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QUANTIFYING THE RADIONUCLICID IMPURITIES AND UNCERTAINTY COMPONENTS OF ^{99m}Tc ELUATE BY LIQUID SCINTILLATION SPECTROMETRIC METHOD

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^{99m}Tc ELUATINDA BULUNAN RADYONÜKLİDİK SAFSIZLIKLARIN VE BELİRSİZLİK BİLEŞENLERİNİN SIVI SİNTİLASYON SPEKTROMETRİ YÖNTEMİYLE BELİRLENMESİ

Abstract:

Radionuclidic impurities, especially long-lived pure alpha, and beta-emitters are of significant concern regarding the quality of radioisotopes used in medical imaging and diagnosis Therefore, the radioisotopes must have appropriate quality control (QC) parameters to prevent the patient from being exposed to excessive radiation doseIn this study, the determination of ^{89}Sr, ^{90}Sr, and total alpha/beta emitters in ^{99m}Tc eluate produced from ^{99}Mo/^{99m}Tc generator was done by sequential separation followed by sensitive measurement using the Liquid Scintillation Counting (LSC) system. The sequential separation method was validated with standard solutions of the radionuclides used, and the measurement uncertainty of the components was evaluated in detail. The uncertainty associated with the activity concentration has been calculated to combined to (may be better?) give a combined standard uncertainty. The parameters contributing to the uncertainty budget include the uncertainties in the counting statistics, detector efficiency, misclassification (PSA), the mass of the sample, and activities of the standard radionuclide solutions, respectively. The significant contributions come from the counting statistics, as expected.

Özet

Radyonüklidik safsızlıklar, özellikle uzun ömürlü saf alfa ve beta yayıcılar, tıbbi görüntüleme ve tanıda kullanılan radyoizotopların kalitesiyle ilgili başlıca endişelerdir. Hastanın genel radyasyon dozuna önemli ölçüde katkıda bulundukları için, kabul edilebilir kalite kontrol (QC) parametrelerine sahip bir ürüne sahip olmak önemlidir. Bu çalışmada, ^{99}Mo/^{99m}Tc jeneratöründen sağılan ^{99m}Tc eluatındaki radyonüklidik safsızlıklar, ^{89}Sr, ^{90}Sr ve toplam alfa/beta yayıcıların ardışık olarak ayrılması ve hemen ardından Sıvı Sintilasyon Sayımı sisteminde yapılan hassas ölçümlerle tayin edilmiştir. Ardışık ayırma yönteminin doğrulaması radyonüklidlerin standart çözeltileri kullanılarak yapılmış ve ölçüm belirsizliği parametreleri

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ayrıntılı olarak değerlendirilmiştir. Aktivite derişiminin hesaplanan belirsizliği, bileşik standart belirsizlik olarak verilmiştir. Belirsizlik bütçesine katkıda bulunan parametreler sırasıyla sayım istatistikleri, detektör verimi, pulse-şekil ayırımı (PSA), numune kütlesi ve radyoaktif standart çözeltilerinin aktivitelerindeki belirsizliklerdir. En büyük katkı beklendiği gibi sayım istatistiklerinden gelmektedir.

Keywords: Radionuclidic impurity, uncertainty, ^{99m}Tc, liquid scintillation spectrometry, sequential separation, strontium.

Anahtar Kelimeler: Radyonüklidik safsızlık, belirsizlik, ^{99m}Tc, sıvı sintilasyon spektrometresi, ardışık ayırım, stronsyum.

1. Introduction

Technetium-99m (^{99m}Tc) is one of the most important radioisotopes used in medical applications. It emits gamma photon with energy of 140 keV. Gamma rays with this property are ideal for gamma detectors. The half-life of 6 hours provides an advantage in diagnosis and is also convenient in terms of the low radiation dose for the patient. Because of all these superior features almost 80% of nuclear medical radioisotopes used all over the world is ^{99m}Tc. It is mainly produced either through ^{99}Mo/^{99m}Tc generator or proton irradiation of stable ^{100}Mo in a cyclotron (IAEA, 2013).

^{99}Mo used for nuclear medical purposes are produced by irradiation of enriched ^{235}U in a nuclear reactor and then loaded onto alumina column in the ^{99}Mo/^{99m}Tc generator. The Tc-99m is eluated by passing a saline solution through the generator. The total concentration of technetium in the eluent is in the range of 10^{-7} to 10^{-6} M, and usually, they are not wholly pure and contain some contaminants during the production process or decay of the parent radioisotope. To control the adverse effects of these contaminants, limits should be set at the maximum permissible levels. According to European Pharmacopy Monograph the radionuclides in the sodium pertechnetate injection consist of ^{99}Mo, ^{131}I, ^{103}Ru, ^{89}Sr, ^{90}Sr, alpha-emitting, and other gamma-emitting impurities (European Pharmacopeia, 2008). Radiopharmaceuticals must be tested for quality control before they are given to patients like all medicines. Radionuclidic impurity distorts the scintigraphic image due to the biodistribution difference.

The measurement uncertainty is an essential part of evaluating the measurement results (Jerome & Eccles, 2007). An analytical procedure's quality assessment often has a degree of uncertainty (Taylor, Ramsey & Potts 2005; Boon & Ramsey, 2012). Estimating uncertainty involves taking into account all steps of the method and all possible sources of uncertainty. Therefore, this study aims to determine the individual uncertainty components for the whole radioanalytical method, starting from the sample preparation up to the radioactivity measurement using the liquid scintillation spectrometry.

The aim of this work is quantifying the radionuclicid impurities and uncertainty components of ^{99m}tc eluate by liquid scintillation spectrometric method and to evaluate the contribution of each parameter to the results separately. The parameter that contributes the most to the uncertainty of the results will be determined. Thus, necessary adjustments or measures can be taken to minimize the contribution of this component to the overall uncertainty.

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2. Material and Method

2.1. Materials, standards and chemical reagents

Strong basic anion exchange resin (AG1×4, Cl- form, 50-100 mesh), plastic empty column, and Sr-resin column (2 mL, 100-150 μm) were purchased from Eichrom Technologies LLC. 20 mL glass vials and Ultima Gold LLT scintillation cocktail which was supplied by Perkin Elmer Inc. were used. Analytical-grade chemicals were used with deionized water. ^{241}Am, ^{85}Sr, ^{90}Sr, and ^{90}Y standard solutions were obtained from the National Institute of Standard and Technology (NIST, USA).

2.2. Instrumentation

The gamma-ray spectrometric system with an n-type coaxial high purity germanium (HPGe) detector (Canberra Industries, 2009) was used with 50 % relative efficiency. Spectra were analyzed with Canberra digital electronics and Genie 2000 software.

Wallac Quantulus 1220 low background liquid scintillation counter was used for gross alpha/beta, ^{85}Sr, ^{90}Sr, and ^{90}Y isotopes activity measurements. The instrument was consisted of a Pulse Shape Analyser (PSA) and ^{152}Eu external standard to get external spectral quench parameter [SQP(E)]. EASY View Spectrum Analysis Software for analyzing spectra was used. The counting windows for alpha and beta spectra were set to channels 500–800 and 50–900, respectively.

2.3. Sequential separation procedure for the determination of impurity radionuclides in ^{99m}Tc eluate

The concentrations of the radionuclide impurities usually are much lower than ^{99m}Tc in the ^{99m}Tc eluate. So, these impurities of radionuclides can't directly be measured by using radiometric methods. Most of the radionuclides need to be separated before the measurement of alpha emitters. All other radionuclides except strontium must be removed to determine the low-level ^{89}Sr and ^{90}Sr radionuclides. In this study, a sequential separation/removal method was performed to determine the levels of multiple radionuclide impurities in Tc-99m generator eluates, according to literature (Hou, 2017; Aslan & Özçayan, 2019). A schematic diagram of the sequential separation procedure is given in Figure 1. The separation procedure in detail was given in our previous article (Aslan & Özçayan, 2019).

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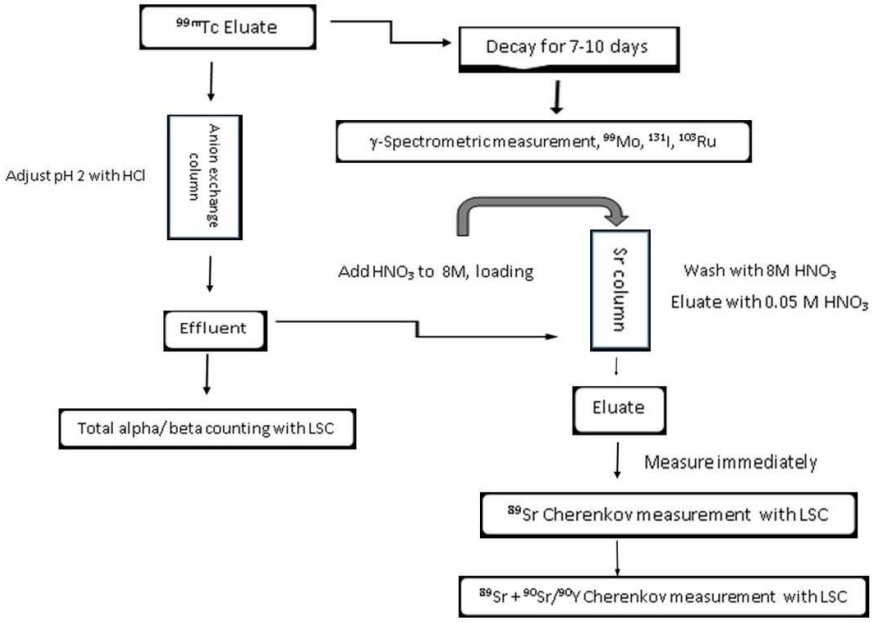

Figure 1. Sequential separation procedure of the impurity radionuclides in ^{99m}Tc eluate.

In the first separation step, TcO_4^- and MoO_4^{2-} in the Tc-99m eluate were removed by using anion exchange chromatography. The adsorption of TcO_4^- and MoO_4^{2-} on the anion exchange resin was excellent during the separation procedure but, all other radionuclides passed into effluent without adsorption. Approximately 2 mL of Tc effluent collected from the anion exchange column was added to one vial containing a 10 mL UG LLT cocktail. Then, measurement was performed with LSC at optimum PSA value for total alpha/beta analysis.

After gross beta activity measurement, if the total beta activity value is higher than 6×10^{-6} % of total activity regarding the date and hour of eluting of ^{99m}Tc, strontium in the anion column effluent has to be separated by using Sr resin column for the measurement of ^{90}Sr and ^{89}Sr. The eluate was immediately measured by LSC with Cherenkov protocol and activity concentration value of ^{89}Sr was calculated by using the count rate. Later, the same sample was re-measured after 6-10 days for Cherenkov counting of ^{90}Y + ^{89}Sr. The second measurement provides the sum of the count rates of ^{90}Y (with ingrowth correction) and ^{89}Sr (with decay correction) to determine ^{90}Sr in the sample.

The radiochemical separation was done to remove total alpha and beta-emitting radionuclides from the ^{99m}Tc eluate. Each of the ^{241}Am, ^{85}Sr, ^{90}Sr/^{90}Y, and ^{90}Y spike solutions as tracers was prepared in 0.45% NaCl-0.1 M HCl solution to determine the chemical recovery of the separation procedure. The same separation procedure for spike solutions was applied, and as a result of all measurements performed with γ-spectrometry and LSC, the chemical recoveries of these radionuclides were calculated.

2.4. Calculation of the total alpha/beta activity concentration

To optimize the α/β discrimination level, the pulse shape analysis must be set correctly. Alpha and beta events were separately recorded in alpha and beta windows with the adjustment of the PSA value in LSC. PSA level represents a dividing line to distinguish alpha events from

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beta ones or vice versa. For this purpose, pure ^{241}Am and ^{90}Sr/^{90}Y standard solutions was prepared and measured using LSC with alpha/beta separation mode at different PSA values between 50 and 120. As a result of these measurements, the percent misclassification values of α-signals into the β-channel and β-signals into the α-channel were calculated and plotted against the PSA values (Figure 2). The optimum PSA value was calculated as 68 from this graph in this study.

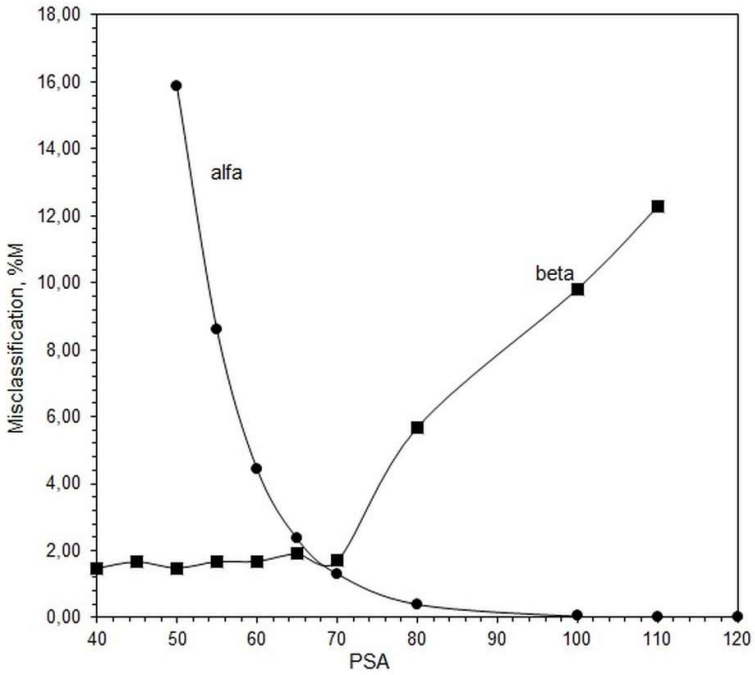

Figure 2. Percent misclassification for ^{241}Am and ^{90}Sr/^{90}Y in Ultima Gold LLT-water scintillation cocktail.

The total alpha and total beta activity concentrations in the sample were calculated the following formula.

$$Activity\ (Bq/g) = \frac{(N - N_{bkg})(cps)}{\varepsilon * m\ (g)} \quad (1)$$

where;

N : gross counting rate for the sample (counts per second, cps)

N_{bkg} : counting rate for the blank vials (counts per second, cps)

ε : counting efficiency

m : sample mass (gram)

The components contributing to the combined measurement uncertainty were estimated as count rates of the sample and background, the recovery of alpha emitters in chemical separation, spillover of beta counts to the alpha window (PSA), counting efficiency, and sample mass.

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2.5. Calculation of the activity concentrations of strontium isotopes

After the first measurement of Sr eluate, ^{89}Sr can be quantified according to the following equations;

$$A_{89Sr} = \frac{\left(N - N_{bkg}\right)}{\varepsilon_{89Sr} \times R \times m} \quad (2)$$

where;

A_{89Sr} : activity concentration of ^{89}Sr

N and N_{bkg} : total count rate (cps) and background count rate (cps) for the ^{89}Sr measurement

R_{chem} : chemical yield of the strontium

ε_{89Sr} : measurement efficiency for ^{89}Sr using Cherenkov counting (cps/Bq)

The activity concentration of ^{90}Sr was calculated by using the following equations:

$$A_{90Y} = \frac{\left(N - N_{bkg}\right)}{\varepsilon_{90Y}} \quad (3)$$

The parameters in Eq. 3 are the same as in Eq. (2) but here ^{90}Y is used instead of ^{89}Sr. The activity of ^{90}Y at any time after separation was calculated, and then the activity of ^{90}Sr can be determined from the formula below

$$A_{90Sr} = \frac{(A_{90}\ ) \times}{(1 - e^{-\lambda 90\ \times \Delta t}) \times R_{chem}} \quad (4)$$

where;

A_{90Sr} : activity concentration of ^{90}Sr

λ_{90Y} : decay constants of ^{90}Y in s^{-1}

Δt : time interval between the separation of ^{89}Sr and the time at the end of counting in s^{-1}.

2.6. Uncertainty budget

Uncertainty components for all measurements and calculations were performed according to the Guide to the Expression of Uncertainty in Measurement (GUM) (ISO, 1995) and using the formula for total alpha/beta ^{89}Sr and ^{90}Sr isotopes. Several computational and mathematical tools are used for determining uncertainty.

The combined standard uncertainty is defined as the estimated standard deviation equal to the sum of the uncertainty components' positive square root for one measurement result (ISO, 1995). Expanded uncertainty is obtained from the combined standard uncertainty multiply by a chosen coverage factor in the final stage. In cases where the coverage factor is chosen as 2, the distributions are normal, and the distribution of values will remain in the range of approximately 95 % confidence level.

3. Results and Discussion

The measurement result is an estimate of the measured quantity and contains uncertainty. Because the measurement uncertainty is considered to include the factors that affect the measurement result (NPAAC, 2007), several parameters can contribute to the uncertainty of the measurement results, such as the composition of the sample, environmental

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effects, assumptions within the measurement method, uncertainties in mass and volume measurement (ISO 15189, 2003). Before calculating the measurement uncertainty, it is necessary to determine all the parameters that may affect the result and to associate each of them with the basic uncertainty concepts. The uncertainty value from each uncertainty component is then calculated as the standard uncertainty (u(x)).

In this study, a validated separation method was applied for the simultaneous determination of radionuclide impurities of ^{89}Sr, ^{90}Sr, and total α-emitters in the ^{99m}Tc eluate. The total measurement uncertainty is evaluated based on Equations 1 to 10.

Tables 1 to 3 present all uncertainty budgets obtained with statistical parameters and their contribution to total uncertainty, for the determination of total alpha/beta, ^{89}Sr, and ^{90}Sr in ^{99m}Tc eluate. Most sources of uncertainty were classified as a normal probability distribution. A rectangular probability function was chosen when calculated uncertainty was associated with mass, according to (ISO 1995).

The parameters contributing to the uncertainty budget of total alpha/beta activity concentration include the uncertainties in the counting statistics, detector counting efficiency, misclassification (PSA), and mass of the solutions. Uncertainty in the net count rate is calculated by using the following equations.

$$Net\ count = N_{total\ counts} - N_{bkg} \tag{5}$$

$$U_{net\ count} = \sqrt{N_{total\ counts} + N_{bkg}} \tag{6}$$

Three repeated counting were done to evaluate the variation on counting rates, and the standard uncertainty was calculated and entered into the uncertainty budget. The same procedure was done for background uncertainty contribution. In this case, ten measurements were carried out to calculate the uncertainty contribution due to background measurement.

The uncertainty of the detector efficiency was estimated from a series of repeated observations by calculating the standard deviation of the mean (3 measurements for ^{89}Sr and ^{90}Sr efficiency and 10 measurements for total alpha/beta efficiency).

The uncertainty associated with the PSA value was estimated using the misclassification equation given below;

$$\%\, M_{\beta} = \frac{N_{\beta}\ in\ \alpha\ MCA}{N_{\beta}\ in\ \beta\ MCA + N_{\beta}\ in\ \beta\ MCA} \times 100 \tag{7}$$

$$\%\, M_{\alpha} = \frac{N_{\alpha}\ in\ \beta\ MCA}{N_{\alpha}\ in\ \beta\ MCA + N_{\alpha}\ in\ \beta\ MCA} \times 100 \tag{8}$$

$$\left[\frac{Umissclasification_{beta}}{missclasification_{beta}}\right]^2 = \left[\frac{\sqrt{counts_{12}}}{counts_{12}}\right]^2 + \left[\frac{\sqrt{counts_{11}+counts_{12}}}{counts_{11}+counts_{12}}\right]^2 \tag{9}$$

$$\left[\frac{Umissclasification_{alpha}}{missclasification_{alpha}}\right]^2 = \left[\frac{\sqrt{counts_{11}}}{counts_{11}}\right]^2 + \left[\frac{\sqrt{counts_{11}+counts_{12}}}{counts_{11}+counts_{12}}\right]^2 \tag{10}$$

Table 1. Uncertainty budget and contribution of the major components for total alpha activity calculations in spike ^{241}Am and ^{90}Sr/^{90}Y solution.

Parameter	***Value***	***Standard Uncertainty***	***Distribution***	***Uncertainty contribution, %***

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Net counts	2401	49.37	normal	2.06
Counting efficiency, ε	1	1	normal	1
Missclasification, PSA	0.0137	0.5326	normal	1.27
Chemical recovery, R_{chem}	92.97	0.94	normal	1.59
Weighing, g	2.0248	0.00009	rectangular	0.0071
Activity, $Bq.g^{-1}$	1.25			5.65

Table 2. Uncertainty budget and contribution of the significant components for total beta activity calculations in spike ^{85}Sr, ^{241}Am and $^{90}Sr/^{90}Y$ solution.

Parameter	***Value***	***Standard Uncertainty***	***Distribution***	***Uncertainty contribution, %***
Net counts	115843	341	normal	0.29
Counting efficiency, ε	0.95	0.75	normal	1
Missclasification, PSA	0.7814	0.1044	normal	1.27
Chemical recovery, R_{chem}	81.26	0.97	normal	1.59
Weighing, g	2.0248	0.00009	rectangular	0.0071
Activity, $Bq.g^{-1}$	65.58			2.57

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Table 3. Uncertainty budget and contribution of the major components for Sr-89 and Y-90 activity calculations.

Parameter	***Uncertainty contribution, % (89Sr)***	***Uncertainty contribution, %(90Y)***
Counting statistics (incl. weight)	13.43	10.14
Counting efficiency, ε	1.27	3.99
Chemical recovery, R_{chem}	4.51	4.51
Weighing, g	0.0021	0.0021
Combined standard uncertainty (quadratic sum), $\Sigma\sqrt{((u(x)/(x)^2)}$	14.22 (k = 1)	11.82 (k = 1)

Uncertainty components for total alpha and total beta emitters are the statistic error of LS counting in the sample, blank and standard, spillover of beta counts into the alpha window and alpha counts in the beta window, counting efficiency, recovery of the chemical separation procedure, and sample weight. For ^{89}Sr and ^{90}Sr, the uncertainty mainly comes from the statistic error of LSC counting, counting efficiency calibration, procedure blank, recovery in the chemical separation steps (anion exchange and Sr-column chromatography), and sample weight.

The sequential separation method was used to analyze ^{99m}Tc eluate obtained from the four batches of ^{99}Mo/^{99m}Tc generator and to determine radionuclidic impurity. Results were given in Table 4. The measured analytical impurities are lower than the limitation of European pharmacopeia (European pharmacopeia, 2008). Uncertainties presented in the analytical results are expanded uncertainties using a coverage factor of k=1 which was estimated considering all possible contributions.

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Table 4. Analytical results of impurity radionuclides in ^{99m}Tc eluate from some batches of ^{99}Mo/^{99m}Tc generators for quality control

		Gross Beta		Gross Alpha		^{89}Sr		^{90}Sr	
Sample code	**^{99m}Tc GBq/ mL**	**A, Bq/g**	**Ratio, %**	**A, Bq/g**	**Ratio, %**	**A, Bq/g**	**Ratio, %**	**A, Bq/g**	**Ratio, %**
Tc_1	1. 012	528.28 (13.58)	5.22×10^{-05}	10.15 (0.57)	1.00×10^{-06}	0.484 (0.069)	4.79×10^{-08}	0.088 (0.010)	8.71×10^{-09}
Tc_2	1.028	272.17 (6.99)	2.65×10^{-05}	5.32 (0.30)	5.17×10^{-07}	0.387 (0.055)	3.76×10^{-08}	0.085 (0.010)	8.27×10^{-09}
Tc_3	1. 022	56.34 (1.45)	5.51×10^{-06}	2.77 (0.16)	2.71×10^{-07}	1.815 (0.258)	1.78×10^{-07}	0.093 (0.011)	9.07×10^{-09}
Tc_4	1.022	103.41 (2.66)	1.03×10^{-05}	5.59 (0.32)	5.57×10^{-07}	3.548 (0.505)	3.54×10^{-07}	0.098 (0.012)	9.75×10^{-09}

Ratio: *The radionuclidic purity is defined as the ratio between the activity of the base radionuclide and the total activity of a radioactive compound*

In all samples, the content of radio strontium and total α-emitters are very low, i.e. close to the detection limit, causing the analytical uncertainties to be relatively high. This is mainly because of the counting uncertainty for samples and blanks.

4. Conclusion

Radionuclidic impurities can have significant effects on the patient's overall radiation dose and also on image quality. In this study, the determination of radionuclidic impurities was done by sequential separation of ^{89}Sr, ^{90}Sr, and total alpha/beta emitters in ^{99m}Tc eluate obtained from ^{99}Mo/^{99m}Tc generator. The total alpha/beta and ^{89}Sr, ^{90}Sr activities were measured using LSC by employing the α/β discrimination function and Cherenkov radiation. The measurement uncertainty components were evaluated in detail, and the major sources of uncertainty were identified as uncertainties associated with the counting rates as expected.

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