Determination of Lutetium In Radiopharmaceutical Samples Using High Resolution ICP-AES Technique

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Abstract:

An analytical method was developed for the determination of Lutetium in dilute nitric acid medium using high resolution ICP-AES analytical technique. These studies were required for the determination of Lutetium contents in radiopharmaceutical samples. For the patients suffering from cancers, ^{177}Lu DOTA-TATE peptide receptor radionuclide therapy is used. This necessitates the use of ^{177}Lu and obviously the quantification of Lutetium for its efficient application during medical therapy which is used for the preparation of the patients suffering from cancers. Due to short half life of ^{177}Lu of 6.67 days, it is most likely to get added up with Hf, as it is build up on storage, the undesired impurity element. Hence the effect of Hf on the determination of Lu was studied. Subsequently seven actual samples of ^{177}Lu were analysed for Lu contents after taking into account Hf contribution if any.

Key words : Lutetium, ^{177}Lu, Hafnium, HR- ICP-AES, Radiopharmaceutical samples

Introduction:

Radioisotopes are being used worldwide for their applications in healthcare, industry, agriculture and research fields for many decades. For healthcare applications, the radioisotopes used are for Radiation Oncology (Teletherapy and Brachytherapy) and Nuclear Medicine (NM). NM is a special branch of medicine in which radioisotopes are used in the form of radiopharmaceuticals which are injected inside human body for the diagnostic purposes or for the treatment to cure the disease. Various radiopharmaceuticals are selected in such way that they have short half-life of few days or weeks. They are well examined and established before being used as nuclear medicine. During the process, lot of studies are undertaken till they are being accepted as `radiopharmaceuticals' mainly for it's radiochemical purity and for the determinations of exact concentration as it is used directly

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on human beings for the purpose of cure who are affected due to various health issues. The radiopharmaceuticals being used in India are ^{99m}Tc, ^{131}I, ^{32}P, ^{51}Cr, ^{153}Sm, ^{90}Y and ^{177}Lu for the purpose of diagnosis and treatment for various types of cancers. India is one of the pioneers in the world to use ^{177}Lu for it's therapeutical applications.

To acquire ^{177}Lu by direct method, ^{176}Lu target which is > 76% enriched is irradiated in the reactor. Due to high thermal neutron absorption cross section (2100 barns) of ^{176}Lu, it gives the production of ^{177}Lu with high specific activities (>20 Ci/mg) for receptor based radionuclide therapy using peptides and monoclonal antibodies. At present, the enriched ^{177}Lu target is procured from the international market but efforts are going on to produce this enriched target material using laser induced electromagnetic separation technology in BARC. With increased demand for ^{177}Lu over the years, few countries developed alternate technological methods for producing ^{177}Lu via indirect irradiation methods involving ^{176}Yb targets. Second alternative involves the separation of no-carrier-added (nca) ^{177}Lu, where the specific activities achieved are near to the maximum theoretical specific activity (110 Ci/mg).

Lutetium-177 decays in 76% of events ($E_{\beta(max)}$ = 0.497 MeV) to the stable ground state of ^{177}Hf with a half-life of 6.65 days and decays in 9.7% of events ($E_{\beta(max)}$ = 0.384MeV) and 12% of the time ($E_{\beta(max)}$ = 0.176 MeV) to an excited state of ^{177}Hf that has 0.24967MeV) and 0.32132 MeV above the ground state, which de-excites to the ground state with the photon emission. During these radioactive decay events, ^{177}Lu emits β- particles with an $E_{\beta(max)}$ of decay events, ^{177}Lu emits β- particles with an $E_{\beta(max)}$ of 497 KeV (78.6%), 384KeV (9.1%) and 176KeV(12.2%) and low energy gamma photons [Eγ = 113 KeV (6.6%), 208 KeV (11%)].

During the production of ^{177}Lu by direct route in a reactor, due to continuous irradiation ^{177}Lu absorbs neutrons leading to the formation of $^{177/178}$Hf. The presence of $^{177/178}$Hf (IV) does not affect in the efficiency of ^{177}Lu(III)- labelling reactions, but accumulation of hafnium atoms decreases the specific activity. Also ^{176m}Lu ($T_{1/2}$ = 3.66h) and ^{177m}Lu ($T_{1/2}$ = 160.4 d) are formed from ^{175}Lu and ^{176}Lu. ^{177m}Lu with longer half-life poses problem from radioactivity point of view, hence is needed to be handled accordingly.

^{177}Lu is being used towards the preparation of complex,^{177}Lu DOTA-TATE(1,4,7,10-tetraazacyclodecane-14,7,10-tetraacetic acid coupled Tyr3-Octreotate) which is used for peptide receptor radionuclide therapy to cure patients suffering from various types of cancers. Quantitative determination of Lu becomes highly important for its effective application during medical therapy. ^{177}Lu-labeled radiopharmaceuticals for peptide receptor radionuclide therapy (PRRT) involved administering of 7.4 GBq (200mCi i.e. 22.182 µg of ^{177}Lu) per course for the patient. It is bound to 180 to 300 μg of the peptide with the chelator DOTA, [DOTA0, Tyr3] octreotate[1-4].Technology for producing nca ^{177}Lu has now been developed within BARC, Mumbai and is awaiting regulatory approval for clinical deployment.

Inductively Coupled Plasma – Atomic Emission Spectroscopic technique (ICP-AES) which scores over many techniques has been utilised for the determination of Lu during the present studies. It is well known that ICP-AES being multielemental technique has many advantages, namely, high sensitivity, reproducibility, accuracy, large linear dynamic range, practically no interferences and lower detection limits[5-7]. Due to these benefits, the technique is used in diversified fields including nuclear industry. In literature, some authors have reported the application of ICP-AES for the determination of ^{177}Lu by ICP-AES[8-14]. Jeff D. Vervoot et. al have reported the isotopic composition of Yb and the determination of Lu concentrations and Lu/Hf ratios by isotope dilution using MC-ICPMS in geological samples at sub-ppm levels [15]. ICP-MS can be a better technique provided the instrument is modified suitably for the handling of radioactive Lutetium samples and also should be available at nearby site just after the preparation of ^{177}Lu-DOTA-TATE sample, for analysis.

In our laboratory the commercial Jobin-Yvon ICP-AES instrument which was adapted in-house to glove box facility to analyse the radioactive samples for the determination of trace elements, being available nearby was used for the present studies[16]. Using this unit, we have reported the determinations of lanthanides, trace elements in HLW solutions, irradiated thoria bundle samples, radioactive aqueous dilute nitic samples containing Lu[17-18]. Using CCD based ICP-AES unit, we have reported the determination of trace elements including lanthanides in uranium, zirconium, thorium and lutetium matrices[19-22]. We had initiated and reported the determination of Lutetium by HR ICP-AES[23-24].The present studies were undertaken further on the similar lines and are described in detail here.

It is essential to determine the amounts of Lu in actual radiopharmaceutical samples accurately, as based on these values the final dose level to be administered to the patients was adjusted.The ICP-AES analysis results for Lu and Hf samples, were obtained for the actual samples received just before being transported to be administered for the patients, which were at sub-ppm levels. At such a low level, ^{177}Hf does not compete in the radiolabeling of ^{177}Lu-DOTAtate synthesis. But with higher amounts it does affect. Jose' de Souza Calderia had studied the interference of ^{177}Hf, a decay product of ^{177}Lu in the preparation of ^{177}Lu-DOTAtate. The studies included the built up of ^{177}Hf at various $^{177}Lu_{t1/2}$ values. The molar ratio of Lu-DOTAtate was calculated each day without considering the effect of ^{177}Hf and with consideration of ^{177}Hf built up. The yield was found to be more when ^{177}Hf influence was considered, which implies that ^{177}Hf, a decay product of ^{177}Lu, competes for the formation of the DOTA binding site. The author conclude that, these data will be relevant in the synthesis of the radiopharmaceuticals ^{177}Lu-DOTAtate with high specific activity to be used in peptide receptor radionuclide therapy[24].

Experimental:

Instrumentation

All the experiments were performed using in-house glove box adopted JY Ultima high resolution inductively coupled plasma atomic emission spectrometer, the details of which have been given elsewhere[16].

Reagents and Standard solutions

Individual elemental stock solutions at 1 mg/ml each of Lu and Hf high purity (E-Merck, Darmstadt, Germany) were used for the studies. To prepare 0.5M HNO_3, Suprapur® (E-Merck) HNO_3 and distilled water re-distilled in quartz distillation unit were used. For profiling and for calibrations, 50µg/ml and 20µg/ml each of Lu and Hf were prepared after appropriate dilutions from stock solutions in 0.5M HNO_3.

Method

The determinations of Lu and ^{177}Lu including Hf built up in actual radiopharmaceutical samples were carried out by ICP-AES. In our laboratory, the commercially procured Jobin-Yvon Ultima high resolution inductively coupled plasma – atomic emission spectrometer unit was suitably modified and was adopted to glove box to carry out the analysis of radioactive samples [10]. To be able to identify suitable analytical lines of Lu and Hf, 50 ppm each of individual solutions of Lu and Hf were aspirated into the plasma, while for calibration purposes, 0.5M HNO_3 and 20 ppm each of individual 20 ppm of Lu and Hf were used as low standard and high standard respectively. As the amounts of Lu in actual samples were expected at low levels, the calibration was limited to 20 ppm only and being pre-treated already, were analysed directly as received.

Results and Discussion:

Peak Search and Profile of Spectral Lines of Lu and Hf

For this purpose, 50 ppm of individual Lu and Hf were aspirated through the plasma under standardized plasma operating conditions followed by peak search, auto-attenuation and profile of the lines. For Lu, three analytical lines, viz., 261.542nm, 261.926nm and 264.14nm, while for Hf, 264.141nm and 282.022nm were selected for studies. Taking into account the intensity response (S/N) i.e. sensitivity and free from spectral interferences, the best analytical lines chosen for Lu and Hf were 261.542 nm and 282.022 nm respectively.

Calibration of Lutetium and Hafnium

The calibration curves were obtained using 20 ppm and 0.05 ppm individual solutions of Lu, Hf as high and low standards. In Table-2, intensity values for Lu and Hf were presented. Based on these values, the calibration curves for Lu 261.542 nm and Hf 282.022 nm were obtained and are shown in Fig.1. Detection limits for Lu and Hf were calculated as (x+3σ), where `x' is the concentration equivalent to the average of intensity of blank solution at the specified wavelength and `σ ' is the standard deviation of the blank measurements. The sensitivity was calculated based on the emission counts per concentration which is the slope of the calibration curve. The detection limits for Lu and Hf were 0.02mg/L and 0.07 mg/L respectively which are presented in Table-2 along with sensitivity values.

Study of spectral interference of Hafnium on determination of Lutetium in dilute nitric acid medium

Lu-177 isotope has a half-life of 6.65 days. This on storage builds up Hf in the samples to be used for medical purposes. Hence it was necessary to study the effect of Hf on the determination of Lu. The ICP-AES determination of Lu and Hf was performed using 261.542nm and 282.022nm analytical lines respectively. Though 282.022nm Hf line is wide apart from 261.542nm Lu line, and was not expected to interfere in the determination of Lu in presence of small quantities of Hf, but at higher levels of Hf built up after sufficient decay of ^{177}Lu, it will cause matrix interference on the determination of Lu at sub-ppm, few ppm levels by ICP-AES.

The amounts of Lu and Hf determined by ICP-AES were at sub-ppm levels. At the Lu concentration level of 0.05 µg/ml, the effect of Hf in the range of 0.05 µg/ml to 50 µg/ml was studied and the results are shown in Table – 3. It was found that even at 50 µg/ml level of

Hf, i.e., 1000 times that of the amount of Lu (at 0.05µg/ml), Lu determination was unaffected. One control sample of Lu at 0.65 µg/ml in presence of 16.67 µg/ml of Hf gave exact value of 0.65 µg/ml for Lu, which showed that this method has high accuracy with good precision. At such low levels, no inferences were observed.

Analysis of real life samples by ICP-AES

Seven real life radiopharmaceutical samples were analysed for Lu contents by ICP-AES. For Lu, 261.542 nm analytical line being the most sensitive one, was used for this purpose. The final radiopharmaceutical products were expected to be highly pure with respect to no elemental impurities(non-radioactive) and also free from other radionuclide impurities, so ICP-AES analysis for Lu contents, beyond 50 µg/ml Hf and also for the determination of any other elemental impurities was not performed. These analyses results were obtained based on the requirements of the final product about to be administered to the patients, which were free from impurities but possibility of built up of Hf was expected due to transportation time. The results are shown in Table-4 and were found to be satisfactory with precision better than 2% RSD.

Conclusions:

Using the developed method, it is possible to determine Lu in the range of 0.05-20 µg/ml by ICP-AES technique in presence of up to 50 µg/ml of Hf i.e. 1000 times that of the analyte without any spectral interferences with precision better than 2% RSD. The best emission lines chosen for Lu and Hf were 261.542 nm and 282.022 nm respectively. Subsequently, the analysis of the actual radio-pharmaceutical samples was carried out satisfactorily as was observed from the analysis data of control samples.

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Figure:

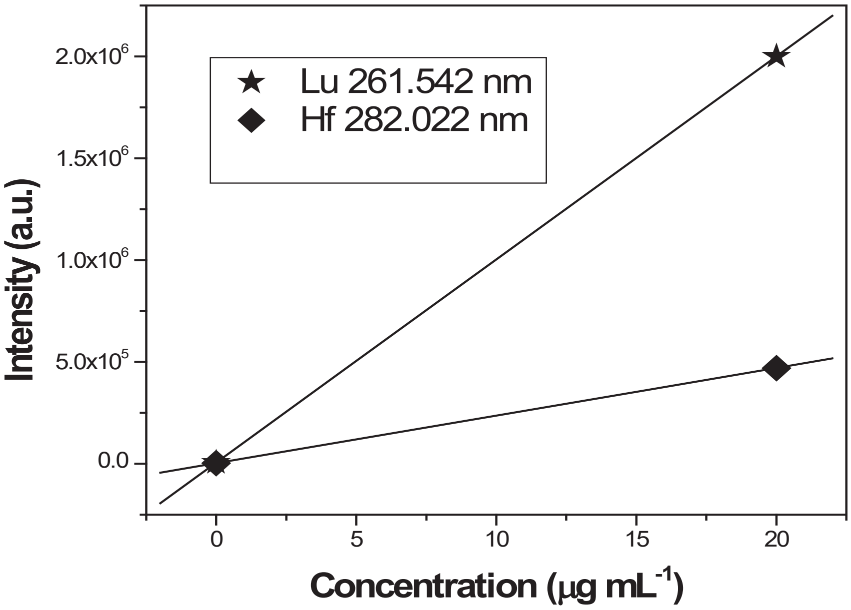

Fig.1 Calibration curves for Lu and Hf
Lu: Slope= 99682; Intercept=6354; Regression coefficient $\chi^2 = 1$
Hf: Slope=23354; Intercept=2907; Regression coefficient $\chi^2 = 1$

Tables:

TABLE 1: Calibration (intensity) data for Lu and Hf

Solution	Lu 261.542nm	Hf 282.022nm
Std Blank (0.5M HNO_3)	6354	2907
Std. 1 (20 ppm Lu)	2044660	-
Std.2 (20 ppm Hf)	-	469642

TABLE 2 Detection limit, sensitivity for Lu and Hf

Element	Detection limit (mg/L)	Sensitivity (counts/mg/L)
Lu 261.542nm	0.02	9.99 x 10^4
Hf 282.022nm	0.07	2.09 x 10^4

TABLE – 3: Effect of Hf on Lu determination

Lu + Hf (µg/ml) Added	**Lu** (µg/ml) Estimated
0.05+0.05	0.04
0.05+0.1	0.04
0.05+1	0.05
0.05+5	0.06
0.05+10	0.05
0.05+50	0.04
0.65+16.67	0.65

TABLE–4 : ICP-AES analysis results for Lu in real samples

Sample	Conc. (µg/ml)
S-1	0.26
S-2	0.13
S-3	0.79
S-4	0.11
S-5	0.18
S-6	0.09
S-7	0.01

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