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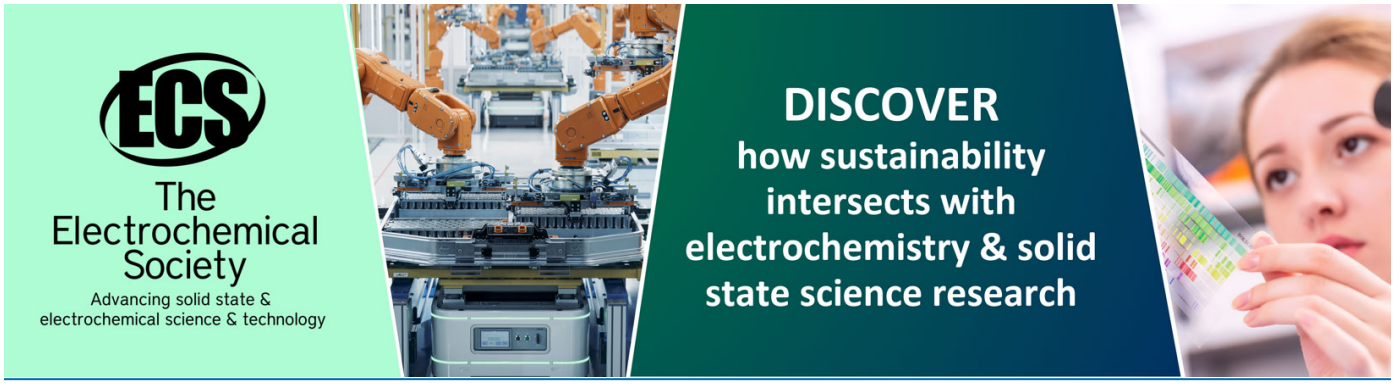

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Physico-chemical characterization of the terbium-161 radioisotope through separation based on cartridge LN resin column from irradiated of enriched Gd_2O_3 target

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Abstract. According to WHO, cancer is the second leading cause of death in the world and the seventh cause of death in Indonesia. Currently, cancer sufferers are increasing every year and become a national problem in health. Terbium-161 (^{161}Tb) is a low β^--emitter of radiolanthanide (E_{β^-} *an average* of 0.150 MeV and $t_{1/2}$ for 6.9 days) that is potential for cancer therapy as an alternative to ^{177}Lu which has been widely used in nuclear medicine. Physico-chemical characterization of ^{161}Tb radioisotope in the form of $^{161}TbCl_3$ final product solution has been studied including radiochemical purity, radionuclide purity, clarity, acidity (pH), and its stability. Irradiation of the Gd_2O_3 enriched target (98.4% ^{160}Gd isotope enrichment) was carried out at Bandung TRIGA 2000 reactor for ± 3 days. The separation of ^{161}Tb radionuclide from the Gd/Tb matrix has been done by the extraction chromatography method using two pieces of LN (Eichrom) resin cartridge column. The radiochemical purity of the final product of $^{161}TbCl_3$ radioisotope solution was determined using paper chromatography and paper electrophoresis methods. Radionuclide purity of fractions resulted from separation as well as the final products of radioisotope $^{161}TbCl_3$ was determined through analysis using a γ-ray spectrometer equipped with a multichannel analyzer (MCA) and HP-Ge detector. The clarity of the solution was determined visually, while the determination of acidity (pH) was carried out using the universal pH indicator paper. In this study, the final product of $^{161}TbCl_3$ solution has Physico-chemical characteristics that meet the requirements for nuclear medicine application, namely clear, has a pH of ~ 1, radiochemical purity of 99.31 ± 0.62%, and radionuclide purity of 99.96 ± 0.03%. The stability of radionuclide purity still meets the requirements (> 99%) for 2 weeks after preparing the final product, but $^{161}TbCl_3$ solution with radiochemical purity more than 95% was stable until 3 weeks at room temperature.

1. Introduction

Currently according to WHO, cancer is the second leading cause of death in the world and the seventh leading cause of death in Indonesia. The number of cancer sufferers is increasing every year, therefore it becomes a national problem in health. The nuclear technique using targeted radionuclide therapy (endoradiotherapy) can be applied to overcome this problem. This technique is very promising for cancer treatment. Various types of tumor-targeted biomolecules namely peptides, antibodies and antibody fragments have been used to be labeled with the appropriate radionuclides which are selectively send therapeutic doses to the target tissue [1 – 3]. The selection of radionuclides appropriately is very promising to improve therapeutic abilities by endoradiotherapy [4].

Radiolanthanides (a radioisotope of lanthanides) are suitable in the development of radiopharmaceuticals for therapy because they have similar chemical properties, but have different nuclear properties [5]. Various radiolanthanides have been used routinely for therapeutic applications. Lutetium-177 (^{177}Lu) is one of the radiolanthanides with a weak β^- emitter that has been available commercially for medical applications [6, 7]. Although the various therapeutic results using ^{177}Lu have been encouraging, it is not yet known whether ^{177}Lu is the optimal radionuclide therapy. Therefore, the study on various other radiolanthanides for therapy is needed [7].

Terbium-161 (^{161}Tb) is a weak-β^- emitter radiolanthanide ($E_{\beta-}$ = 0.150 MeV, $t_{1/2}$ = 6.9 days) which is very similar to ^{177}Lu ($E_{\beta-}$ = 0.140 MeV, $t_{1/2}$ = 6.7 days). ^{161}Tb also emits low-energy photons ($E\gamma$ = 45 keV) which is useful for monitoring the progress of therapy [8]. In addition, ^{161}Tb also releases Auger electrons and internal conversion electrons which can lead to greater radiocytotoxicity, thus providing better therapeutic results compared to ^{177}Lu [3, 9].

Radioisotope of ^{161}Tb can be produced in the form of carrier-free so that it has a high specific activity which is suitable for use in the labeling of biomolecule as a specific target of the radiopharmaceutical for cancer therapy. Based on its nuclear properties, ^{161}Tb can be used as an alternative to ^{177}Lu for the treatment of small tumors/ cancer [3, 10]. Terbium-161 can be produced indirectly through (n,γ) nuclear reaction in the reactor using gadolinium-160 (^{160}Gd) isotope as a target with high specific activity [3, 11]. In addition, using the enriched ^{160}Gd isotope as a target can further increase ^{161}Tb specific activity.

In order to obtain ^{161}Tb as a daughter radionuclide, it is necessary to separate ^{161}Tb from the mixture of parent-daughter radionuclides in the Gd/Tb matrix. The ease and possibility of separating a daughter radionuclide from a mixture of parent-daughter radionuclides are one of the criteria that need to be considered in the production of carrier-free radioisotopes.

Separation of a daughter radiolanthanide from the mixture of parent-daughter radiolanthanides can be carried out using extraction chromatography method [12, 13]. In previous studies, ^{161}Tb radioisotope was separated from Gd/Tb matrix based on extraction chromatography using LN (Eichrom) resin [14, 15]. The separation conditions can determine in the results of ^{161}Tb separation from the Gd/Tb matrix. In this study, ^{161}Tb has been obtained from irradiated Gd_2O_3 enriched target (98,4% of ^{160}Gd isotope enrichment) and separated from the Gd/Tb matrix based on LN resin cartridge column. In order to determine Physico-chemical characteristics the final product of $^{161}TbCl_3$ radioisotope solution, clarity, acidity (pH), radiochemical purity, radionuclide purity, and its stability at room temperature (pH, clarity, radiochemical purity and radionuclide purity stability) after preparation were examined. The solution of $^{161}TbCl_3$ radioisotope obtained from the separation is expected to have Physico-chemical characteristics that meet the requirements for nuclear medicine application.

2. Experimental procedure

2.1 Materials

Materials that used in this research were gadolinium oxide (Gd_2O_3) enriched with 98.4% ^{160}Gd isotope enrichment (Trace Science), LN (50-100 micron) resin cartridge column (Eichrom), hydrochloric acid (Merck), nitric acid (Merck), acetic acid (Merck), sodium hydrogen phosphate (Merck), disodium hydrogen phosphate (Merck), sterile aquabidest (IPHA Laboratory), 0.9% NaCl solution (IPHA Laboratory), Whatman 3MM chromatographic paper (Whatman), pH indicator paper (Merck).

The equipment that used in this research was dose calibrator (Capintec), a γ-spectrometer with an HP-Ge detector equipped with multichannel analyzer / MCA (Canberra), a γ-spectrometer with NaI-Tl detector (Ortec), hot and magnetic stirrer (Thermolyne) and micropipettes (Thermo Scientific).

2.2. Irradiation of Gd_2O_3 enriched target

The target for irradiation was carried out by weighing 5 mg of Gd_2O_3 (98,4 % ^{160}Gd isotope enrichment) and put into quartz ampoule, then the quartz ampoule was closed by welding of the glassware and put into an aluminum capsule. The target material was irradiated at the Bandung TRIGA 2000 Reactor for ± 3 days at CT (Central Thimble) irradiation facilities with thermal neutron flux ~ 10^{13} $n.cm^{-2}.s^{-1}$. After irradiation, the irradiated target material was cooled for ± 1 day.

2.3. Dissolution of irradiated Gd_2O_3 enriched target

The dissolution of the irradiated target was carried out in a box process of beta emitter which is also equipped with lead shielding. The irradiated Gd_2O_3 target was put into a 50 mL beaker, then dissolved in 2 mL of 2 N HCl solution with gently warming and evaporated until it was almost dry. Then the residue was redissolved in 1 mL of sterile aquabidest.

2.4. Separation of the ^{161}Tb radioisotope from Gd/Tb matrix

In this experiment was used 2 pieces (tandem) of LN (50-100 micron) resin cartridge columns as a stationary phase for separation of ^{161}Tb from irradiated Gd_2O_3 enriched target. The column was washed using a 0.15 N HNO_3 solution and kept immersed in the eluent overnight. The irradiated radioisotope solution containing $^{161}Gd/^{161}Tb$ matrix with 5 – 10 mCi activity was loading into the LN resin cartridge column. Furthermore, the column was eluted with 0.8 N and 3 N HNO_3 eluent solutions to elucidate Gd and Tb isotopes, respectively. Each mL of the eluate was entered in 10 mL glass vials. Then the separated eluate was counted using a γ-spectrometer with an HP-Ge detector equipped with a multichannel analyzer (MCA).

2.5.Preparation of the final product of $^{161}TbCl_3$ radioisotope

The separated eluate containing ^{161}Tb fractions were collected and evaporated until it was almost dry, then the residue was redissolved in 1 mL of 0.1 N HCl solution, so that the final product of the ^{161}Tb radioisotope solution was obtained in the chemical form of $^{161}TbCl_3$.

2.6. Physico-chemical characterization of the final product of $^{161}TbCl_3$ radioisotope solution

The Physico-chemical characterization of the final product of $^{161}TbCl_3$ radioisotope solution was carried out including the determination of its clarity, acidity (pH), radiochemical purity, radionuclide purity, and its stability (pH, clarity, radiochemical purity and radionuclide purity stability) at room temperature for several days after preparation.

2.6.1. Determination of radionuclide purity of $^{161}TbCl_3$ radioisotope solution. The radionuclide purity of the final product of $^{161}TbCl_3$ radioisotope solution was determined using a γ-spectrometer with an HP-Ge detector equipped with multichannel analyzer (MCA). A total of 5 µL of $^{161}TbCl_3$ radioisotope solution was put into a 2 mL glass vial, then counted for 15 minutes.

2.6.2. Determination of radiochemical purity of $^{161}TbCl_3$ radioisotope solution. The radiochemical purity of the final product of $^{161}TbCl_3$ radioisotope solution was determined using two methods, namely the paper chromatography and the paper electrophoresis methods. Determination of the radiochemical purity of $^{161}TbCl_3$ radioisotope solution by paper chromatography method was carried out using Whatman 3MM as a stationary phase and 50% acetic acid solution as well as 0.9% NaCl solution as mobile phases. Determination of radiochemical purity of $^{161}TbCl_3$ solution by paper electrophoresis method was carried out using a stationary phase of Whatman 3MM (2x38 cm) and as an electrolyte solution was used 0.02 M phosphate buffer with pH of 7. Electrophoresis was carried out for 1 hour at an electrical voltage of 350 V. The chromatograms and electropherograms were dried in the oven at 40 ^{0}C, and then was cut into 1 cm length. Every 1 cm piece of paper was counted using a single channel analyzer (SCA) with a NaI-Tl detector.

2.6.3. Determination of acidity (pH) of $^{161}TbCl_3$ radioisotope solution. The acidity (pH) of the final product of $^{161}TbCl_3$ radioisotope solution was determined using a pH indicator paper by comparing the changes of color that occurred on the pH paper with the colors indicated on the standard at pH indicator paper.

2.6.4. Determination of $^{161}TbCl_3$ clarity. A total of 1 mL the final product of $^{161}TbCl_3$ radioisotope solution was put into a 10 mL glass vial. The clarity of $^{161}TbCl_3$ solution was determined visually in front of a lamp with a black background to see the presence of particles in the radioisotope solution.

2.6.5. Determination of $^{161}TbCl_3$ stability. The stability of the final product of $^{161}TbCl_3$ radioisotope solution was carried out including stability of its radiochemical purity, radionuclides purity, pH and clarity for several days at room temperature.

3. Result and discussion

In this study, irradiation of Gd_2O_3 enriched target with 98.4% ^{160}Gd isotope enrichment (n = 5) at the Bandung TRIGA 2000 reactor was carried out. The irradiated target material that was dissolved in 2 N HCl solution produces a clear solution in the form of the mixture solution of $^{161}GdCl_3$ /$^{161}TbCl_3$. The radioisotope mixture solution was passed into the LN (50-100 micron) resin cartridge column which was tandem in two pieces to separate ^{161}Tb radioisotope from the Gd/Tb matrix using the nitric acid solution as eluent. Separation of ^{161}Tb from the Gd/Tb matrix based on LN resin cartridge columns was obtained that the terbium isotope (Tb) can be separated successfully from gadolinium isotopes (Gd) with a ^{161}Tb yield of 100% with the final product in the form of $^{161}TbCl_3$ solution [3].

The radioisotope solution to be applied in the health should have Physico-chemical characteristics that meet the requirements for nuclear medicine application, i.e. a radiochemical purity > 95%, radionuclide purity > 99%, and have adequate specific activity according to its application, quite stable after preparation and a clear solution [16]. Therefore, the final product of $^{161}TbCl_3$ radioisotope solution that was obtained in this experiment should have Physico-chemical characteristics that meet the requirements with high stability.

To determine the clarity of the final product of $^{161}TbCl_3$ radioisotope solution that was obtained, visual observation was carried out and the results showed that $^{161}TbCl_3$ radioisotope was a clear solution and colorless. Radioisotope of $^{161}TbCl_3$ that was obtained has an acidity with a pH of 1 - 1.5. The acidity of $^{161}TbCl_3$ radioisotope solution was similar to $^{177}LuCl_3$, $^{166}HoCl_3$ and $^{153}SmCl_3$ which have been used in the field of nuclear medicine with the pH of 1-2 [17-19]. The final product of $^{161}TbCl_3$ that was obtained in this research was also similar to the final product of the $^{161}TbCl_3$ radioisotope solution that was obtained in the previous study from irradiated of the natural Gd_2O_3 target [20].

Based on the characterization that has been carried out, the Physico-chemical characteristics of the final product of $^{161}TbCl_3$ radioisotope solution were summarized in table 1.

Table 1. Physico-chemical characteristics of the final product of $^{161}TbCl_3$ radioisotope solution

Physico-chemical characteristics of $^{161}TbCl_3$	Results
Clarity	clear, colorless
Acidity (pH)	1 – 1.5
Radiochemical purity (RCP)	99.31 ± 0.62%
Radionuclide purity (RNP)	99.96 ± 0.03%
Stability at room temperature (pH, clarity and RCP)	still stable for 3 weeks at room temperature
Stability of RNP	still stable for 2 weeks after preparation of $^{161}TbCl_3$ solution

Based on table 1, it can be seen that the final product of $^{161}TbCl_3$ radioisotope solution has a radiochemical purity more than 95%. The chromatogram of $^{161}TbCl_3$ radioisotope solution using paper chromatography method was shown in figure 1 and figure 2. The chromatogram in figure 1, using Whatman 3MM (2x10 cm) as a stationary phase and 50% acetic acid solution as the mobile phase showed that there was only a single peak in the form of $^{161}TbCl_3$ compound in the final product of $^{161}TbCl_3$ radioisotope solution. The solution did not have radiochemical impurities in the form of other chemical compounds from ^{161}Tb radioisotopes. In this paper chromatography system, $^{161}TbCl_3$ compounds migrate to the solvent migration with Rf 0.8 - 0.9. The chromatogram did not show the presence of $^{161}Tb(OH)_3$ compound as an impurity in $^{161}TbCl_3$ solution which was proven by the absence of radioactivity distribution at Rf = 0.

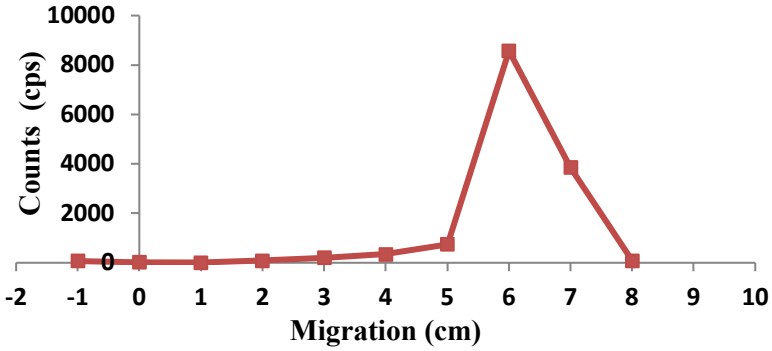

Figure 1. Chromatogram of $^{161}TbCl_3$ radioisotope using Whatman 3MM (2x10 cm) as a stationary phase and 50% acetic acid solution as a mobile phase.

The radiochemical purity determination of the final product of $^{161}TbCl_3$ radioisotope solution was also supported by the chromatogram shown in figure 2, which was eluted using Whatman 3MM (2x20 cm) as a stationary phase and 0.9% NaCl solution as a mobile phase. The result showed that there was only a single peak in the form of $^{161}TbCl_3$ compound in the final product of $^{161}TbCl_3$ radioisotope solution. In this paper chromatography system, $^{161}TbCl_3$ compounds migrate to the solvent migration with Rf 0.8-0.9. The chromatogram that was obtained using this system also did not show the presence of $^{161}Tb(OH)_3$ impurity in $^{161}TbCl_3$ radioisotope solution which was proven by the absence of radioactivity distribution at Rf = 0.

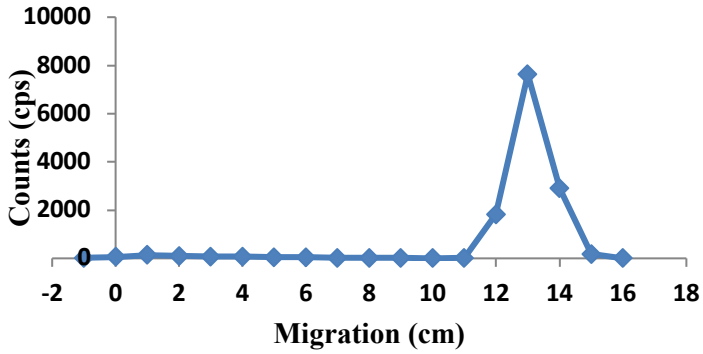

Figure 2. Chromatogram of $^{161}TbCl_3$ radioisotope using Whatman 3MM (2x20 cm) as a stationary phase and 0.9% NaCl solution as a mobile phase.

Besides the paper chromatography method, the radiochemical purity of $^{161}TbCl_3$ solution was also determined using the paper electrophoresis method. The electropherogram of $^{161}TbCl_3$ radioisotope using this method as shown in figure 3. Based on the electropherogram in figure 3, using Whatman 3MM (2x38 cm) as a stationary phase and 0.02 M phosphate buffer solution with pH 7 as an electrolyte indicates that there was only a single peak in the form of compound $^{161}TbCl_3$ in the final product of $^{161}TbCl_3$ radioisotope solution. Therefore, $^{161}TbCl_3$ solution did not have radiochemical impurity in the form of other chemical compounds from ^{161}Tb radioisotopes. In this paper electrophoresis system, $^{161}TbCl_3$ compound has remained at the point with Rf = 0.

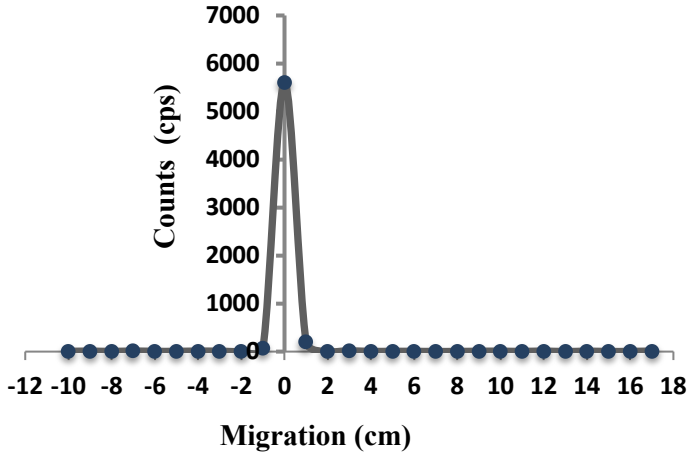

Figure 3. Electropherogram of $^{161}TbCl_3$ radioisotope using Whatman 3MM (2x38 cm) as a stationary phase and 0.02 M phosphate buffer solution with pH 7 as an electrolyte.

Based on the results, the radiochemical purity determination of $^{161}TbCl_3$ radioisotope by paper chromatography and paper electrophoresis methods showed that the final product of $^{161}TbCl_3$ radioisotope solution had a radiochemical purity of 99.31 ± 0.62%. The results obtained indicate that the final product of $^{161}TbCl_3$ radioisotope has met the requirements in terms of its radiochemical purity, which is above 95%. The result obtained from this experiment was similar to the radiochemical purity of the final product of $^{161}TbCl_3$ radioisotope solution that was obtained in the previous study from irradiated natural Gd_2O_3 target [20].

Based on table 1, it can be seen that the final product of $^{161}TbCl_3$ radioisotope solution has a radionuclide purity > 99%. Radionuclide purity determination of $^{161}TbCl_3$ radioisotope solution was carried out using a γ-spectrometer with an HP-Ge detector equipped with Multichannel Analyzer (MCA). The gamma spectrum of $^{161}TbCl_3$ radioisotope solution was shown in figure 4. The result did not show the presence of ^{161}Gd parent radionuclides as a result of irradiation of ^{160}Gd isotope target. This was due to ^{161}Gd radionuclide has a very short half-life, which is 3.66 minutes. Therefore, by cooling for ± 1 day before the separation process, the parent radionuclides (^{161}Gd) have been decayed into daughter radionuclide (^{161}Tb). Based on the spectrum in figure 4, it can be seen that there was ^{161}Tb radionuclide ($E\gamma$ = 45; 49.1; 57.7; 74.9 and 88 keV) as expected radionuclide in $^{161}TbCl_3$ radioisotope solution . Besides that, there were ^{160}Tb radionuclides ($E\gamma$ = 197.03 and 215.64 keV) as radionuclide impurity in the final product of $^{161}TbCl_3$ radioisotope solution. Radionuclide of ^{160}Tb is isotopic with ^{161}Tb that can not be separated from ^{161}Tb radionuclide chemically. The presence of ^{160}Tb radionuclides in $^{161}TbCl_3$ solution was very low, which is less than 1%. The results obtained indicate that the final product of $^{161}TbCl_3$ radioisotope solution has radionuclide purity of 99.96 ± 0.03%. Therefore, it meets the requirements which are> 99%. Radionuclide purity of $^{161}TbCl_3$

radioisotope solution was similar to $^{177}LuCl_3$ radiolanthanide solution that has been widely used in biomolecules labeling for cancer therapy, which has a radionuclide purity of $\geq 99.9\%$ [17].

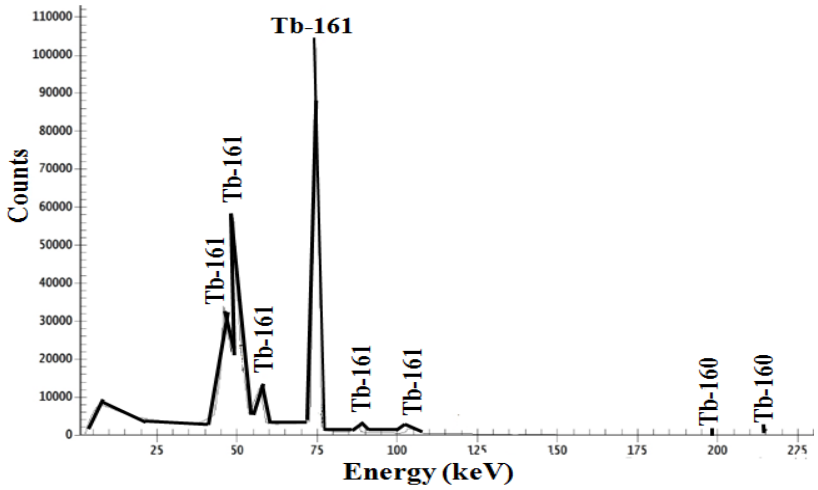

Figure 4. The γ-rays spectrum of $^{161}TbCl_3$ radioisotope solution**.**

The radioisotope solution must be stable during storage. Stability tests have also been carried out on the final product of $^{161}TbCl_3$ radioisotope to determine its stability for several days, including its radiochemical purity, radionuclide purity, clarity and acidity (pH). Based on the stability test, it was obtained that the final product of $^{161}TbCl_3$ radioisotope solution was still stable for 3 weeks at room temperature i.e its acidity (pH), clarity and radiochemical purity. The stability test for the radiochemical purity of the final product of $^{161}TbCl_3$ radioisotope solution after 3 weeks at room temperature was presented in figure 5. Based on figure 5, it can be seen that $^{161}TbCl_3$ radioisotope solution had high radiochemical purity stability. Radioisotope of $^{161}TbCl_3$ still meets the requirements after 3 weeks of preparation for the final product, with radiochemical purity still above 95%.

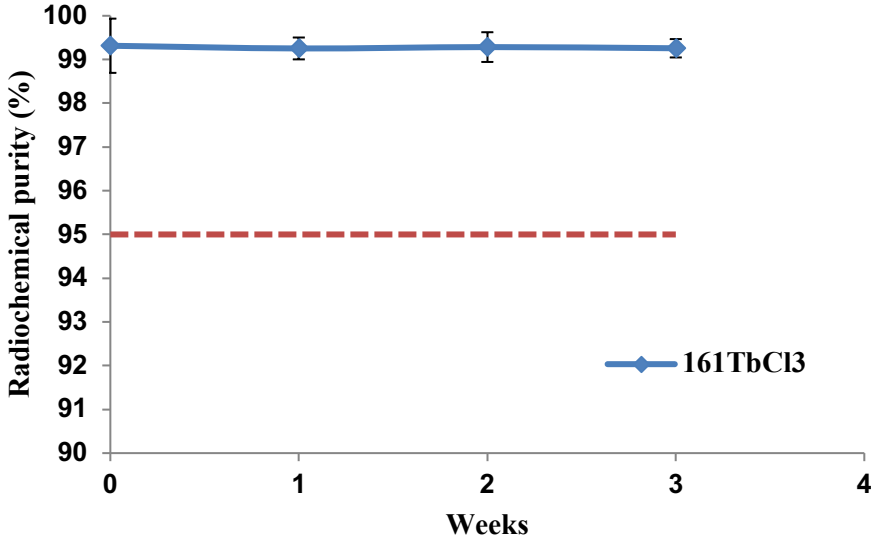

Figure 5. Stability of radiochemical purity of $^{161}TbCl_3$ radioisotope solution.

The radionuclide purity stability of $^{161}TbCl_3$ radioisotope solution was presented in Figure 6. The presence of ^{160}Tb in $^{161}TbCl_3$ radioisotope solution with very low radionuclide impurity levels (<1%) is still acceptable for medical applications [19]. However, the presence of ^{160}Tb ($t_{1/2}$ = 72.4 days) radionuclide can cause a decrease in the radionuclide purity of $^{161}TbCl_3$ radioisotope solution during storage, because this radionuclide has a longer half-life than ^{161}Tb radionuclide [6]. In figure 6 can be seen that the stability test for radionuclide purity of $^{161}TbCl_3$ radioisotope solution showed that $^{161}TbCl_3$ radioisotope only meets the requirements for up to 2 weeks after preparation of final product of $^{161}TbCl_3$ radioisotope, with the radionuclide purity still above 99%.

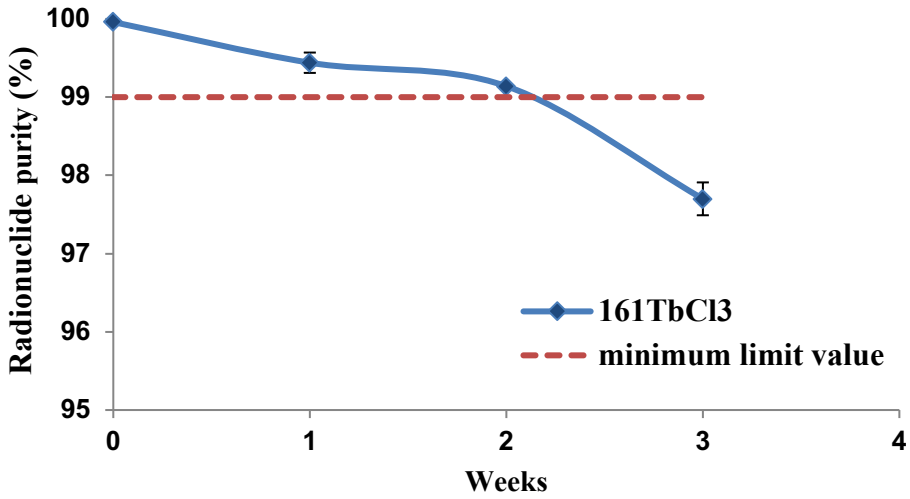

Figure 6. Stability of radionuclide purity of $^{161}TbCl_3$ radioisotope solution.

Based on the Physico-chemical characteristics obtained, it showed that the final product of $^{161}TbCl_3$ radioisotope solution has Physico-chemical characteristics that meet the requirements for nuclear medicine application. Radioisotope of $^{161}TbCl_3$ was a clear solution with acidity (pH) close to the pH of other radiolanthanides solution that was used in nuclear medicine i.e $^{177}LuCl_3$. In addition, $^{161}TbCl_3$ radioisotope solution also has radiochemical purity and radionuclide purity that meet the requirements, with radiochemical purity > 95% and radionuclide purity > 99% [21]. The final product of $^{161}TbCl_3$ radioisotope solution is quite stable during storage at room temperature with Physico-chemical characteristics that meet the requirements for up to 2 weeks after preparation.

4. Conclusion

Physico-chemical characteristics of the final product of $^{161}TbCl_3$ radioisotope solution have been obtained from irradiated of gadolinium oxide (Gd_2O_3) enriched target (98.4% enrichment of ^{160}Gd isotope) through ^{161}Tb separation from Gd/Tb matrix based on column chromatography method using LN resin cartridge columns. The solution of $^{161}TbCl_3$ radioisotope obtained from the separation has Physico-chemical characteristics that meet the requirements for nuclear medicine application and stable for 2 weeks at room temperature after preparation for the final product.

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