Evaluation of radiochemical purities of routinely used radiopharmaceuticals: Three years' experience of a single institute

Original Article

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ABSTRACT

Introduction: Radiochemical purity (RCP) is a routine quality control test carried out at nuclear medicine to determine the concentration of various chemical species present in the radiopharmaceuticals (RPs). The present work describes three years of experience in a single institute for the measurement of these impurities in the RPs preparations.

Methods: The RCP of different cold kit preparations were performed by chromatographic methods. Specifically, a small drop of the aliquot was spotted on the specific paper acting as the stationary phase and then developed in different solvents as mobile phases. The developed chromatograms were then quantified for various chemical species by Mini TLC scanner or well type counter.

Results: The retention factor (R_f) values for the different chemical species in the labeling of RP were measured by using single, double or triple solvent systems. It was observed that 2.70% of the kits had RCP less than the acceptable limit whereas 97.30% kits were found within the permissible levels.

Conclusion: Chromatographic techniques used for the assessment of RCP offer sufficiently good results for identification and separation of different chemical impurities.

Key words: Radiochemical purity; R_f values; Chromatogram; Stationary phase; Radiopharmaceuticals

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INTRODUCTION

Technetium-99m based Radiopharmaceuticals (^{99m}Tc RPs) are widely used in nuclear medicine, often in tandem with cold kits [1]. The imperatively required quality control (QC) tests of the cold kits towards the assessment of composition, purity, apyrogenecity, sterility and particle size are typically guaranteed by the manufacturer [2, 3]. However, the assessment of the labeling process of the Technecium-99m with the cold kits, which may be affected by multiple factors, is generally the responsibility of the end user. Although various radiopharmaceuticals kits have been developed for the diagnosis of several common diseases, the reliable outcome of these kits depends upon the quality, purity, radiolabeling techniques and safety of the radiopharmaceuticals product [4, 5]. Thus strict QC regarding the determination of radiochemical purity (RCP) is mandatory for all in-house preparations [6-8].

The US Pharmacopeia (USP) has set limits for labeling yields of each kit vial (i.e., minimum 90% for most RPs) before dispensing to the patients [9, 10]. Hence, it is imperative that all RPs should undergo different QC measures. The various analytical techniques commonly employed for the determination of RCP of RPs includes Paper Chromatography (PC), Instant Thin Layer Chromatography (ITLC), High-Performance Liquid Chromatography, Thin Layer Chromatography (TLC), Electrophoresis, Gel permeation and solvent extraction methods [11, 12]. Among these, PC is considered as a relatively appropriate method to determine different species in the ^{99m}Tc formulations. In this technique, each component of the sample is characterized by the specific retention factor (R_f) value used for the identification of the species. R_f is the ratio of the distance traveled on the medium (stationary phase) by a given radiochemical species to the distance traveled by the mobile phase's solvent front.

The PC separation techniques depend on the type of paper and solvent used, hence different information can be obtained with different systems. That said, each institute has its own experience for separation and identification of various impurities, as determined by the availability of the specific procedures, equipment, and expertise [13]. The present study describes our experience at the Institute of Radiotherapy and Nuclear Medicine (IRNUM), one of the busiest medical centers in the north-west of Khyber Pakhtunkhwa, Pakistan, for the RCP of the routinely used ^{99m}Tc RPs during 2014-2016. Specifically, we discuss various techniques and solvent systems used for the assessment of different RPs at our institute.

METHODS

All the chemicals and solvents used in this study were of analytical grade and were purchased from Merck, Germany and Sigma, UK. The $^{99}Mo/^{99m}Tc$ generator and majority of the cold kits were purchased from Isotope Production Division, PINSTECH, Islamabad (Pakistan), MAA kits from GE Healthcare (UK), EDDA/HYNIC-Tyr^3-Octreotide from Pars Isotope Company (Iran), dose calibrator 15-CRC from Capintech (USA), TLC Scanner from Bioscan, Inc, (USA) and well type counter from Nuclear Enterprises Ltd, Edinburgh, Scotland. The commercial cold kits were reconstituted and complexed with ^{99m}Tc pertechnetate as per the manufacturer's instructions. A summary of the total number of cold kits used at the institute during this period has been presented in Table 1.

Table 1: Quantity of individual radiopharmaceutical kits used in 3 years at our institute.

^{99m}Tc-RPs	Total
^{99m}Tc MDP	180
^{99m}Tc DTPA	144
^{99m}Tc DMSA	36
^{99m}Tc MAG-3	8
^{99m}Tc MIBI	12
^{99m}Tc Phytate	36
^{99m}Tc Octreotide	7
^{99m}Tc Nanocolloid	6
^{99m}Tc MAA	12
^{99m}Tc HIDA	36
^{99m}Tc DMSA(V)	13
Others	28

All the RPs used were classified into the following three groups on the basis of techniques and solvent systems:

A) RCP yield of radiopharmaceuticals using single strip system

The RCP of the ^{99m}Tc RPs in this group was analyzed by PC using ITLC, TLC-SG or Whatman paper No. 1 or 3 strips as the stationary phase. The RPs included in this group were ^{99m}Tc sestamibi (^{99m}Tc -MIBI), ^{99m}Tc-MAA, ^{99m}Tc-sulphur colloid (^{99m}Tc-SC), ^{99m}Tc phytate and ^{99m}Tc-nanocolloid. To assess the RCP, the paper strips were cut into 1.5×12 cm^2 and a small drop (2-5 µl) of the prepared RP was spotted on it at the origin. The strip was developed in a particular solvent (mentioned in Table 2) as the mobile phase. The chromatogram was then quantified for various chemical species by Mini TLC scanner. The hydrolyzed reduced technetium (HR-^{99m}Tc) impurities remained at the origin (R_f=0-0.1), free pertechnetate (TcO^-_4) stayed at R_f=0.5 while the desired complex moved towards the solvent front (R_f=0.9-1) in case of ^{99m}Tc -MIBI.

Table 2: The R_f values, types of techniques and single solvent systems for RPs.

Sr.No	^{99m}Tc-RP	St. Ph	Mob. Ph	R_f Values
1	^{99m}Tc- MIBI	TLC-Al_2O_3	C_2H_5OH	Complex=1; TcO^-_4 =0.5; HR-Tc =0
2	^{9m}Tc-MAA	TLC-SA	85% CH_3OH /H_2O	Complex=0; TcO^-_4 =1
3	^{99m}Tc Nanocolloid	ITLC-SG	Acetone	Complex=0; TcO^-_4 =1
4	^{99m}Tc SC	ITLC-SG	Acetone	Complex=0; TcO^-_4 =1
5	^{99m}Tc Phytate	W.P. No.	Acetone	Complex=0; TcO^-_4 =1

^{99m}Tc-RPs= Technecium-99m Radiopharmaceuticals, St. Ph= Stationary phase, Mob. Ph= Mobile phase, R_f = Retention factor

Table 3: The Rf values, types of techniques and double solvent systems for RPs.

		System I			System II		
S.No	^{99m}Tc RPs	St. Ph	Mob. Ph	R_f Values	St. Ph	Mob. Ph	R_f Values
1	^{99m}Tc-DISIDA/BrIDA	TLC-SG (or) ITLC-SA	20% NaCl	Complex=0 TcO^-_4 =1 HR- Tc =0	TLC-SG	85% CH_3OH	Complex=1 TcO^-_4 =1 HR-Tc =0
2	^{99m}Tc-DMSA	TLC-SG	Acetone	Complex=0 TcO^-_4 =1 HR-Tc =0	TLC-SG	5% Glycine	Complex=1 TcO^-_4 =1 HR-Tc =0
3	^{99m}Tc-DTPA	W.P. No.3	Acetone	Complex=0 TcO^-_4 =1 HR-Tc =0	W.P. No.3	0.9% NaCl	Complex=1 TcO^-_4 =1 HR-Tc =0
4	^{99m}Tc-Octreotide	W.P. No.3	Acetone	Complex=0 TcO^-_4 =1 HR-Tc =0	ITLC-SG	Dist. H_2O	Complex=1 TcO^-_4 =1 HR-Tc =0
5	^{9m}Tc-MAG 3	W.P. No.1	Ace/Chl.(8/2)	Complex=0 TcO^-_4 =1 HR-Tc =0	W.P. No.1	0.9% NaCl	Complex=1 TcO^-_4 =1 HR-Tc =0
6	^{99m}Tc-MDP	W.P. No.3	Acetone	Complex=0 TcO^-_4 =1 HR-Tc =0	W.P. No.3	0.9% NaCl	Complex=1 TcO^-_4 =1 HR-Tc=0

^{99m}Tc-RPs= Technecium-99m Radiopharmaceuticals, St. Ph= Stationary phase, Mob. Ph= Mobile phase, R_f = Retention factor

Table 4: The R_f values, types of techniques and triple solvent systems for ^{99m}Tc-(V) DMSA.

Kit ^{99m}Tc- (V) DMSA	**System I** R_f=1 for TcO^-_4 R_f=0 for DMSA III, DMSA V & HR-Tc		**System II** R_f= 1 for TcO^-_4, DMSA-III & DMSA-V R_f= 0 for HR-Tc		**System III** R_f= 1 for TcO^-_4, R_f= 0.5 for DMSA-V R_f= 0 for HR-Tc & DMSA-III	
	St. Ph	**Mob. Ph**	**St. Ph**	**Mob. Ph**	**St. Ph**	**Mob. Ph**
	TLC-SG	Acetone	TLC-SG	5% Glycine	TLC-SG	n-Butanol/acetic acid/ Dist.H_2O

Ph= Stationary phase, Mob. Ph= Mobile phase, R_f = Retention factor

However, the complex remained at R_f=0-0.1 and the free pertechnetate, TcO^-_4 moved with the solvent front (R_f=0.9-1) for ^{99m}Tc-MAA, ^{99m}Tc-SC, ^{99m}Tc-phytate and ^{99m}Tc-nanocolloid. The R_f values and different types of techniques and solvent systems of RPs included in this group are summarized in Table 2.

B) RCP yield of radiopharmaceuticals using double strip system

The RCP tests in this group were carried out by PC, TLC or ITLC techniques using the dual mobile systems according to Table 3. The RPs included in this group were ^{99m}Tc-DTPA, ^{99m}Tc-MDP, ^{99m}Tc-DMSA, ^{99m}Tc-DISIDA/BrIDA and ^{99m}Tc-Pyrophosphate. For the solvent system I, the desired RP complex and HR-^{99m}Tc remained at the origin (R_f=0-0.1) while the free pertechnetate moved to the solvent front (R_f=0.9-1). However, for solvent system II, the free pertechnetate and RP complex migrated to the solvent front and the HR-^{99m}Tc remained at the origin.

The different species were quantified mostly by Mini TLC scanner. However, in some cases, the developed strips were cut in half at a preset cut line and the radioactivity in each half was measured by well type counter using cut and count method. In the latter case the percentage of each species was calculated according to the following equations:

Pertechnetate (%) =

$$\frac{\text{Counts in the upper piece}}{\text{Counts in both upper and lower pieces}} \times 100$$

HR-^{99m}Tc (%) =

$$\frac{\text{Counts in the lower piece}}{\text{Total counts in both upper and lower pieces}} \times 100$$

% RCP of Complex = 100 - (free Pertechnetate% + HR-^{99m}Tc%)

C) RCP yield of radiopharmaceuticals using triple strip system

The RCP of RPs in this group was performed by TLC method on silica gel (TLC-SG). This group included RPs like ^{99m}Tc (V)-DMSA and ^{99m}Tc-HMPAO. In the case of ^{99m}Tc(V)-DMSA, the solvent system I was used for determination of free pertechnetate, $^{99m}TcO^-_4$. Solvent system II, for separation of hydrolyzed $^{99m}TcO_2$, while a solvent system III, containing n-butanol/acetic acid/ distilled water in the ratio of 3:2:2 by volume was used to separate ^{99m}Tc(V)-DMSA from $^{99m}TcO^-_4$ and ^{99m}Tc(III)-DMSA (Table 4). The developed strips were then analyzed for different fractions using TLC scanner.

RESULTS

A wide variety of RPs has been used for evaluation of various pathological or physiological processes of body organs at our institute. Figure 1, summarizes the total number of cold kits used at the institute during a three year period. Specifically, out of all 518 kits, only 14 (2.70%) preparations were found with RCP less than the acceptable limit in the indigenous kits as presented in Figure 1. In terms of the number of individual kits, 180(34.75%) were MDP, 144 (27.80%) DTPA, 36 (6.95%) renal DMSA, 8 (1.54%) MAG-3, 12 (2.32%) MIBI, 36 (6.95%) Phytate, 7(1.35%) Octreotide, 6(1.16%) Nanocolloid, 12(2.32%) MAA, 36 (6.95%) HIDA/BrIDA, 13 (2.51%) Pentavalent DMSA (V) and 28 (5.40%) were Miscellaneous kits used during this period.

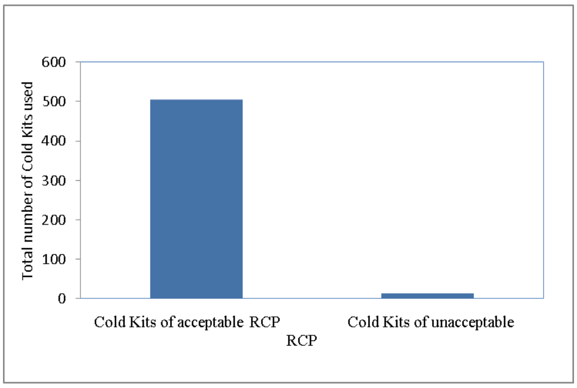

Fig 1. Radiopharmaceuticals with acceptable RCP vs. Kits with RCP less than 90%.

Any type of undesired chemical species in the above mentioned RPs was segregated using single, double or the triple solvent systems of paper chromatography. The range of R_f values for different chemical species found in the labeling of ^{99m}Tc based RPs are summarized in Table 2, 3 and 4. In the single solvent system, RPs such as ^{99m}Tc -MIBI, ITLC or TLC-Al_2O_3 paper was used as a stationary phase and ethanol as a mobile phase; the HR-^{99m}Tc remained at R_f=0-0.1, TcO^-_4 stayed at R_f=0.5 and the complex moved to the solvent front at R_f=0.9-1, as shown in Figure 2.

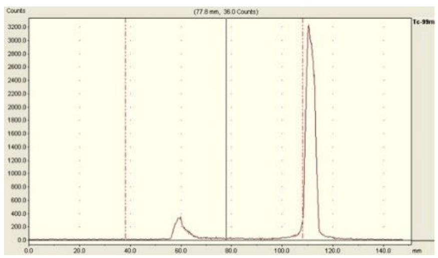

Fig 2. Typical chromatogram of ^{99m}Tc-MIBI showing peaks of HR-^{99m}Tc at R_f=0-0.1, TcO^-_4 at R_f=0.5-0.6 and bound complex at R_f=0.9-1.

However, the ^{99m}Tc-MAA, ^{99m}Tc Nanocolloid, ^{99m}Tc Phytate and ^{99m}Tc SC that were insoluble in saline; organic solvent was used as a mobile phase and ITLC-SG paper was used as a stationary phase. We observed two peaks, one at R_f=0-0.1 for the complex and other at R_f=0.9-1 for TcO^-_4, as shown in Figure 3.

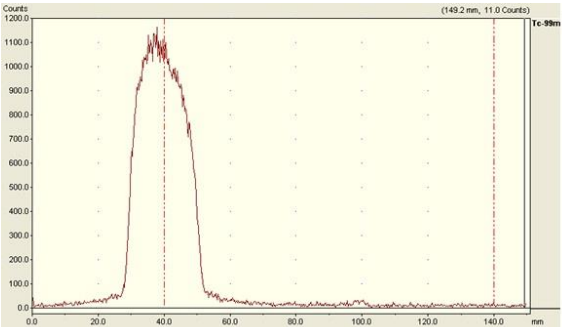

Fig 3. Chromatogram of ^{99m}Tc Phytate indicating two peaks: one at R_f=0-0.1 for the complex and other at R_f=0.9-1 for free pertechnetate, TcO^-_4.

The double solvent system was used in RPs like ^{99m}Tc-DTPA, ^{99m}Tc-MDP, ^{99m}Tc-DMSA, ^{99m}Tc-DISIDA/BrIDA and ^{99m}Tc-Pyrophosphate for the RCP tests using instant TLC method. In this case, the HR -^{99m}Tc and complex remained at R_f=0-0.1 while the free pertechnetate, TcO^-_4 migrated to solvent front, R_f=0.9-1 as illustrated in Figure 4. In solvent system II, HR -^{99m}Tc remained at R_f=0-0.1 but free pertechnetate, TcO^-_4 and complex migrated to solvent front, R_f=0.9-1 as illustrated in Figure 5.

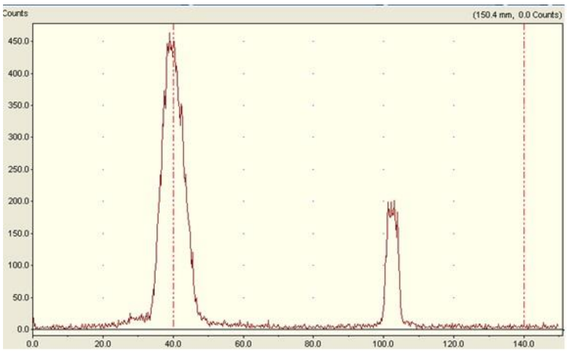

Fig 4. Chromatogram of ^{99m}Tc-DMSA showing peaks: one at R_f=0-0.1 for the HR -^{99m}Tc and the desired complex and the other at R_f=0.9-1 for free pertechnetate, TcO^-_4.

The triple solvent system was used for the segregation of RP exhibiting four different species. Specifically, in the first phase, the single and double solvent systems were used for determination of free pertechnetate, $^{99m}TcO^-_4$ and HR-^{99m}Tc in RPs such as ^{99m}Tc(V)-DMSA; while in the second phase, the triple solvent system was used to separate ^{99m}Tc(V)-DMSA from $^{99m}TcO^-_4$ and ^{99m}Tc(III)-DMSA. The R_f of HR-^{99m}Tc and ^{99m}Tc(III)-DMSA was at the origin (0-0.1), a peak of ^{99m}Tc(V)-DMSA was seen at R_f=(0.5-0.6), while a small peak of free pertechnetate, $^{99m}TcO^-_4$ was noted at R_f=0.9-1 (solvent front) as presented in Figure 6 and 7.

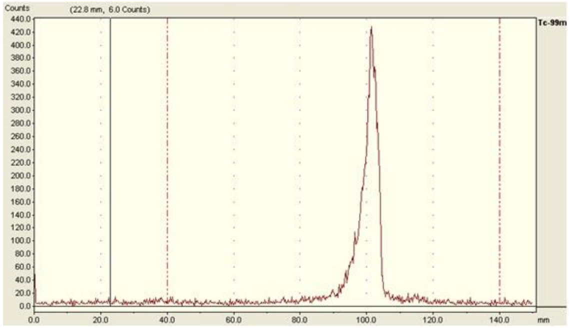

Fig 5. Chromatogram of ^{99m}Tc-DTPA indicating peaks: one at R_f=0-0.1 for the HR -^{99m}Tc and the other at R_f=0.9-1 for complex and free pertechnetate, TcO^-_4.

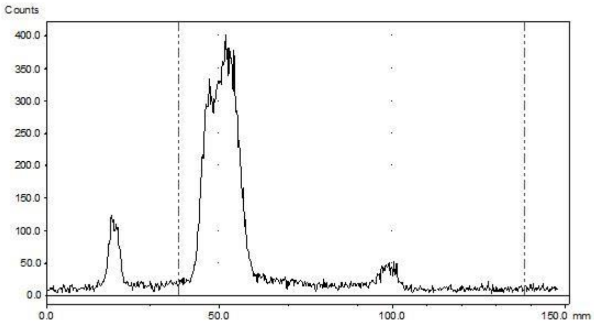

Fig 6. Chromatogram of ^{99m}Tc-DMSA at pH 5 in triple solvent system showing three peaks: one at R_f=0-0.1 for ^{99m}Tc-DMSA(III) & HR -^{99m}Tc, the second small peak at R_f=0.5-0.6 indicates poor labeling of ^{99m}Tc-DMSA(V) while the third peak at R_f=0.9-1 shows free pertechnetate, TcO^-_4.

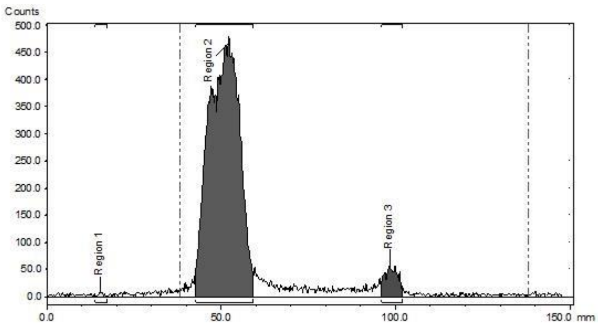

Fig 7. Chromatogram of ^{99m}Tc-DMSA obtained at pH 8.4 in triple solvent system showing peaks: at R_f=0-0.1 for ^{99m}Tc-DMSA(III) & HR -^{99m}Tc, at R_f=0.5-0.6 for bound^{99m}Tc-DMSA(V) and a small peak at R_f=0.9-1 for free pertechnetate, TcO^-_4.

DISCUSSION

Labeling of the ^{99m}Tc with the given cold kit usually results in three important chemical species, the desired RP complex accompanied by two radiochemical impurities- hydrolyzed reduced technetium (HR-^{99m}Tc) and free pertechnetate TcO_4^- [14]. Specifically, the former impurity is formed when pertechnetate is reduced to lower oxidation state and instead of forming a complex with the chelating agent, react with water molecules and form the colloidal impurity (i.e., HR-^{99m}Tc). Alternatively, the free pertechnetate impurity results from the incomplete reduction of the +7 oxidation state of Technetium to lower oxidation state. These impurities may not only increase the radiation exposure of the patient but may also alter the biodistribution pattern of RP (and subsequently the specificity), ultimately leading to possible confusion and complexity in the correct diagnosis [15-17]. In this context, the implementation of RCP is imperatively required for the qualification of any RP intended for clinical use [6, 7].

During the chromatographic process, various species of the RP sample distribute themselves between the stationary phase (paper or silica gel) and the mobile phase (solvent) depending upon their distribution coefficients. Electrostatic forces of the stationary phase tend to retard, while the mobile phase carries these species along. This effect and the varying solubility of the various component in a particular solvent together with solvents polarity lead the individual components to move at different speeds and form peaks at different distances along the paper or strip [15, 18].

We carried out the assessment of RCP for all the radiopharmaceuticals with ITLC, TLC, and paper chromatography using different stationary and mobile phases according to the procedures described in Table 1, 2 and 3. In our study, a single solvent system was used for RCP of ^{99m}Tc -MIBI, because all the three species were at different R_f values. Moreover, for RPs insoluble in saline, only two species were found that were easily separated by the single solvent system. Likewise, for RPs expressing three chemical species with two species having the same R_f value, a double solvent system was used to discriminate their positions. However, for RPs expressing three types of impurities along with the desired complex such as ^{99m}Tc(V)-DMSA), a third solvent system was used where, in the single solvent system, ^{99m}Tc(III)-DMSA), ^{99m}Tc(V)-DMSA) and HR -^{99m}Tc remained at the origin (R_f=0-0.1) while free pertechnetate $^{99m}TcO_4^-$migrated to solvent front. In the double solvent system, the HR -^{99m}Tc stayed at the origin and the other species i.e., ^{99m}Tc(III)-DMSA, ^{99m}Tc(V)-DMSA, and $^{99m}TcO_4^-$ moved with the solvent front (R_f=0.9-1). The triple solvent system was used in order to separate both ^{99m}Tc(V)-DMSA from $^{99m}TcO_4^-$ and ^{99m}Tc(III)-DMSA.

We routinely observed that several factors affect the precision and accuracy of the RCP results in the quality control process, and are thereby essential to be considered for avoiding any possible artifacts. For instance, streaking of the solvent along the edge of the paper strip should be prevented. The size of the sample drop should be kept small enough as permitted by the sensitivity of the equipment. Long air drying of the chromatographic paper should be avoided to prevent re-oxidation of ^{99m}Tc [18-20]. These factors can alter the migration pattern of radioactive species and hence lead to lower RCP results [16, 17]. Other important factors that affect the quality and purity of the RPs are incubation time, temperature and heating period, pH, the introduction of air into the reaction vial during preparation, the amount of ^{99m}Tc added to the kit and interference of chemical and radionuclide impurities [16, 19]. Keeping in view these results, it is evident that all technicians involved in the RP formulations must adhere to preparation instructions to reduce the chances of impurities and poor labeling. In the present work, we found a limited number of the RPs with unacceptable RCP in the indigenously manufactured cold kits. Since the labeled cold kits with unacceptable RCP cannot be used for clinical imaging procedures, the patient waiting time presumably prolongs in such situations [3, 16]. In order to avoid such patient inconvenience, the RCP of one vial was performed in each batch of the cold kits to declare the subsequent vials for the continuation of the imaging services.

CONCLUSION

In this study, the radiochemical purity (RCP) of routinely used radiopharmaceuticals in the nuclear medicine was evaluated with chromatographic techniques. Specifically, paper chromatography (PC), thin layer chromatography (TLC) and instant thin layer chromatography (ITLC) were used to determine the concentration of various chemical species present in the radiopharmaceuticals. It was observed that only a limited number of the cold kits (i.e., 2.70%) had RCP less than the permissible levels, ensuring that chromatographic techniques used for the assessment of RCP offer sufficiently good results for identification and separation of different chemical impurities.

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