Validation of $[^{99m}\text{Tc}]\text{Tc}$-DTPA radiochemical testing method using one-system paper chromatography

Amal Rezka Putra, Enny Lestary, Maskur Maskur and Yayan Tahyan

Center for Radioisotope and Radiopharmaceutical Technology, National Nuclear Energy Agency, Tangerang Selatan, Indonesia, 15314.
E-mail: amalrezka@batan.go.id

Abstract. Kidney failure is a degenerative disease that has a prevalence of nearly 12 to 15% of the total population in the world. Renal scans are one of many diagnostic means which refers to several examinations using radiopharmaceuticals that evaluate the function and anatomy of the kidneys. Technetium-$99m$-diethylenetriaminepetaacetic acid ($[^{99m}\text{Tc}]\text{Tc}$-DTPA) is a commonly used radiopharmaceutical for kidney scans. Since the half-life of technetium-$99m$ radioisotope, one component of this radiopharmaceutical, is only about 6.0 hours, so an efficient and effective quality control techniques is a necessity. Up to now, two-system thin layer chromatography (TLC) is a common method used for radiochemical purity (RCP) test of $[^{99m}\text{Tc}]\text{Tc}$-DTPA. Recently one-system TLC has been successfully developed for this purpose. Therefore prior to its application, it is necessary to validate as well to compare this method with an established method (WHO Pharmacopeia). These methods were two-system used Whatman-1 paper as static phase and methyl ethyl ketone (two-system-A) and 0.9% sodium chloride (two-system-B) as mobile phases and one-system used Whatman-1 paper as static phase and acetone: 0.9% sodium chloride (11:9) as a mobile phase. RCP of $[^{99m}\text{Tc}]\text{Tc}$-DTPA was then tested using these methods. The retrieved data were processed and validated with some variables like accuracy, precision, and compared using t-test to see whether the above-mentioned TLC systems show a significant difference or not. The analysis results of RCP test of $[^{99m}\text{Tc}]\text{Tc}$-DTPA using two-system method was 99.37± 0.48% while using one-system method was 99.20 ± 0.41%. The percentage accuracy of the data between two methods was 99.83%. The t-stat value for both methods was 0.84 so it can be concluded that the results of measurement using one-system method are not significantly different from two-system method.

1. Introduction

Infectious disease as well as degenerative diseases have become a serious burden of well-being of Society. One of degenerative diseases is kidney disease which is mainly suspected to be caused by unhealthy lifestyles and junk food consumption. Kidney disease might also be caused by hypertension, decreased blood supply, genetic disorders, toxins or chemicals in the body, and diabetes. Kidney disease can be classified as follows: kidney failure, kidney infection, kidney stones, chronic renal failure. In recent publication 2018, H. Htay et al., reported that chronic kidney disease (CKD) is a common cause of noncommunicable diseases that had a global prevalence of about 12 to 15% [1]. Jessica also mentions that 20 to 40% of diabetics have chronic renal failure (CRF) [2]. Management of handling kidney disease could be taking anti-hypertensive drugs, antibiotics, increase iron intake, reduce phosphate intake, and change to be a healthy lifestyle [3].

Handling of CKD and CFR should not only refer to treatment but should also consider effective ways to prevent the occurrence of the disease. In the 1960s the application of nuclear medicine could readily...
be used after the first research reactor in Indonesia began to be operated [4]. Utilization of nuclear medicine can identify the physiological, pathophysiological and metabolic processes of the organ or system under study up to the molecular level. Measurable variables are the amount and distribution of radioactive substances. Computerized diagnostic methods can read radioactive material information such as clearance rate, total radioactivity, metabolism in organ patterns (calculate glomerulus filtration rate of the kidneys and know the motion of blood flow in heart) [5,6].

Kidney scans for kidney disorders can be performed in nuclear medicine with an examination time of 20 to 30 minutes. In general, renal examination in nuclear medicine uses radiopharmaceutical [131I]-Hippuran (iodine-131 has a half-life of 8.04 days, gamma energy 364.48 KeV, intensity 81.2%) and [99mTc]-DTPA (technetium-99m has a half-life 6.0 hours, gamma energy 140 KeV, intensity 87.2%) [7,8]. Among of these, [99mTc]-DTPA is commonly used for the application of diagnosis of renal abnormalities due to fewer organ received radiation dose compared to [131I]-Hippuran [9,10].

Prior to its use in hospitals, radiopharmaceutical kits such as DTPA kit firstly tested for its quality. One of the most important test parameters is radiochemical purity (RCP). This parameter aims to determine whether the radiopharmaceutical substance produced is in accordance with pharmacopeia acceptance. The requirement for RCP of [99mTc]-DTPA is not less than 90% [11]. The rest would be impurities in form of free [99mTc]O4- and [99mTc]O2- of about 5 to 10% [12]. An excess amount of radiochemical impurities from a particular radiopharmaceutical will result in a changing biodistribution and poor image scan quality.

In general, RCP of radiopharmaceuticals is measured by using chromatography such as paper chromatography [13,14], thin layer chromatography (TLC), high-performance liquid chromatography (HPLC) [15] and electrophoresis. For [99mTc]-DTPA, RCP testing uses two-system paper chromatography. Two-system-A uses Whatman-1 paper as a static phase and methyl ethyl ketone as mobile phase for measuring [99mTc]O4- and two-system-B uses Whatman-1 paper as static phase and 0.9% sodium chloride as the mobile phase for measuring [99mTc]O2-. [16]. However, this method is inefficient as its process is time-consuming. Therefore, a new method which is faster and simpler is needed. In 2013 Maria et al. conducted a validation of alternative RCP testing methods for [99mTc]-DTPA [16]. In the process of developing the method for RCP test of [99mTc]-DTPA obtained a more efficient testing method using one-system. Maskur et.al in 2019 has developed a new method for testing [99mTc]-DTPA with one TLC system [17]. However, in that study RCP [99mTc]-DTPA tests were not carried out on products that had been incubated within 24 hours. Therefore, validation of the [99mTc]-DTPA RCP method using one system must be done. The purpose of this study is to determine whether the new method (one-system) gives valid results in terms of measurement results compare with the standard method (two-system).

2. Methods

2.1. Materials
DTPA radiopharmaceutical kit and technetium-99m radioisotope retrieved form an in-house produced molybdenum-99/technetium-99m generator (Center for Radioisotope and Radiopharmaceutical Technology, PTRR – BATAN), 0.9% sodium chloride (PT. Otsuka Indonesia) methyl ethyl ketone for analysis 99.5% and acetone for analysis 99.8% (Merck), plastic film, 1 x 11 cm Whatman-1 paper strips (Schleicher & Schuell).

2.2. Equipment
Equipment used in this research was glass cylinder tube 10 x 29 cm, stopwatch, gamma counter (Capract), micropipette (Eppendorf).

2.3. Radiolabelling
The radiolabeling procedure for the DTPA radiopharmaceutical kit was performed according to the manufacturer’s instructions. Approximately 74 – 370 MBq of a technetium-99m solution was added to a DTPA kit (5.0 mg, dry powder) vial. Each vial was shaken firmly and then let it stand at room temperature for at least 15 minutes before its analysis [18].

2.4. Radiochemical purity test

The RCP testing was performed by 2 methods: two-system method and one-system method. Each method used the static phase Whatman-1 paper. Method two-system-A using methyl ethyl ketone as mobile phase to determine free [99mTc]TcO$_4^-$ (Rf 1.0), two-system-B using 0.9% sodium chloride as mobile phase to determine [99mTc]Tc-colloidal impurity ([99mTc]TcO$_2$) located at Rf 0.0. While one-system method using mixture solvent acetone: 0.9% sodium chloride (11:9) to determine RCP of [99mTc]Tc-DTPA. Free [99mTc]TcO$_4^-$ will be at Rf 1.0; [99mTc]Tc-DTPA at Rf 0.5; and [99mTc]TcO$_2$ at Rf 0.0 [17]. The Rf value is calculated using Eq. 1 [15].

$$R_f = \frac{\text{distance travelled by the component}}{\text{distance of the solvent front}}$$  

(1)

The radiochemical purity of 99mTc-DTPA is calculated using the Eq. 2.

$$\%[99mTc]Tc\text{−DTPA} = 100 - (\%[99mTc]TcO_4^- + \%[99mTc]TcO_2)$$  

(2)

2.5. Data analysis

Determining the accuracy percentage of the two methods is calculated by using the Eq.3 and 4. The higher the %accuracy the smaller the difference between the two methods tested.

$$\%\text{Accuracy} = 100 - \%\text{Error}$$  

(3)

Where

$$\%\text{Error} = \left(\frac{\%\text{RCP(A)}-\%\text{RCP(B)}}{\%\text{RCP(A)}}\right) \times 100\%$$  

(4)

Where

- % RCP(A) = % RCP [99mTc]Tc-DTPA with two-system method
- % RCP(B) = % RCP [99mTc]Tc-DTPA with one-system

The retrieved data were compared by using two-sample assuming equal variance to test for significant differences between two methods with the assumption that both samples had the same variance. The t-test of two independent samples with the same variance is calculated by the Eq.4 [19].

$$t = \frac{x_1 - x_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$  

(5)

Where

- $t$ = t-value,
- $x_1$ = average data of sample 1,
- $x_2$ = average data of sample 2,
- $s_1$ = sample varian 1,
- $s_2$ = sample varian 2,
- $n_1$ = sample size 1, and
- $n_2$ = sample size 2
The percentage of RCP of the \[^{99m}\text{Tc}]\text{Tc-DTPA}\) with 2 methods (two-system and one-system) was analysed by using the t-test. The difference between both methods is not significant if the t-stat of t-test statistic is less than 2.10 with significance level \((P) = 0.05\) with number of degrees freedom \((df) = 18\).

3. Results
The chromatograms constructed from two-system method data are shown in Fig. 1 and 2. The mobile phase for two-system-A is methyl ethyl ketone to find out the percentage of \[^{99m}\text{Tc}]\text{TcO}_4^-\) free impurities. Then in the two-system-B phase using 0.9% sodium chloride to see \[^{99m}\text{Tc}]\text{TcO}_2^-\) impurities.

![Figure 1. Chromatogram of the two-system method developed by methyl ethyl ketone.](image)

![Figure 2. Chromatogram of the two-system method developed by 0.9% sodium chloride.](image)

Fig. 1 shows the chromatogram of \[^{99m}\text{Tc}]\text{Tc-DTPA}\) developed using Whatman-1 paper as stationary phase and methyl ethyl ketone as the mobile phase. In this system both \[^{99m}\text{Tc}]\text{Tc-DTPA}\) and \[^{99m}\text{Tc}]\text{TcO}_2^-\) do not migrate with the solvent front so both remain at the origin \((Rf 0.0)\). \[^{99m}\text{Tc}]\text{TcO}_4^-\) however migrated with the solvent to give Rf value 1.0. This is because \[^{99m}\text{Tc}]\text{TcO}_4^-\) is small ion so it migrates quickly and easily separated from the larger complexes \([16,20]\).

Fig. 2 presents the chromatogram of \[^{99m}\text{Tc}]\text{Tc-DTPA}\) developed using Whatman-1 paper as a stationary phase and 0.9% sodium chloride as the mobile phase. In this system, due to its chemical properties, \[^{99m}\text{Tc}]\text{Tc-DTPA}\) which is very soluble in the polar solvent (0.9% sodium chloride), migrate with solvent to give an Rf value of 1.0 joining \[^{99m}\text{Tc}]\text{TcO}_4^-\) free. While \[^{99m}\text{Tc}]\text{TcO}_2^-\) remain in the spotting position of Rf 0.0 \([16,20]\).

Generally, the migration of \[^{99m}\text{Tc}]\text{TcO}_4^-\) free can be influenced by the choice of different mobile and stationary phases. When silica gel or paper is used as a stationary phase, the migration of \[^{99m}\text{Tc}]\text{TcO}_4^-\) free depends on the solubility of this anion in the solvent. In a polar solvent such as 0.9% sodium
chloride, 80% methanol, acetone or methyl ethyl ketone, \([\sim \text{Tc}]\text{TcO}_4\) migrates with solvent front (Rf 0.9-1.0) while the \([\sim \text{Tc}]\text{TcO}_2\) is always on the initial spot Rf 0.0. Determination of \([\sim \text{Tc}]\text{Tc-DTPA RCP}\) also used this method [20]. The Rf of these compounds can be adjusted by changing the dielectric constant or the polarity of a mobile phase.

**Figure 3.** Chemical structure of \([\sim \text{Tc}]\text{Tc-DTPA} [11].

Fig. 3 shows the chemical structure of \([\sim \text{Tc}]\text{Tc-DTPA}.\) Polar bonds occur when 2 atoms form molecules with covalent bonds. In the case of \([\sim \text{Tc}]\text{Tc-DTPA compound there are two free ions (Na- and CO_2-). Free ionic bonds can be easily carried away with polar solvents. There are also covalent bonds in \([\sim \text{Tc}]\text{Tc-DTPA compound between carbon and oxygen, C-O (electronegativity 1.0), nitrogen and technetium-99m, N-[\sim \text{Tc]} (electronegativity 1.1), oxygen and technetium-99m, O-[\sim \text{Tc}] (electronegativity 1.6). If the electronegativity more than 0.4, it means the molecule has polar character. These bonds will raise the dipole moment differences in the outer shell of the compound. Polar molecules such as \([\sim \text{Tc}]\text{Tc-DTPA can be separated by using a polar or high dielectric constant solvent such as 0.9% sodium chloride. Polar molecules tend to attract each other even less strongly. The molecule interacts with hydrogen bonds and dipoles between the molecules. However, low dielectric constant molecules like methyl ethyl ketone do not have this charge so there is no attraction between \([\sim \text{Tc}]\text{Tc-DTPA [21].

The chromatograms constructed from the one-system method shown in Fig. 4. The mobile phase used is a mixture of acetone: 0.9% sodium chloride (11:9) to determine the percent RCP of \([\sim \text{Tc}]\text{Tc-DTPA}.

**Figure 4.** Chromatogram of the one-system method using by mixture solvent aseton: 0.9% sodium chloride as mobile phase (11:9).
When using eluent methyl ethyl ketone with a dielectric constant value of 18.5, the position of $[^{99m}\text{Tc}]\text{Tc-DTPA}$ was at Rf 0.0. However, when using 0.9% sodium chloride solvent with dielectric constant value of 79.3 the $[^{99m}\text{Tc}]\text{Tc-DTPA}$ migrated with solvent front to give an Rf value of 1.0. The development of one-system method using a mixture solvent acetone: 0.9% sodium chloride (11:9) with dielectric constant of 47.1 would place the $[^{99m}\text{Tc}]\text{Tc-DTPA}$ complex at Rf 0.5 (Fig. 3.) while $[^{99m}\text{Tc}]\text{TcO}_2$ stay at origin at Rf 0.0 and $[^{99m}\text{Tc}]\text{TcO}_4$ free migrate with solvent front to give a Rf of 1.0 [17,21,22].

The total test time for measuring RCP of $[^{99m}\text{Tc}]\text{Tc-DTPA}$ using chromatography two-system was of 117.0 minutes ± 8.7% while chromatography one-system was of 96.7 minutes ± 4.2%. It can be seen that the one-system method has a relatively shorter test time than using two-system method. One-system method not only has a shorter test time but more efficient in terms of the used chemicals. Therefore, one-system method is more economical.

This study also tested the validity of the new test method. The results of RCP of $[^{99m}\text{Tc}]\text{Tc-DTPA}$ using standard method (two-system) and new method (one-system) presented in Table 1.

| Table 1. Comparison of % RCP $[^{99m}\text{Tc}]\text{Tc-DTPA}$ between two-system and one-system methods. |
|--------------------------------------------------|-------------------|
| two-system method                                 | one-system method |
| 99.24                                            | 99.19             |
| 99.26                                            | 99.14             |
| 99.00                                            | 99.48             |
| 99.83                                            | 99.38             |
| 99.87                                            | 99.38             |
| 99.58                                            | 99.51             |
| 99.80                                            | 99.48             |
| 99.76                                            | 99.52             |
| 98.74                                            | 98.51             |
| 98.59                                            | 98.43             |
| Mean                                             | 99.37             |
| %RSD                                             | 0.48%             |
| %Accuracy                                        | 99.83%            |
| p-value                                           | 0.21              |
| t-stat value                                      | 0.84              |

It can be seen from Table 1. that the percent RCP of $[^{99m}\text{Tc}]\text{Tc-DTPA}$ tested with the two above-mentioned methods were of 98.59 to 99.87% (percent RSD = 0.48%) for one-system method and 98.43 to 99.52% (percent RSD = 0.41%) for two-system method. The data variation from both methods showed a precise value because the percentage of SD did not exceed 1%. The 1% limit of the percent RSD value indicates a variation of data that does not differentiate between one experiment to another [23]. The percent accuracy value indicates 99.83%. This confirms that the one-system method has good accuracy with comparison of two-system method. High percent accuracy indicates proximity of test results of one-system method with two-system method [24].

Hypothesis 0: The one-system method is not significantly different from two-system method if p-value greater than 0.05 and t-stat value less than 2.10. Hypothesis 1: one-system method is significantly different from two-system method if p-value less than 0.05 and t-stat value greater than 2.10.

In order to have statistically acceptable data, in this study 10 experiments were performed for each method with the df value of 18 and t-table value is 2.10. Table 1 shows that p-value is 0.21 which is greater than 0.05, while t-stat value is 0.81 which is smaller than 2.10. Based on these data it can be
concluded that Hypothesis 0 is accepted. The results of percent RCP test of $[^{99}\text{m}]\text{Tc-DTPA}$ using one-system method did not differ significantly from two-system method.

A further test for both methods was performed for measuring the percent RCP of $[^{99}\text{Tc}]\text{Tc-DTPA}$ which was prepared with various incubation time. This study aims to validate whether one-system method gives a similar result to that of two-system method at different incubation times. The percent RCP of $[^{99}\text{Tc}]\text{Tc-DTPA}$ which was incubated at various time is shown in Fig. 5.

![Figure 5](image-url)

**Figure 5.** Comparison of % RCP $[^{99}\text{Tc}]\text{Tc-DTPA}$ using by two-system and one-system at some variation of incubation time.

Fig. 5 shows the percent RCP of $[^{99}\text{Tc}]\text{Tc-DTPA}$ developed using one-system is not different from the two-system. The t-stat values from t-test of RCP of $[^{99}\text{Tc}]\text{Tc-DTPA}$ which were incubated for 15 min, 1, 4, and 24 h were of 0.09, 0.62, 0.04, and 0.87 (df=4, t-table value=2.78) respectively. These t-stat values approved that both methods (two-system and one-system method) are not different from one to another and might be used for determination of high as well as low RCP of $[^{99}\text{Tc}]\text{Tc-DTPA}$.

4. Conclusion
Validation of the radiochemical purity testing method for $[^{99}\text{Tc}]\text{Tc-DTPA}$ has been successfully performed. The validation results shows that one-system chromatography method where Whatman-1 paper used as static phase and acetone : 0.9% sodium chloride (11:9) used as mobile phase is not significantly different from two-system method where Whatman-1 paper used as static phase and methyl ethyl ketone as a mobile phase (two-system-A) and Whatman-1 paper used as static phase and 0.9% sodium chloride as a mobile phase (two-system-B) in term of precision, accuracy and t-test.

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