Routine Radiochemical Quality Control of ^{99m}Tc eluate and ^{99m}Tc-Labeled Radiopharmaceuticals

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ABSTRACT

Technetium-99m (^{99m}Tc)-labeled radiopharmaceuticals are indispensable tools in nuclear medicine, playing a vital role in various diagnoses such as myocardial perfusion imaging (MPI), bone scintigraphy, thyroid imaging, renal scintigraphy, lung perfusion and ventilation scans, gastrointestinal imaging, parathyroid imaging, tumor imaging, etc. Quality control plays a key role in ensuring the safety and efficacy of radiopharmaceuticals, particularly in the case of radiopharmaceuticals. The production of Tc-99m-labeled radiopharmaceuticals involves a complex series of steps, from generator elution to final patient administration. The Nuclear Regulatory Commission (NRC), United States Pharmacopeia and National Formulary (USP-NF), British Pharmacopeia (BP), and European Pharmacopeia (EP) limit the amount of radionuclide contamination allowed in ^{99m}Tc solutions for patient use. Various methods have been used to ensure the quality of the ^{99m}Tc-eluate. The radiochemical purity of various ^{99m} Tc radiopharmaceuticals is checked by Instant Thin Layer Chromatography (ITLC), and radio-nuclide identity was confirmed by obtaining a gamma spectrum from a High Purity Germanium (HPGe) detector and measuring the half-life of the radiopharmaceuticals. pH and sterility testing are also performed before administration to the patient's body. These QC methods collectively help verify the quality and safety of ^{99m}Tc radiopharmaceuticals, ensuring that they meet the necessary standards for clinical use and patient care as per IAEA guidelines.

Keywords: Technetium-99m (^{99m} Tc), Radiopharmaceuticals, Quality control, Scintigraphy

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INTRODUCTION

The field of radiopharmacy in medicine deals with the development, manufacturing, processing, quality control, and distribution of radiopharmaceuticals used in nuclear medicine for imaging, diagnosis, and/or treatment (1). The diagnosis and treatment of anatomical and biochemical physiology are specialties of nuclear medicine, which draws on the unique characteristics associated with radiopharmaceutical compounds and radioisotopes (RI). The RI is generated by a generator, cyclotron, or reactor. To increase picture resolution in nuclear medicine imaging, a certain radiation dosage is required. Because of its low patient dose, it is preferable to utilize a RI with a relatively short half-life; nevertheless, this has the drawback of rapidly attenuating during examination. By isolating the milked 99mTc from the mother nuclide molybdenum-99 (^{99}Mo), the generator produces technetinum-99m (^{99m}Tc), which is simple to use and obtain (2-4). Radiopharmaceutical practices in Bangladesh are subject to the guidelines set out by the Bangladesh Atomic Energy Commission (BAEC) and the Bangladesh Atomic Energy Regulatory Authority (BAERA). Nowadays, a significant number of radiopharmaceuticals used in nuclear medicine are freeze-dried kits for in situ sodium pertechnetate radio labeling (Na99mTcO4-). The goal of freeze-dried formulations is to improve product stability, enabling an effective process and simple reconstitution for radiopharmaceuticals (5). Because products are generally administered intravenously and contain radionuclides in their composition, radiopharmaceuticals have unique production and quality control requirements (1). RCP is the total percentage of radioactivity in a radiopharmaceutical that is present in the intended chemical form, i.e., bound 99mTc to the target ligand. Radiochemical impurities include both free ^{99m}Tc (^{99m}TcO4-) and hydrolyzed-reduced ^{99m}Tc (^{99m}TcO2). Because of their great counting sensitivity, instruments like gamma counters and thin-layer chromatography (TLC) scanners are used in industrial radiopharmacy to determine RCP. However, even though it has a lower sensitivity than the formers, dose calibrators are frequently utilized in hospitals to quantify chromatographic stripes once they are typically available. This brief note attempts to evaluate dose calibrator reliability for routine

nuclear medicine testing and to propose the most cost-benefit chromatographic techniques for the RCP evaluation of ^{99m}Tc-eluate and ^{99m}Tc-radiopharmaceuticals.

MATERIALS AND METHODS

The chromatographic systems that were already reported in the literature were redesigned to accomplish the objectives. All the steps such as cost, time, ease of operation, performance, and consistency were carried out in the same research laboratory to compare the technical criteria. simple modifications were made in certain systems to improve routinely, compared to the relevant references. These adjustments include shifting the stationary and mobile phases as well as the cutoff of the chromatographic strip. Thin-layer chromatography (TLC) was the primary quality-control method used in this investigation as, in our opinion, it is the most appropriate method to measure the quality of short-half-life radiopharmaceuticals. The thin-layer chromatography media used were Gelman silica gel ITLC, instant thin-layer chromatography strip. The solvents used were 0.9% w/v sodium chloride solution and Ethyl Methyl Ketone (MEK). The TLC paper is heated to 120°C for approximately 20 minutes prior to the aliquot of radiopharmaceuticals being dropped. It is noteworthy to emphasize that all radiopharmaceuticals in this study were radiolabeled with ^{99m}TcO4- in four distinct batches, and duplicate ascendant chromatography was used for RCP analysis. The radioactivities of the strips were measured using an automatic gamma-counter (Gamma Multi Channel Analyzer Mucha-raytest), a dose calibrator (ATOMLABTM 500), and a TLC-scanner (miniGITA Elysia Raytest).

RESULT AND DISCUSSION

The chromatographic systems were chosen with a few technical considerations in mind. In addition to the chromatographic development time, we have also considered the stationary and mobile phases of the chromatographic system. As thin layer chromatography (TLC)-silica gel (SG) strips are the least expensive chromatographic strips available for ascendant chromatography, most of the systems selected used them for stationary phases. With regard to mobile phases, we have considered easy preparation, purchasing control by authorities, high availability, and waste disposal with minimum cost, minimum risk, and toxicity to the professional. Additionally, shorter chromatographic developments were given priority in order to accelerate radiopharmaceutical dispensing for patients. In addition, the cutoffs of the strips were verified using the TLC scanner, the gold standard for counting chromatographic strips (6). Usually, cutoffs in the stationary phase were prioritized for standardizing counting in dose calibrators.

Table 1: The relevant chromatographic parameters, chromatographic systems, cutoff, and Rf for the 99mTc-eluate Radiochemical purity (RCP) studies and the evaluated ^{99m}Tc-radiopharmaceuticals.

Radiopharmaceuticals (Rpharma)	Chromatographic system		Retention factor (R_f)		
	Stationary phase	Mobile phase	Labeled Rpharma	TcO_4^-	TcO_2
Sodium Pertechnetate $Na^{99m}TcO_4$	TLC-SG	MEK	-	0.0-0.1	0.9-1.0
^{99m}Tc-Sestamibi (^{99m}Tc-MIBI)	TLC-SG	Saline	0.0-0.1	0.9-1.0	0.0-0.1
^{99m}Tc-Medronate (^{99m}Tc-MDP)	TLC-SG	MEK	0.0-0.1	0.9-1.0	0.0-0.1
^{99m}Tc-Pentetate (^{99m}Tc-DTPA)	TLC-SG	MEK	0.0-0.1	0.9-1.0	0.0-0.1
^{99m}Tc-Succimer (^{99m}Tc-DMSA)	TLC-SG	MEK	0.0-0.1	0.9-1.0	0.0-0.1
^{99m}Tc-Albumin colloid (^{99m}Tc-Nanocolloid)	TLC-SG	MEK	0.0-0.1	0.9-1.0	0.0-0.1
^{99m}Tc-pyrophosphate (^{99m}Tc-PYP)	TLC-SG	MEK	0.0-0.1	0.9-1.0	0.0-0.1

Compared to dose calibrators, TLC scanners and automated gamma counters are more sensitive instruments (6). However, dose calibrators are most commonly used in the routine activities of hospital radiopharmacy, and they are usually available to measure chromatographic strips for RCP analysis. Therefore, the radiopharmaceuticals ^{99m}Tc -eluate, ^{99m}Tc -DTPA, ^{99m}Tc -MDP, ^{99m}Tc-nanoscan, ^{99m}Tc -DMSA, ^{99m}Tc -MIBI, and ^{99m}Tc -PYP were assessed in the aforementioned radioactivity counting devices in order to validate the efficacy of the dose calibrator as a trustworthy counting instrument for RCP assays. These results are summarized in Table 2.

The dose calibrator can be used for routine RCP evaluation, according to our data, even though it is not as sensitive as an automatic gamma counter and a TLC scanner. It's also important to note that the dose calibrator is less expensive and simpler to use than the alternatives, and it can already be found at a hospital radio pharmacy for other uses.

Table 2: Comparative RCP data from different radioactive counting instruments

Radiopharmaceutical	Radiochemical purity (RCP)		
	Dose calibrator	TLC-scanner	Gamma-counter
Sodium Pertechnetate ($Na^{99m}TcO_4^-$)	99.78 ± 0.12	98.74 ± 0.24	99.20 ± 0.68
^{99m}Tc-DTPA	98.25 ± 1.42	98.46 ± 0.41	99.13 ± 0.85
^{99m}Tc-MDP	96.25 ± 2.42	98.26 ± 0.63	98.89 ± 0.51
^{99m}Tc-nanocolloid	99.42 ± 0.53	99.61 ± 0.34	99.57 ± 0.42
^{99m}Tc-DMSA	98.86 ± 0.84	99.11 ± 0.69	99.24 ± 0.61
^{99m}Tc-MIBI	99.11 ± 0.67	99.32 ± 0.64	99.21 ± 0.49
^{99m}Tc-PYP	97.27 ± 1.76	98.27 ± 0.86	99.12 ± 0.52

The strip of TLC plate, which had already been developed with an ethyl methyl ketone (MEK) solvent, was placed on a detector of the Gamma Multi Channel Analyzer Mucha-raytest in order to confirm the energy of ^{99m}Tc. The gamma energy of 99mTc is indicated by the peak in Figure 1 and is located at 136 keV. Every radiopharmaceutical, including ^{99m}Tc MDP, ^{99m}Tc DTPA, ^{99m}Tc PYP, ^{99m}Tc MIBI, ^{99m}Tc DMSA, ^{99m}Tc nanocolloid, likewise has a peak at 136 KeV.

A high-performance thin-layer chromatography (TLC) scanner was used for the quick and precise assessment of radiochemical purity. The MEK-developed TLC strip is exposed to the detector, and by shifting the TLC plate, it forms a peak and provides the Rf value. The Rf value for ^{99m}Tc DTPA, ^{99m}Tc MDP, ^{99m}Tc nanocolloid, ^{99m}Tc MIBI, ^{99m}Tc DMSA and ^{99m}Tc PYP is determined to be 0.0-0.1 for the same mobile phase MEK and the purity percentage of all radiopharmaceuticals is greater than 95% (Figure 2).

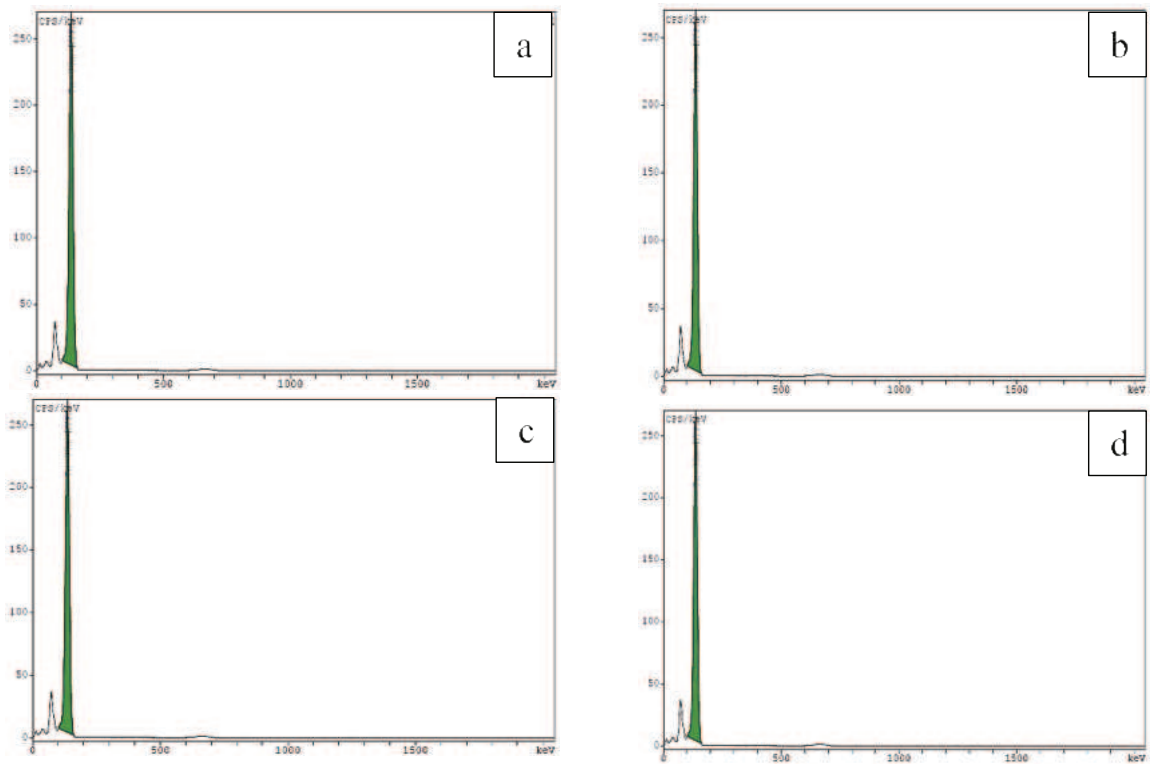

Figure 1: Gamma ray spectrum of (a) Na99mTcO4; (b) 99mTc-DTPA; (c) ^{99m}Tc-MDP; (d) 99mTc-Nanocolloid; the procedure was carried out by Gamma Multi Channel Analyzer Mucha-raytest.

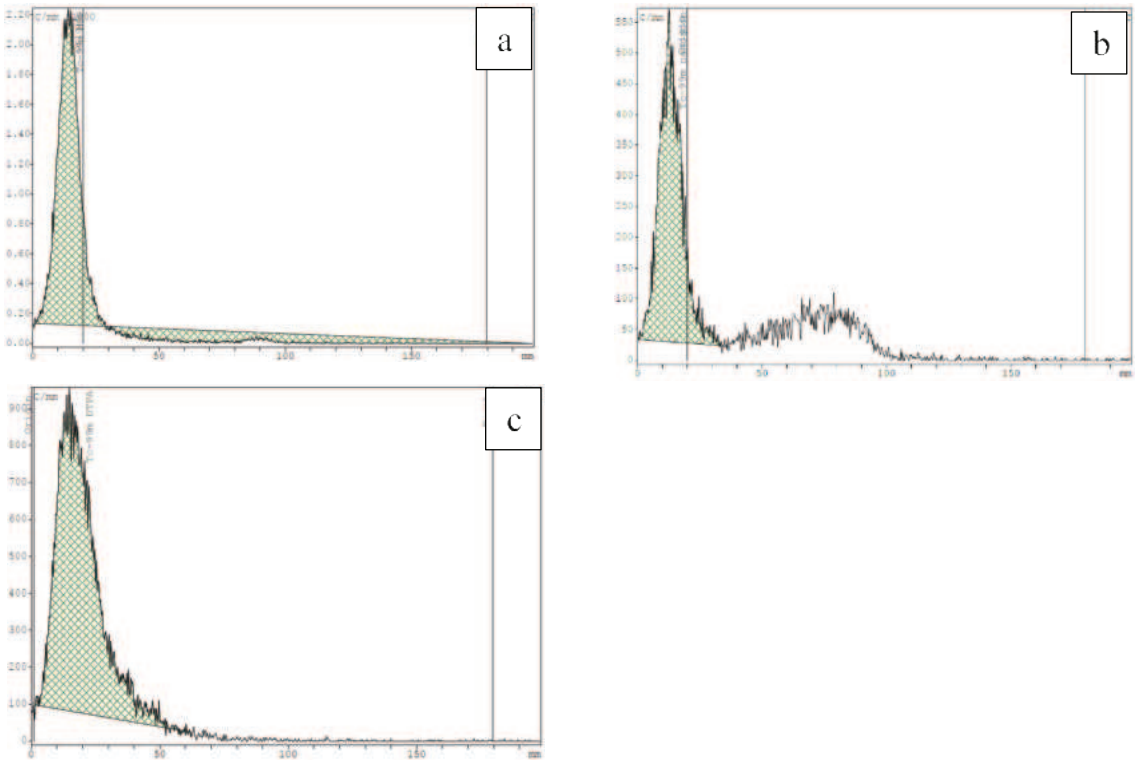

Figure 2: profiles of radio chromatography obtained through a TLC scanner (miniGITA Elysia Raytest): (a) ^{99m}Tc-MDP; (b) ^{99m}Tc-nanocolloid; (c) ^{99m}Tc-DTPA. All have developed in the same solvent/mobile phase: Ethyl Methyl Ketone (MEK).

CONCLUSION

Nuclear medicine mostly uses ^{99m}Tc-radiopharmaceuticals for diagnostic applications. Radionuclidic/radiochemical purity is an important consideration in the quality control of radiopharmaceuticals. In order to achieve a good-quality scintigraphy image, the radionuclide needs to meet the limitations specified by the impurities for localization only in the intended organ and have specific nuclear properties. It also needs to be relatively safe. Because ITLC chromatography produces the most accurate and rapid chromatographic findings, it is currently the most widely utilized chromatographic technique. In order to verify the results of the routine tests carried out in the NINMAS hot lab, we also have two additional devices in the cyclotron QC room: a TLC scanner and a gamma counter. So, the outcomes are roughly the same as what we consistently achieve.

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