

IS IT POSSIBLE TO DO RADIOPHARMACEUTICAL QUALITY CONTROL WITH A GAMMA CAMERA

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ABSTRACT

All of the imaging studies in nuclear medicine start with a suitable radiopharmaceutical preparation step. In radiopharmaceutical synthesis, an organic or biochemical molecule is combined with a radioactive element to form a complex. This process is known as radiolabeling (1). In a radiopharmaceutical labeling study, it is important to realize that whether or not the radiolabeled chemical complex is in the expected radiochemical form has a vital role for all the nuclear medicine imaging processes. The common method of radiopharmaceutical quality control is the chromatographic analysis such as PC, TLC, and HPLC. In nuclear medicine practice, application of these methods is called radiopharmaceutical quality control(2). The agreement of results obtained from such chromatographic analysis methods with the criterions given in United States Pharmacopeia (USP) means the regulatory permission of the use of that radiopharmaceutical in proposed applications(3).

In this study separation of several labeled radiopharmaceuticals were demonstrated by using standard support materials and solvents. After drying the chromatographic support material, a gamma camera (TOSHIBA GCA-602A) was used to do radiation counting and static imaging for 2 minutes. These images, then, was divided into rectangular pieces (5 x 25 in pixel) and Region of Interest (ROI) process was applied to them. The percent labeling yields were calculated by plotting total count for each area against the number of area. It was also demonstrated that the Rf values obtained from gamma camera studies were in agreement with the Rf values obtained with classical methods.

INTRODUCTION

Nuclear medicine is an interdisciplinary program which combines physics, chemistry, electronic and medicine. Today the developments in nuclear medicine, in terms of imaging technology, performance and speed have reached to their highest level where further new developments may only be achieved with the synthesis of new radiopharmaceuticals and the determination their organ/pathology specific imaging performances. It is widely believed that studies for new radiopharmaceutical synthesis are very important for further developments in this field(4).

Molybdenum (Mo-99) isotope which is generated from naturally occurring Molybdenum (Mo-98) isotope by radiating in a reactor, is transmuted to Technetium (^{99m}Tc) with a half-life of 66

hours. This synthetic ^{99m}Tc radioisotope emits pure gamma rays of 140 keV and has been used extensively in nuclear medicine. Today, ^{99m}Tc is the most commonly used radioisotope for diagnosis purposes in medicine(4). The reason for this is the fact that specifically designed organo-metallic complexes of this particular isotope have very specific accumulation characteristics for a number of organs, abce and tumors. These complexes which are administered to the body by intra-venous (i.v.) at very low concentrations, can provide physiologic information about the organs that they are accumulated. Also they can help to evaluate the functionality of the organs under study(5).

In order to synthesize organo-metallic complexes of ^{99m}Tc , first it is necessary to reduce pertechnetate with Sn^{++} to a reduced form. Several parameter such as pH, temperature and stirring rate have an important role on complexation process and theretofore these parameters must be optimized to achieve a good complexation yield(2). Once the reaction medium is optimized, the resulted radiocomplex of ^{99m}Tc with such ligands are called radiopharmaceuticals. It is very important to evaluate the quality and labeling yield of these radiopharmaceuticals in order to approve their further use in nuclear medicine applications. Otherwise it may result in false diagnosis and unnecessary exposure of the patient to radiation.

A number of conventional chromatographic radiopharmaceutic quality control methods have been described in literature (6-7). These are paper chromatography, TLC, and Single Step ITLC or Two Strip ITLC. Instant TLC is a fast method and used for preliminary identification of labeling yield in routine applications(3). In the synthesis of new pharmaceuticals, initial studies are carried out with TLC to obtain preliminary results. Once the initial studies confirms that the results are promising then a Radio-HPLC with radiation and uv combined detectors is used to gather accurate and acceptable results. With the conventional methods, first the samples are spotted on origin. After the solvent is migrated to the top of the plates and drying is completed, support materials are cut into 0.5 or 1.0 cm pieces (a few pieces in ITLC) and counted on a appropriate radioactivity counting system. Then, the data were plotted as counts versus distance in cm. These plots are used to determine labeling yield and R_f values of radiopharmaceuticals. However, there is the possibility of contamination due to contact of cutted pieces with each other, contamination of cutting device, and the contamination of counting system in these methods. In addition, It can be difficult to evaluate the agreement of the results in terms of accuracy and precision with the USP criterions due to these possible source of contamination factors.

In this study, quality control of a number of radiopharmaceuticals labeled with ^{99m}Tc which are used for routine nuclear medicine imaging were studied. The aim was to determine whether the radioactive counting of plates can be performed with different methods as opposed to the conventional chromatographic analysis. The separation of several labeled radiopharmaceuticals were demonstrated by using standard support materials and solvents. After dying the chromatographic support material, a gamma camera (TOSHIBA GCA-602A) was used to do radiation counting and static imaging for 2 minutes. These images, then, was divided into

rectangular pieces (5 x 25 in pixel) and Region of Interest (ROI) process was applied to them. Here it is worth to mention that these pieces corresponds to each individual piece obtained by cutting whole chromatographic plates in classical radiochromatography. Because mm/pixel calibration of gamma camera was performed earlier, the area length of these pixel were obtained with the help of pixel to cm conversion. Thus, percent labeling yield and were calculated by plotting total count for each area against the number of area.

It was also demonstrated that the Rf values obtained from gamma camera studies were in agreement with the Rf values obtained with classical methods. Therefore, it may be possible to use a gamma camera as a tool for chromatographic quality control for the clinics that do not have a counting instrument like Single or Multi Channel Analyzer (SCA or MCA).

EXPERIMENTAL SECTION

All chemicals and solvents used in this study were reagent grade. ^{99m}Tc sodiumpertechnetate NaTcO_4 solution was obtained from a $^{99}\text{Mo}/^{99m}\text{Tc}$ generator (CIS bio international, Cedex/France). DTPA (Diethylenetriaminepentaacetic acid) and Nanocolloids cold kits purchased from Amersham (Amersham plc. England) and used as starting material for quality control of radiopharmaceuticals. Whatman 31-ET chromatography paper and other chromatographic plates were purchased from Whatman Ltd. (Maidstone/England). After chromatographic processes, strips and layers were acquired and imaging processes performed by using Toshiba GCA-602A circular gamma camera imaging system. Measurement were made in static imaging mode with 256x256 matrix size for 2 minutes scan time.

RESULTS AND DISCUSSION

The aim of this study was to investigate the applicability of a gamma camera for radiopharmaceutical quality control. The same chromatographic procedure described above has been followed except the counting stage where a gamma camera (TOSHIBA GCA 602A) was used instead of a radioactivity counting system. Figure.1. shows gamma camera image of a sample radiopharmaceutical labeled with ^{99m}Tc and other impurities on a Whatman 31-ET chromatographic paper developed in Saline solution (bottom left and right). Upper left part of the Figure.1 illustrates the ROI processed image of the radioactive complex. It can be seen from the figure that this process generated 17 identical rectangular pieces having the are of 125 pixel² (5 x 25 in pixel). The table on the upper right part of the figure shows total counts with their statistical evaluation for each area. Figure.2 shows gamma camera image of free pertechnetate ($^{99m}\text{TcO}_4^-$) on the same chromatographic paper with same development solution. In order to indicate the paper on the camera head a rectangle was drawn by the software of the system with the help of the pixel calibration of the camera. Also, as can be seen on the figure, a marker was used to indicate the origin. It is clear from these figures that spot images of both radio-labeled compound and free pertechnetate can easily be seen. Figure.3 illustrates the smoother version of the image shown in Figure.2 by subtracting the background noise. In order to show how reduced form of the ^{99m}Tc behaves in same chromatographic system, images of reduced ^{99m}Tc were also

collected as shown in Figure.4. As seen from this figure, reduced form of the ^{99m}Tc do not migrate at all in this system.

Figure.5 shows the gamma camera image of the ^{99m}Tc -DTPA on the same type of the chromatographic paper under same conditions. As shown on the figure there are three separated region labeled as 1, 2, and 3. Region 1 corresponds to the free pertechnetate which was either not reduced or reoxidized with time. The region labelled as number 2 shows the radiolabeled DTPA compound and the region 3 represents whole paper. As can be seen on the table, shown on the upper left of the figure, the total count for radiolabeled compound was about ten times higher than those for pertechnetate. The labeling yield of ^{99m}Tc -DTPA was given as 90.1% and the free pertechnetate was 8.59% which indicates a very good labeling yield. It was also possible to determine the Rf values of both labeled compound and free pertechnetate with high precision as shown on the right side of the image. Finally Figure.6 shows gamma camera image of ^{99m}Tc -nanocolloid under the same conditions. Since the nanocolloids do not migrate in this solvent system most of the activity were observed on just above the origin. However the spot at the top of the plate indicates the presence of free reoxidized ^{99m}Tc . The reason for this is that the labeled compound was waited for a long time before the images were taken.

The results shows that this method eliminates the need of cutting chromatographic plates into small pieces since the software of the gamma camera allows the user to do the same process on the images obtained from camera and thereby eliminating the possible sources of contamination. This new modified method as an alternative to the conventional methods can provide much faster repeatability, higher accuracy and better precision when compared with classical methods for radiopharmaceutical quality control in both research and routine applications. As a result, it can provide an enormous time saving especially in process of determining the labeling yield studies. It is also important to note that many nuclear medicine clinics may not have a radioactivity counting system where a gamma camera can be easily used for this purpose.

CONCLUSION

It was demonstrated that a gamma camera can be used as a means of radiopharmaceutical quality control. It can provide much faster analysis, higher accuracy and better precision for both labeling yield and Rf values by eliminating many of the possible contamination sources. This method can also be very useful for routine applications especially for the clinics that do not own a radioactivity counting system.

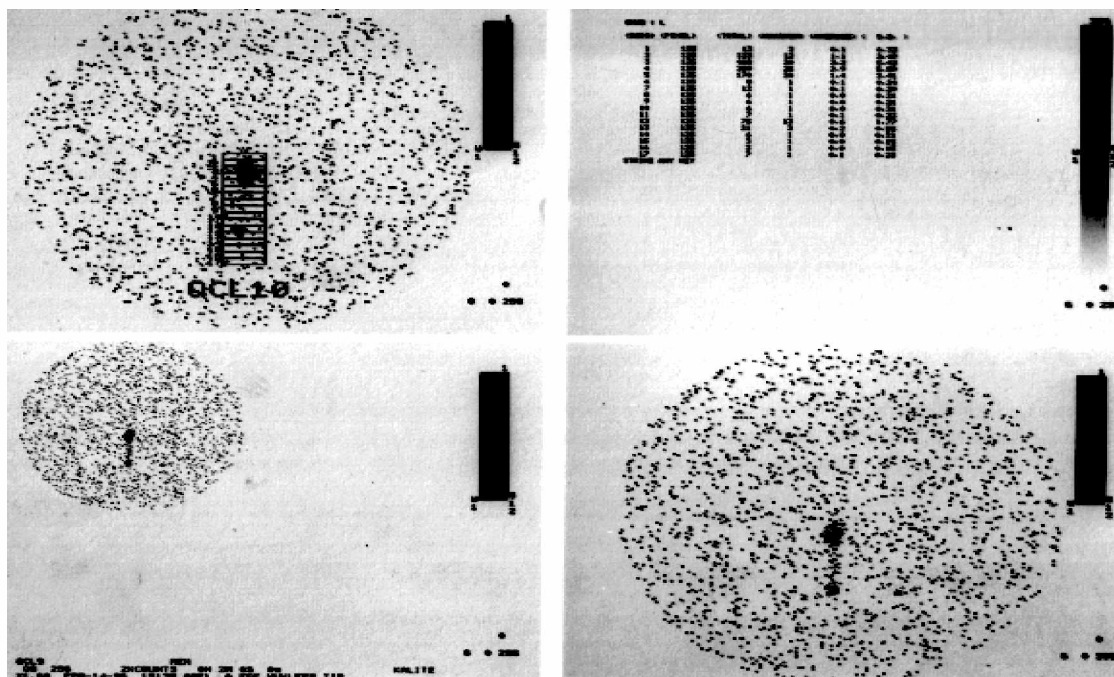


Figure.1. Gamma camera image of a sample compound radiolabeled with ^{99m}Tc and other impurities on a Whatman 31-ET chromatographic paper developed in Saline solution.

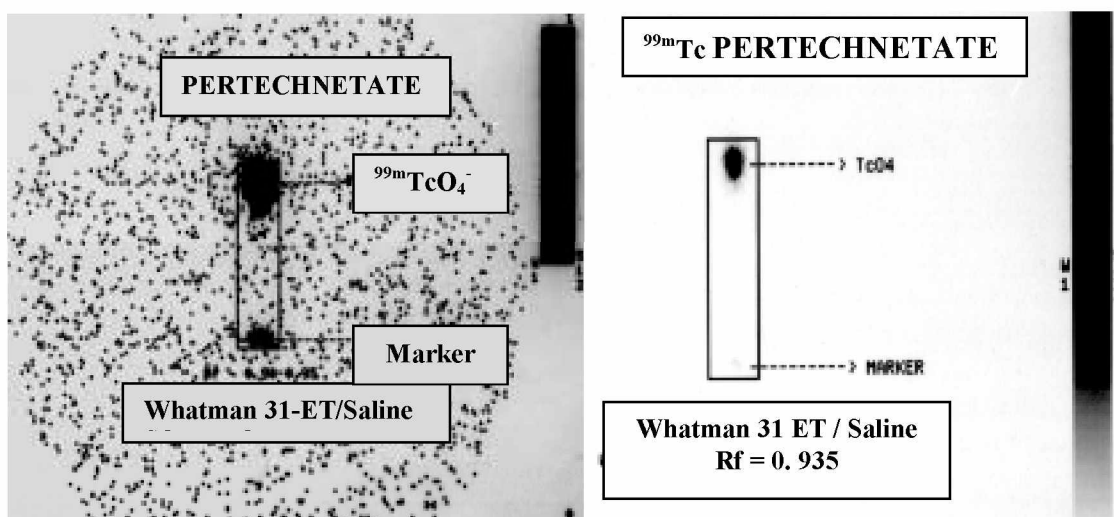


Figure.2. Gamma camera image of free pertechnetate ($(^{99m}\text{TcO}_4)^-$) on the same chromatographic paper with same development solution.

Figure.3. The smoother version of the image shown in Figure.2 by subtracting the background noise.

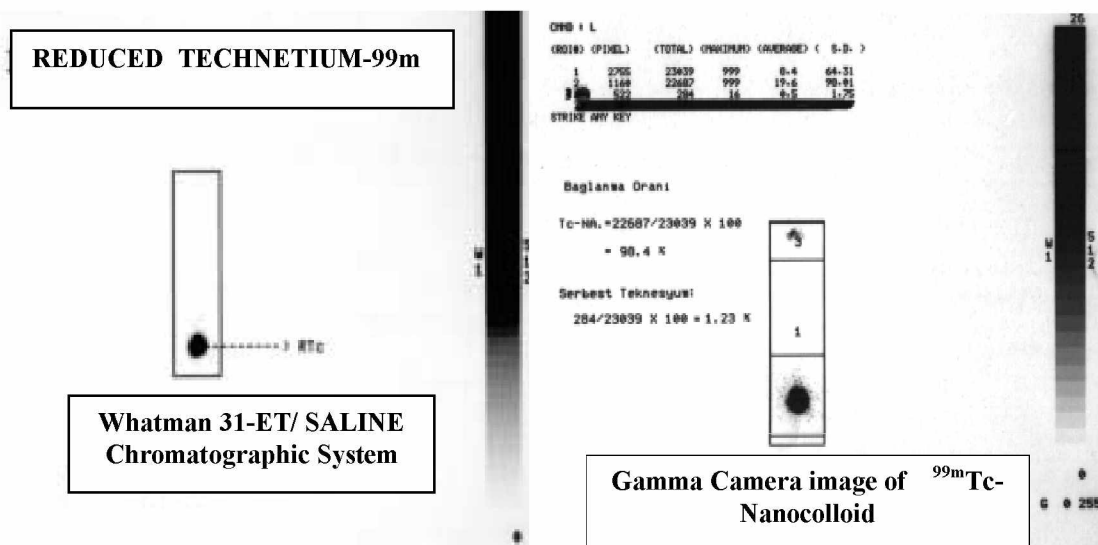


Figure.4. Gamma camera image of reduced form of the ^{99m}Tc on the same chromatographic paper with same development solution (Left).

Figure.6. Gamma camera image of ^{99m}Tc -nanocolloid under the same conditions (Right).

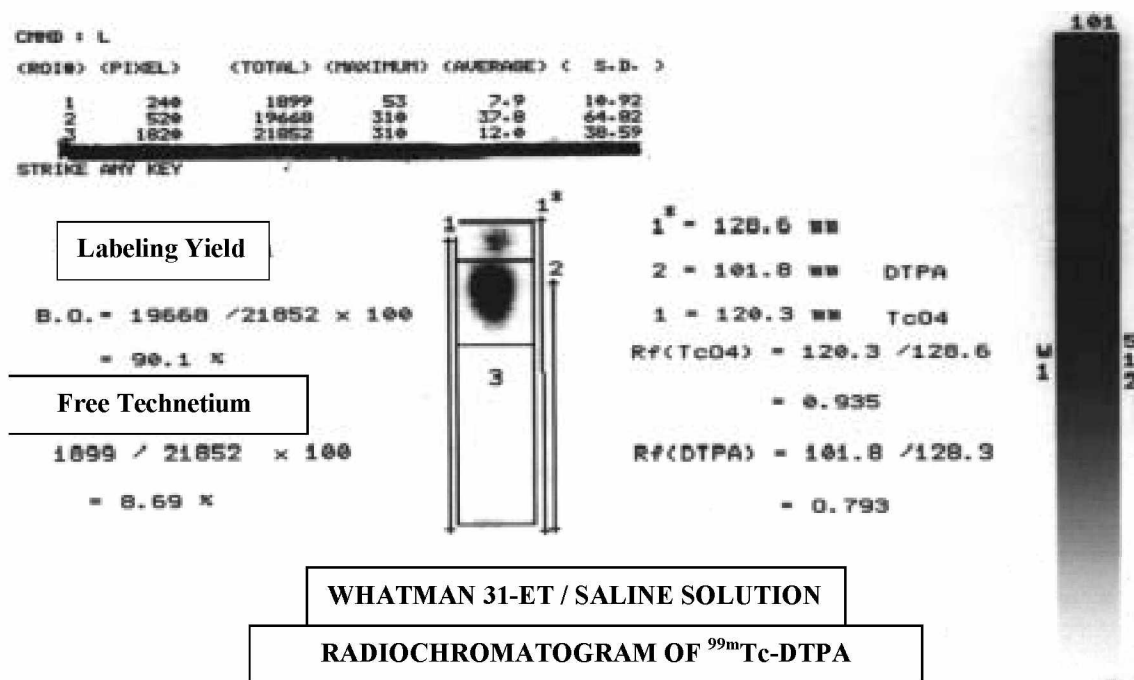


Figure.5. Gamma camera image of the ^{99m}Tc -DTPA on the same type of the chromatographic paper under same conditions.

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