured either in an isotope dose calibrator or in a NaI(Tl) crystal scintillation counter. The total retained dose (%TRD) is calculated as follows:

$$\%\mathrm{TRD(organ)} = \frac{\mathrm{A}}{\mathrm{B}} \mathrm{x100}$$

where *A* is the activity or counts in the organ, and *B* is the activity or counts in all organs and the carcass except for the tail. To accurately estimate the activity and to account for decay corrections in the ^{99m}Tc activity, standard solutions of the radiophar-maceuticals are prepared.

A typical experiment is given below.

Preparation of standard solution

Draw 0.5 ml of the ^{177}Lu–DOTATATE in a syringe and estimate its weight by weighing the empty syringe and the syringe with solution and calculating the difference. Dispense this ^{177}Lu–DOTATATE solution into a clean 100 ml glass beaker and add 20 ml of distilled water. This solution is taken as the standard for estimation of the total activity that is injected into the animals. The activity retained in the organs is calculated as follows:

$$\%\text{injected activity in the organ} = \frac{\text{Activity obtained in the organ}}{\text{Total activity injected}} \mathrm{x100}$$

If using a NaI(Tl) scintillation counter, the activity retained in the organs

is calculated as:

$$\%\ \text{injected activity in the organ} = \frac{\text{Counts in organ x 100}}{\text{Counts in standard x}(\mathrm{W_i}|\mathrm{W_s})}$$

where *W*i is the weight of injection and *W*s is the weight of the standard. All the

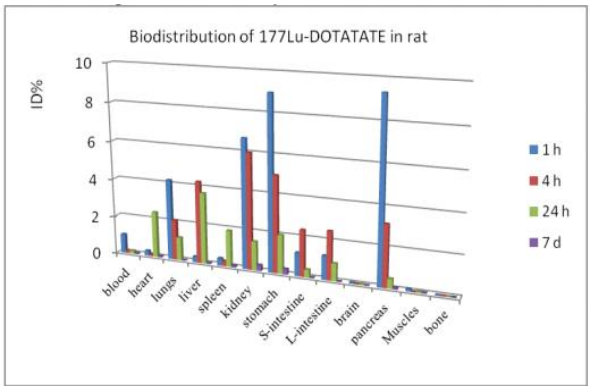
counts are corrected for background activity.

Rabbits scans

To examine the in-vivo retention, white rabbits (7 week-old) were used. The animals were kept individual cages at 20 ± 1^{o}C with a relative humidity of $75 \pm 10\%$ and 12 h light/dark cycle. The amimals were allowed free access to food and water, and left to acclimatize for 1 week. ^{177}Lu–DOTATATE was administered intraven-ously to the rabbit via an ear vein for the image tests such as dynamic kinetics and serial images scan using a gamma camera (SPECT-GE).

The experimental

Seven weeks old white male rabbits (2023.4 ± 100g, n=3), which were anesthe-tized with Ether, were used for imaging studies. Each rabbit was injected with ^{177}Lu-DOTATATE via an ear vein with 111 MBq-/0.5ml. All the rabbit were placed in a posterior position.To confirm the dynamic kenitics of ^{177}Lu-DOTATATE, whole body dynamic images for 4h and some static images at the predeteminated time intervals were obtained using a gamma camera fitted with a low energy all purpose collimator. Window was centered around 208KeV. Images were scanned by system of (GE-SPECT).



Order	Organ	Time after injected (%)			
		1 h	4 h	24 h	7 d
1	Blood	0,94±0,35	0,13±0,05	0,15±0,03	0,04±0,005
2	heart	0,26±0,05	0,083±0,02	0,24±0,06	0,05±0,01
3	lungs	**4,27±0,37**	**2,10±0,17**	**1,14±0,39**	0,023±0,02
4	liver	0,29±0,03	**4,27±0,033**	**3,70±0,54**	0,046±0,01
5	spleen	0,38±0,06	0,26±0,06	**1,90±1,00**	0,10±0,04
6	**kidney**	**6,70±0,60**	**6,05±1,00**	**1,50±0,30**	**0,33±0,07**
7	**stomach**	**9,00±1,00**	**5,12±0,71**	**2,09±0,18**	**0,28±0,077**
8	S. ntestine	1,20±0,30	2,38±0,42	0,41±0,11	0,031±0,01
9	Big intestine	1,23±0,15	2,51±1,20	0,94±0,10	0,13±0,02
10	brain	0,032±0,00	0,028±0,01	0,031±0,01	0,015±0,00
11	**pancreas**	**9,34±3,45**	**3,18±1,31**	**0,50±0,05**	**0,099±0,02**
12	muscle	0,12±0,02	0,10±0,11	0,054±0,01	0,03±0,005
13	bone	0,00±	0,00±	0,00±	0,10±0,05

Figure 9: Biodistribution of ^{177}Lu-DOTATATE in rat

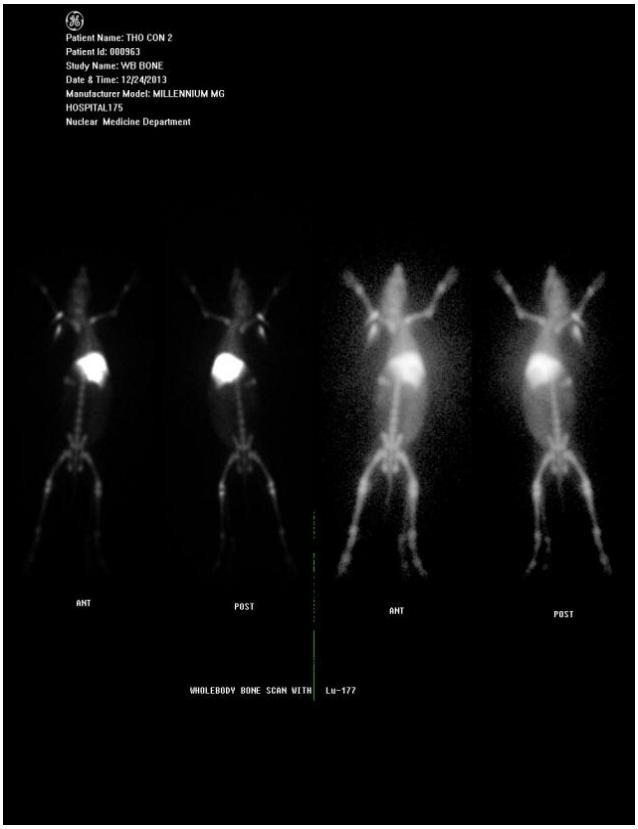


Figure 10: Biodistribution of ^{177}Lu-DOTATATE in rabbit

Comment: ^{177}Lu-DOTATATE was stable than 72 hours after labeling. The results indicate that high labelling yield of ^{177}Lu-DOTATATE was obtained at pH=5 with incubation for 25-30 min at a temperature of 80-90^{o}C. The effect of varying the molar ratio of Lu to DOTATATE is shown in Fig. 7. The stability of the ^{177}Lu-DOTA-Tyr^{3}-octreotate was followed by 3 days, and in procedure, the radiochemical purity was over 99%. Biodistribution studies showed fast blood clearance and the kidneys were the critical organs.

IV. CONCLUSION

Through the study results can be concluded that the Da Lat Nuclear Reactor in can only be prepared with carriers ^{177}Lu using highly enriched target of $^{176}Lu_2O_3$> 64%. In this study, subject developed the production processes and institutional standards, ensuring all quality control criteria of radiopharmaceuticals have met the application requirements.

The radiolabelling procedures for DOTATATE using ^{177}Lu were optimized, and relevant quality control parameters were standardized. According to this labeling procedure, the

radiochemical purity is more than 99%. In vivo biodistribution studies in normal mice revealed that the ^{177}Lu-DOTATATE have suitable pharmacokinetic properties.

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