Talanta 114 (2013) 1–4

Contents lists available at ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

Determination of ^{90}Sr traces in medical ^{90}Y after separation on DGA column

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ARTICLE INFO

Article history:
Received 15 October 2012
Received in revised form
21 March 2013
Accepted 28 March 2013
Available online 9 April 2013

Keywords:
^{90}Sr
^{90}Y
Solid phase extraction
DGA resin

ABSTRACT

A new analytical procedure for ^{90}Sr determination in freshly milked ^{90}Y from a ^{90}Sr/^{90}Y generator is described. To a solution containing 125 mg of Sr a 200 to 400 MBq sample of ^{90}Y is added and strontium is separated from ^{90}Y using DGA column of 1 mL volume. ^{90}Sr is recovered in a yield close to 100% and counted in a liquid scintillation spectrometer (LSC). The separated strontium is slightly contaminated with ^{90}Y in the range from 7 to 19% of ^{90}Sr activity. The separation and counting can be completed within 30 min. The detection limit in 900 s counting time is equal to about 0.2 Bq. This corresponds to ^{90}Sr/^{90}Y activity ratio of 10^{-8} level.

1. Introduction

^{90}Sr has a high affinity to the bone and a long half-life and is a very dangerous radioactive isotope when it is introduced into the human body. Its decay daughter ^{90}Y is also radioactive and decays with a half-life of 64 h to stable ^{90}Zr. ^{90}Y is a pure beta emitter of 2.26 MeV maximum particle energy. It is more and more often used in nuclear medicine for radionuclide therapy of some cancers and for radiosynovectomy of the large joints. The ^{90}Sr content in ^{90}Y produced from ^{90}Sr/^{90}Y generators must therefore be low and it should be determined before the ^{90}Y pharmaceutical is administered to a patient. According to US Pharmacopoeia monograph recommendation the activity ratio of ^{90}Sr/^{90}Y for Yttrium Y-90 Ibritumomab Tiuxetan (Zevalin®) should not exceed 10^{-5} [1]. The same value is recommended by European Medicines Agency for ^{90}Y as radiopharmaceutical precursor [2,3]. To determine the ^{90}Sr content it is necessary to separate it with a very high yield from ^{90}Y. Chromatographic methods can fulfill these requirements. Two approaches are possible: either to immobilize ^{90}Y or ^{90}Sr. In the internationally recommended procedure [1] a cellulose phosphate strip retains ^{90}Y at a starting point when developed with 3 M HCl and ^{90}Sr ascends with the solvent front. Some of ^{90}Y is migrating together with ^{90}Sr and the part of the cellulose strip containing ^{90}Sr is contaminated with ^{90}Y, hence the detection limit of ^{90}Sr is relatively low. In the paper chromatography method [4] the 12 cm strip of Whatman 1 paper was used. At the starting point 10 µl of 2-ethylhexylphosphonic acid mono-2-ethylhexyl ester (KSM-17) was deposited and after air-drying a 5 µl of ^{90}Y/^{90}Sr analyte was dispensed on it and chromatogram developed using 0.9% NaCl solution in ascending mode. One centimeter pieces of developed paper were counted using an LSC. The authors claimed that ^{90}Sr/^{90}Y radioactivity ratio equal to 10^{-6} could be determined. Commercially available Sr-resin produced by Eichrom Technologies LLC, IL USA, consisting of 4, 4′(5′)-di-t-butylcyclohexano-18-crown-6 (crown ether) in 1.0 M concentration in 1-octanol loaded onto an inert chromatographic support has a very high affinity for strontium at pH < 1. Strontium is quantitatively retained on the column from 6 to 8 M HNO_3 solution whereas most of the yttrium is not retained and elutes off. Besides strontium other beta emitting nuclides are also retained (^{35}S, ^{36}Cl, ^{63}Ni, ^{99}Tc, and ^{45}Ca). Strontium can be stripped from the column using dilute (0.01 M) nitric or hydrochloric acid [5–7]. However, in this approach ^{90}Y first needs to be eluted from the column to allow ^{90}Sr determination. If ^{90}Y is not removed quantitatively, even small contamination with it lowers the detection limit for ^{90}Sr, because it is eluted together with ^{90}Sr. In all mentioned methods no systematic studies of ^{90}Sr recovery yields from ^{90}Y were carried out. The contamination of ^{90}Sr with ^{90}Y was also not evaluated.

We developed a new analytical procedure using DGA resin for ^{90}Sr separation from ^{90}Y. The Eichrom DGA resins are extraction chromatographic materials in which the extractant system is either N,N,N′,N′-tetra-n-octyldiglycolamide (DGA Resin, Normal) or N,N,N′,N′-tetrakis-2-ethylhexyldiglycolamide (DGA Resin, Branched) [8].

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http://dx.doi.org/10.1016/j.talanta.2013.03.081

The bed density of both DGA resins is approximately 0.38 g/mL, with a working capacity of 7.23 mg of Sr per mL of resin and 11 mg of yttrium per mL of resin. All alkaline earth cations normally are not retained on the DGA resin from HCl, and only strontium and calcium show moderate uptake from nitric acid concentrations from 0.5 to about 5 M. Yttrium is much more strongly retained on the resin than Sr from nitric and hydrochloric acids across all concentrations. A large excess of Sr carrier was used for two reasons: to minimize the retention of ^{90}Sr on the column bed and to minimize the losses of ^{90}Sr by adsorption on the glassware. The amount of Sr carrier was about 60 times the capacity of DGA column, similarly as in Ref. [8].

2. Experimental part

2.1. Reagents and materials

DGA Resin, Normal, 50–100 μm, Eichrom Technologies LLC, IL USA. Polypropylene columns 1 mL, Varian Inc., USA. Nitric and hydrochloric acids of various concentrations: strontium nitrate solution of 31.25 mg Sr/mL in 5 M HNO_3; ^{85}Sr solution of chloride in 1 M HCl with 42.6 MBq/mL radioactivity concentration and a specific radioactivity of 156 MBq/mg Sr; RSr-90-1 solution—standard reference solution of ^{90}Sr of 10.62 kBq/g $\pm$ 0.6% radioactivity concentration (POLATOM, Poland); RSr-90-2 solution working standard reference solution of 1558 Bq/g $\pm$ 0.8% prepared from RSr-90-1 solution by dilution of 0.1493 g with 5 M HNO_3 to 1.0176 g mass.

2.2. Instrumentation

1) Wallac 1411 liquid scintillation counter (Wallac Oy, Turku, Finland).
2) Ionization chamber (Capintec Inc., NY, USA).
3) HPGe spectrometer, 15 cm^3 (Canberra-Packard).
4) Analytical balance, 0.1 mg accuracy (Radwag, Poland).

2.3. Radioactivity measurements using Wallac 1411 LS

Activity measurements were performed using only a fraction of the eluate which was in the range from 0.10 to 0.15. The results of measurements were obtained by multiplying the aliquot activity by the dilution factor. The measurement time was 900 s for all samples and the background count number in ^{90}Sr channel during this time was about 1200. The counting efficiency was 0.96 and 0.98 for ^{90}Sr and ^{90}Y respectively.

The counts were registered in 2 measurement windows: 1 to 1024 channel comprising the whole spectrum, CPM_{tot}; 1 to 650 channel comprising the spectrum of ^{90}Sr, CPM_{1-650}.

During measurements the Spectral Quench Parameter-External (SQPE) was registered using an external source of ^{152}Eu. For calculation of the number of ^{90}Sr counts in an overlapped spectrum of ^{90}Sr+^{90}Y a linear function was used of a formula

$$CPM_{Sr-90}/CPM_{tot} = k_1 CPM_{1-650}/CPM_{tot} + k_0 \tag{1}$$

where $CPM_{Sr\text{-}90}/CPM_{tot}$ is the fraction of counts from ^{90}Sr, CPM_{1-650} is the number of counts in ^{90}Sr channel, CPM_{tot} is the total number of counts in spectrum, k_0, k_1 are the coefficients for SQPE value of 730 are equal to -0.83 and 1.83, respectively.

To determine the values of k_0 and k_1 coefficients the following spectra have to be accumulated: (i) spectrum of pure ^{90}Sr in the shortest time after ^{90}Y separation, (ii) spectrum of pure ^{90}Y spectrum free of ^{90}Sr, (iii) spectrum of ^{90}Sr+^{90}Y in secular equilibrium. Having these 3 spectra a set of new spectra with the different ratios of ^{90}Sr and ^{90}Y was mathematically generated and k_0 and k_1 were calculated using the least square method.

2.4. Preparation of DGA column

DGA resin was soaked in 1 M HNO_3 (100 mg resin per 1 mL of acid) for at least 24 h. Agitation with a magnetic stirrer was applied for 10 min prior to column preparation and 1 mL of DGA suspension was introduced onto 1 mL polypropylene column having fritted glass at the bottom. The column bed was covered with another fritted glass. *Note*: the resin bed had to be free of air bubbles and it had always to be covered with the acid solution.

3. Results and discussion

3.1. Determination of strontium recovery from DGA column using ^{85}Sr as a tracer

To 8 mL of 5 M HNO_3 125 mg Sr and 25 μL of ^{85}Sr solutions were added. The volume of solution was then increased to 10 mL by adding 5 M HNO_3. One mL of this solution was taken for ^{85}Sr activity measurement by gamma spectrometry. Two similar solutions were prepared by adding 114.8 and 120.7 kBq of ^{85}Sr. The solutions were loaded onto 2 columns. A peristaltic pump ensured a flow rate of 1 mL/min. Each column was rinsed in turn using 6 mL 5 M HNO_3, 8 mL 0.1 M HNO_3 and 10 mL 0.1 M HCl. Two mL fractions were collected and measured by gamma spectrometry. A void volume of the setup was 1.5 mL (column and tubing). Two runs were performed. The eluate profile of Sr and ^{85}Sr recovery is shown in Fig. 1. The mean value of ^{85}Sr recovery was 99.86% (SD = 0.135, RSD = 0.14%).

3.2. Preliminary studies of strontium recovery from DGA column with addition of ^{90}Sr in presence of a large excess of ^{90}Y

To each of eight weighed aliquots (150 mg) of ^{90}Y solution from a production lot of ^{90}Sr/^{90}Y generator 125 mg of Sr (500 μL of strontium chloride solution) was added. Six aliquots were spiked with different activities of ^{90}Sr standard reference solution: 2 with 100 Bq, 2 with 250 Bq and 2 with 500 Bq. Two additional aliquots were used as ^{90}Sr blanks. To all aliquots 5 mL of 5 M HNO_3 was added to give a final volume of about 6 mL. Each aliquot was loaded onto a DGA column and the column was rinsed consecutively with 4 mL 5 M HNO_3, 4 mL 0.1 M HNO_3 and 6 mL 0.1 M HCl. The flow rate was 1 mL/min. Two mL fractions were collected and about 1 g was weighed for LSC measurement. After addition of 1.5 mL of deionized water and 10 mL of Ultima Gold AB Scintillator to 20 mL counting vial the aliquot was measured. ^{90}Sr was completely eluted in five 2 mL fractions. ^{90}Y was removed using diluted HCl solution. In blank

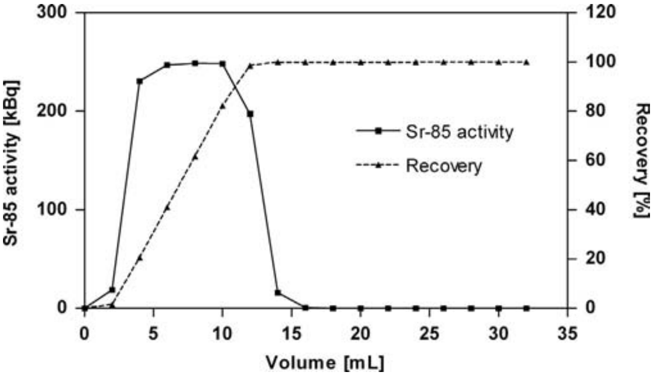

Fig. 1. Strontium elution profile and its recovery from DGA column.

Table 1
Preliminary results of ^{90}Sr recovery from DGA column.

Sample	^{90}Sr activity added [Bq]	^{90}Sr activity measured [Bq]	^{90}Sr activity after blank substraction [Bq]	^{90}Sr recovery [%]
Blank 1	0.0	25.2	–	–
Blank 2	0.0	26.3	–	–
Mean ± SD		*25.8 ± 0.55*		
Sample 1	113.8	138.5	112.7	99.1
Sample 2	113.8	137.6	111.8	98.3
Sample 3	282.2	304.4	278.7	98.8
Sample 4	281.0	311.3	285.5	101.6
Sample 5	527.3	555.3	529.5	100.4
Sample 6	527.3	559.8	534.1	101.3
Mean ± SD				*99.9 ± 1.26*

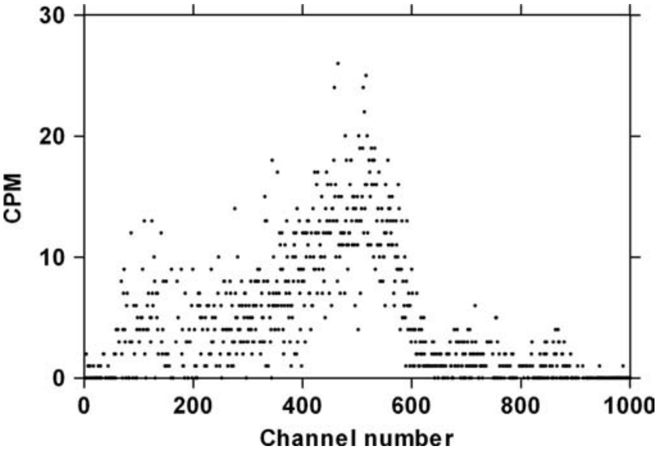

Fig. 2. LSC spectrum of strontium fraction from DGA column. Approximate ^{90}Sr activity—60 Bq.

aliquots the LSC measurement was done directly after elution. The blanks contained some ^{90}Sr originating from the ^{90}Sr/^{90}Y generator. Table 1 summarizes the data for all 8 aliquots: activity of ^{90}Sr added, in Bq, activity of ^{90}Sr measured, in Bq, ^{90}Sr activity after blank subtraction, in Bq, ^{90}Sr recovery in percent. The average recovery of ^{90}Sr was equal to 99.9% (SD = 1.26, RSD = 1.26%). Fig. 2 shows spectrum of ^{90}Sr fraction containing about 60 Bq of ^{90}Sr.

3.3. Validation of ^{90}Sr determination from a DGA column

To validate the ^{90}Sr recovery from ^{90}Y solution the method of standard addition was used. All aliquots were prepared by weight. First, to each of 29 vials 4 mL of Sr solution containing 31.25 mg Sr/mL in 5 M HNO_3 was pipetted. The standard solution of ^{90}Sr in equilibrium with ^{90}Y was added: to 6 aliquots—50 Bq, to 6 aliquots —100 Bq and to 5 aliquots—250 Bq. To 6 aliquots no standard was added. In next step about 230 MBq of ^{90}Y from the same production lot was added to each aliquot. The separation procedure was performed as follows: the aliquots were loaded on DGA columns each containing 100 mg of DGA resin. The columns were rinsed consecutively with 4 mL of 5 M HNO_3, 2 mL of 5 M HNO_3 and 2 mL of 0.1 M HNO_3. The flow rate was 1 mL/min. Three fractions were collected from the column, first fraction of 8 mL (4 mL of loaded sample and 4 mL of 5 M HNO_3 column rinsing), second fraction of 2 mL of 5 M HNO_3 column rinsing, third fraction of 2 mL of column rinsing with 0.1 M HNO_3. From each fraction a 1 g aliquot was added to a 20 mL LSC vial followed by 1.5 mL of deionized water and finally 10 mL of Ultima Gold AB liquid scintillator. Measurements of ^{90}Sr activity in all 29 aliquots were carried out with Wallac 1411 spectrometer and the results are presented in Table 2 showing a mean recovery with SD and ^{90}Sr content in blanks. Table 3 shows the parameters of calibration curve.

Table 2
Data for calibration curve.

Sample	^{90}Sr activity added [Bq]	^{90}Sr activity measured [Bq]	^{90}Sr activity after blank substraction [Bq]	^{90}Sr recovery [%]
Blank1	0	12.1	–	–
Blank2	0	10.3	–	–
Blank3	0	11.0	–	–
Blank4	0	9.8	–	–
Blank5	0	11.0	–	–
Blank6	0	11.5	–	
Mean ± SD		*10.9 ± 0.8*		
Sample 50/1	58.1	67.5	56.5	97.3
Sample 50/2	57.7	72.4	61.4	106.5
Sample 50/3	58.6	70.1	59.1	100.9
Sample 50/4	58.2	71.1	60.1	103.2
Sample 50/5	57.9	64.6	53.6	92.6
Sample 50/6	57.9	70.9	59.9	103.4
Sample 100/1	104.8	120.1	109.1	104.1
Sample 100/2	106.0	114.1	103.1	97.3
Sample 100/3	106.9	120.9	109.9	102.8
Sample 100/4	104.8	116.4	105.4	100.6
Sample 100/5	105.3	117.9	106.9	101.5
Sample 100/6	106.0	116.7	105.7	99.8
Sample 250/1	261.9	270.6	259.6	99.1
Sample 250/2	257.2	264.2	253.2	98.4
Sample 250/3	276.0	285.2	274.2	99.4
Sample 250/4	264.9	272.2	261.2	98.6
Sample 250/5	266.6	280.0	269.0	100.9
Mean ± SD				*100.4 ± 3.1*

Table 3
Parameters of calibration curve ($p = 0.05$).

Parameter	Value
Slope	0.9926 ± 0.0052
Y-intercept	11.69 ± 0.72
X-intercept	−11.77
Goodness of fit r^2	0.9994

Table 4
Results of ^{90}Sr determination in two production batches. Activity at shipping time.

Approx. ^{90}Y activity [MBq]	^{90}Sr/^{90}Y activity ratio	
	Batch 1	Batch 2
200	1.24×10^{-7}	1.85×10^{-7}
200	1.33×10^{-7}	1.82×10^{-7}
200	1.35×10^{-7}	1.88×10^{-7}
400	1.33×10^{-7}	1.86×10^{-7}
400	1.35×10^{-7}	1.83×10^{-7}
400	1.31×10^{-7}	1.85×10^{-7}
Mean ± SD	$1.32\times10^{-7}\pm3.76\times10^{-9}$	$1.85\times10^{-7}\pm1.95\times10^{-9}$

3.4. Detection and determination limits

Assuming normal distribution of random errors and Poisson distribution for counting of pulses a formula for detection limit, C_D, with a probability of 95% is [9,10]

$$C_D = 3.29(\eta N_b)^{1/2}/St \tag{2}$$

where η has value 1 when the background is well defined or 2 for a single measurement, N_b is the number of counts of background, t is the counting time, [s], S is the sensitivity of measurement, number of Bq added to number of Bq measured.

For determination limit, C_Q, the following expression is used

$$C_Q = 10f(\eta N_b)^{1/2}/St \tag{3}$$

where $f=(1+(25/\eta N_b))^{1/2}+(25/N_b)^{1/2}$ or $f\approx 1$ when $N_b > 2500$.

N_b increases as a square root of measurement time, so increasing the measurement time n times, the C_D and C_Q increase $n^{1/2}$ times. For ^{90}Sr measurements using LSC the value of S is close to 1 because of counting efficiency near to 100%. For 900 s measurement time of both sample and background (approximately 1200 counts), $S=0.96$ and $\eta=2$ the detection limit calculated from formula (2) was equal to 0.19 Bq assuming negligible contribution of ^{90}Y. The determination limit, C_Q, obtained from formula (3) with $f=1.15$ was equal to 0.65 Bq. As mentioned earlier 7 to 19% of Sr eluate was taken for measurements, so the detection and determination limits in the ^{90}Y product have to be increased accordingly. Extending the measurement time would not improve the detection limit due to in growth of ^{90}Y from the decay of ^{90}Sr.

3.5. *Example of routine determination. Final test of the method*

From two lots of ^{90}Y separated from ^{90}Sr/^{90}Y generator 6 aliquots from each lot of ^{90}Y were evaluated—3 of them contained approximately 2 times more ^{90}Y than the other three. The activity of ^{90}Y was measured in ionization chamber. It was about 200 MBq and 400 MBq. Twelve DGA columns were prepared. To each aliquot 125 mg of natural strontium carrier was added (4 mL of 5 M HNO_3 solution, 31.25 mg Sr/mL). All 6 separations were carried out in approximately 2 h of time. Three fractions were collected from each column—8 mL in 5 M HNO_3, 2 mL in 5 M HNO_3 and 4 mL in 0.1 M HNO_3. Approximately 1 mL by weight of each fraction was taken for measurement. It was diluted using 1.5 mL of deionized water and 10 mL of Ultima Gold AB scintillator. Measurements of ^{90}Sr were started on the day of separation. Each measurement lasted 15 min. The values of SQPE parameter were equal to 730 ± 3 and ^{90}Sr activity calculated from formula (1) was accordingly corrected. Practically all of the ^{90}Sr was eluted in the first fraction. In the second fraction the amount of ^{90}Sr was less than 1%. The activity of ^{90}Y was also calculated from the spectrum. It grew in with the elapsed time to the end of each measurement and was in the range of 6–12% of ^{90}Sr activity. Results are shown in Table 4. The ^{90}Sr/^{90}Y activity ratios were 1.32×10^{-7} for batch 1 (SD$=3.76 \times 10^{-9}$, RSD$=2.85\%$) and 1.85×10^{-7} for batch 2 (SD$=1.95 \times 10^{-9}$, RSD$=1.05\%$). The initial activity of ^{90}Y in ^{90}Sr fraction originating from the leakage of ^{90}Y from the column was in the range of 7–19% of ^{90}Sr activity. It should be mentioned here that approximately 61% of counts in ^{90}Y spectrum was free from the ^{90}Sr spectrum interference. Therefore the correction of ^{90}Y interference in ^{90}Sr spectrum could easily be calculated.

4. Conclusion

The single separation of ^{90}Sr from ^{90}Y on a DGA column takes no more than 10 min. Preparing an aliquot for LSC and its counting requires 20 min, so ^{90}Sr can be determined in 30 min assuming the precise value of background was measured earlier. The risk of aliquot contamination with ^{90}Y is negligible which can happen when chromatographic strips are used. Using this procedure routinely, the determination limit of 1 Bq of ^{90}Sr per 10^7 Bq of ^{90}Y can easily be achieved. The presented method is superior in comparison with procedures described earlier in two aspects: (i) ^{90}Sr is separated quantitatively and (ii) the remaining small activity of ^{90}Y can be accounted for and corrected.

References

[1] Yttrium Y-90 Ibritumomab Tiuxetan Injection, US Pharmacopeia 29.
[2] Yttriga: EPAR Scientific Discussion, European Medicines Agency, 29.10.2006.
[3] Ytracis: EPAR Scientific Discussion, European Medicines Agency, 21.10.2005.
[4] U. Pandey, P.S. Dhami, P. Jagesia, M. Venkatesh, M.R.A. Pillai, Anal. Chem. 80 (2000) 801–807.
[5] R. Mikolajczak, M. Zuchlinska, A. Korsak, E. Iller, D. Pawlak, Z. Zelek, M. Konior, J.L. Parus, (2009).
[6] P. Juntunen, T.K. Nikula, Eur. J. Nucl. Med. Mol. Imaging 34 (2007) S336.
[7] M.L. Bonardi, L. Martano, F. Groppi, M. Chinol, Appl. Radiat. Isot. 67 (2009) 1874–1877.
[8] E.P. Horwitz, D.R. MCalister, A.H. Bond, R.E. Barrans, Solvent Extr. Ion Exch. 23 (2005) 319–344.
[9] L.A. Currie, Anal. Chem. 40 (1968) 586–593.
[10] L.A. Currie, Detection and quantitation in X-ray fluorescence spectrometry, in: T.G. Dzubay (Ed.), X-ray Fluorescence Analysis of Environmental Samples, Ann Arbor Science, Ann Arbor, 1977.