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Radiochemical separation of no-carrier-added ^{177}Lu as produced via the ^{176}Yb(n,γ)^{177}Yb$\rightarrow^{177}$Lu process

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Abstract

The ^{176}Yb(n,γ)^{177}Yb–$\beta^-\rightarrow^{177}$Lu process was investigated to provide no-carrier-added (nca) ^{177}Lu. The radiochemical separation of the ^{177}Lu from the macro-amounts of the ytterbium target based on the cementation process, i.e. the selective extraction of Yb by Na(Hg) amalgam from Cl^-/CH_3COO^- electrolytes, followed by a final cation exchange purification. The cementation separation process provides a decontamination factor of Yb(III) of 10^4, the cation exchange purification adding a decontamination factor of $>10^2$. The nca ^{177}Lu is available in radiochemically pure form despite the chemical similarity of the lanthanides with $75 \pm 5\%$ overall separation yield within 4–5 h. It can be used to synthesise nca ^{177}Lu labelled radiotherapeuticals. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: ^{177}Lu; Endoradiotherapy; Specific activity; Cementation

1. Introduction

The β^- emitter ^{177}Lu is a promising therapeutic radioisotope for the curative treatment of cancer using labelled proteins (Schlomm et al., 1991; Mulligan et al., 1995) or peptides (Erion et al., 1999; Bugaj et al., 1999). It has a half-life of $T_{1/2} = 6.71$ days and maximum and average β^- energies of 421 and 133 keV, resulting in a short range of radiation in tissue. The decay is accompanied by the emission of low energy γ-radiation with $E_\gamma = 208.3$ keV (11.0%) and 113 keV (6.4%) suitable for simultaneous imaging. Moreover, ^{177}Lu attracted a special interest because of the very high cross-section of 2100 barn of the ^{176}Lu(n, γ) ^{177}Lu production process. ^{177}Lu thus can be produced at nuclear reactors with high yield and high specific activity. Irradiation of 100 mg of ^{nat}Lu at reactors providing 10^{14} n cm^{-2} s^{-1} for 100 h yields specific activities of 1.15 GBq/μmol, which can be increased by a factor of 36 in the case of 95% isotopically enriched ^{176}Lu. Nevertheless, a minimum amount of stable ^{176}Lu cannot be avoided and might cause some problems concerning the labelling of tumor affine biomolecules, in particular monoclonal antibodies, fragments or small peptides. These specific activities determine the upper limit of the correspondingly ^{177}Lu labelled radio-

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therapeuticals. However, the required specific activity needs to be evaluated individually. To investigate these parameters, a no-carrier-added (nca) ^{177}Lu seems to be useful, providing the maximum specific activity of 720 GBq/μmol ($1.0994 \cdot 10^5$ Ci/g).

For this purpose, an alternative production route of this isotope, namely the $^{176}\mathrm{Yb}(n,\gamma)^{177}\mathrm{Yb}\,(T_{1/2} = 1.9\,\mathrm{h}){-}\beta^{-}{\rightarrow}^{177}\mathrm{Lu}$ process was investigated, providing a nca state of ^{177}Lu. It was the aim of this work to develop an efficient separation of nca ^{177}Lu from macroscopic amounts of the ytterbium target material despite the chemical similarity of these neighboured lanthanides. Recently, Lahiri et al. (1998) proposed an extraction technique using 1% HDEHP in cyclohexane to isolate nca lutetium isotopes from macroscopic ytterbium targets as produced in Yb(p,xn)- or Yb(p,pxn)Lu-reactions. They claim that 30% of the nca radiolutetium are extracted already in a first step from 1 N HCl solutions without any trace of ytterbium.

In the present work a Na(Hg) cementation process was investigated. The separation of the nca ^{177}Lu from the macro-amounts of the ytterbium target based on the cementation process, i.e. the selective extraction of Yb by Na(Hg) amalgam from Cl^-/CH_3COO^- electrolytes, followed by a final cation exchange purification. The basic principles of the separation of nca radionuclides of rare earth metals from macro-amounts of the target materials using the cementation process have been described by Marsh (1942, 1943), Novgorodov et al. (1966, 1968), Nguen et al. (1985), Denzler et al. (1997) and others.

Experiments were done to optimise the experimental parameters such as the sodium content of the amalgam, the concentration of the electrolyte anions, the pH of the solutions, the volumes of both the Na(Hg) and the electrolyte solution, the period per cementation and the number of the successive cementations. Further experimental details have been published in a work on the chemically similar separation of nca ^{147}Gd from macroscopic samarium targets, cf. Denzler et al. (1997).

2. Materials and methods

2.1. Materials

Natural Yb_2O_3 of high chemical purity (99.999%) was supplied by Alfa, Johnson Matthey GmbH. In the case of an isotopically enriched ^{176}Yb, the isotopic composition was 0.0034% ^{168}Yb, 0.114% ^{170}Yb, 0.634% ^{171}Yb, 1.157% ^{172}Yb, 1.014% ^{173}Yb, 2.355% ^{174}Yb and 94.72% ^{176}Yb. Hg, Na, α-hydroxyisobutyric acid (α-HIB) and acetic acid (p.a.) were purchased from Merck, Darmstadt. Pt foil and Pt wire were obtained from ChemPar, Karlsruhe. Aminex A6 was obtained from Bio-Rad, Hercules.

2.2. Irradiations

^{177}Lu was produced in a neutron capture reaction on natural ytterbium (12.7% ^{176}Yb, 31.8% ^{174}Yb, 0.13% ^{174}Yb). 200 mg ytterbium oxide Yb_2O_3 of high chemical purity (99.999%) were irradiated for 6 h at the TRIGA II reactor Mainz at a neutron flux of 2×10^{12} cm^{-2} s^{-1}. In another irradiation, 12.4 mg of 94.72% enriched ^{176}Yb in the form of $^{176}Yb_2O_3$ were irradiated for 2 days at the HMI neutron source BERII at 2×10^{14} n cm^{-2} s^{-1}, resulting in 8.1 GBq ^{177}Lu at one day after EOB.

2.3. Preparation of sodium amalgam

Sodium amalgam was prepared via electrolysis of a 20% solution of NaOH, with mercury as cathode and a 25 cm^2 Pt-foil as anode (10 V). The Hg(Na) was washed with water and ethanol. As at lower pH, the amalgam starts decomposing, a higher Na content is needed. In a slightly neutral medium the lanthanides begin to precipitate as hydroxides, which prevents their transfer to the amalgam. The amount of sodium in the amalgam was determined by decomposition of 1 ml of the amalgam with 1 ml of 4 M HCl, followed by titration with 0.1 M NaOH.

2.4. Cementation

The optimum conditions for this separation technique are as follows: 200 mg Yb_2O_3 were dissolved in 1.4 ml 4 M HCl. Next, 3 ml 4.5 M CH_3COONa and H_2O were added to a total volume of 6 ml of pH ≈3.4. This solution is transferred into a special stirring vessel. 4 ml of Na(Hg) amalgam (0.4% Na) were added and this system is stirred for 90 s. The amalgam is removed from the system. Preparatory to the next cementation, 0.2 ml 8 M CH_3COOH were added in order to keep the pH at 3.4. The period of each of the following cementation cycles is increased by 30 s.

2.5. Purification

Finally, ^{177}Lu must be purified from the amount of Yb(III) remaining (< 30 μg) using cation exchange chromatography. The nca ^{177}Lu is co-precipitated as La/^{177}Lu, Yb/$(OH)_3$. After centrifugation to remove the possible mercury compounds Hg_xCl_y the hydroxides were dissolved in 0.1 M HCl. From this solution, the lanthanides are absorbed on the head of an Aminex A6 column (2.0 × 80 mm). After the resin is brought to the NH_4^+-form, ^{177}Lu is eluted using 0.07 M α-HIB, pH 4.7.

2.6. *Activity measurements*

Fractions were collected in 0.03 ml volumes and analysed via γ-ray spectrometry on a calibrated HPGe detector. For ^{177}Lu, the photo peaks at $E_\gamma = 208.3$ keV (11.0%) and 113 keV (6.4%) were used. To analyse the distribution of ytterbium, ^{175}Yb ($T_{1/2}$ = 4.2 d) was used as formed in the neutron capture of ^{174}Yb.

3. Experiments and results

3.1. *Cementation*

After a total of four of these cementation cycles, about 99% of the ytterbium were removed from the aqueous solution. The nca ^{177}Lu is isolated from this solution by precipitation as the hydroxide using 4 M NaOH. The hydroxide is isolated by centrifugation and dissolved in 2.5 ml 0.1 M HCl. After adding of 2.5 ml 4.5 M CH_3COONa, another four cementations with 3 ml of Na(Hg) each are performed in a new vessel. After this procedure, the amount of Yb(III) is reduced to about 0.01–0.02% of the initial mass, cf. Fig. 1, while about 85 ± 5% of the nca ^{177}Lu are remaining in the solution.

3.2. *Purification*

The ^{177}Lu was separated both from the amount of Yb(III) still present after the cementation cycles as well as from the La$^{(III)}$ carrier added for co-precipitation. The nca ^{177}Lu was eluted using 0.07 M α-HIB, pH 4.7 of an Aminex A6 column (2.0 × 80 mm).

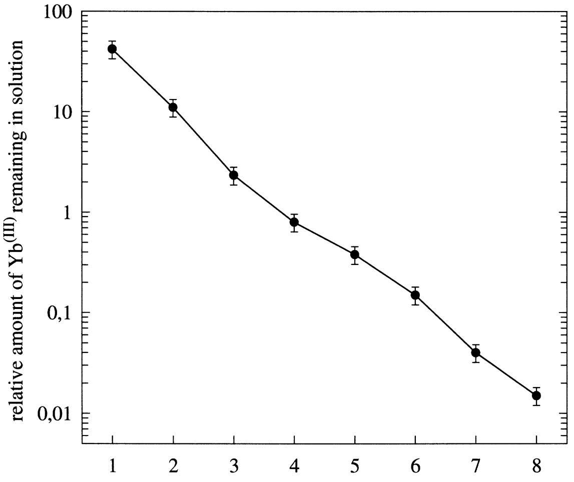

Fig. 1. Successive separation of macro-amounts of Yb(III) in individual cementation cycles.

The capacity of the column was evaluated using different amounts of Yb(III), namely 10, 50 and 200 µg. The results of the elution experiments are summarised in Fig. 2. They indicate, that nca ^{177}Lu can effectively separated in the presence of ≤50 µg Yb(III), which corresponds to the efficacy of the cementation cycle. For low initial amounts of ≤50 µg Yb(III) about 90 ± 5% of the nca ^{177}Lu can be isolated with Yb(III) contaminations of <0.1% of the initial Yb(III) traces, i.e. <10 ng Yb(III) for the 10 µg Yb(III) experiment. If only the maximum of the nca ^{177}Lu elution peak of about 80% is considered, the amount of Yb(III) can be reduced to levels of <1 ng. Fig. 3 shows an elution profile of the chromatographic separation of the original separation process starting with 100 mg irradiated ^{nat}Yb.

The ^{177}Lu sample obtained from the processing of the 12.4 mg $^{176}Yb_2O_3$ irradiated at high neutron flux was investigated for its content of ytterbium using γ-spectroscopy on HPGe-detectors within two days after

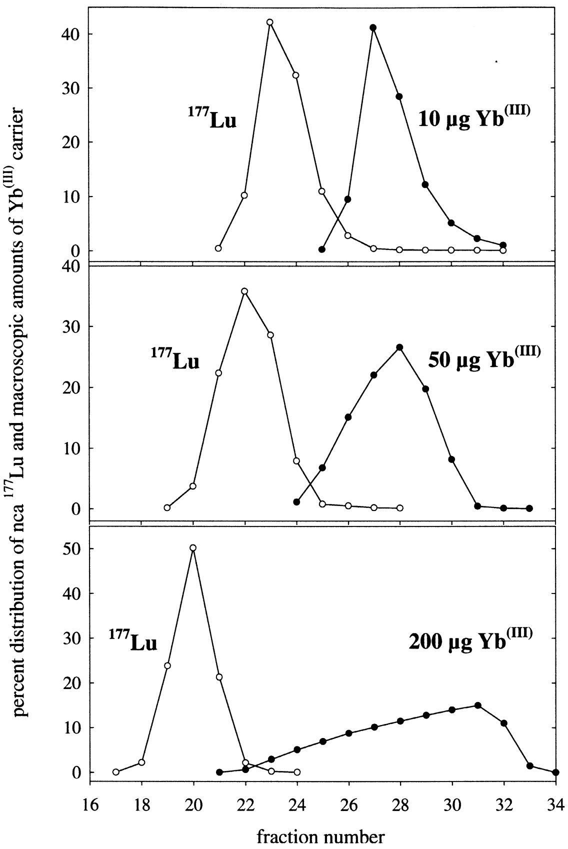

Fig. 2. Elution profiles from model experiments with nca ^{177}Lu and Yb(III) carrier in amounts of 10, 50 and 200 µg using 0.07 M α-HIB, pH 4.7; column: Aminex A6, 4.3 × 95 mm; three drops per fraction.

the separation. The amount of ytterbium was determined comparing the γ-lines of ^{177}Lu ($E_\gamma = 208$ keV) and ^{175}Yb ($E_\gamma = 396$ keV) of the irradiated sample and of the separated ^{177}Lu fraction. The ytterbium present amounted to $\leq 5\%$ of the mass of the nca ^{177}Lu itself.

3.3. Recovery of the enriched target material

If isotopically enriched ^{176}Yb is used in the irradiations, the target material should be recovered from the sodium amalgam. In acidic medium the Na(Hg) is destroyed using 0.5 M HCl. Some mercury(I) chlorides, if formed, are removed by centrifugation. The ytterbium is then precipitated as oxalate at pH ~1 and is converted to the oxide by heating at 1000°C for several hours during which the residual mercury traces are removed. The recovery of ytterbium is nearly quantitative.

This material can be used for the subsequent irradiation. It is even recommended to run a first inactive separation cycle before, in order to separate any traces of lutetium eventually present in the Yb_2O_3 target material supplied.

4. Conclusion

The total activity of ^{177}Lu available from the ^{176}Yb(n,γ)^{177}Yb$\rightarrow$^{177}Lu process on 100 mg of 94.72% isotopically enriched ^{176}Yb amounts to >370 MBq per hour at thermal neutron fluxes of $1 \cdot 10^{14}$ cm^{-2} s^{-1}, for example. Batch yields of >10 GBq of nca ^{177}Lu can be produced.

The cementation separation process provides a decontamination factor of Yb(III) of 10^4, i.e. <10 µg Yb(III) remaining for an 100 mg amount of ytterbium irradiated. The final cation exchange purification is able to remove any traces of Yb(III) and adds a decontamination factor of $>10^2$. Thus, nca ^{177}Lu is available in radiochemically pure form despite of the chemical similarity of the neighboured lanthanides. In conclusion, the radiochemical separation process developed provides radiochemically pure nca ^{177}Lu within a total volume of less than 0.5 ml with an overall separation yield of $75 \pm 5\%$ within 4–5 h, with an Yb contamination of $<10^{-6}\%$, i.e. <1 ng Yb(III) for a 100 mg ^{176}Yb target. It thus can be used to synthesise nca ^{177}Lu labelled radiotherapeuticals.

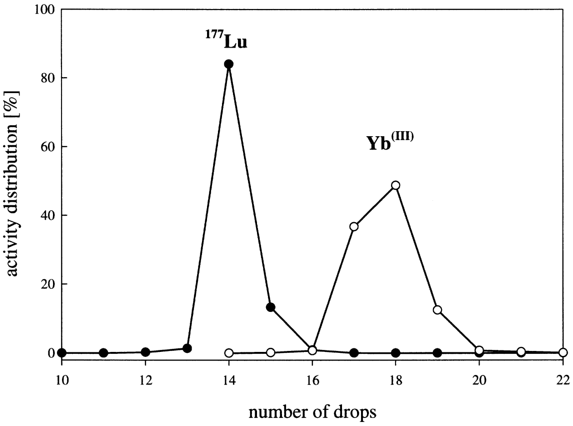

Fig. 3. Optimum ion exchange purification ^{177}Lu from Yb(III) using 0.07 M α-HIB, pH 4.7; column: Aminex A6, 2 × 80 mm.

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