

QUALITY CONTROL STUDIES OF ^{99}Mo USED IN $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ GENERATORS PRODUCED AT IPEN-CNEN/SP

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ABSTRACT

$^{99\text{m}}\text{Tc}$ is the most used radionuclide in nuclear medicine. In Brazil, the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators are produced exclusively by the Center of Radiopharmacy at IPEN-CNEN/SP, by importing ^{99}Mo from different suppliers. ^{99}Mo ($t_{1/2} = 66$ h) is a fission product of ^{235}U , therefore, it can be accompanied by several radioisotopes that are highly prejudicial for human health, demanding a strict quality control of this product for generators safe use. The European Pharmacopoeia established some parameters and limits that evaluate the quality of the solution of sodium [^{99}Mo]molybdate, that is used as raw material for generator's production. The European Pharmacopoeia also recommends some analytical methods to perform these evaluations, however, it has been observed difficulties on the implementation of these methods by the generator's producers. These difficulties are probably related to the lack of practicability of the proposed methods and the extensive list of utilized reagents. In this work some procedures of the European Pharmacopoeia's quality control method for ^{99}Mo were evaluated. Different types of solid phase exchanger cartridges were tested for retention of ^{99}Mo in 3 different conditions. Cartridges that presented percentages of retention higher than 90% were also tested for separation of ^{99}Mo from possible contaminants (Ru e Te). The results shown that solid phase exchanger cartridges that presented percentages of retention of Mo higher than 90% also presented significant percentages of retention of Ru and Te. An alternative method for separation of ^{99}Mo from ^{131}I (other contaminant) are also proposed.

1. INTRODUCTION

Nuclear medicine is a medical modality in which nuclear properties of various radioisotopes are utilized for diagnosis and therapy of various pathologies. More than 90% of all procedures are diagnostic imaging, and more than 80% of the images are obtained by using $^{99\text{m}}\text{Tc}$ [1]. The chromatographic generator $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ is the most used source of $^{99\text{m}}\text{Tc}$ of high quality and adequate activities [2]. This generator is based on the $^{99\text{m}}\text{Tc}$ radioactive father, ^{99}Mo ($t_{1/2} = 66$ h), obtained through the nuclear fission of ^{235}U in nuclear research reactors, which ensures high specific activity of ^{99}Mo required for the production of the generator. For generators safe use a strict quality control of ^{99}Mo is necessary, including chemical, radionuclidic and radiochemical purity analysis. The European Pharmacopoeia [3] established some parameters and limits that evaluate the quality of the solution of sodium [^{99}Mo]molybdate, to be used as raw material for generator's production. The European Pharmacopoeia also recommends some analytical methods to perform these evaluations. Table 1 shows the main ^{99}Mo impurities, their limits and the recommended quantification method by European Pharmacopoeia.

Table 1. European Pharmacopoeia limits for main radionuclidic impurities of ^{99}Mo and recommended quantification methods.

Radionuclides	Maximum activity allowed	Quantification method
^{131}I , ^{103}Ru e ^{132}Te	5×10^{-3} % of the total radioactivity	Gamma-ray spectrometry
Total radioactivity due to ^{90}Sr and ^{89}Sr	6×10^{-5} % of the total radioactivity	Liquid scintillation spectrometry
Total of gamma emitting radionuclides other than ^{99}Mo , $^{99\text{m}}\text{Tc}$, ^{131}I , ^{103}Ru e ^{132}Te	1×10^{-2} % of the total radioactivity	Gamma-ray spectrometry
Total radioactivity due to alpha-particle emitting impurities	1×10^{-7} % of the total radioactivity	Alpha spectrometry

The main gamma emitting contaminants of ^{99}Mo are ^{131}I , ^{103}Ru and ^{132}Te . For the detection and quantification of these impurities at the maximum allowed level the removal of bulk activity of ^{99}Mo is necessary, since it has been verified that ^{99}Mo gamma energies peaks can easily overlap impurities peaks at low activity on a gamma spectrum. For ^{99}Mo separation the European Pharmacopoeia recommends the use of strongly basic anion-exchange resin. A practical solution for a routine procedure is the use of commercial solid phase exchanger cartridges. For that reason, the ideal cartridge property would be to retain at maximum ^{99}Mo with, at the same time, none retention of the impurities. In fact, these devices are very effective on retention of ^{99}Mo but the retention of part of the impurities cannot be overlooked. The European Pharmacopoeia recommendation is to estimate impurities retention on cartridges or resins by using radioactive tracers of known activity of each impurity on each elution. For example, to estimate ^{131}I retention is recommended the use of a reference solution of ^{123}I and to estimate ^{103}Ru retention is recommended the use of ^{106}Ru reference solution. Due to the disadvantages of handling radioactive tracers on a quality control routine, an alternative method of separation of ^{99}Mo from its contaminants was studied. The thin layer chromatography (TLC) technique showed an important advantage that is the possibility of separate ^{99}Mo from its contaminants without any loss of contaminant, thus eliminating the use of radioactive tracers for estimate impurities loss during the procedure. After developing the strip, it is possible to cut the strip in segments and count these segments singly at a hiperpure germanium (HPGe) detector. The aim of this work is to develop and adapt the ^{99}Mo quality control technology in order to implement this procedure in Center of Radiopharmacy at IPEN-CNEN/SP, whereas quality control of the imported ^{99}Mo is not yet a routinely practice on this institution. Moreover, it is expected that the developed method could be adapted for the routine production of ^{99}Mo at the new Brazilian Multipurpose Reactor in the future.

2. MATERIALS AND METHODS

2.1. Retention of ^{99}Mo on Solid Phase Exchanger Cartridges

Six types of solid phase exchanger cartridges were tested for the retention of ^{99}Mo :

- Sep-Pak QMA Light
- Sep-Pak Plus Silica
- Maxi-Clean SCX 600 mg
- Sep-Pak Plus Alumina-N
- Maxi-Clean Alumina-A 1800 mg
- Sep-Pak Plus Alumina-B

On each cartridge, 2 mL of a sodium [^{99}Mo]molybdate solution with a radioactive concentration of 50 $\mu\text{Ci/mL}$ was applied with a syringe. The ^{99}Mo solutions were prepared in 3 different conditions:

- Diluted in $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$; concentration: 2.42 g/L in aqueous solution (pH=5.5);
- Diluted in HCl pH 1.5;
- Diluted in a mixture of glacial acetic acid and H_2O_2 prepared according European Pharmacopoeia 8.0 (pH=2).

After applying ^{99}Mo solution on each cartridge, the eluted solution was collected and the cartridge was rinsed with 2 mL of a mixture of equal volumes of glacial acetic acid and water. The rinse fraction was also collected. Then, cartridge, eluted fraction and rinse fraction were measured one at a time at a CRC – 10BC dose calibrator by Capintec Inc., USA, to determine the percentage of retention of ^{99}Mo on each cartridge.

2.2. Retention of ^{99}Mo Contaminants on Solid Phase Exchanger Cartridges

Solid phase exchanger cartridges that presented percentage of retention of ^{99}Mo higher than 90% were tested for retention of possible contaminants – ^{131}I , ^{103}Ru and ^{132}Te . For ^{103}Ru and ^{132}Te analysis, non-radioactive assays have been performed by using Mo, Ru and Te ICP-OES standards solutions and an ICP-OES spectrometer model Varian Vista – MPX by Varian Inc., USA. Non-radioactive standards solutions containing Mo, Ru and Te of known concentrations were prepared in 3 different conditions, similar to the conditions described on item 2.1:

- Diluted in water with pH 5.5;
- Diluted in HCl pH 1.5;
- Diluted in a mixture of glacial acetic acid and H_2O_2 prepared according European Pharmacopoeia 8.0.

2 mL of the standards solutions were applied on the selected cartridges with a syringe. The eluted was collected and the cartridge was rinsed with 2 mL of a mixture of equal volumes of glacial acetic acid and water. The rinse fraction was also collected. Then, an aliquot of the standard solution (the same that was applied on cartridge), eluted fraction and rinse fraction

were measured at ICP-OES spectrometer, to determine the percentage of retention of each element on the selected cartridges.

2.3. Separation of ^{131}I from ^{99}Mo by Thin Layer Chromatography

The preliminary tests on separation of ^{131}I from ^{99}Mo by TLC were performed on 2 types of stationary phases: Whatman 3MM chromatography paper (1.5 x 12 cm) and Silica gel on TLC Al foil (1.5 x 12 cm). The mobile phase utilized was methanol 70% in aqueous solution [4]. The idea of the experiment was to keep ^{99}Mo on the origin of the strip and to carry up ^{131}I to the top. In order to hold ^{99}Mo species on the origin its precipitation was performed by dripping a single spot of 20% KSCN in aqueous solution before dripping the ^{99}Mo sample [5]. In order to be precipitated, ^{99}Mo sample in the form of sodium molybdate must be reduced to Mo(V) before applying it on the strip [5]. The reducing agent utilized was saturated solution of SnCl_2 diluted in 2 mol/L HCl. After developing the strip, it was cut in 10 segments and each one was counted at a HPGe detector during 120 seconds. Two different strips were tested in 3 conditions:

- The spot contained only ^{99}Mo with activity of 5.55 kBq (0.15 μCi);
- The spot contained only ^{131}I with activity of 5.55 kBq (0.15 μCi);
- The spot contained a mixture of ^{99}Mo and ^{131}I with activity of 5.55 kBq (0.15 μCi) each one.

The main gamma energies of each radionuclide (For ^{99}Mo , 739.5 keV and for ^{131}I , 364.5 keV) were used for identification and quantification.

3. RESULTS AND DISCUSSION

3.1. Retention of ^{99}Mo on Solid Phase Exchanger Cartridges

Table 2 shows the percentages of retention of ^{99}Mo on the 6 types of solid phase exchanger cartridges studied at 3 different conditions. The following cartridges that presented percentage of retention higher than 90% were selected for tests of contaminants retention:

- At molybdate aqueous solution: Sep-Pak Plus Alumina-N, Maxi-Clean Alumina-A 1800 mg and Sep-Pak Plus Alumina-B.
- At HCl pH 1.5: Sep-Pak QMA Light, Maxi-Clean SCX 600 mg, Sep-Pak Alumina-N, Maxi-Clean Alumina-A 1800 mg and Sep-Pak Plus Alumina-B.
- At acetic acid and H_2O_2 : Sep-Pak Plus Alumina-N, Maxi-Clean Alumina-A 1800 mg and Sep-Pak Plus Alumina-B.

Table 2: Percentages of retention of ⁹⁹Mo on solid phase exchanger cartridges.

Cartridge	Percentages of Retention of ⁹⁹ Mo (%)		
	Molybdate aq. sol.	HCl pH 1.5	Acetic acid + H ₂ O ₂
Sep-Pak QMA Light	0.8	98.2	8.7
Sep-Pak Plus Silica	0.4	9.7	1.2
Maxi-Clean SCX 600 mg	34.7	97.5	0.8
Sep-Pak Plus Alumina-N	99.1	99.5	94.7
Maxi-Clean Alumina-A 1800 mg	99.7	99.8	99.1
Sep-Pak Plus Alumina-B	99.2	100.0	98.0

3.2. Retention of ⁹⁹Mo Contaminants on Solid Phase Exchanger Cartridges

Figure 1, 2 and 3 shows the percentages of retention of the contaminants Ru and Te and the percentage of retention of Mo on the selected solid phase exchanger cartridges for each condition.

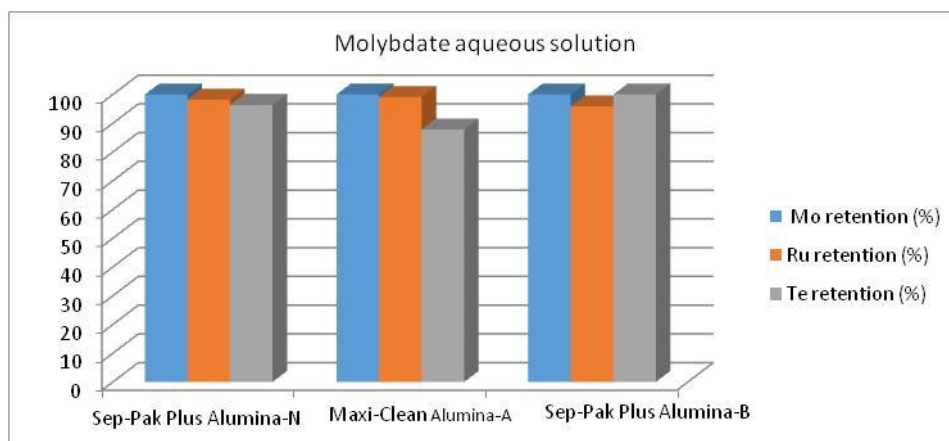


Figure 1. Percentages of retention at molybdate aqueous solution.

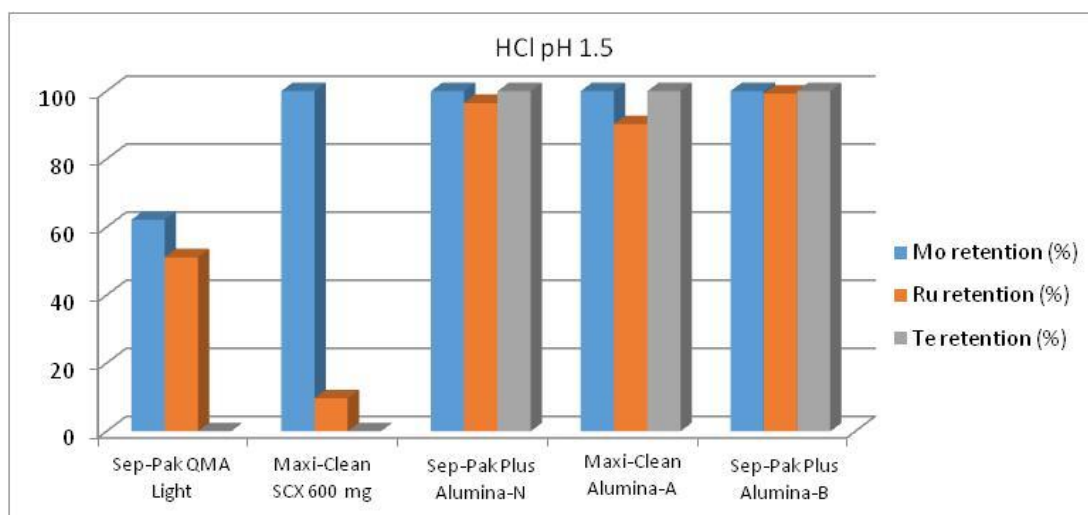


Figure 2. Percentages of retention at HCl pH 1.5.

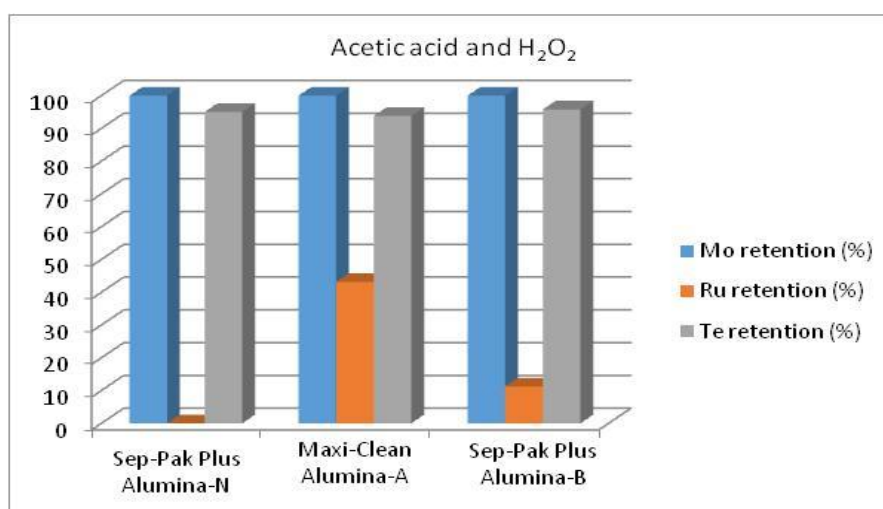


Figure 3. Percentages of retention at acetic acid and H₂O₂.

Sep-Pak Plus Alumina-N and Sep-Pak Plus Alumina-B cartridges, at mixture of glacial acetic acid and H₂O₂, presented the lowest percentages of retention for Ru, but their percentages of retention for Te were high, close to Mo values. At HCl pH 1.5, Maxi-Clean SCX 600 mg cartridge showed the most promising performance with a percentage of retention of Ru close to 10% and for Te, close to 0%.

3.3. Separation of ¹³¹I from ⁹⁹Mo by Thin Layer Chromatography

Figures 4, 5 and 6 show the distribution of ⁹⁹Mo and ¹³¹I alone and mixed on Whatman 3MM chromatography paper.

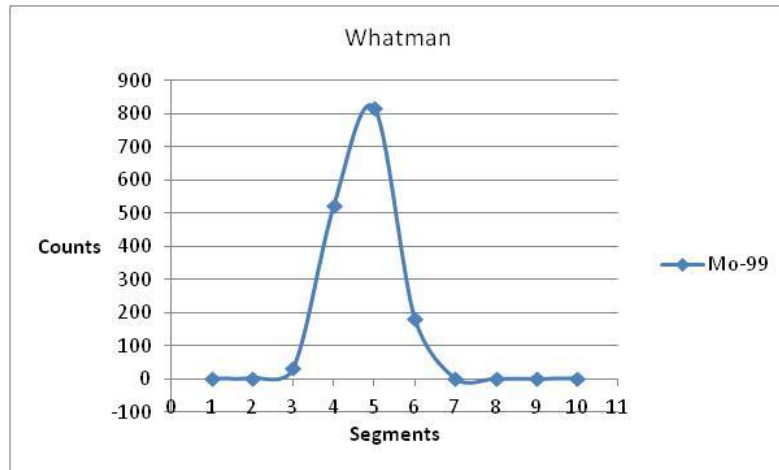


Figure 4. Distribution of ^{99}Mo on Whatman 3MM chromatography paper.

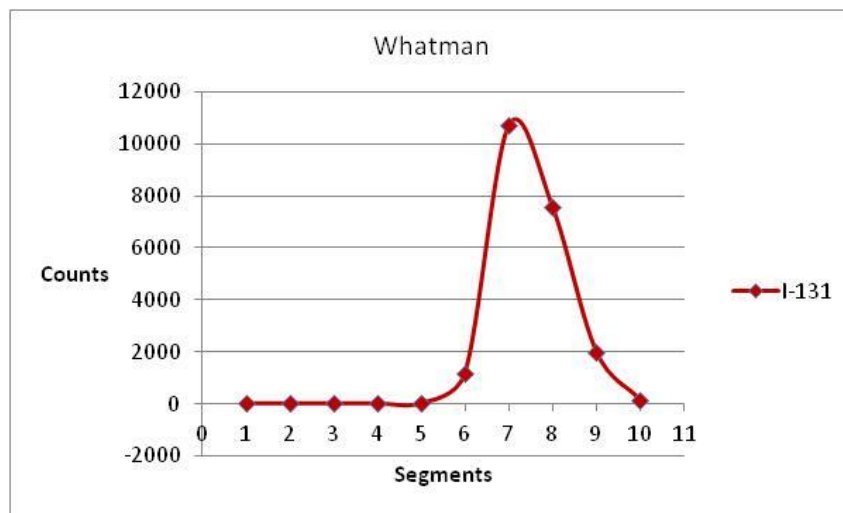


Figure 5. Distribution of ^{131}I on Whatman 3MM chromatography paper.

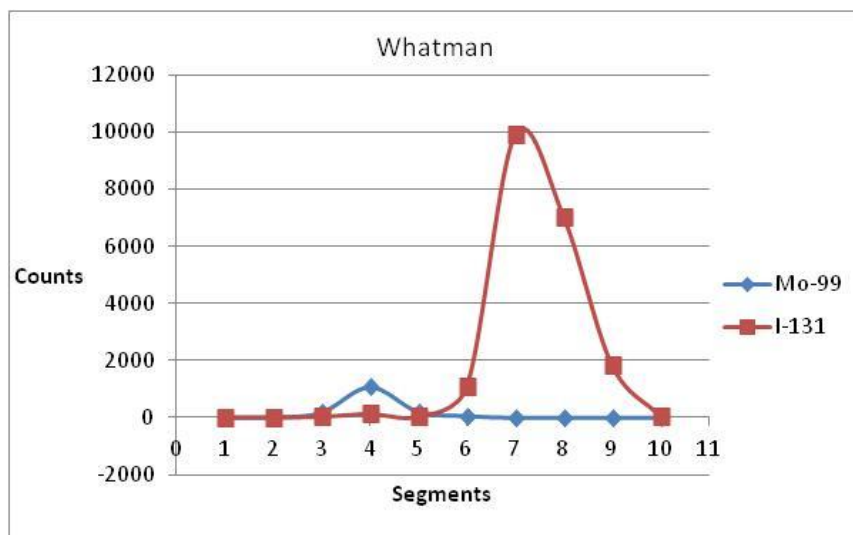


Figure 6. Distribution of a mixture of ^{99}Mo and ^{131}I on Whatman 3MM chromatography paper.

Although Whatman 3MM chromatography paper enabled a separation of ^{99}Mo and ^{131}I , the peaks of distribution are very close to each other. Figures 7, 8 and 9 shows the distribution of ^{99}Mo and ^{131}I alone and mixed on Silica gel on TLC Al foil.

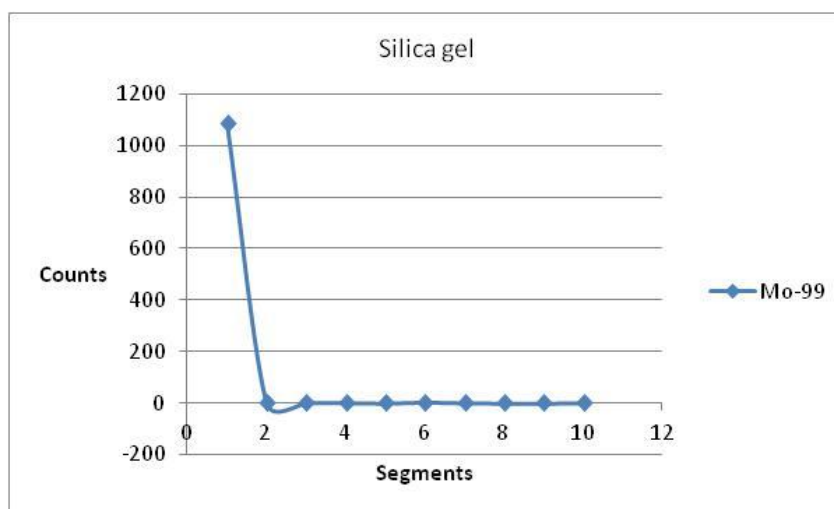


Figure 7. Distribution of ^{99}Mo on Silica gel on TLC Al foil.

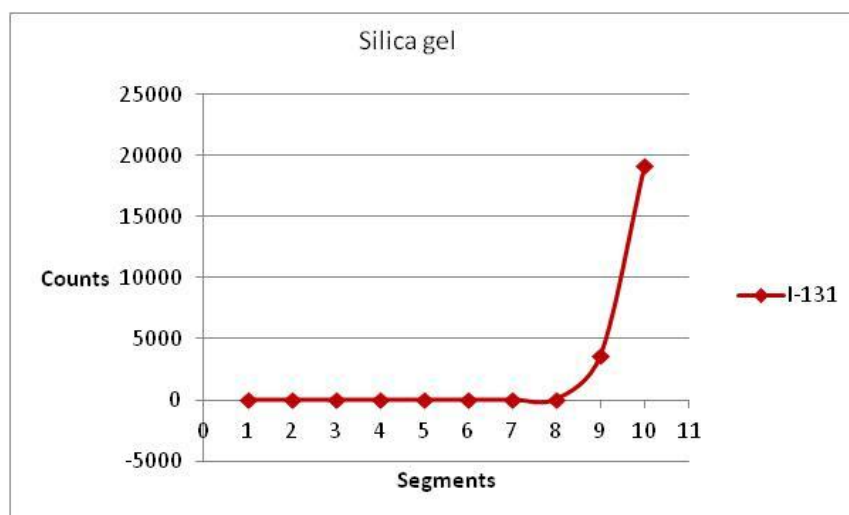


Figure 8. Distribution of ^{131}I on Silica gel on TLC Al foil.

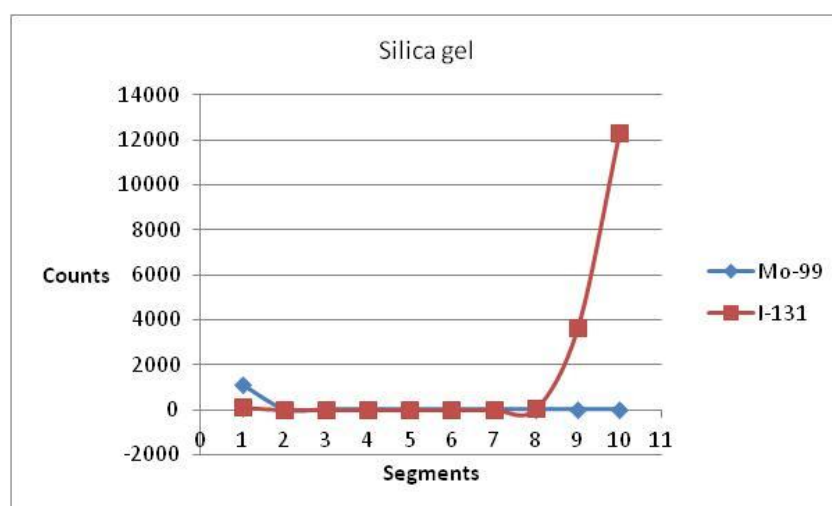


Figure 9. Distribution of a mixture of ^{99}Mo and ^{131}I on Silica gel on TLC Al foil.

The tests with Silica gel on TLC Al foil as stationary phase showed higher performance on separation ^{131}I from ^{99}Mo , with more distant distributions peaks which avoids overlapping.

4. CONCLUSIONS

Separation of main gamma emitting impurities from the bulk activity of ^{99}Mo is a necessary step on quality control analysis of ^{99}Mo as raw material for generator's production. Maxi-Clean SCX 600 mg cartridge showed superior performance on separate Ru and Te from Mo compared to others commercial cartridges. However, this cartridge still retains a fraction of Ru. The alternative method of separation of ^{99}Mo from others impurities by TLC presented promising results in the case of ^{99}Mo and ^{131}I separation.

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