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Production of No-Carrier Added Lutetium-177 by Irradiation of Enriched Ytterbium-176

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Abstract: Two methods of Lu-177 production are reviewed: irradiation of isotopically enriched Lu-176 (direct way) and irradiation of ytterbium enriched with Yb-176 (indirect way). Based on neutron-physical calculations Lu-177 yield and specific activity were estimated for both methods. Lu-177 specific activity strongly depends on neutron flux density in the direct way, that is 75,000 Ci/g for 10-days irradiation in a neutron flux of $2 \cdot 10^{15} \text{ cm}^{-2} \text{ s}^{-1}$, and only 13,000 Ci/g after 30 days irradiation at neutron flux $1 \cdot 10^{14} \text{ cm}^{-2} \text{ s}^{-1}$. Irradiation of Yb-176 provides Lu-177 specific activity close to theoretical value (110,000 Ci/g). Neutron flux density effect Lu-177 yield, that is 530 Ci/g for $2 \cdot 10^{15} \text{ cm}^{-2} \text{ s}^{-1}$ neutron flux density after 30 days irradiation. A procedure of isolation and purification of Lu-177 from irradiated targets is described based on combination of galvanostatic extraction of ytterbium followed by cation-exchange chromatography from alfa-hydroxyisobutyrate solutions on BioRad AG[®] 50W-X8 resin.

Keywords: High specific activity, Lutetium-177, non-carrier added, purification, reactor production.

INTRODUCTION

The specific activity of lutetium-177 (^{177}Lu) is a key parameter defining application of this important therapeutic radioisotope for radiopharmaceuticals production. To produce high specific activity ^{177}Lu two methods may be used [1, 2]:

- neutron irradiation of the target material containing ^{176}Lu (so-called "direct" method)
- neutron irradiation of the target material containing ytterbium-176 (^{176}Yb , "indirect" method).

The nuclear transformations scheme describing these processes is presented in Fig. (1).

In an ideal case of irradiation of isotopically pure ^{176}Yb containing no admixtures of ^{174}Yb or lutetium, the indirect method provides for production of ^{177}Lu with specific activity equal to the theoretical value ($\sim 110000 \text{ Ci/g}$). In such a case, the ^{177}Lu yield is only a function of the neutron flux density and duration of irradiation. In practice, enriched ^{176}Yb typically contains some amount of ^{174}Yb and lutetium, which may lead to a decrease in specific activity. The extent to which these isotopic impurities affect the product parameters depends on the target material treatment prior to irradiation, the irradiation conditions and the efficiency of further radiochemical processing. From the point of view of further application of ^{177}Lu (i.e. for synthesis of radiopharmaceuticals), one should consider possible competition with the matrix ytterbium, traces of which may be present in the final product.

Therefore, all stages of ^{177}Lu production technology through irradiation of ^{176}Yb should be optimized to provide for the required product quality. The results of our studies are presented in this paper.

^{177}Lu ACCUMULATION IN A NUCLEAR REACTOR

Patterns of ^{177}Lu accumulation in a reactor were initially compared for the "direct" and "indirect" methods by calculation. Modeling of nuclide transmutation was performed using the ORIP_XXI software package [5] including the NKE digital database of nuclear data, module for automated search of nuclide formation chains (ChainFinder), and module for calculation of nuclide formation kinetics (ChainSolver). In computation of transmutation indexes, the non-stationary effect of self-shielding was taken into account. Besides, the absence of the effect of changes in composition of the irradiated material on the characteristics of neutron flux was assumed. It should be noted, reliable data on neutron cross-sections for a number of nuclides (^{175}Yb , ^{177}Yb , etc.) are unavailable, but this does not practically affect the accuracy of calculations due to low activation rate compared to the rate of radioactive decay.

Production of ^{177}Lu from ^{176}Lu

The results of calculations of ^{177}Lu generated from ^{176}Lu for different values of thermal neutron flux density are presented in Fig. (2).

Maximal values of ^{177}Lu specific activity are proportional to the density of thermal neutron flux and are rapidly achieved. After 10-day irradiation of ^{176}Lu with a flux of $2 \times 10^{15} \text{ cm}^{-2} \text{ s}^{-1}$ (such thermal neutron flux is exclusively available in two reactors: HFIR, Oak Ridge, TN, and SM, Dimitrovgrad, Russia), the maximum value of specific activ-

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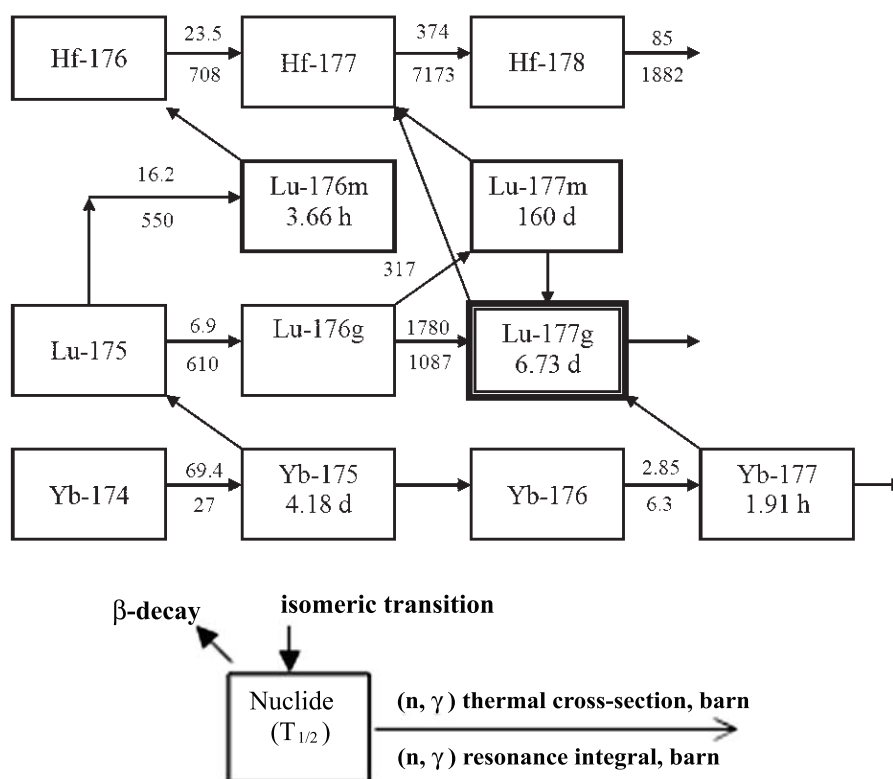


Fig. (1). Scheme of ^{177}Lu production chain (cross-section data taken from [3,4]).

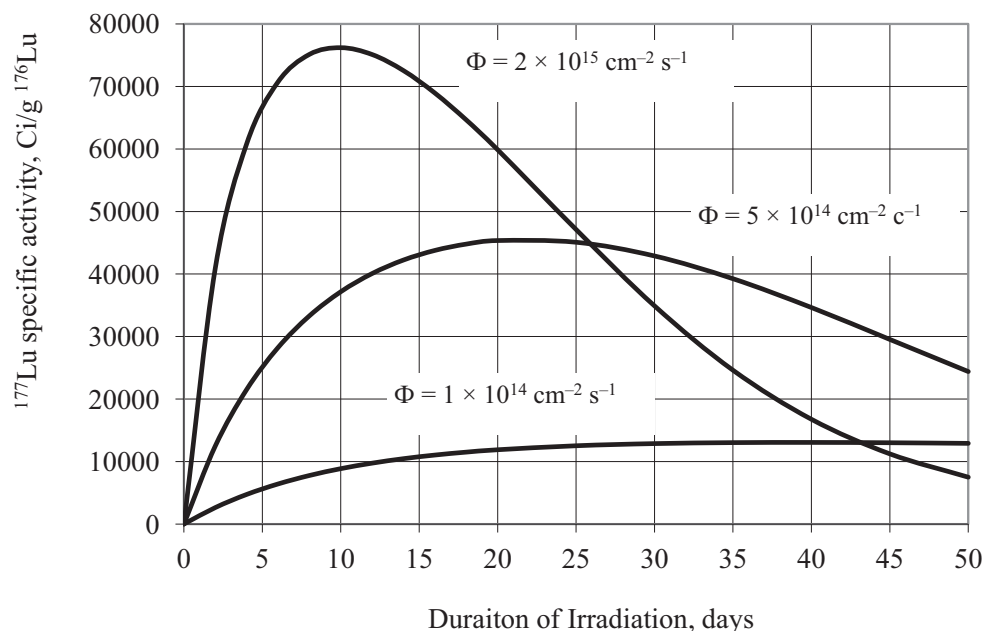


Fig. (2). Specific activity of ^{177}Lu as a function of time of irradiation for different values of thermal neutron flux density (Φ).

ity achieved is 76,000 Ci/g. This corresponds to approximately 70% of the theoretical specific activity of ^{177}Lu (~110,000 Ci/g) and, apparently, is the upper limit for the reactor method of ^{177}Lu produced by the “direct” method.

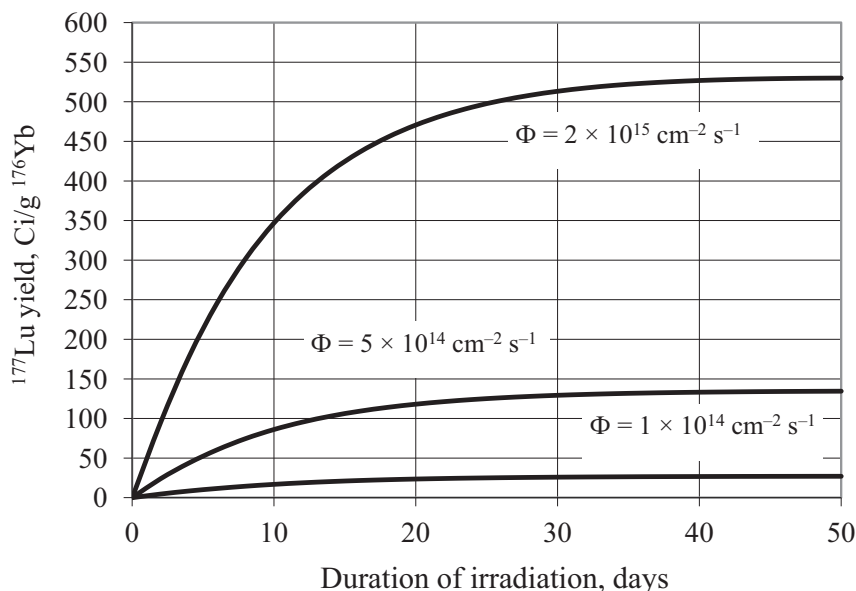
During irradiation, ^{176}Lu intensively burns up, therefore the maximum yield of ^{177}Lu (activity per gram of irradiated material) is reached earlier than the maximum specific activity and is much lower (Table 1). For example, 10-days irradiation at a flux of $2 \times 10^{15} \text{ n cm}^{-2} \text{ s}^{-1}$, yields in ~44,000 Ci

^{177}Lu with specific activity of 76,000 Ci/g Lu. The maximum yield of ^{177}Lu is 55,000 Ci and is reached after 5 days of irradiation, but the corresponding specific activity is somewhat lower, at a value of ~66,000 Ci/g.

The relative amount of the long-lived $^{177\text{m}}\text{Lu}$ isomer is another factor determining the quality of the ^{177}Lu preparation (together with the specific activity). In the range of thermal flux values under consideration (1×10^{14} – $2 \times 10^{15} \text{ cm}^{-2} \text{ s}^{-1}$), the ratio of $^{177\text{m}}\text{Lu}/^{177}\text{Lu}$ activities changes

Table 1. Parameters of ^{177}Lu production upon irradiation of 1 g of ^{176}Lu for different values of thermal neutron flux density.

Thermal Neutron Flux Density, $\text{n cm}^{-2} \text{ s}^{-1}$	Max. ^{177}Lu Specific Activity, Ci/g	Time to max. Specific Activity, Days	Lu Content in a Target after Irradiation, g	Max. ^{177}Lu Yield, Ci	Time to max. Yield, Days	^{177}Lu Specific Activity at max. Yield, Ci/g
1×10^{14}	13 000	40	0,68	10 000	20	12 000
5×10^{14}	45 000	20	0.54	30 000	12	40 000
2×10^{15}	76 000	10	0.58	55 000	5	66 000

Fig. (3). ^{177}Lu yield as a function of duration of ^{176}Yb irradiation for different values of the thermal neutron flux density (Φ).

from 0.03 to 0.01 (the data are valid at the moment when ^{177}Lu maximum specific activity is reached; further irradiation results in a sharp increase in the amount of $^{177\text{m}}\text{Lu}$).

Production of ^{177}Lu from ^{176}Yb

Fig. (3) presents the ^{177}Lu yield (Ci per gram of starting ^{176}Yb) as a function of the duration of irradiation with thermal neutron fluxes of different densities. In contrast to the “direct” method, the dependencies (Fig. 3) have no pronounced maxima over the ranges of irradiation cycle under consideration, which provides for the possibility of variation of the time over the ranges without loss in the ^{177}Lu yield. It is important that neutron flux density determines the ^{177}Lu yield, as well as its specific activity, which is always close to the theoretical value. This allows for a ^{177}Lu production in any reactor, including the low- and intermediate- neutron flux density.

It is important to note that after isolation of ^{177}Lu , the ^{176}Yb target may be recycled and used for repeated irradiation. This substantially increases the efficiency of utilization of the expensive target material. The value of total ^{177}Lu yield upon complete utilization of 1 g of ^{176}Yb may be used as a qualitative measure of the efficiency, taking into account ytterbium repeated irradiation after chemical treatment of an irradiated target.

Let us introduce the following designations:

- y_{max} , ^{177}Lu yield per cycle of irradiation, Ci/g ^{176}Yb ;
- B_{irr} , ^{176}Yb fraction remaining upon a cycle of irradiation, a.u.

The total yield of ^{177}Lu (Y_{max} , Ci) per 1 g of ^{176}Yb should be

$$Y_{\text{max}} = y_{\text{max}} + y_{\text{max}}(B_{\text{irr}}) + y_{\text{max}}(B_{\text{irr}})(B_{\text{irr}}) + \dots + y_{\text{max}}(B_{\text{irr}})^n.$$

Taking into account that $B_{\text{irr}} < 1$,

$$Y_{\text{max}} = y_{\text{max}} \sum_{n=0}^{\infty} (B_{\text{irr}})^n = y_{\text{max}} / (1 - B_{\text{irr}}).$$

Calculated values of ^{177}Lu total yields for different values of thermal neutron flux density are presented in Table 2.

According to the estimations, ^{177}Lu integral yield upon complete utilization of one gram of ^{176}Yb does not depend on the level of neutron flux, but upon numbers of irradiation cycles (increase in the ^{177}Lu yield is “balanced” by the increased rate of ^{176}Yb burning out per cycle).

The specific activity of ^{177}Lu upon production *via* the “indirect” protocol depends on the amount of lutetium in the target material. Calculations demonstrated that even upon irradiation with a high-density neutron flux ($\Phi = 2 \times 10^{15} \text{ cm}^{-2} \text{ s}^{-1}$) as little as $\sim 4.8 \text{ mg}$ ^{177}Lu (0.48% by mass) is generated from 1 g of the target material. Obviously, the presence of stable lutetium isotopes in the target material, even at the levels of several tenth of a mass percent, would lead to a notable decrease in the ^{177}Lu specific activity.

Table 2. ^{177}Lu total yield per 1 g of ^{176}Yb .

Thermal Neutron Flux Density, $\text{cm}^{-2} \text{s}^{-1}$	^{177}Lu Yield Per One Irradiation Cycle, y_{max} , Ci/g ^{176}Yb	^{176}Yb Fraction Remaining upon a Cycle of Irradiation, B_{irr} , a.u.	^{177}Lu Integral Yield (Required Number of Cycles $1/(1 - B_{\text{irr}})$), Ci
1×10^{14}	27	0.99873	~21 000 (790)
5×10^{14}	134	0.99368	~21 000 (160)
2×10^{15}	530	0.97495	~21 000 (40)

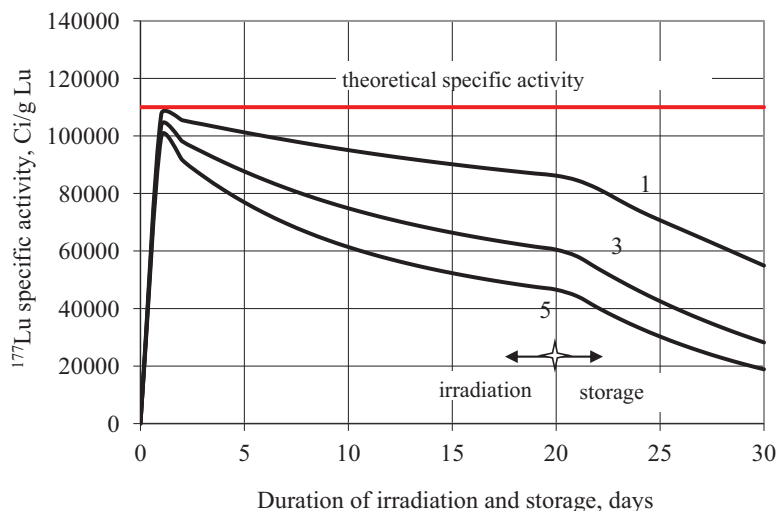
Fig. (4). ^{177}Lu specific activity as a function of duration of irradiation and post-reactor storage (irradiation of the ^{174}Yb and ^{176}Yb mixture with a neutron flux of $\Phi = 2 \times 10^{15} \text{ cm}^{-2} \text{s}^{-1}$) at various content of ^{174}Yb in the target (weight %).

Table 3. Isotope composition of the ytterbium-176 oxide samples, %

Mass number	168	170	171	172	173	174	176
Sample 1	<0.01	0.12	0.58	0.91	0.78	2.47	95.15
Sample 2	<0.02	<0.02	<0.02	<0.05	<0.05	0.13	99.80

An important factor for kinetics of ^{177}Lu specific activity is the presence of a stable isotope of ^{174}Yb in the target material. ^{174}Yb forms stable isotopes of lutetium during irradiation via the $^{174}\text{Yb}(n, \gamma)^{175}\text{Yb}(\beta^-)^{175}\text{Lu}(n, \gamma)^{176}\text{Lu}$ reaction (see Fig. 1). The accumulated short-living ^{175}Yb ($T_{1/2} = 4.18$ days) generates the ^{175}Lu stable isotope after irradiation (until chemical separation of lutetium from ytterbium).

Fig. (4) provides time dependencies of ^{177}Lu specific activity for various compositions of the starting ytterbium isotope mixtures. For the sake of simplicity, the mixture was considered to comprise only two ytterbium isotopes, ^{174}Yb and ^{176}Yb . The curves clearly demonstrate that the problem of the presence of ^{174}Yb plays the defining role in ^{177}Lu production via ^{176}Yb irradiation.

Indeed, when a monoisotopic ^{176}Yb is used, the resulting ^{177}Lu specific activity (equal to the theoretical value) does not change with time and only the total activity changes. The presence of ^{174}Yb in the target mixture and, consequently, the rise of stable isotopes of lutetium during irradiation lead to a completely different kinetics. Specific activity rapidly reaches its maximum, which is somewhat lower than the theoretical one, and then, with the growth of stable ^{175}Lu

content, the specific activity decreases. This means that radiochemical processing of the targets should be performed as soon as possible after end of irradiation.

Experimental Study of Reactor Production of ^{177}Lu

To determine experimentally the presented patterns in ^{177}Lu production, targets of ^{176}Yb were irradiated in one of the peripheral cells of the central neutron trap in the SM-3 reactor.

The parameters of the neutron field used for irradiation (disturbed value) were as follows:

- thermal neutron flux density, $\Phi = 1.65 \times 10^{15} \text{ cm}^{-2} \text{s}^{-1}$;
- epithermal neutron flux density, $\Phi = 1.16 \times 10^{14} \text{ cm}^{-2} \text{s}^{-1}$;
- neutron gas temperature, 475 K.

Two samples of ^{176}Yb -enriched ytterbium oxide significantly different in their enrichment were evaluated. The isotope composition (mass %) of the samples are summarized in Table 3.

After irradiation samples were analyzed using gamma- and mass-spectrometry. The results are presented in Table 4.

Table 4. The results of radiometric and mass spectrometry analysis of the irradiated ytterbium-176 oxide

Starting Material	Sample 1	Sample 2	Sample 2
Effective irradiation time, eff. days	7.60	9.04	8.07
^{177}Lu yield at the end of irradiation, Ci/g Yb	210	229	226
^{177}Lu specific activity at the end of irradiation, kCi/g Lu	94	106	107
^{177}Lu specific activity after radiochemical processing, kCi/g Lu	64	103	106
Total time of storage of irradiated activity and time of radiochemical processing, days	3	5	2

To determine the efficient cross-section of the $^{176}\text{Yb}(n, \gamma)^{177}\text{Yb}(\beta^-)^{177}\text{Lu}$ reaction, neutron physics studies on the conditions of sample irradiation were conducted. The calculations were performed using the MCNP [5] software designed for determination of the space-energy distribution of neutrons, photons, and electrons by means of the Monte Carlo method. In these calculations, the model of the reactor used was specifically elaborated for precision neutron physics calculations. The following results were obtained for the effective cross-sections of the $^{176}\text{Yb}(n, \gamma)^{177}\text{Yb}$ reaction in thermal and epithermal regions of the neutron spectra (taking into account the real geometry of the target sample):

- Maxwell spectrum-averaged thermal cross-section, ~ 1.98 barn;
- Effective resonance integral ($E_n > 0.5$ eV) taking into account self-shielding of the nuclei, ~ 5.6 barn.

Using the values of neutron flux densities and the effective cross-section of the target reaction, ^{177}Lu accumulation kinetics were calculated. The results of the calculations are excellent and agree with the experimental data within the 5% error limit.

RADIOCHEMICAL PROCESSING OF IRRADIATED TARGETS

Depending on the irradiation conditions, content of produced ^{177}Lu falls into range of (0.05–0.30)%. Assuming the ytterbium content in the final product should not exceed 5% of the ^{177}Lu mass, the separation factor of these two elements should be at least 1×10^4 .

One of the most efficient methods of ytterbium and lutetium separation is based on the ability of ytterbium to be reduced to the bivalent state on a mercury cathode in basic solutions in the presence of a chelator [6]. The ytterbium forms an amalgam while lutetium remains in solution.

To evaluate this approach, a pilot unit has been constructed for electrolytic separation of ytterbium from lutetium remotely operated in a “hot” cell (Fig. 5).

The main constructive nodes of the unit are as follows.

- Electrolysis cell (Fig. 5) made of quartz with three cathode current lead platinum wires placed at the bottom. The volume of mercury for electrolysis was 100 mL and the volume of the electrolyte 250 mL. The surface area of mercury and the electrolyte was 95 cm².
- The electrolysis cell cap (Fig. 5) has a platinum wire helical anode installed. A compact electromotor to stir

mercury, laboratory thermometer (or a thermocouple) to control the temperature of the electrolyte, and a sampling tube to collect sample of electrolyte, were also installed on the cap.

The optimal conditions of galvanostatic extraction of ytterbium into mercury cathode were studied using ^{177}Lu and ^{175}Yb as radioactive tracers. Solutions containing 0.10–0.15 mol/L lithium citrate and ytterbium chloride at concentration of 0.4 g/L ytterbium were used as electrolytes. Selected results are presented in Fig. (6). Optimal cathode current density was found to be in the range of 25–40 mA/cm² and under these conditions, the ytterbium isolation coefficient reached $\sim 99\%$ after 3–5 h of electrolysis.

The described unit was used to purify a sample of isotopically enriched ^{176}Yb from a mixture of natural lutetium isotopes. Purified ^{176}Yb was then used as a target material to study features of ^{177}Lu accumulation in the reactor *via* $^{176}\text{Yb}(n, \gamma)^{177}\text{Yb}(\beta^-)^{177}\text{Lu}$ nuclear reaction.



Fig. (5). The prototype unit for separation of ytterbium and lutetium *via* electrolysis on a mercury cathode.

Isolation of ^{177}Lu from Solution after Electrolytic Separation of Ytterbium

After electrolytic removal of ytterbium, lutetium solution containing lithium citrate at a concentration range of 0.10–0.15 mol/L and is characterized by a pH value in the range of

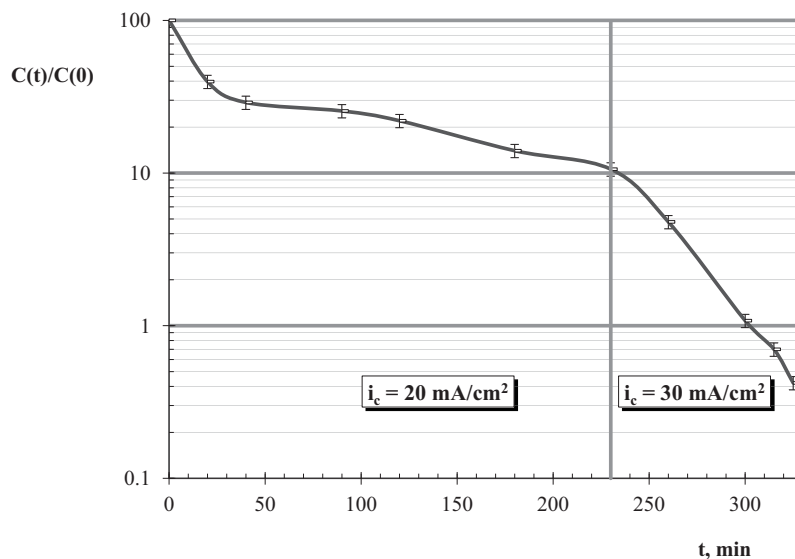


Fig. (6). Changes in ytterbium relative concentration in the electrolyte, $C(t)/C(0)$, %, in the process of electrolysis. Electrolyte composition: 0.15 mol/L Li_3Cit ; $C(0) = 0.4$ mg/mL.

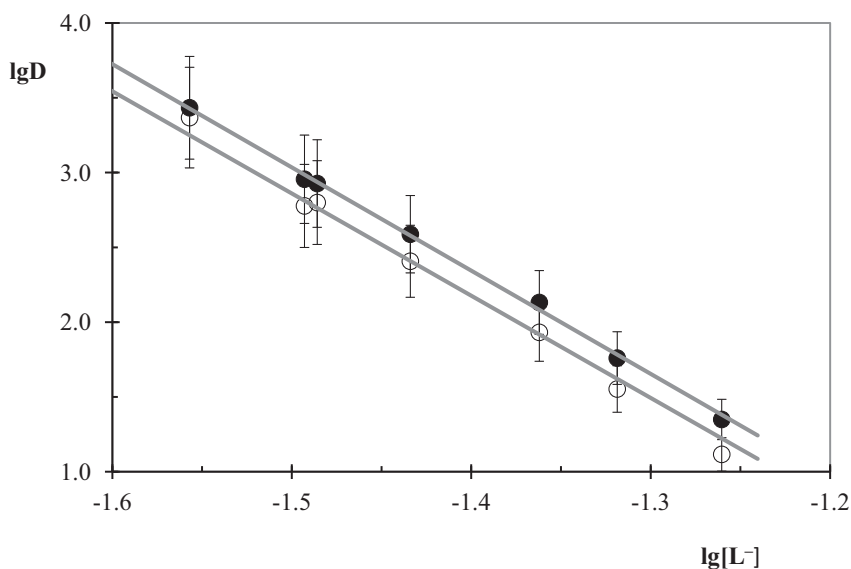


Fig. (7). Distribution of Yb (●) and Lu (○) on BioRad AG[®]50Wx8 from $(\alpha\text{-HIB})\text{NH}_4$ solution as a function of the free $\alpha\text{-HIB}$ anion concentration (L^- , mol/L).

$5 \leq \text{pH} \leq 7$. To concentrate ^{177}Lu in the form of citrate and purify it from the components of electrolyte *via* chromatography, a strongly acidic sulfocationite BioRad AG[®]50W-X8 was used. In the case of electrolyte pH value ranging within $1 \leq \text{pH} \leq 2$, the effect of citric acid on sorption behavior of lutetium is insignificant and it is readily adsorbed on the cationic column. The following subsequent washing of the column with solution of nitric and hydrochloric acids at concentrations of 0.1, and then 1.0 mol/L provided removal of electrolyte solution together with the admixtures of alkaline and alkaline earth metals. To elute lutetium solutions of mineral acids at concentrations of (4–6) mol/L may be used.

Chromatographic Purification of ^{177}Lu

Electrolysis on a mercury cathode provides for initial separation of the major fraction (~99%) of the target element, which allows for utilization of a wide spectrum of

methods for subsequent further purification of ^{177}Lu since masses of the components to separate remain comparable. One of the efficient methods is the cationic exchange chromatography in the presence of chelating agents. The method is widely used for separation of rare earth elements (REE). It is well known that the most successful separation of the neighboring REE, in particular, Yb–Lu, is achieved on styrol-divinylbenzene sulfocationites using salts of α -hydroxyisobutyric ($\alpha\text{-HIB}$) acid as eluent, providing a separation factor 1,4 for tracer amounts of Yb and Lu [7].

The possibility of chromatographic separation of ytterbium and lutetium on the BioRad AG[®]50W-X8 resin has been experimentally studied. The distribution ratio of ytterbium and lutetium, determined in batch experiments, are presented in Fig. (7). Based on these results, the lutetium distribution ratio was calculated as a function of $\alpha\text{-HIB}$ concentration and pH of the solution (Fig. 8).

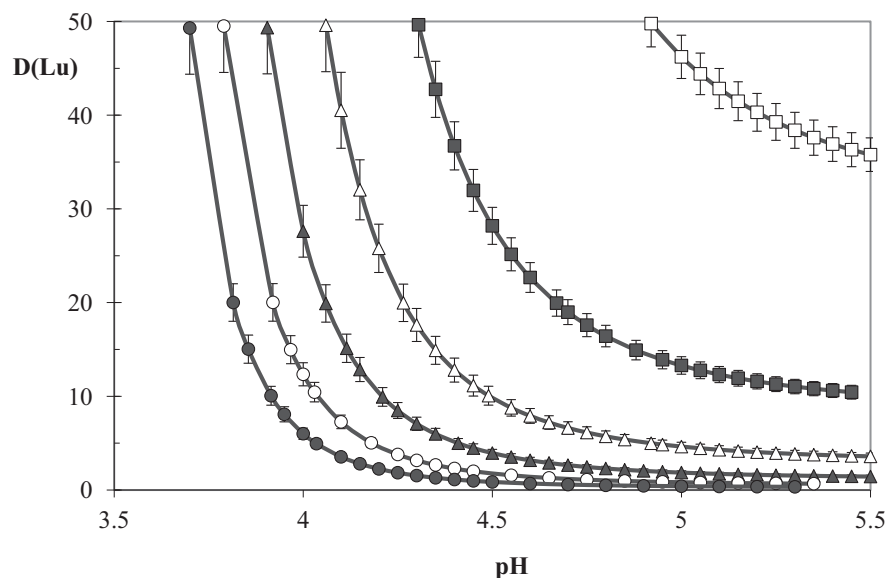


Fig. (8). Calculated distribution ratio of lutetium on BioRad AG[®]50Wx8 as a function of α -HIB analytical concentration (C_a) and pH. C_a , mol/L: \square – 0.05; \blacksquare – 0.06; \triangle – 0.07; \blacktriangle – 0.08; \circ – 0.09; \bullet – 0.10.

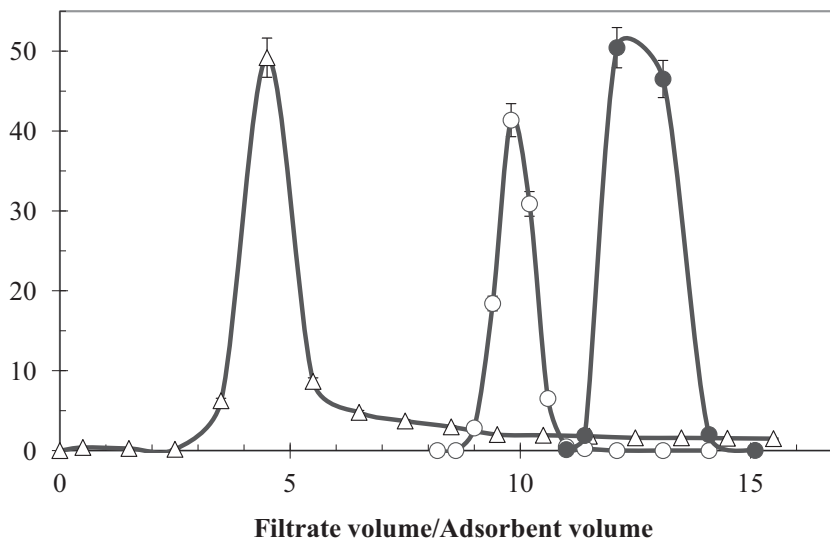


Fig. (9). Elution curves of tracer amounts of hafnium (Δ), lutetium (\circ), and ytterbium (\bullet) from the BioRad AG[®]50Wx8 with 0.057 mol/L solution of α -HIB, pH 5.0.

The dependencies presented in Fig. (8) allow for selection of α -HIB analytical concentration and pH of the solution providing for the required coefficient of distribution of lutetium. From the practical point of view, elution of the first of the separated components is reasonable under conditions when its distribution ratio has values in the range of 10–20. To perform chromatography experiments, we chose the combination of values $C_a = 0.057$ mol/L and pH 5.0. Calculated values of equilibrium coefficient of distribution and separation of elements under the conditions were as the follows:

$$D(\text{Lu}) = 18; D(\text{Yb}) = 27; \alpha(\text{Yb/Lu}) = 1.50.$$

The resulting elution curves of tracer amounts of lutetium, ytterbium, and hafnium under the chosen conditions are presented in Fig. (9). Values of dynamic coefficients of

distribution and separation calculated basing on the curves were

$$D_{\text{dyn}}(\text{Hf}) = 9; D_{\text{dyn}}(\text{Lu}) = 16; D_{\text{dyn}}(\text{Yb}) = 21; \alpha_{\text{dyn}}(\text{Lu/Hf}) = 1.77; \alpha_{\text{dyn}}(\text{Yb/Lu}) = 1.31.$$

Experimental values of dynamic distribution ratio and separation of lutetium and ytterbium turned out to be lower than the relevant equilibrium values. The separation resulted in a fraction of filtrate containing 98.5% of the initial quantity of lutetium. The coefficient of lutetium purification from hafnium was ~ 20 and from ytterbium, 5×10^3 . As follows from Fig. (9), somewhat low coefficient of lutetium purification from hafnium is caused by the broadening of the back of the peak of hafnium elution.

It has been demonstrated in [2], that increased content of ytterbium in the mixture (10 to 200 μg) leads to decreased

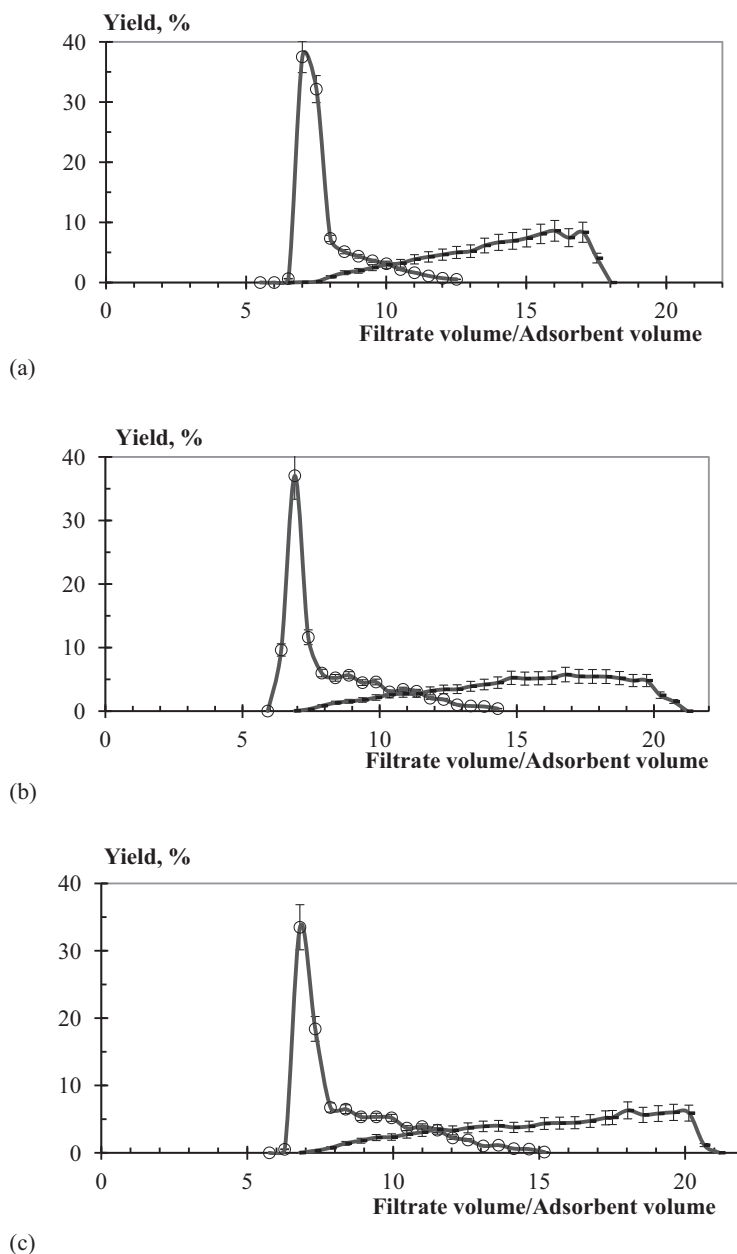


Fig. (10). Elution curves of lutetium (○) and ytterbium (●) from the BioRad AG[®] 50Wx8 cationite with 0.07 mol/L α -HIB solution (pH 5.0). Ytterbium mass, mg: 4.7 (a); 8.3 (b); 9.8 (c).

efficiency of purification of lutetium from ytterbium. To evaluate the effect of ytterbium mass on efficiency of its separation from lutetium, we have carried out experiments on separation of indicator amounts of lutetium from 5 to 10 mg ytterbium. The separation was performed on a column filled with 1.5 cm³ adsorbent volume; height of adsorbent layer was 22 cm, filtration rate 1.0 cm/min. A solution of 0.07 mol/L (α -HIB)NH₄ at pH 5.0 was used as eluent. The experiment demonstrated that approximately 90% lutetium is eluted with the purification factor of ytterbium of about 10³. The results of the experiments on separation of lutetium (microcomponent) from ytterbium (macrocomponent) are presented in Fig. (10).

Elution curves presented in Fig. (10) demonstrate the considerable decrease in the quality of separation of the Lu–

Yb mixtures upon increase in ytterbium content therein. For example, under the investigated conditions, as little as 50% of the initial amount of lutetium may be isolated with coefficient of purification from ytterbium of $\sim 10^3$. Depending on desired radionuclide yield, purification factors vary. For example, for the yield of 70%, purification factor from ytterbium are 470 (4.7 mg Yb), 30 (8.3 mg Yb), and 17 (9.8 mg Yb).

Isolation of ¹⁷⁷Lu from α -HIB Solutions after Separation from Ytterbium

Solutions obtained after chromatographic separation of ytterbium, contain (α -HIB)NH₄ at concentrations of (0.06–0.07) mol/L and pH 5.0. A BioRad AG[®] 50W-X8 was used

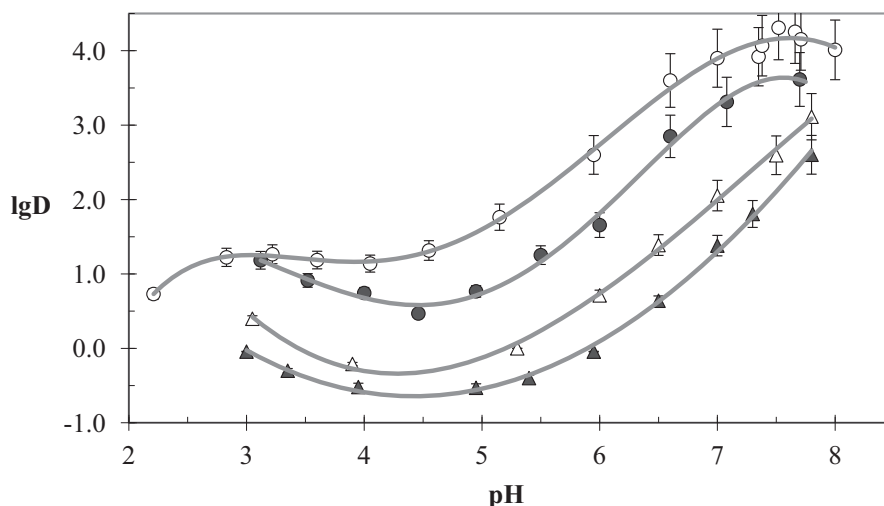


Fig. (11). Equilibrium distribution ratio of lutetium between the Chelex®100 resin and α -HIB solution as function of its analytical concentration (C_a) and pH. C_a , mol/L: \circ – 0.0057; \bullet – 0.10; Δ – 0.20; \blacktriangle – 0.30.

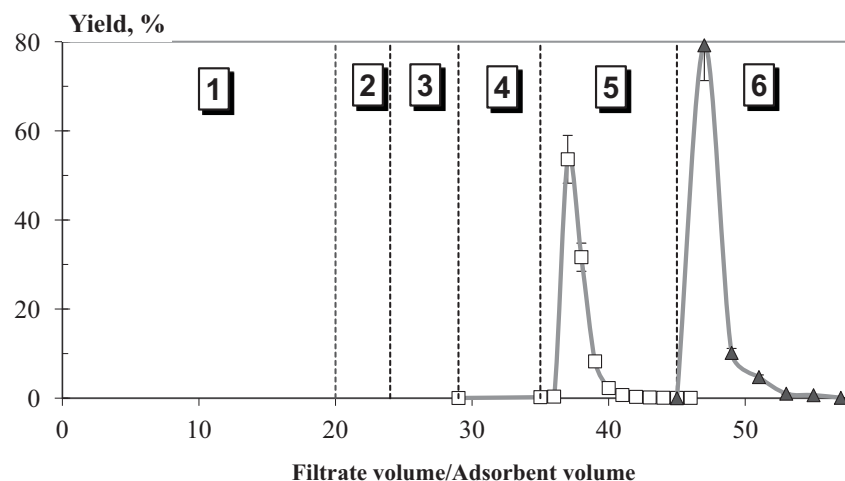


Fig. (12). Chromatographic concentrating and separation of tracer amounts of ^{177}Lu (\square) and ^{55}Fe (\blacktriangle) on the Chelex®100 resin. Column: adsorbent volume, 1 cm³; adsorbent layer height, 6 cm; filtration rate, 1.0 cm/min. Stages of the process: **1** – adsorption from solution of 0.20 mol/L α -HIB (pH 8.0); **2, 4** – washing with water; **3** – washing with 1 mol/L CH_3COOH ; **5** – elution of ^{177}Lu with 0.05 mol/L HCl ; and **6** – elution of ^{55}Fe with 2 mol/L HNO_3 .

as an adsorbent and Chelex®100 as a chelating resin. Chromatographic behavior of ^{177}Lu on these adsorbents was studied as function of acidity of the aqueous phase and the corresponding $(\alpha\text{-HIB})\text{NH}_4$ concentration.

The strongly acidic BioRad AG®50W-X8 cation exchange resin was found to be suitable for chromatographic concentrating of ^{177}Lu from α -HIB solutions and purification of the radionuclide from the eluent components. The conditions of separation are the same as the conditions for ^{177}Lu isolation from citric acid solutions. The disadvantage of the method of ^{177}Lu isolation from α -HIB solutions is the use of high concentration mineral acids for elution of the radionuclide, which leads to the necessity of removal of excessive acid (typically, by means of evaporation) prior to further radiochemical processing. Besides, use of this adsorbent does not allow for separation of the desired radionuclide from the admixture of iron due to low differences in the coefficients of distribution of the three-valence REE ions and iron (III) on strongly acidic sulfocationites.

The distribution ratio of lutetium on the Chelex®100 resin as a function of solution composition are presented in Fig. (11). As follows from the data, lutetium is efficiently adsorbed on the resin at α -HIB solution acidity values of $7 \leq \text{pH} \leq 8$. Use of the Chelex®100 amphotite allows for simultaneous concentrating of lutetium from its solutions in α -HIB solution and purification from iron admixtures. Another advantage of the adsorbent is the possibility of lutetium elution with mineral acid solutions of (0.05–0.10) mol/L.

The example of utilization of the Chelex®100 resin for isolation of ^{177}Lu from its solution in α -HIB, desalting of the desired radionuclide, and its purification from admixtures of iron (III) is presented in Fig. (12).

^{177}Lu QUALITY SPECIFICATIONS

Major specifications for a quality product of Lu-177 include activity, radionuclide impurities content, and specific activity. The first parameter is determined with standard

Table 5. Detection limits of radioactive impurities in the ^{177}Lu preparation.

Radionuclide	Relative Content of Impurity (by Activity), %
Lu-177m	$\leq 1.0 \times 10^{-2}$
Yb-175	$\leq 4.8 \times 10^{-3}$
Yb-169	$\leq 6.0 \times 10^{-3}$
Tb-160	$\leq 5.0 \times 10^{-4}$
Eu-152	$\leq 3.0 \times 10^{-4}$
Eu-154	$\leq 2.0 \times 10^{-4}$
Co-60	$\leq 1.0 \times 10^{-4}$
Co-58	$\leq 1.0 \times 10^{-4}$
Zn-65	$\leq 1.0 \times 10^{-4}$
Mn-54	$\leq 1.0 \times 10^{-4}$
Fe-59	$\leq 1.0 \times 10^{-4}$
Cr-51	$\leq 5.0 \times 10^{-4}$

gamma spectrometry protocols. To determine the specific activity of ^{177}Lu we used mass spectrometry.

Gamma Spectrometry

Two types of detectors were used for gamma spectrometry. The high purity germanium detector was used for the energy range of 1–400 keV (energy resolution of the detector at the 59.5 keV line is 0.7 keV). For higher-energy gamma rays, spectrometer equipped with Ge(Li) detector with energy resolution 4 keV at the 1332 keV line was used. The detection limits of radioactive impurities are presented in Table 5.

Determination of ^{177}Lu Specific Activity by Mass Spectrometry

Determination of component concentration in ytterbium and lutetium solutions was performed by isotope dilution

mass spectrometry. Standard solutions of lutetium and ytterbium of natural isotopic composition were used as isotope labels. Rare earth elements have relatively low values of ionization energy, therefore produce high yield of ions in the thermal ionization ion source used in the work. Ion currents were registered on MI-1201 mass spectrometer. Rhenium metal foil, 3- μm thick, was used as an ionizer and tungsten foil, 4- μm thick, as an evaporator. To enhance the ion current in the registration system, VEU-2A multipliers with multiplication coefficient of at least 10^5 were used.

The effect of the evaporator temperature on intensity and stability of ion currents for Me^+ , MeO^+ , and MeO^{2+} , was studied for various inorganic (nitrates, chlorides) compounds of lutetium and ytterbium of natural isotope composition. The experiments were performed in the concentration range of 1 to 1000 mg/L of metal analyzed.

The optimal concentration for analysis of the elements in solution was found to be 10–100 mg/L, with mass spectrometer sensitivity to lutetium approximately 10 times higher than for ytterbium. Optimal evaporator loading is ~ 100 ng of ytterbium and ~ 10 ng of lutetium. The sensitivity for ytterbium was ~ 10 ng, and for lutetium, ~ 1 ng. The correctness of the lutetium and ytterbium isotope composition was verified by comparison of measurement results with the known literature data. It was found that the relative error of the isotope composition determination for the elements did not exceed 1%.

The presence of ^{176}Lu and ^{176}Yb isobars may considerably complicate the analysis in the case of simultaneous presence of lutetium and ytterbium isotopes in the sample. To find the conditions excluding their mutual effect in the course of analysis, artificial Yb and Lu mixtures with mass ratios varying in the range from 1 : 100 to 100 : 1 were studied. Intensities of element ions current as function of evaporator heating current are presented in Fig. (19). As follows from the figure, at evaporator current of (3.5–3.6) A, a mass spectrum of practically pure Lu may be registered. The behavior of ion currents of ytterbium and lutetium chlorides was found to be similar to that of nitrates.

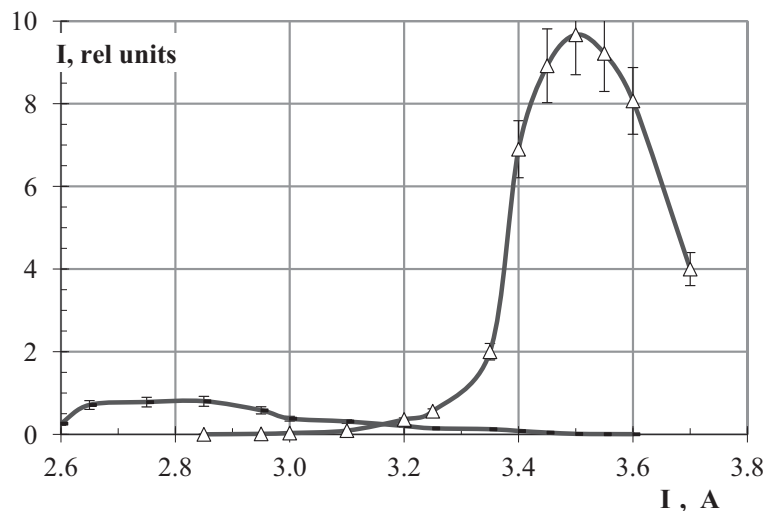
**Fig. (13).** Intensities of ytterbium (\blacktriangle) and lutetium (\triangle) ion currents in function of evaporator heating current (I_{ev}).

Table 6. Typical parameters of the ^{177}Lu produced from ^{176}Yb .

No.	Parameter	Certified Value
1	Chemical form	Lutetium chloride
2	Solvent	HCl, 0.1 mol/L
3	Batch activity, Ci	10–20 Ci (calibrated at delivery date)
4	Bulk activity, Ci/mL	5–10
5	^{177}Lu specific activity, kCi/g	80–90
6	$^{175}\text{Lu}/^{177}\text{Lu}$ ratio	<0.01
7	Radioactive impurities content, %	<0.001

As a result of ^{177}Lu beta decay, a stable isotope of ^{177}Hf is generated, which is an isobar with respect to the parent ^{177}Lu . The experiments on the effect of hafnium on the correctness of lutetium isotope composition determination were also performed. The presence of hafnium in lutetium preparations at mass ratio of $\text{Hf/Lu} \leq 100$ was found to produce no considerable effect on the results of lutetium isotope composition analysis.

In the course of isotope dilution, concentration of the measured component was preliminarily evaluated in the solution to be analyzed. Mixing of aliquots of the analyzed sample and the standard solution was performed in such a way that the component mass ratio would be 0.2–5. Calculation of the concentration of measured component in the preparation was performed using the obtained mass spectra of the analyzed sample and the prepared isotope mixture and the following formula:

$$X = \frac{\left(m \cdot \frac{C_{i/j} - B_{i/j}}{1 - A_{j/i} \cdot C_{i/j}} \cdot \frac{\sum M_j \cdot A_{j/i}}{\sum M_j \cdot B_{i/j}} \right)}{V_{al}},$$

where X is metal concentration in the sample, g/mL;

V_{al} , volume of the aliquot of analyzed sample, mL;

m , mass of the metal in standard solution of isotope label, g;

$A_{j/i}$, ratio between the isotope j and isotope i content in the sample;

$B_{i/j}$, ratio between the isotope j and isotope i content in the isotope label;

$C_{i/j}$, ratio between the isotope j and isotope i content in the isotope mixture of the sample and standard solution;

M_j, M_i , atomic masses of isotopes j and i .

Specific and bulk activity of the ^{177}Lu were determined from the data on isotope composition. The characteristics of the preparation were calculated according to the formula:

$$A_{sp} = A_{sp}^{theor} * q$$

and

$$A_v = A_{sp} X$$

where A_{sp} is the specific activity of the preparation, Bq/g;

A_{sp}^{theor} , theoretical specific activity of ^{177}Lu , Bq/g;

q , mass fraction of ^{177}Lu in the preparation;

A_v , bulk activity of the preparation, Bq/mL.

SUMMARY

The method of ^{177}Lu production by irradiation of isotopically-enriched ^{176}Yb was elaborated in the JSC State Research Center Research Institute of Atomic Reactors beginning in 2007. The performance capabilities of the described stages of radiochemical processing has been demonstrated in production of over 50 batches of the product used for radiopharmaceutical synthesis. Typical parameters of the product are presented in Table 6.

The product was supplied to customers as a radiochemical product used for production of radiopharmaceuticals after additional purification at special facilities, so no additional requirements to non-radioactive impurities content were applied. Obviously, these parameters are defined by purification procedure/conditions used at radiopharmaceutical plant.

It should be noted that the developed technology is not tied to a specific reactor. It may be used successfully for processing of targets irradiated in reactors with medium level of neutron flux density. Decrease in the yield of ^{177}Lu upon utilization of such reactors may be easily compensated by the increase in the mass of ytterbium irradiated. In this case, the technology of irradiated target processing should be adapted to the changing mass of the irradiated material. The changes in the technology touch upon the first stage of the processing, that is, electrochemical isolation of ytterbium. Also, the influence of mass of separated components on the efficiency of chromatographic methods of separation should be taken into account.

Also, the possibility (and feasibility) of the target material recycling should be emphasized. This would decrease the production expenses that may be extremely high due to the need for significant amount of expensive ytterbium-176 target material. The recycling procedure used at this work (galvanostatic extraction of Yb followed by ion-exchange chromatography) were applied to several batches of used (irradiated and processed) ytterbium after long-term storage. These

results have demonstrated technical possibility of the approach and will be reported separately.

Obviously, the choice between the direct and indirect methods of production should be made based upon the balance between the requirements to final product which include its specific activity and the allowed production costs.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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