

GAMMA-RAY SPECTROMETRIC MEASUREMENT OF RADIONUCLIDE PURITY OF RADIOPHARMACEUTICALS CONTAINED IN BOTTLE SAMPLES

by

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The radionuclide purity of a radiopharmaceutical product is usually measured by gamma-ray spectrometry with various measurement geometries. The importance of this test is that the radionuclide impurities, if present, result in an increase in the radiation dose to the patient without contributing to diagnostic information and in some cases may also interfere with the marking molecules and affect the proper conduct of diagnostic examination. In this work, gamma-ray spectrometry is used to determine the amounts of impurities by adopting as measurement geometry the same bottle containing eluted or prepared radiopharmaceuticals. In addition to high-purity germanium semiconductor detectors, the usefulness of NaI(Tl) and LaBr₃(Ce) scintillators in routine operation is also examined. For the latter detectors, an evaluation of the minimum detectable activity was carried out and compared with the activity limits established by the regulation rules. The main cases considered are related to the first elution of ⁹⁹Mo-^{99m}Tc generators and samples of ¹⁸F-FDG (fluoro-deoxy-glucose) to be used for positron emission tomography diagnostics.

Key words: radionuclide purity, PET, SPECT, gamma-ray spectrometry, dose

INTRODUCTION

The increasing occurrence of diagnostic techniques based on the use of radiopharmaceuticals, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), has made some safety conditions more restrictive for administration of radioactive substances to patients. The rules of good preparation of radiopharmaceuticals in nuclear medicine, contained for example in European Pharmacopoeia [1], have identified criteria and control procedures for the quality management of radiopharmaceutical preparations, achieved through a series of tests to assess physical, chemical, and biological parameters. Among these, particular attention was paid to assess the radionuclide purity, defined as the fraction of the radioactivity of a given radionuclide compared to the amount of the final product used for diagnostics. The importance of this test is that the radionuclide impurities, if present, result in an increase in the radiation dose to the patient without contributing to the information and in some cases may also interfere with the marking molecules and affect the examination [2].

The most often employed technique in determining radionuclide purity of a given radiopharmaceutical is gamma-ray spectrometry with the use of high-purity germanium (HPGe) detectors [3-7] or scintillation detectors [8]. In order to improve the efficiency of the spectrometric system, it is often necessary to use enveloping geometries (*e. g.* Marinelli beakers). The preparation of these samples can involve a radiation risk to the operators, particularly if it requires a handling procedure of open radioactive substances or mixing of small quantities into a liquid matrix. To avoid such procedures, we developed in this work a gamma-ray spectrometric procedure to determine the activities (or concentrations) of impurities in the same bottle that used to contain eluted or produced radiopharmaceuticals. In particular, we examined some gamma-ray spectrometric measurements carried out on samples resulting from the first elution of ⁹⁹Mo-^{99m}Tc generators used for SPECT or samples from synthesis of ¹⁸F-FDG (fluoro-deoxy-glucose) to be used for PET diagnostics. The importance of these measurements is related to the recommendation of national and international agencies [1, 9-11] to measure the content of ⁹⁹Mo and aluminum in the first eluate of a new generator, to verify that the ⁹⁹Mo fraction does not exceed 0.01% of the initial ^{99m}Tc activity. FDG

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preparation requires a purity of 99.9%, *i. e.* the total amount of quantity of other radionuclides must not exceed 0.1% of the total activity. To assess the concentration of radionuclides and verify compliance with these quantities, a calibration procedure of the efficiency of the spectrometer was carried out by measuring samples of a calibrated solution of $^{152-154}\text{EuCl}_3$ contained in the same bottles.

In all measurements, quantities determined were still below the percentage of the primary product as the limit indicated by the Pharmacopoeia [1]. We also considered the possibility of using other detectors, such as NaI(Tl) and LaBr₃(Ce) scintillators. However, the use of scintillation detectors is less advisable because of their detection limits which prevent detection of the photopeaks related to the main radionuclides present as impurities in a sample. In this case, an assessment of MDA allows the verification of the compliance with the activity limits indicated by the standard rules.

MATERIALS AND METHODS

Samples of FDG and of ^{99}Mo - $^{99\text{m}}\text{Tc}$ generator first elution were provided from the “San Gaetano” Nuclear Medicine Center, located at Bagheria, a little city near Palermo, Italy, while other samples originate from the “Villa Sofia Nuclear Medicine Center”, located in the city of Palermo and annexed to a public hospital. The quantities of radio pharmaceuticals, 10 ml of residual solution for the sample of FDG and 10 ml of the first elution from the ^{99}Mo - $^{99\text{m}}\text{Tc}$ generator, were provided in glass vials of the shape and size normally used by nuclear medicine departments.

The same samples, with no further action except closure by a plastic bag to avoid the spread of contamination, were subjected to gamma spectrometric analysis using a measurement system based on a HPGe detector ORTEC GEM 50195S, a detector with a very low background and high relative efficiency (60%). The samples were placed directly on the top of the detector, without any material between the detector end-cap and sample. An amplifier ORTEC mod. 672 and a multichannel analyzer ORTEC mod. 919E connected to a personal computer in the Ethernet environment were used to analyze signals. Figure 1 shows a photograph of the glass bottle used for samples of FDG.

Calibration of efficiency, taking into account variable forms of vials for FDG and those of $^{99\text{m}}\text{Tc}$ eluate used in various nuclear medicine departments, was performed with standards prepared with the procedure described below. Bottles of the same shape, with a self-sealing rubber stopper, were filled with about 10 ml of distilled water and then a small amount (one or two drops) of a concentrated europium chloride solution containing a large amount of ^{152}Eu and ^{154}Eu was added. Similarly other standards were pre-



Figure 1. Photograph of a 10 ml glass bottle containing a sample of FDG solution

pared containing 5, 15, and 20 ml of solution to determine the activities contained in samples of different heights (*i. e.* different thickness), as the ones from different centers. Figure 2 shows a photograph of some of the calibration vials, sealed in suitable plastic bags.

The activity of ^{152}Eu and ^{154}Eu in each bottle is unknown *a priori*; to determine ^{152}Eu and ^{154}Eu activities a comparison between a measurement of the vial placed at 25 cm from the detector and the corresponding calibrated point source of ^{152}Eu provided by Amersham was performed.

The value of activity of each radionuclide is then determined by using a weighted average of the values related to the gamma-ray with a higher emission rate. Then, the calibration bottle is measured in contact with the detector, in the same location of the samples to be measured. Measurements at small distances from the detector are affected by errors due mainly to the self-absorption in the matrix of the sample and coincidence-summing effects associated with multi-energy emissions of ^{152}Eu (and less for ^{154}Eu), whose impor-



Figure 2. Photograph of calibration bottles containing $^{152-154}\text{Eu}$ aqueous solution

tance depends on the efficiency of the detector. While the self-absorption effects are taken into account by using the same bottle, matrix, and height of the samples, an evaluation of the importance of coincidence-summing errors is not easy to perform, and only specific programs can be used. Suitable corrections for the main ^{152}Eu and ^{154}Eu gamma emissions were obtained by using the CORCO program [12] able to evaluate efficiency values of water cylindrical sources in the presence of coincidence-summing errors. However, the values of correction factors and the ones given in literature for a detector with a similar volume and "bottle" type measurement geometry do not exceed 10% [13] and this error range can also be accepted for the evaluations of radionuclide purity even though it must still be taken into account in the evaluation of overall uncertainties.

The determined activities of the vials were 1663 ± 45 Bq for FDG type and 1240 ± 40 Bq for the eluate type. Such activities are small enough and do not affect measurements due to the dead time of the detector even for sources located near the detector.

RESULTS AND DISCUSSION

The analysis of the spectrometric measurements on different samples shows the presence of some radionuclides in all measurements and enabled the determination of their related activities. For example, figs. 3 and 4 show the spectra recorded in a sample of FDG (10 ml) measured after 30 days from its production and a sample of $^{99\text{m}}\text{Tc}$ (first elution). The use of a detector of the type "low background" and a "cleaning" operation of the measurement cavity with exhausted nitrogen (or with a nitrogen gas from a cylinder) before measuring, eliminates the characteristic peaks of environmental radionuclides, and results in an improvement of spectrometer performances. Main radionuclides highlighted are: ^{56}Co , ^{57}Co , ^{58}Co for the sample of FDG and only ^{99}Mo for the second sample. We note that the identification and quantification of specific radionuclides (*e. g.*, ^{103}Ru , ^{131}I , and others) is related to the type of generator and method of production of the source, *i. e.* for example ^{99}Mo extracted as a fission product. A typical example is the spectrum

Figure 3. Gamma-ray spectrum of an FDG sample

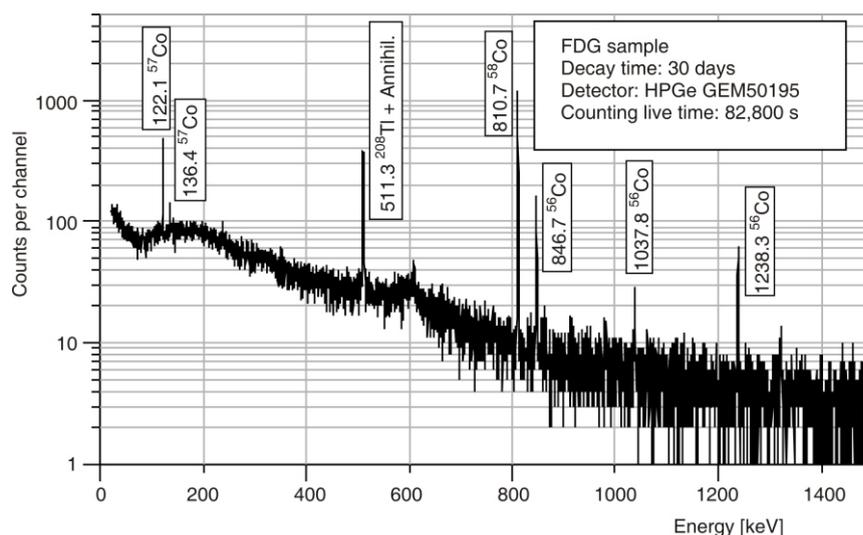
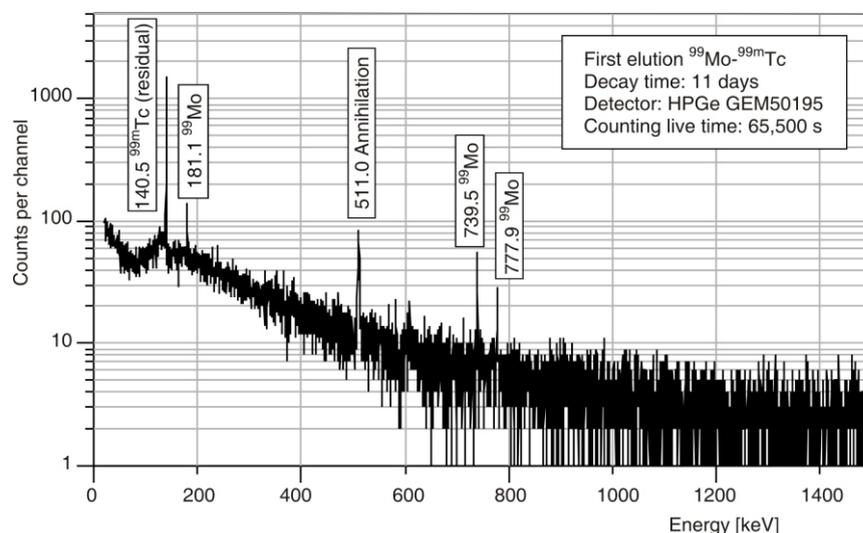


Figure 4. Gamma-ray spectrum of $^{99\text{m}}\text{Tc}$ sample derived from a first elution of a ^{99}Mo - $^{99\text{m}}\text{Tc}$ generator (first manufacturer)



shown in fig. 5, detected in a sample (first elution) extracted from a generator of a different manufacturer, where it shows the presence of ^{103}Ru , a fission product associated with ^{99}Mo .

The activities determined in all the measured samples are of the order of 1 to 2 Bq for ^{99}Mo , 0.2 to 0.5 Bq for ^{56}Co and ^{57}Co , while having a value of about 3 Bq for ^{58}Co . Relatively higher values are due to the second type of generator, with values at least 3 times higher. The activity values, regardless of generator type, are always quite small and it is already difficult to identify them except by long time spectrometric counting. This shows the consistency with the requirements of the technological processes of production used by the manufacturers of generators and the goodness of synthesis procedures for the production of radiopharmaceuticals for PET. Regarding the latter application, we have been able to verify that the small concentrations of impurities in the samples also depend on the effectiveness of filters and synthesis tech-

niques used. For example, fig. 6 shows a gamma-ray spectrum detected on a QMA filter provided with an IBA synthesis module. Several events related to the presence of impurities are identified whose quantity is significantly higher than that determined for FDG samples, with the uncertainties due to different measurement geometry. This confirms the goodness of filters provided with synthesis module from IBA.

The little amount of impurities in radiopharmaceuticals, a percentage much lower than the ones provided in good preparation procedures of radiopharmaceuticals, is difficult to detect with low energy resolution detectors. As tested experimentally, the use of a NaI(Tl) scintillator, with dimensions $3'' \times 3''$, typical energy resolution 7%, did not allow us to detect activities with the abovementioned order of magnitude, which are lower than the detection limits of the spectrometer system. Even an innovative type $\text{LaBr}_3(\text{Ce})$ scintillator, whose energy resolution is very high (2.8% to ^{137}Cs), does not yield significant

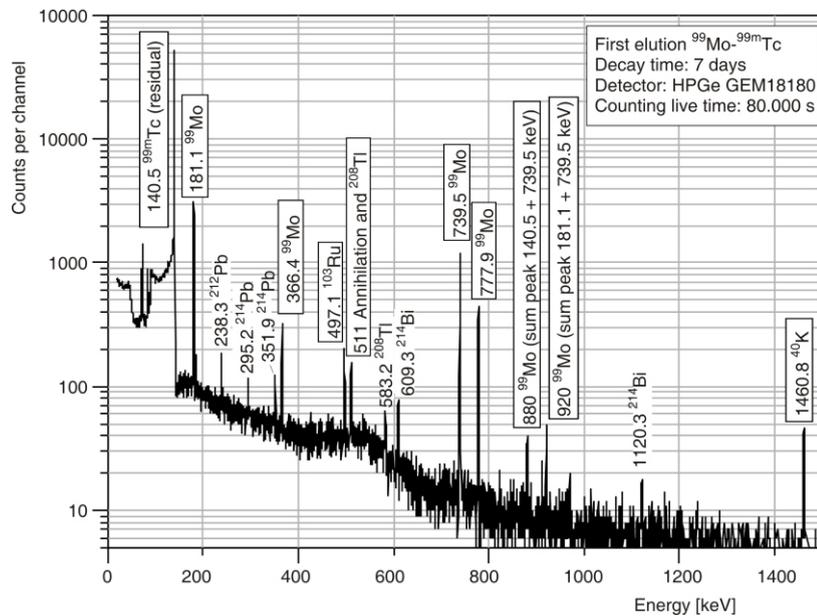


Figure 5. Gamma-ray spectrum of $^{99\text{m}}\text{Tc}$ sample derived from a first elution of a second manufacturer generator

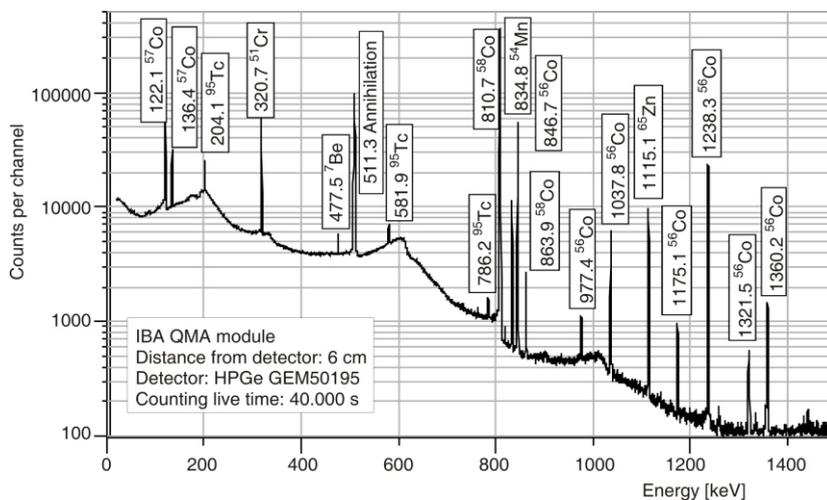


Figure 6. Gamma-ray spectrum of QMA filter provided in an IBA synthesis module

counts in desired energy ranges because of the inherent high background of the spectrum which increases the minimum levels of detection [14-17].

However, a system based on a scintillation detector, properly shielded, may be useful for a rapid assessment of the purity degree if the detection limits are still lower than the percentage amounts imposed by the Pharmacopeia. However, it is possible to compute the minimum detectable activity (MDA) value, *i. e.* the lowest activity of a radionuclide that can be determined for a reference energy with a spectrometric system in a given counting time. To confirm that, measurements of the same samples were made with both spectrometric systems based on a Tennelec NaI (TI) 3"× 3" scintillator and with a LaBr₃(Ce) detector, supplied by Saint-Gobain™, Brilliance-380 type, size 2"× 2", directly coupled to a photomultiplier PMT XP5500 Photonis. For both detector systems, scintillator, photomultiplier and the magnetic shield are hermetically sealed in an aluminum container to avoid hygroscopic problems. Both detectors are used in connection with an Ortec Nomad Plus Multichannel Buffer or an Ortec DigiBase (1024 channels) multi-channel unit connected via USB to a personal computer. Data acquisition and analysis are performed by using ScintiVision™ software supplied by Ametek [18].

The spectra obtained with both spectrometric systems did not highlight photopeaks of interest, even for long periods of counting. Therefore, we assessed MDA related to the efficiency of each detector and the background counting in the region-of-interest (ROI) corresponding to the reference energy in the spectrum. The relation for MDA computation, given by Currie [19] for background and sample spectra measured for the same counting time, is

$$MDA[\text{Bq}] = \frac{2.71 \cdot 4.65\sqrt{B}}{\varepsilon I T_c} \quad (1)$$

where B is the ROI background (computed as the product of the average value of the channel counting in the $2 \times \text{FWHM}$ range of channels, with the full width at half maximum (FWHM) inferred from the calibration curve), ε – the photoelectric efficiency (counts/photon), I – the emission probability, and T_c – the active time of counting. The efficiency values are determined by measuring the same standard bottle with ¹⁵²⁻¹⁵⁴Eu used for the calibration of HPGe detectors. The MDA evaluations for the system based on the NaI (TI) 3"× 3" scintillator vary both with counting time and shielding of the detector against environmental radioactivity, *i. e.* background level of the detector.

Just in relation to the variability of the measurement conditions that can be realized in various nuclear medicine centers, we have evaluated a range of MDA assessments with reference to measurements made in

different conditions and with counting time of 3,600 s (which corresponds to the highest MDA) and 80,000 s. The results, with reference to main gamma emissions of some radionuclides, are reported in tab. 1. The last column contains the ratio (in %) between the value of MDA and a reference activity of 370 MBq (10 mCi), which accounts for the dose given to patients for many diagnostic tests.

Table 1. MDA for 3" 3" NaI(Tl) spectrometric measurements, counting time ranged from 1 hour (3.600 s) and 80.000 s

Nuclide	Energy [keV]	Emission probability [%]	MDA [Bq]	Ratio (with reference to a 370 MBq activity) [%]
⁹⁹ Mo	181.1	5.99	3-57	8 10 ⁻⁵ -2 10 ⁻³
	739.5	12.13	4-29	1 10 ⁻⁴ -8 10 ⁻⁴
⁵⁶ Co	846.8	99.97	0.5-3.5	1 10 ⁻⁵ -9 10 ⁻⁵
	1238.3	66.41	1-6	2 10 ⁻⁵ -2 10 ⁻⁴
⁵⁷ Co	122.7	85.51	0.2-3	4 10 ⁻⁶ -8 10 ⁻⁵
⁵⁸ Co	810.9	99.45	0.5-4	1 10 ⁻⁵ -1 10 ⁻⁴

As regards the LaBr₃(Ce) scintillator, a range of MDA values is reported in tab. 2, which are nevertheless consistent with those determined above, and in some cases, slightly higher. That fact, in some ways surprising, can be justified because of the high intrinsic background of the scintillator [14-17] that, for some gamma emissions, significantly affects the MDA value.

Table 2. MDA ranges for 2" 2" LaBr₃(Ce) spectrometric measurements; counting time ranged from 1 hour (3.600 s) and 80.000 s

Nuclide	Energy [%]	Emission probability [%]	MDA [Bq]	Ration (with reference to a 370 MBq activity) [%]
⁹⁹ Mo	181.1	5.99	4-34	1 10 ⁻⁴ -9 10 ⁻⁴
	739.5	12.13	5-27	1 10 ⁻⁴ -7 10 ⁻⁴
⁵⁶ Co	846.8	99.97	1.2-5.8	3 10 ⁻⁵ -2 10 ⁻⁴
	1238.3	66.41	1-7	3 10 ⁻⁵ -2 10 ⁻⁴
⁵⁷ Co	122.7	85.51	0.25-2	6 10 ⁻⁶ -5 10 ⁻⁵
⁵⁸ Co	810.9	99.45	1.2-6	3 10 ⁻⁵ -2 10 ⁻⁴

We can note that MDA values with short counting times are smaller than the percentages listed in the Pharmacopoeia. Therefore, it may still be sufficient to carry out a measurement with this type of detectors to check that the condition do not exceed the percentage limits described above.

CONCLUSIONS

Radionuclide purity of a radiopharmaceutical can be assessed through various methods, but it is ad-

visible to use gamma spectrometry with HPGe detectors for initial validation of a new procedure, for example after a replacement of an important component in a FDG production chain or to test a new type of generator, and for subsequent confirmation tests. This can be checked at regular time intervals and can be considered an off-line monitoring of the stability of the generator or the quality of the radiopharmaceutical production process.

A second test, capable of ensuring compliance with regulatory rules, can be performed using a spectrometric systems based on scintillating detectors, although these are less sensitive than the semi-conducting detectors.

These conclusions may be useful for optimizing the procedures for quality assessment of radiopharmaceuticals and as guidelines in establishing the frequency of performing these checks.

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Елио ТОМАРЧИО

ГАМА СПЕКТРОМЕТРИЈСКО МЕРЕЊЕ ЧИСТОЋЕ РАДИОНУКЛИДА РАДИОФАРМАЦЕУТИКА У БОЦАМА

Чистоћа радионуклида радиофармацеутског производа обично се одређује гама спектрометријом при различитим геометријама мерења. Важност оваквог теста је у томе што нечистоће радионуклида, уколико постоје, увећавају дозу зрачења пацијента не доприносећи дијагностичкој информацији, а у неким случајевима могу се и помешати са молекулима за обележавање и утицати на правилно спровођење дијагностичког прегледа. У овом раду је коришћена гама спектрометрија ради одређивања количине нечистоће усвајајући за геометрију мерења исту боцу која садржи елуиране или припремљене радиофармацеутике. Поред полупроводничких детектора са германијумом високе чистоће (HPGe), испитивана је и употребљивост NaI(Tl) и LaBr₃(Ce) сцинтилационих детектора у рутинским поступцима. За сцинтилационе детекторе извршена је процена прага детекције и упоређена са граничним активностима које су утврђене регулаторним правилима. Главна разматрања тичала су се прве елуције ⁹⁹Mo-^{99m}Tc генератора и узорак ¹⁸F-FDG (флуоро-дезоксиглукозе) који се користе у позитронској емисионој томографији – PET дијагностици.

Кључне речи: чистоћа радионуклида, PET, SPECT, гама спектрометрија, доза
