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Evaluation of Radiochemical Purity of Received ^{99m}Tc-^{99}Mo Generator using Paper Chromatography Test

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Abstract

Chromatography is a technique for separating mixtures into the components that they are made from in order to analyze, identify, quantify, or purify the mixture or components. This study was performed in Nuclear medicine Department - National Cancer Institute (NCI) University of Gazeria in period of March to May 2011. Quality control testing of the eluate from the generator was tested for the presence of molybdenum breakthrough, and radiochemical purity. These impurities was easily be detected by simple methods. The determination of Aluminum which is a non radioactive agent in the eluate needs indicator paper which could be obtained commercially. The results of chromatography were 98.48% and 98.45%, 98.44%, 98.42%, 98.40% and 98.40%. Finally the quality control of radiopharmaceuticals, if given attention in the department, will result in improving the diagnostic information, reducing the radiation doses to patients and staff, and reducing costs through effective use of radiopharmaceuticals.

Key Words: Chromatography, Radiochemical, Radiopharmaceuticals, Quality Control (QC) and Technetium-99.

INTRODUCTION

Technetium, the 43rd element in the periodic table, belongs to the group of transient metals. Owing to its electron configuration of 4D5 5S2, technetium provides several opportunities for complex formation with a large number of different ligands, and its oxidation state (OS) can change from +1 up to +7. The OS is considered to be a main parameter determining the chemical nature of the complexes. Technetium can form chemical bonds consisting of both sigma and pi electrons, and the sigma bonds can be of colligative and coordinative types when spin compensation and electron pair donation occur, respectively. The structure of technetium complexes can also be characterized by the coordination number (N), which can vary from 4 to 7, allowing tetrahedral (N = 4), tetragonal pyramidal (N = 5), octahedral (N = 6), capped octahedral (N = 7) or pentagonal bipyramidal (N = 7) geometry. The third parameter for characterization of technetium complexes is the electric charge (Z) of the whole molecule, which may provide an anionic (Z = –1), neutral (Z = 0) or cationic (Z = +1) character. A summary of the different kinds of complexing centre and the parameters OS, N and Z. The high variability of the complexing centers results in different stabilities for the various complexes. Pertechnetate (N = 4, OS = +7, Z = –1) is the most stable form of technetium in aqueous media. The presence of free pertechnetate in the solution of a technetium compound is possible, especially after long periods of post-labeling storage. At lower oxidation states, the Tc-S, Tc-P (III) and Tc-C (II) chemical bonds are quite stable in the appropriate geometry. At the same time, phosphonates, in which six oxygen atoms are bound to technetium, are of a lower stability and are liable to form oligomers, that is, polynuclear complexes. The hexacoordinated

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N2O4 and N3O3 complexes such as DTPA, EDTA or HIDA derivatives are also of a relatively low stability and partially transform to heptacoordinated pentagonal bipyramidal geometry, which might be an alternative structure provided by these complexing centers and an additional oxo-oxygen. All starting materials, including active pharmaceutical ingredients (active substances), recipients and primary packaging materials used for kit production; need to be approved before use. Generally, the starting materials such as buffer salts and reducing agents are used in many types of kit and are to be analyzed when a new bottle is opened. The specifications for such substances are described in various pharmacopoeias.[1] However, it should be borne in mind that 99mTc radiopharmaceuticals are a special class of products in which 'no carrier added' grade 99mTc is used to form a complex with ligands, most often in the presence of a reducing agent such as Sn+2 salts. The presence of even small quantities of competing metal ions or oxidants could cause problems in the formation of the desired radiopharmaceutical. Thus it is difficult to provide complete specifications for all the starting materials with respect to the components that should not be present. Often, the use of high quality materials from reputed manufacturers is adequate to ensure good quality products. QA for the material that forms the radiopharmaceutical (along with the ligand and other materials, which are pretested) is advisable.[2] A QC certificate from the manufacturer should be procured. Although the compliance certificate from the manufacturer may appear to be adequate, compliance with the rules laid out by the local regulatory authorities is desirable. Throughout the world, the laws governing the manufacture and sale of medical and pharmaceutical products are modified from time to time, becoming progressively more stringent and specific. In most countries, when a new product is manufactured for use in humans, all the starting materials are to be tested for their quality. This can be done by having the starting materials analyzed at an approved laboratory; alternatively, the QC analysis can be done in the manufacturer's own laboratory. The quality of all the materials should comply with the specifications in the pharmacopoeias or recommended by the regulatory body of the country.[3] The preparation of radiopharmaceuticals in a

hospital radiopharmacy is considered a manufacturing process. This is especially true for technetium-99m labeled radiopharmaceuticals because when a label- ling kit is reconstituted with eluate from a technetium-99 m generator, a new chemical entity is being formed. Therefore, it is logic that such activity should be a subject of EU directives or at least guidelines. However, in the nuclear medicine laboratories (radiopharmacies) in Europe, quality assurance varies from almost non-existent to good manufacturing practice level. In order to set uniform standards, the Radiopharmacy Committee of the EANM took the initiative to provide the nuclear medicine community in Europe with guidelines which would ensure a necessary and sufficient level of safety and efficacy in the production, reconstitution and handling of radiopharmaceuticals in nuclear medicine. Preparation of all radiopharmaceuticals requires adherence to regulations on radiation protection.[4] In the case of radiopharmaceuticals for parenteral use (a large majority), also rules of working under aseptic conditions must be followed. The handling of radioactive materials is potentially hazardous. The radiation protection rules, including storage, handling and waste disposal of radioactive materials, are commonly known and generally applied. On the other hand, the pharmaceutical requirements as described in the principles and guidelines on Good Manufacturing Practice (are not yet very well known nor generally applied. Therefore, a Quality Assurance system established in the hospital radiopharmacy should cover these two aspects of radiopharmaceutical preparation. Continuous assessment of the effectiveness of the Quality Assurance system is essential in order to prove that the procedures applied in the radiopharmacy lead to the expected results. The most important of these procedures are briefly described below.[5]

^{99}MTC-^{99}MO GENERATOR

^{99}mTc species (10 not elute from the column. This problem has been addressed by purging the saline reservoir with O2 Previous attempts to add oxidizing agents to the column to decrease reduction of ^{99}mTc species resulted in ^{99}mTC radiopharmaceuticals formulation problems. The dry column generator ss1ei was developed to alleviate poor elution yields of ^{99}mTcO4 by removing saline alter elution. This decreases the amount of radiolysis products formed. The dry column generator employs a 5-20 ml saline charge, which is applied to au exterior part of the generator. An evacuated vial draws saline through the generator to remove ^{99}mTcO4, followed by air I o dry the column I caving the air on the column promotes oxidation of any reduced Tc99m species back to +7 valence state of ^{99}mTcO4 which can then be eluted. There are two types of parent - daughter relationships. Firstly, transient equilibrium is where the parent's half-life is a factor 10— 100 times greater than that of the daughter (e.g.: Mo/^{99}mTc generator, where the parent, ^{99}mMo, has a half-Life of 67 hours, compared to 6 hours for the daughter, ^{99}mTc). The second equilibrium stale is known as secular, this is where the half—life of the parent is many times greater (100 times) that of the daughter's half-life, e (Supination). Plantaro dorsal external oblique (Pronation).

^{90}Sr â - $^{-90}$ã (29.1 yrs) - 2.67 days).

The three curves of Fig.4, are demonstrating what happens with the growth and decay of a daughter radionuclide in a transient equilibrium situation Curve X indicates the radioactivity of the parent radionuclide at subsequent lime intervals, showing its radioactive, decay. Curve Y indicates the radioactivity of the ^{99}mTc daughter. Curve Z is the radioactivity of^{99}mTc 1resent in ^{99}o/^{99}mTc generator, i.e. it demonstrates how the radioactivity of ^{99}Tc grows to a maximum value and then gradually decays away. Before this maximum value, ^{99}mTc is growing into the system faster than it is decaying, which leads to a progressive build-up of the level of ^{99}mTc. After the maximum value, the ^{99}mTc growth rate equals its decay rate. However from this point on, the growth rate of ^{99}mTc gets progressively smaller as the parent ^{99}Mo decays away but the system is self - compensating by reducing the rate of decay of ^{99}mTc. The overall net effect is the establishment of transient equilibrium in which the ratio of ^{99}Mo radioactivity ^{99}mTc radioactivity remains at a constant value.

The daughter radionuclide can he separated from the parent by chemical means. In the case of the ^{99}Mo/^{99}mTc generator, ^{99}mTc is separated from ^{99}Mo by passing saline through the column. The ^{99}mTc is eluted off the generator column as sodium pertechnetate (NaCl ^{99}mTc O4). The ^{99}Mo remains immobilized on the column. Alternative separation techniques include solvent extraction and sublimation.[11]

The columns contain a small alumina bed allowing elution of ^{99}mTc O_4^- in small volumes (high specific activities). The elution profile indicates the volume of elute which removes all the ^{99}mTc activity out of the column. The bulk of ^{99}mTc activity is eluted in the first half of the elution volume.

The first 1 mL contains no activity (dead space of the tubing). An elution volume of 6 mL will remove approximately 90% of available ^{99}mTc, so the larger volumes serve only to dilute the bulk of activity already eluted. Thus high specific activity solutions can be obtained by collecting only over the peak of the elution profile (2-6mL).

The process of elution can be repeated as many limes as is thought necessary; however, the percent yield will vary. After the daughter has been eluted, the daughter activity remaining on the column is low but begins to increase (regenerate) until it eventually approximates the activity of the parent again. If the column has completely regenerated, the usual yield is approximately 70% of the parent activity. In the case of ^{99}Mo/^{99}mTC generator, regeneration requires 24 hours. Any elutions that are performed before that time will result in lower yields per elution; however a large net yield can be realized if several premature elutions are performed over any period of time. This is caused by the exponential buildup of the daughter product after elution but concentration is reduced. [12]

The plot of ^{99}Mo/^{99}mTc decay shown as a dotted line and ^{99}mTc shown as a solid line. The generator is eluted on days 1, 3 and 5, changing in no way the course of decay of ^{99}Mo. Following each elution, it requires approximately four physical half-lives [25hours] to return to equilibrium. Regeneration is an exponential function with approximately 50% regeneration during the first half-life, 25% during the second half-life and So on.[13]

Correct handling of radiopharmaceuticals ensures good aseptic techniques. All procedures in the hot laboratory are designed to optimize patient care and minimize radiation exposure to all personnel in the department. The patient must receive the correct radiopharm-aceiitica1 at the correct dose with high radiochemical purity. This requires that accurate and sterile doses are prepared for patient administration by well trained and qualified personnel. Aseptic techniques and sterile and pyrogen - free ingredients are

used at all times to minimize bacterial and pyrogen contamination. Appropriate records must he maintained to document the receipt, patient use, and ultimate disposition of all radioactive materials. To minimize the chance of errors, be sure the work area is clear. Work with only one radiopharmaceutical agent at a time. In addition, check the dose calibrator setting when assaying the patient's dose.

Urbano et al. (2005) mentioned in their study of evaluation of fresh and old eluate of ^{99}Mo-^{99}mTc generators used for labeling of different pharmaceutical kit that that these "risky" elutions might be appropriately used, in "emergency" conditions, for labeling radiopharmaceuticals although their radiochemical purity control is recommended prior to patient administration. Sixty ^{99}Mo-99mTc wet column generators, loaded with two different ^{99}Mo activities, were analyzed in order to assess the quality of their elutes. Each elution was used for labeling of different radiopharmaceuticals, in order to evaluate whether "risky" elutions, namely those performed just after generator delivery and at 72 hours or more from the last elution, could be conveniently employed when fresh available radioactivity is not enough for the planned labeling or when shipping problems arise, or delay in delivery of a new generator occurs. Radiochemical quality control of all radiopharmaceuticals labeled with these elutions was performed. The elutions differed mainly in ^{99}Tc ground state (^{99}gTc) and amounts of oxidizing impurities. Radiolabelling procedures, however, were not affected, suggesting that these "risky" elutions might be appropriately u s e d , i n " e m e r g e n c y " c o n d i t i o n s , f o r l a b e l i n g radiopharmaceuticals although their radiochemical purity control is recommended prior to patient administration.

MATERIALS AND METHODS

In paper chromatography the stationary phase is the filter paper and the mobile phase is the solvent. The filter paper holds the components until the solvent dissolves them and carries them up the filter paper. The solvent travels up the filter paper by capillary action. The solvent's attraction to itself pulling it up is greater than the force of gravity pulling it down. The separation of components depends on their solubility with the solvent and their affinity to the solvent and filter paper. The solvent can only move the components if they are soluble in it and the more soluble a component is the more there is available to move up the filter paper. Solutes will dissolve into solvents that have similar properties. Polar solvents dissolve polar solutes and non-polar solvents dissolve non-polar solutes. (Like dissolves like.) A component will travel up the filter paper at a rate that is determined by its affinity to the filter paper and solvent. Since each component has its own solubility with the solvent and its own affinity to the solvent and filter paper, they can be separated in multiple ways by using mixtures of different solvents and different filter papers.

For nuclear medicine, each generator was being tested for radiochemical purity testing, chemical purity and pH determination, where the acceptable level of the tests will be determined.

A.Paper Chromatography: Experiment

1.Purpose

· To introduce students to the terminology and principles of chromatography and demonstrate separation of the dyes in Sharpie Pens with paper chromatography.

2.Time Required

- Preparatory time – 10 minutes
- Experiment time – 25

minutes Material List .Material

Required 1)Tc-99m DTPA

2)Two ITLC-SG paper (1cm x 8 cm)

3)Two Small 10mL or 20 mL vials with cover

4)Normal saline

5)acetone

6)pencil

7)Scissor

8)Counting tubes

9)1mL with 27 G needle or TB syringe

10)Forceps (Figure 1)

11)Gamma counters (if not available, can be replaced by thyroid probe or gamma camera) (Figure 2).

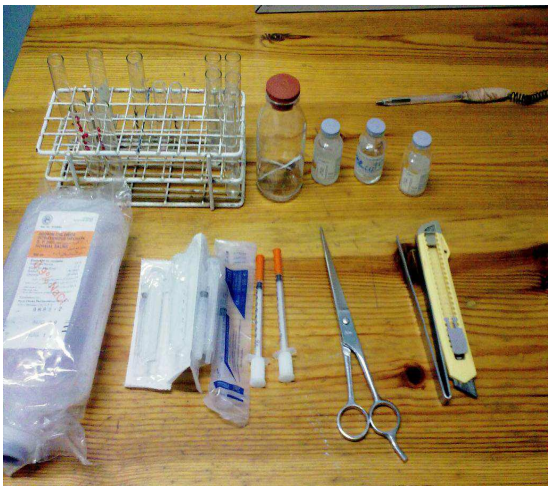

Figure 1.QC Test Tools

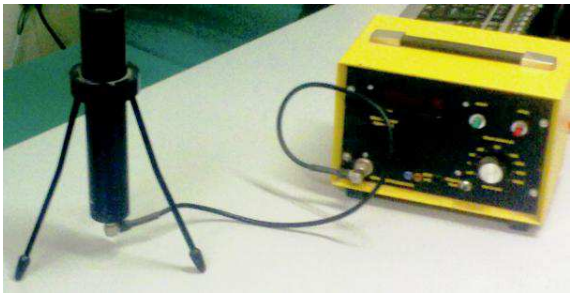

Figure 2. Shows Gamma Counter

Radiopharmaceutical

- Tc-99m DTPA
- Activity: 203 mCi in 6 ml (elution)
- Time of Mixture: 8:17 am
- Generator type: Dry Mo99-Tc99 Generator
- Dose: 1.2 mCi at 8:30 am

Steps

1. Normal saline was added to one of the vials (to about 0.5 cm from the bottom) and acetone to another one. To make sure that researcher must put the cover on (Fig. 3).

Figure 3. Addition normal saline and acetone

1. Researcher added normal saline to one of the vials (to about 0.8 cm from the bottom) and acetone to another one. To make sure, he put the cover on (Fig. 4).

Figure 4. Shows the researcher adding Normal saline in one vial and acetone in other one

3. Researcher drew no more than 0.1 mL of the Tc-99m DTPA using 1mL syringe or the TB syringe (Fig.5).

Figure 5. Shows Tc-99m DTPA syringe

4. Researcher applied a small drop at the origin of both ITLC-SG paper (Fig. 6)

Figure 6. Shows 0.1 mL of Tc-99m DTPA

5. He allowed the spot to dry in air for about 2 to 3 min. (Fig.7)

Figure 7. Shows ITLC paper

6. He placed one of the ITLC paper into the normal saline vial and the other into the acetone vial. He made sure that the radiopharmaceutical spots were above the solvent level and then closed the cap.

7. He allowed the solvent to migrate up the ITLC-paper. When the solvent had reached the 'solvent front line', he removed the ITLC-paper using the forceps.

8. He allowed the ITLC paper to dry in air for about 2 to 3 min (Fig.8)

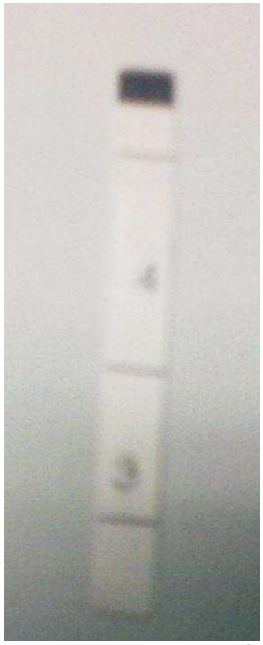

Figure 8. The ITLC paper to dry in air for about 2 to 3 min

9. He cut the ITLC paper along the middle line. He placed each section into separate counting tubes

10. He placed the counting tube into the gamma counter (Fig. 2)

11. He drew a region of interest around the radioactive spots and recorded the counts. Then he recorded background accounts

From the acetone strip:

% of free Tc-99m =

$$\frac{\text{Radioactivity of the upper half} \times 100\%}{\text{Radioactivity of the upper half + radioactivity of the lower half}}$$

From the normal saline strip

% of RH-Tc-99m =

$$\frac{\text{Radioactivity of the lower half} \times 100\%}{\text{Radioactivity of the upper half + radioactivity of the lower half}}$$

% of the radiopharmaceutical = 100% - % of free Tc-99m - % of RH-Tc-99m

RESULTS

QC measures are necessary to ensure that a product complies with all the requirements and specifications laid out for it. The QC unit should have well documented procedures for QC, which is to be undertaken for each starting material used for production as well as for finished products. It is suggested that the manufacturers refer to national pharmacopoeias, the USP, the EP or any other international pharmacopoeia when designing appropriate QC specifications and methods. The main objective of this study is to establish guidelines of procedures of radiochemical purity tests of received Technetium-99m generator.

The main objectives of this study are firstly; to establish quality assurance program for received Tc-99m generator, secondly to highlight the importance of the Quality Control (QC)methods in ensuring that a product complies with all the requirements and specifications laid out for it. Thirdly; to encourage good radiopharmacy practices for the preparation and quality assurance. Finally; to establish a quality management system this encourages continuous update of core competencies in hot laboratory staff.

For nuclear medicine, each 99mTc generator was being tested for radiochemical purity testing, chemical purity and pH determination. The results of chromatography were 98.48% and 98.45%, 98.44%, 98.42%, 98.40% and 98.40%. Finally the quality control of radiopharmaceuticals, if given attention in the department, will result in improving the diagnostic information, reducing the radiation doses to patients and staff, and reducing costs through effective use of radiopharmaceuticals.

PAPER CHROMATOGRAPHY

RESULTS AND CALCULATION

EXPERIMENT NO.1

RADIOPHARMACEUTICAL:

- Tc-99m DTPA
- Activity: 203 mCi in 6 ml (elution)
- Time of Mixture: 8:17 am on 8/6/2011
- Generator type: Dry Mo99-Tc99 Generator
- Dose: 1.2 mCi at 8:30 am

From the acetone strip:

% of free Tc-99m =

$$\frac{\text{Radioactivity of the upper half} \times 100\%}{\text{Radioactivity of the upper half + radioactivity of the lower half}} = \frac{7884}{8084} = 0.97526\%$$

From the normal saline strip:

% of RH-Tc-99m =

$$\frac{\text{Radioactivity of the lower half} \times 100\%}{\text{Radioactivity of the upper half + radioactivity of the lower half}} = \frac{36273}{37927} = 0.95639\%$$

Radiochemical = 100% - % of free Tc-99m - % of RH-Tc-99m

=100% -0.975% -0,956% =98.06 %

CONCLUSION

This is an experimental study deals with evaluation of quality control program of received Technetium-99m (^{99}Mo-^{99m}Tc) Generators. The importance of this study is to highlight the importance of the quality assurance program in nuclear medicine department. In addition to its role to increase diagnosis accuracy and reduce the dose to both patient that is unable to reach by without quality control special in Technetium-99m (^{99}Mo-^{99}mTc)Generators. Chromatography is a technique for separating mixtures into the components that they are made from in order to analyze, identify, quantify, or purify the mixture or components. A scientist will use chromatography; firstly to examine a mixture, its components, and their relations to one another (analyze). Secondly determine the identity of a mixture or components based on known components (identify). Thirdly to separate components in order to isolate one of interest for further study (purify). Finally to determine the amount of the mixture and/or the components present in the sample (quantify). Different types of chromatography are used: liquid chromatography, gas chromatography, paper chromatography, and thin-layer chromatography. While each type of chromatography uses different methods to separate compounds, they all share the same principles. Chromatography utilizes the differential affinities of the components for a gas or liquid mobile medium (mobile phase) and for a stationary adsorbing medium (stationary phase) through which they pass. The stationary phase holds the mixture until the mobile phase passes through, solubilizes the components, and moves them along at their individual rates. Once components are separated from one another, they can be analyzed.

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