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RADIONUCLIDIC PURITY – AN ESSENTIAL PARAMETER IN QUALITY CONTROL OF RADIOPHARMACEUTICALS

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Abstract. Radiopharmaceuticals are radioactively labeled compounds fulfilling the requirements of pharmaceutical products, used in radio diagnosis or radiotherapy. One essential parameter in the quality control of radiopharmaceuticals is the radionuclidic purity. In this work, we present aspects regarding the radionuclidic purity determination for the radiopharmaceutical products: Sodium Iodide (^{131}I) solution; Sodium Iodide (^{131}I) capsules for radiodiagnosis; Sodium Pertechnetate (^{99m}Tc) injection (non-fission).

Key words: radionuclidic purity, radiopharmaceuticals, nuclear medicine, gamma-ray spectrometry.

1. INTRODUCTION

Radiopharmaceuticals are radioactively labeled compounds fulfilling the requirements for pharmaceutical products, used in radiodiagnosis or radiotherapy. In order to become a radiopharmaceutical product, a chemical product undergoes a labeling procedure using a certain radionuclide with the adequate nuclear characteristics for the desired use in nuclear medicine.

The selection of a radionuclide for radiodiagnosis and radiotherapy must take account some aspects:

– the radionuclide must have specific nuclear characteristics, for the gamma radiation energy to allow the aquisition of good scintigraphies;

– the radionuclide must have adequate radiation energies and half-life such that the internal irradiation dose delivered to the patient after administration of radiopharmaceutical, for the whole duration of the medical procedure, to be as low as possible;

– the radionuclide must have certain chemical properties enabling its biological behavior to answer the desired purposes (localization only in the targeted organ) and the time until its clearance form the organism (biologic half-life) to be as short as possible. The product must have a selective affinity toward certain organs or groups of organs and in some specific cases to be metabolized, being physiologically inert and non toxic.

The radionuclides can be classified according to the preparation methods and their characteristics as follows:

a. Radioactive products obtained by target irradiation, with a higher or lower degree of chemical processing.

b. Radiounclides resulted from generators; these products consist of a daughter-radionuclide with short life-time obtained from a parent-radionuclide with longer half-time by elution from a chromatographic column or by solvent extraction.

c. Organic compounds labeled with radioactive isotopes, mainly radiopharmaceutical compounds, which after preparation and before utilization are subjected to radiochemical and radionuclidic purity control. This control is imperative, knowing that all labeled compound and especially labeled organic radiopharmaceutical compounds suffer a decay process over time.

The concept of purity applied to radiopharmaceutical compounds implies three aspects that need to be considered:

– radionuclidic purity;

– radiochemical purity;

– chemical purity.

The paper presents in detail only the radionuclidic purity aspects.

The radionuclidic purity is defined as the ratio between the activity of the base radionuclide and total activity of a radioactive compound, according to the Pharmacopoeia [1]. A compound has absolute radionuclidic purity if it contains no radionuclide other than the one of interest .

The radionuclidic purity is an essential parameter in the quality control of radiopharmaceuticals [2].

In this work, we present several aspects regarding the radionuclidic purity determination for the radiopharmaceutical products: Sodium Iodide (^{131}I) solution; Sodium Iodide (^{131}I) capsules for radio diagnosis; Sodium Pertechnetate (^{99m}Tc) injection (non-fission).

The method of high resolution HPGe gamma-ray spectrometry is, in present, the only fast, precise and complete analytic method available for the radionuclidic purity determination of radioactive mixtures of gamma emitting radionuclides.

2. OBTAINING OF THE RADIOPHARMACEUTICAL PRODUCTS: SODIUM IODIDE (^{131}I) SOLUTION; SODIUM IODIDE (^{131}I) CAPSULES FOR RADIO DIAGNOSIS

^{131}I was the first radionuclide used *in vivo* for hyperthyroidism and different forms of thyroid cancer treatment. Also, it is used for radioactive labeling of some substances for radio diagnosis and radiotherapy procedures [3].

The Sodium Radioiodide solution – Na^{131}I, as radiopharmaceutical product with oral administration is used for the treatment and as raw material in the production of Sodium Radioiodide gelatinous capsules with low activities used in radiodiagnosis of thyroidal diseases and with high activities for thyroid cancer treatment.

One purity condition that need to be fulfilled by radiopharmaceutical products is that radionuclidic purity determined (by gamma-ray spectrometry), must be $P_{RN} \geq 99.9$ %;

^{131}I radionuclide physic nuclear characteristics. ^{131}I is a gamma and beta emitter radioisotope with the main gamma emission energy of 364 keV (79%) and the main beta emission maximum energy of 610 keV (87.2%). The half-life of ^{131}I is 8.02 days.

^{131}I can be obtained by two different methods: by tellurium target irradiation in a nuclear reactor or by separation from the uranium fission fragments.

2.1. ^{131}I OBTAINED BY IRRADIATION OF Te

The nuclear reactions for ^{131}I obtained at nuclear reactor are presented in Fig. 1.

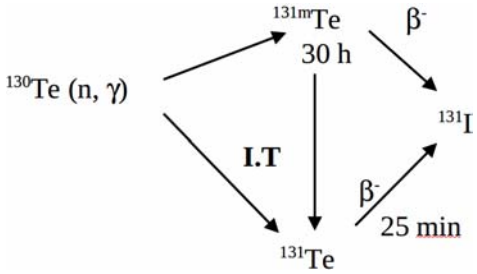

Fig. 1 – Activation and radioactive decay of ^{130}Te.

The target can be either metallic tellurium (Te) or tellurium dioxide (TeO_2). The abundance of tellurium isotopes in natural composition target is presented in Table 1.

Table 1

Abundance of tellurium isotopes in natural target

Isotope	Isotopic abundance [%]
^{120}Te	0.09
^{122}Te	2.47
^{123}Te	0.89
^{124}Te	4.74
^{125}Te	7.03
^{126}Te	18.72
^{128}Te	31.75
^{130}Te	34.24

The useful reaction is the activation of ^{130}Te and the useful radionuclide is ^{131}I. The activation cross section of ^{130}Te nuclide for thermal neutrons is 0.22 barn.

Other isotopes, formed in the composition of the irradiated target (Table 1), can result as radionuclidic impurities or stable isotopes, which are presented in Table 2.

Table 2

Isotopes obtained by natural tellurium irradiation

Isotope	Isotope produced by irradiation	$T_{1/2}$	Disintegration products
^{120}Te	^{121m}Te ^{121}Te	130 days 17 days	$^{121}Te \rightarrow ^{121}Sb$ (stable)
^{122}Te	^{123m}Te	104 days	^{123}Te (stable)
^{123}Te	^{124}Te	stable	
^{124}Te	^{125m}Te	58 days	^{125}Te (stable)
^{125}Te	^{126}Te	stable	
^{126}Te	^{127m}Te ^{127}Te	104 days 9.3 h	$^{127}Te \rightarrow ^{127}I$ (stable)
^{128}Te	^{129m}Te ^{129}Te	33 years 74 min.	$^{129}Te \rightarrow ^{129}I$ ($1.7x10^7$ years)

The sequence of activation reactions and decay mode presented in Fig. 2.

Iodine radioactive isotopes are produced by the following nuclear reactions, from Fig. 2.

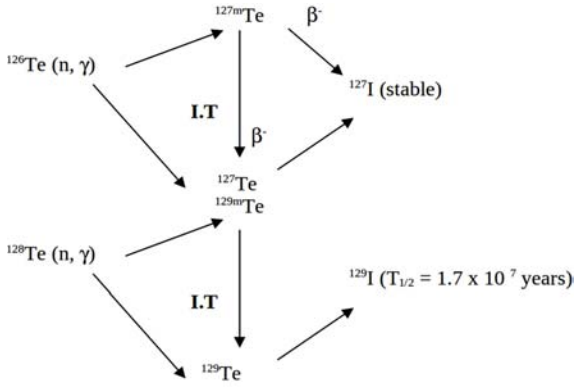

Fig. 2 – The sequence of activation reactions and decay mode.

The possible radionuclidic impurities, to be measured, are from Table 2. Specific activities of ^{131}I radioisotope, resulted after irradiation in a nuclear reactor depend on the irradiation conditions: irradiation time and thermal neutron fluxes (Table 3).

Table 3

Specific activities calculated for ^{131}I at different neutron flux values and irradiation times

Flux [n/cm^{2}s]	Activity after one week irradiation time		Activity after one month irradiation time		Activity at saturation	
	[mCi/g Te]	[GBq/g Te]	[mCi/g Te]	[GBq/gTe]	[mCi/g Te]	[GBq/g Te]
10^{12}	3.9	0.144	8.3	0.307	9.7	0.358
$5x10^{12}$	19.5	0.721	41.5	1.535	48.5	1.794
10^{13}	39	1.443	83	3.071	97	3.589
$2x10^{13}$	78	2.886	166	6.142	194	7.178
$5x10^{13}$	195	7.215	415	15.355	485	17.945
10^{14}	390	14.43	830	30.71	970	35.89

In IFIN-HH – CPR Department, ^{131}I was obtained by irradiation at VVR-S IFIN-HH nuclear reactor (until 1997, when the reactor was shut down in order to start decommissioning procedures) able to supply neutron flux values between 10^{12} n/cm^{2}s and 5×10^{12} n/cm^{2}s, the maximum obtainable activity being 1.794 GBq/g Te (48.5 mCi/g Te) with a minimum two months of target irradiation. After 1997, for a few years, ^{131}I was obtained at Triga SCN-Pitesti nuclear reactor, with the resulting activities being 20 times higher due to the maximum neutron flux of 1.4×10^{14} n/cm^{2}s.

2.2. THE SECOND METHOD OF OBTAINING ^{131}I IS ITS SEPARATION FROM FISSION PRODUCTS OBTAINED ACCORDING TO THE REACTION: $^{235}_{92}U(n,f)^{131}_{53}I+^{92}_{39}Y$+2neutrons [4]

In this case, other parallel reactions may occur and ^{131}I is separated by a complex radiochemical process followed by the advanced purification. Potential impurities originating from the synthesis; the ^{235}U fission generates more than 300 different isotopes that emerge in approximately 90 decay chains. During the time of the fission, many iodine isotopes are generated, as shown in Table 4.

Table 4

Iodine isotopes generated during the time of the fission

Isotope	$T_{1/2}$	Fission yield (*) [%]
^{127}I	Stable	0.13
^{129}I	1.7 x 10^7 [years]	0.8
^{131}I	8.1 [days]	3.1
^{132}I	2.3 [days]	4.7
^{133}I	20.8 [days]	6.62
^{134}I	52.5 [minutes]	8.06
^{135}I	6.7 [days]	6.3

* Yields for the decay chains are expressed without taking into account the decay ratios (Nordion MDS, Belgium)

These isotopes are isolated along with ^{131}I during the process of chemical purification:

– the yields of stable or long lived isotopes are very small and do not reach a value that may cause a significant decrease in the specific activity of ^{131}I.

– after purification, ^{131}I is contaminated with two short lived isotopes ^{133}I and ^{135}I. The ratios $^{135}I/^{131}I$ and $^{133}I/^{131}I$ quickly decrease with time. The usual time between the end of the irradiation and the use of ^{131}I is 12-14 days. This allows a decrease of the contamination level from ^{133}I by a factor of 5 000–2 0000.

Potential impurities are generated during production and purification. The β^- decay of ^{131}I leads to the formation of stable ^{131}Xe. Unavoidably, a small quantity of ^{131m}Xe ($T_{1/2}$=11.93 days) is produced (0.8% probability of decay). ^{131m}Xe is a γ/X emitter with the main radiations: 4 keV (X, 3%), 29–34 keV (X, 54%) and 164 keV (γ, 1.92%). Xe is a noble gas and leaves the solution.

3. OBTAINING OF THE RADIOPHARMACEUTICAL PRODUCT: SODIUM PERTECHNETATE (^{99m}Tc) INJECTION (NON-FISSION) FROM A NEW TYPE OF ^{99}Mo-^{99m}Tc GEL GENERATOR BASED ON ^{99}Mo-Zr GEL TECHNOLOGY USING ^{99}Mo OBTAINED BY IRRADIATION

The ^{99m}Tc radionuclide is nowadays the most used radionuclide in nuclear medicine for radiodiagnosis. ^{99m}Tc is the radionuclide used in 85 % of the nuclear medicine diagnosis procedures; it is due not only to its ideal nuclear properties but also its easy availability throughout the $^{99}Mo/^{99m}Tc$ generator.

A new type of $^{99}Mo/^{99m}Tc$ gel generator is based on a polypropylene column filled up with a zirconium molybdenum matrix ^{99}Mo-Zr. The raw material is ^{99}Mo obtained by irradiation in a nuclear reactor ^{98}Mo (n, γ) ^{99}Mo [5,6,7]. The advantages of "$^{99}Mo/^{m}Tc$ gel generator" are:

– the $^{99}MoO_3$, raw material obtained by (n,γ) nuclear reaction at nuclear reactor, is more reasonable than raw material obtained by separation from fission fragments;

– the raw material is obtained in our country, at Triga Pitesti nuclear reactor, eliminating the need for its import;

– the $Na^{99m}TcO_4$ solution obtained by elution from $^{99}Mo/^{99m}Tc$ gel generator, has higher chemical, radiochemical and radionuclidic purity than the classic generator with the alumina column; the α, β-γ fission impurities are not present;

– the ^{99}Mo binding is stronger in zirconium molybdenum matrix (due to the chemical bonds), than in classical generators where ^{99}Mo is absorbed on the alumina column (^{99}Mo being retained by physical interactions);

– the necessities of $^{99}Mo/^{99m}Tc$ generators in nuclear medicine laboratories from our country are not so high, so that it is not justified to develop the technology for ^{99}Mo separation from fission fragments (which is expensive and generates large quantities of radioactive wastes).

The $^{99}Mo/^{99m}Tc$ classic generator is based on a polypropylene column filled with Al_2O_3.

^{99}Mo obtained by separation from fission fragments is absorbed on the alumina column by physical interactions.

The ^{99}Mo binding is stronger in zirconium molybdenum matrix, due to the chemical bonds, than in classical generator where ^{99}Mo are absorbed on the alumina column as ^{99}Mo is retained by physical interaction.

Obtaining of $^{99}Mo/^{99m}Tc$. Physical-chemical characteristics of ^{99}Mo radionuclide; nuclear reactions leading to ^{99}Mo. ^{99}Mo is a beta/gamma emitter with main beta radiation energy of 1.23 MeV (85%) and main gamma radiation energy of 140 keV (86 %). ^{99}Mo has a half-life of 67 hours. By β^- decay of ^{99}Mo, the "daughter" radionuclide ^{99m}Tc results, with a half-life of 6.007 hours and the main gamma radiation energy of 140 keV [4].

The nuclear reactions for ^{99}Mo production at the nuclear reactor are in the Fig. 3.

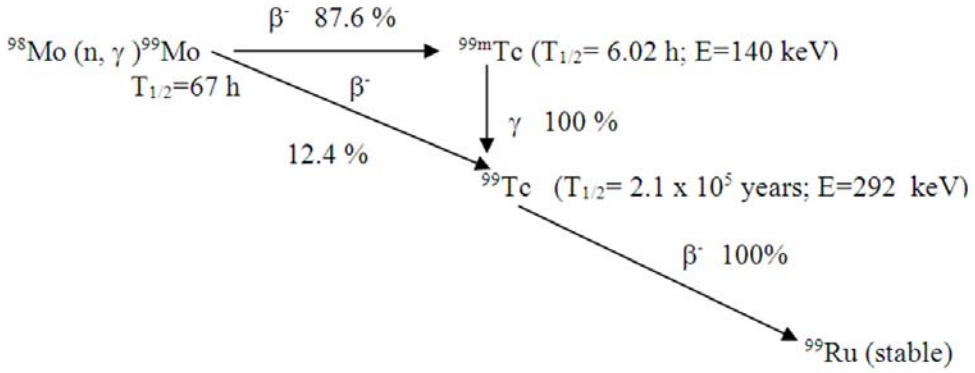

Fig. 3 – The nuclear reactions for the ^{99}Mo production in a nuclear reactor.

The relative abundance of ^{98}Mo is 23.75 %; the activation cross section for thermal neutrons of ^{98}Mo is 0.51 barn; the raw material used for irradiation is molybdenum trioxide.

Some other radionuclides appear after irradiation: ^{101}Mo ($T_{1/2}$=15 min), ^{101}Tc ($T_{1/2}$=15 min.). ^{99}Tc ($T_{1/2} = 2.15 \times 10^5$ years) is the daughter of ^{99}Mo, either direct or *via* ^{99m}Tc decay.

Target (natural MoO_3 with purity > 99 %) preparation for neutron irradiation in the nuclear reactor. The raw material is natural MoO_3, which is weighed with the analytical balance and is closed in a special container (of high purity aluminum, over 99 %). This container is sealed by electron beam welding in an external container (of high purity aluminum, over 99%) for irradiation.

Irradiation of the target in the nuclear reactor. The targets were irradiated in Triga nuclear reactor from SCN Pitesti. The irradiation conditions were: time about 1 week; neutron flux between 5×10^{13} and 10^{14} n/cm^{2}s. In these irradiation conditions, no gamma impurities emerge.

The nuclear reaction is: ^{98}Mo (n, γ) ^{99}Mo. For one week irradiation time and a neutron flux of 5×10^{13} n/cm^{2}s (usual for Triga reactor from SCN Pitesti) one can produce about 800 mCi/g Mo (29.6 GBq/g Mo).

The irradiation location at TRIGA-SSR reactor selected for ^{99}Mo obtaining was XC1; power ~ 5.8 MW.

The characteristics of this location at 1 MW are: thermal neutron flux: $\Phi_{Sc}= 1.36\cdot10^{13}$ n/cm^{2}s; average energy flow: $3.14\cdot10^{-1}$MeV; fast flow ($0.1< E > > 18$ MeV): $\Phi_R= 4.42\cdot10^{12}$ n/cm^{2}s; relation between heat flux and epithermal flux: $f = \Phi_{Th}/\Phi_{Epi} = 19.66$.

In this irradiation conditions, no gamma impurities are suspected to be produced.

The final product – $Na^{99m}TcO_4$, injectable radiopharmaceutical product is a clear, colorless solution.

The radionuclidic purity conditions that must be fulfilled by sodium pertechnetate $Na^{99m}TcO_4$ radiopharmaceutical product obtained from this new type of generator using ^{99}Mo obtaines by irradiation, are:

– radionuclidic purity (by gamma spectrometry), $P_{RN} \geq 99.9$ %;

– radiochemical purity, $P_{RC} \geq 95$%;

4. RESULTS

4.1. RADIONUCLIDIC PURITY DETERMINATION BY GAMMA–RAY SPECTROMETRY

In this part of the work, we present the aspects regarding the radionuclidic purity determination for the radiopharmaceutical products: Sodium Iodide (^{131}I) solution; Sodium Iodide (^{131}I) capsules for radiodiagnosis; Sodium pertechnetate (^{99m}Tc) injection (non-fission) [8].

The gamma-ray spectrometry method is used to determine the radionuclidic purity or radioactive mixtures containing gamma emitters.

In order to determine the radionuclidic purity of radiopharmaceutical products we used a gamma spectrometry installation consisting of:

– HP Ge detector with built-in preamplifier;
– high voltage source (0–4000) V;
– fast spectroscopic amplifier;
– Canberra multichannel analyzer, type MP 2-1 E-Multiport II, Ethernet, USB;
– Canberra S 502C-GENIE 2000 Basic licensed software.

Sample measurements and radionuclidic purity calculation. The optimum distance between the sample and the detector is selected according to sample activity so that the dead time (displayed in GENIE 2000 program window) is less than 10%.

The activity (Bq) of one radionuclide present in the sample can be calculated according to the relation:

$$\Lambda = \frac{A \cdot F_c}{t \cdot \text{eff} \cdot p}, \tag{1}$$

where: A – area of full energy peak (FEP) of interest from the gamma radiation spectrum; t – measuring time (s), eff – the corresponding efficiency for FEP; p – the emission probability of the gamma radiation corresponding to the considered FEP; F_c – correction factor for summing by real coincidences.

The activities for all radionuclides identified in the gamma spectrum of the sample are calculated according to relation (1).

The following relation is used to calculate the radionuclidic purity:

$$P_{RN}(\%) = \frac{\Lambda}{\Lambda_i + \Lambda} \cdot 100, \tag{2}$$

where: Λ_i – activities summing for all the radionuclides present in the sample, considered as impurities; Λ – activity of the radionuclide of interest (for which the radionuclidic purity is being calculated).

All activities values from relation (2) must be calculated at the same moment, when the radionuclidic purity is calculated.

4.2. RADIONUCLIDIC PURITY DETERMINATION FOR RADIOPHARMACEUTICAL PRODUCTS: SODIUM IODIDE (^{131}I) SOLUTION; SODIUM IODIDE (^{131}I) CAPSULES FOR RADIODIAGNOSIS

According to the Work Procedure code AC-PC-CPRLAB-01 [9] the sample consists of 10 μL $Na^{131}I$ test solution dropped on a paper stripe which is placed in a

glass vial closed with a rubber stopper to avoid detector contamination. The $Na^{131}I$ test solution is either the radiopharmaceutical product Sodium Iodide (^{131}I) solution, or a solution obtained by a Sodium Iodide (^{131}I) capsule dissolution in distilled water. The vial containing the paper stripe is placed centered on the detector (0 cm) or at 44.5 cm above it, according to sample activity (so that the dead time is less than 10%).

The measuring time is set to 1000 s and the spectrum acquisition starts. After completing the acquisition, the spectrum is saved on the PC's hard-disk. The whole spectrum is carefully analyzed such that we identify: FEP corresponding to ^{131}I, the background of measuring installation. According to the European Pharmacopoeia [1], impurities such as ^{130}I, ^{133}I, ^{135}I [10] are compulsory to be investigated.

In the same region of the energetic spectrum there are some close values for gamma emission energies of ^{131}I (503.0 keV) and its possible gamma-ray impurities, ^{135}I (half-life 6.55 h, main gamma radiation energies 526.6 and 1260.4 keV, emission probabilities 0.133, respectively 0.289), ^{133}I (half-life 20.8 h, main gamma radiation energy 529.9 keV, emission probability 0.87), ^{130}I (half-life 12.4 h, main gamma radiation energy 536.0 keV, emission probability 0.99). If there are impurities identified in the spectrum, we must calculate (using relation (1)) the activity for each one and also the activity for ^{131}I (half-life 8.02 days, considering FEP area at 503 keV, with the emission probability 0.003589).

The necessary efficiency values for all these calculation are presented in table 5 (for distances of 44.5 cm and 0 cm, with F_c=1), and were determined within the process of HPGe system calibration in efficiency *versus* energy.

Table 5

Efficiency values at different energies

0 cm	Energy [keV]	503.0	526.6	529.9	536.0
	Efficiency	0.0601 ±3.5 %	0.0574 ±3.6 %	0.0571 ± 3.6 %	0.0565±3.6 %
44.5 cm	Energy [keV]	503.0	526.6	529.9	536.0
	Efficiency	0.000234 ± 6 %	0.000223 ± 6 %	0.000222 ± 6 %	0.000219 ± 6 %

The radionuclidic purity is calculated using relation (2).

More than 99.9 % of the total radioactivity is due to ^{131}I and less than 0.1 % of the total radioactivity is due to ^{133}I, ^{135}I and other possible radionuclidic impurities.

In Fig. 5, we present the gamma radiation spectrum for ^{131}I radiopharmaceutical products. In this spectrum, the only one radionuclide identified are: ^{40}K from the background and ^{131}I from the radiopharmaceutical product. The suspect impurities are not identified as visible, by comparison with the ^{131}I to 503.004 keV and emission probability of 0.3589 %.

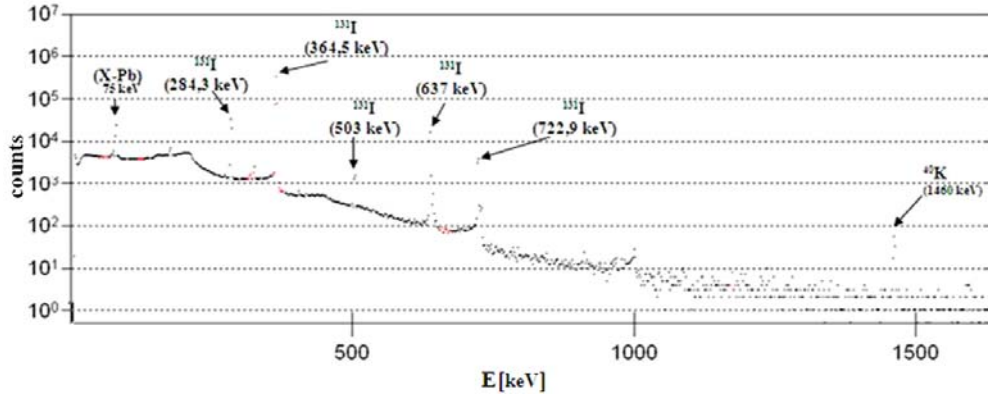

Fig. 5 – Gamma radiation spectrum for radiopharmaceutical products with ^{131}I.

4.3. RADIONUCLIDIC PURITY DETERMINATION FOR RADIOPHARMACEUTICAL PRODUCT: SODIUM PERTECHNETATE (^{99M}Tc) INJECTION (NON-FISSION)

One must fisrt measure the ^{99m}Tc activity in the sample (sodium pertechnetate $Na^{99m}TcO_4$ eluted from the generator, placed in a glass vial closed with rubber stopper) using a radioisotope calibrator, for a certain time.

The sample for analysis (sodium pertechnetate $Na^{99m}TcO_4$ eluted from the generator, placed in a glass vial closed with rubber stopper) is introduced in KT type (from lead and stainless steel) container, in order to absorb selectively the ^{99m}Tc (140 keV) radiations. The sample introduced in this container is measured by gamma-ray spectrometry. The measuring time is 200 s. The KT type container containing the sample is centered placed, at 44.5 cm above the detector and the spectrum acquisition is started (considering the starting time t_0).

Just one impurity ^{99}Mo (half-life 66 h), is possible to exist, with main gamma emission energy 739.5 keV. The most prominent gamma emission of ^{99m}Tc (half-life 6.02 h) has an energy of 140 keV.

After the spectrum acquisition is finished, we determine the 739.5 keV FEP area. The spectrum is saved on the PC's hard-disk.

For the measuring conditions presented above, the ^{99}Mo activity, at the moment $t=t_0+200s$ (considered the final moment) is calculated using the following relation, (3):

$$\Lambda(^{99}\mathrm{Mo}) = \mathrm{Area}(\mathrm{FEP}_{739.5\mathrm{kev}}) \cdot 0.014629. \quad (3)$$

The measured activity values for both ^{99m}Tc and ^{99}Mo are calculated for the generator calibration date and time.

The purity can be calculated according to relation (2) using the QBASIC program named PUR99mTC.bas, or other programs such as ORIGIN, EXCEL, etc.

More than 99.9 % of the total radioactivity is due to ^{99m}Tc and less than 0.1 % of the total radioactivity is due to ^{99}Mo.

The gamma radiation spectrum of Sodium Pertechnetate $Na^{99m}TcO_4$ eluted from ^{99}Mo/^{99m}Tc gel generator is presented in Fig. 6. From Fig. 6 one can conclude that none impurity occurs.

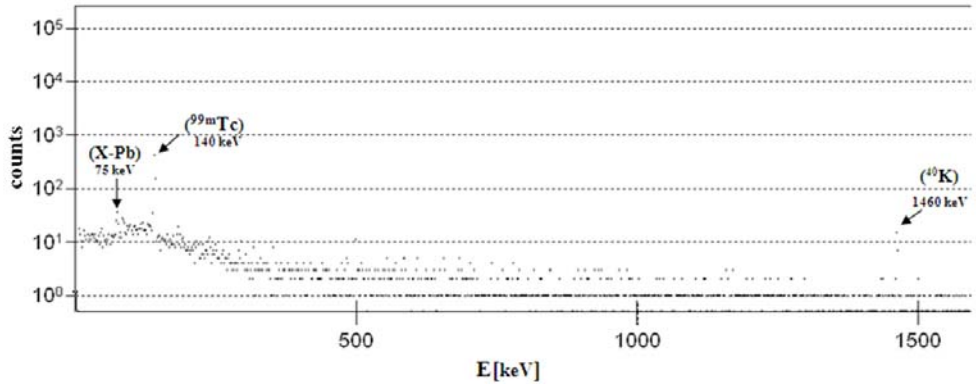

Fig. 6 – Gamma radiation spectrum of Sodium Pertechnetate $Na^{99m}TcO_4$ eluted from ^{99}Mo-^{99m}Tc gel generator.

5. CONCLUSIONS

The radionuclidic purity is an essential parameter in the quality control of radiopharmaceuticals. The radionuclidic purity for radiopharmaceutical products must be higher than 99.9 %, according to the European Pharmacopoeia.

From the presented experiments and based on our own experience in radiopharmaceutical products manufacturing in CPR Department from IFIN-HH, we can conclude that all radiopharmaceutical products presented in this paper fulfill the criteria for radionuclidic purity.

The radionuclidic purity values for the presented compounds were higher than 99.99% proving that they are adequate to be used as radiopharmaceutical products.

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