ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

Nuclear Medicine Review

ISSN: 1506-9680

e-ISSN: 1644-4345

Clinical Efficacy of Sodium [99mTc] Pertechnetate from Low Specific Activity 99Mo/99mTc Autosolex Generator in Hospital Radiopharmacy Centre

Authors: Arpit Mitra, Sankha Chattopadhyay, Ashok Chandak, Sangita Lad, Luna Barua, Anirban De, Umesh Kumar, Rajesh Chinagandham, Trupti Upadhye, Kamaldeep Koundal, Sharmila Banerjee, Ramakrishna Rajan

DOI: 10.5603/NMR.a2020.0001

Article type: Original articles

Submitted: 2018-06-16

Accepted: 2019-11-27

Published online: 2019-12-05

VIA MEDICA

Nuclear Medicine Review 2020, 23, 1: 1–13
DOI: 10.5603/NMR.a2020.0001

ISSN 1506–9680

Original

Clinical Efficacy of Sodium [^{99m}Tc] Pertechnetate from Low Specific Activity ^{99}Mo/^{99m}Tc Autosolex Generator in Hospital Radiopharmacy Center

Arpit Mitra[1], Sankha Chattopadhyay[2], Ashok Chandak[1], Sangita Lad[3], Luna Barua[2], Anirban De[4], Umesh Kumar[2], Rajesh Chinagandham[3], Trupti Upadhye[3], Kamaldeep Koundal[5], Sharmila Banerjee[1,2,3], Ramakrishna Rajan[6]

[1]Medical Cyclotron Facility, Radiation Medicine Center, Board of Radiation and Isotope Technology, Parel, Mumbai, India
[2]Radiopharmaceutical Laboratory, Regional Center, Board of Radiation and Isotope Technology, Variable Energy Cyclotron Center, Kolkata, India
[3]Radiation Medicine Centre, Bhabha Atomic Research Center, Parel, Mumbai, India
[4]Accelerator Technology Group, Variable Energy Cyclotron Center, Kolkata, India
[5]Radiation Safety and System Division, Bhabha Atomic Research Center, Trombay, Mumbai, India
[6]DAE Raja Ramana Fellow, Department of Atomic Energy, Mumbai, India

[Received 24 XI 2018; Accepted 2 VIII 2018]

Abstract

BACKGROUND: Production of ^{99m}Tc from low specific activity (LSA) ^{99}Mo obtained from ^{98}Mo(n,γ)^{99}Mo reaction in research reactor and ^{100}Mo(γ,n)^{99}Mo reaction in accelerator or directly from ^{100}Mo(p,2n)^{99m}Tc nuclear reaction in cyclotron, has been explored [1]. The methyl ethyl ketone (MEK) based solvent extraction technique is a well-known method for the separation of ^{99m}Tc from low specific activity ^{99}Mo. The ^{99}Mo/^{99m}Tc autosolex generator [2], a computer controlled automated module, utilizes the conventional MEK solvent extraction method for extraction of ^{99m}Tc. Herein, we have validated the usage of autosolex by preparing quite a large number of pharmacopoeia grade $^{99m}TcO_4^-$ (No. of batches: 97) using 7.40–27.5 GBq of LSA ^{99}Mo-Sodium Molybdate ($^{99}MoO_4^{2-}$) solution (No. of batches: 31). To check the efficacy of $^{99m}TcO_4^-$ towards radiolabeling, a wide range of ^{99m}Tc-radiopharmaceuticals (^{99m}Tc-RPs) including fourth generation ^{99m}Tc-radiopharmaceuticals has been evaluated. Finally, the clinical efficacy of these ^{99m}Tc-RPs has been evaluated. To make the autosolex generator more versatile, we have studied further some of the important issues relevant to autosolex generator viz. the functionality of conductivity detector with respect to the concentration of sodium hydroxide, purity of reagents/materials used and radiation dose outside the module.

MATERIAL AND METHODS: The $^{99m}TcO_4^-$ was extracted from the autosolex as described in the reported literature [2] using 7.40–27.5 GBq of LSA $^{99}MoO_4^{2-}$. The ^{99m}Tc radiopharmaceuticals prepared from cold kits (^{99m}Tc-cold kits), obtained from our center, using standard procedures [3], subjected to required QC as per Indian Pharmacopeia monograph [4] and used in scintigraphic imaging in patients. The radiation exposure dose to the operator was compared between autosolex and manual MEK based solvent extraction generator.

RESULTS: The extracted $^{99m}TcO_4^-$ from autosolex is a clear and colorless solution with pH between 5.0 and 6.5. The elemental molybdenum (Mo) and aluminum (Al) content < 10 μg/mL, MEK levels < 0.1%, ^{99}Mo breakthrough < 0.026% and radiochemical purity (RCP) > 98%. All the extracted $^{99m}TcO_4^-$ batches complies sterility test, endotoxin limit (EL) < 5 EU/mL. The RCP of all the labeled ^{99m}Tc-RPs > 95%. The autosolex delivers much less radiation dose to the operator than the convention manually handled MEK based solvent extraction generator.

CONCLUSIONS: Autosolex Generator was successfully validated to obtain pharmaceutical grade $^{99m}TcO_4^-$ using LSA $^{99}MoO_4^{2-}$ up to a higher range of activity of 27.5 GBq and the generator is safe in radiological and pharmacological point of view. The work also confirms the suitability for the preparation of various types of ^{99m}Tc-RPs, especially using fourth generation ^{99m}Tc-RPs using autosolex generator and using these ^{99m}Tc-RPs for scintigraphic imaging in patients.

KEY words: autosolex, LSA, $^{99}MoO_4^{2-}$, $^{99m}TcO_4^-$, radiopharmacy, scintigraphic image

Nucl Med Rev 2020; 23, 1: 1–13

Correspondence to: Dr Sankha Chattopadhyay
Radiopharmaceuticals Laboratory, Board of Radiation & Isotope Technology
Variable Energy Cyclotron Center 1/AF, Bidhan Nagar
Kolkata 700 064, India
e-mail: sankha@vecc.gov.in Tel: +91-33-23183214, Mob: +91-9432014537

Introduction

Plans to shut down aging nuclear reactors used for producing HSA ^{99}Mo and the lack of alternate nuclear reactors to meet the demands highlight the need for alternative ^{99m}Tc production methods [5–9]. The international safeguards on the use of HEU have also led to the non-availability of HEU for production of HSA ^{99}Mo. This drives our focus back to produce $^{99m}TcO_4^-$ from LSA ^{99}Mo via ^{98}Mo(n,)^{99}Mo route, a convenient method suitable for hospital radiopharmacy. Several approaches have been evolved for separating $^{99m}TcO_4^-$ from LSA ^{99}Mo for use in hospital radiopharmacy. Two widely used technologies for producing $^{99m}TcO_4^-$ are Zr/Mo gel column and solvent extraction generators. The former requires a multi-step automated mechano-chemical process similar to that used for column generators made with HSA ^{99}Mo [10–13].

Gel-generators have an inherent limitation on the amount of $^{99}MoO_4^{2-}$ that can be loaded, with a maximum being ~350 mCi. Further since a minimum of 10 mL saline is required for elution, considering the size of gel column the radioactive concentration reduces considerably from the fourth day making it unsuitable for labeling several ^{99m}Tc-RPs [10–13]. Hence, the solvent extraction is suited for a typical hospital radiopharmacy center where about 400-500 mCi of $^{99m}TcO_4^-$ is required every day with radioactive concentration (RAC) of 50–60 mCi/mL even on the sixth day of use. The solvent extraction method for producing $^{99m}TcO_4^-$ from 0.75–1.0 Ci of LSA $^{99}MoO_4^{2-}$ requires minimum infrastructure (negative pressure fume hood with adequate shielding) at hospital radiopharmacy center. With the autosolex generator [2], further shielding requirement is minimal, since it is built with adequate shielding and is automated requiring very little human intervention. The aim of this study is to validate autosolex generator in order to scale up the activity level of low specific activity (n,g)^{99}Mo (up to 750 mCi), prepare reliably high radiochemical purity $^{99m}TcO_4^-$ and to prepare various kinds of very sensitive ^{99m}Tc-RPs for elaborate usage in studying human beings. To make the autosolex generator more versatile, we have studied further some of important issues relevant to autosolex generator viz. The functionality of conductivity detector required for separation of aqueous and organic phase, with various concentrations of sodium hydroxide, the water content of the used MEK and leakage radiation dose during operation of autosolex generator.

The clinical and overall suitability of the system could be evaluated only after using the $^{99m}TcO_4^-$ produced to label different cold kits at a hospital radiopharmacy center. Hence, for this we have chosen to label various ^{99m}Tc-cold kits including fourth generation cold kits. The ^{99m}Tc-RPs after QC were used in different oncological and non-oncological investigations in patients referred to our nuclear medicine center, as per prescription of nuclear medicine physicians.

Material and methods

Materials

The self-shielded autosolex generator is shown in Figure 1. The autosolex generator had a minimum of 15 mm lead shielding all around and was housed in negative pressured fume hood (Labguard, India). $^{99m}TcO_4^-$ was extracted in spectroscopy grade MEK (SD Fine-chem Limited, India) and reconstituted with saline (Nirlife, India) and filtered through 0.22 μm hydrophilic polyether sulfone (PES) membrane filter (Millipore, India) in sterile pyrogen free evacuated (< 10 mbar) 10 mL vials. For QC tests of the extracted $^{99m}TcO_4^-$ and various ^{99m}Tc-RPs, analytical reagent grade (AR) chemicals were procured from SD Fine-chem Limited, India. Thin layer chromatography (TLC) (silica gel, 60A°) and Whatman 3MM paper chromatography (PC) strips were from Merck, Germany and Fisher Scientific, India respectively. All the ^{99m}Tc-cold kits were obtained from BRIT, DAE, India. The RCP were determined either using BGO (V) coupled radio-chromatogram scanner (Raytest GmbH, Germany) or by NaI(Tl) coupled well type -ray spectrometer (ECIL, India). Universal narrow range pH papers (Merck, Germany) were used for checking pH of the solutions. Residual ethanol and MEK in the product were quantified by gas chromatography (Chemito Instruments, India) equipped flame ionization detector (FID), a split less injector system and a 0.53 mm × 30 m fused silica column coated with a 0.25 μm, chemically cross-linked G16 stationary phase. For radionuclide purity (RNP) detection, multiple-channel analyzer (MCA) from Baltic Scientific Instrument, Russia was used.

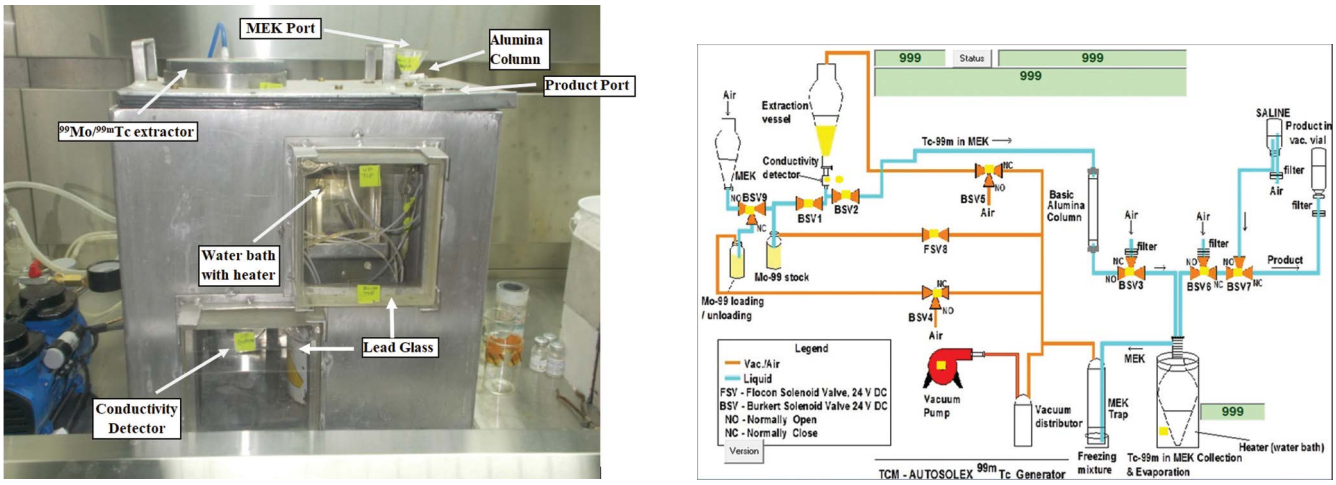

Figure 1. Autosolex Generator

Bacterial endotoxin (BE) assay (gel clot method) was performed using lysate (LAL) and control standard endotoxin from Charles River Inc, USA while sterility test was performed with fluid thioglycolate (FTM) and soya casein digest (SCD) media from Hi-media labs, India. Scintigraphy imaging (dynamic and static) was performed with various ^{99m}Tc-RPs in patients employing two different dual head gamma camera equipped with eSoft and Xeleris work station from Siemens, USA and GE, USA respectively. Radiation fields were measured using survey meter (Atomtex, India), whereas personal instant exposure was measured using direct reading pocket dosimeter developed by Bhabha Atomic Research Center (BARC), Mumbai, India. LSA $^{99}MoO_4^{2-}$ in 0.3–0.5 N sodium hydroxide (NaOH) (specific activity 400–500 mCi/g, RAC 60–70 mCi/mL) was supplied by Board of Radiation and Isotope Technology (BRIT) Mumbai, India. Three different batch sizes (200, 500 and 750 mCi) of LSA $^{99}MoO_4^{2-}$ were used in the autosolex generator.

Methods

Extraction of $^{99m}TcO_4^-$

The solution of ^{99}Mo obtained in dilute NaOH solution and was made to 5N NaOH concentration. The extraction of $^{99m}TcO_4^-$ from LSA $^{99}MoO_4^{2-}$ (batch size of 200, 500, and 750 mCi) solution in 5 N NaOH was done with MEK using automated autosolex generator as described [2] earlier.

Physico-chemical and Biological quality control of $^{99m}TcO_4^-$

The clarity and color of the extracted $^{99m}TcO_4^-$ were observed visually, pH was checked by narrow range universal pH paper. ^{99}Mo content (breakthrough) was quantified using the 0.7 mm lead canister method, while RCP was determined by TLC and RNP was checked by using spectroscopy employing MCA. The MEK levels in the extracted $^{99m}TcO_4^-$ were quantified by iodoform test. Colorimetric tests were employed to determine the content of Mo and Al. The EL of $^{99m}TcO_4^-$ was quantified by gel clot BE assay using LAL reagent and sterility testing by direct inoculation method using FTM and SCD media.

Determination of residual Ethanol and MEK levels in $^{99m}TcO_4^-$ by gas chromatography

The concentration of residual ethanol and MEK levels in the extracted $^{99m}TcO_4^-$ were detected by gas chromatography (GC) equipped with a flame-ionization detector, a split less injector system, and a 0.53 mm × 30 m fused-silica column coated with a 0.25 μm, chemically cross-linked G16 stationary phase. The chromatograph is programmed for an oven temperature of 70°C and the injection port and detector temperatures are maintained at 200°C. Equal volume (0.5 μL and 0.1 μL) of standard (5000 ppm and 1000 ppm) for ethanol and MEK respectively, along with test solutions are injected and GC recorded to measure the peak responses. The percentage of residual ethanol and MEK in the injection is calculated by the formula: C (rI/rS) in which C is the percentage of the relevant analyte obtained from the test solution (rI) and the standard solution (rS) respectively.

Labeling of various ^{99m}Tc-cold kits with $^{99m}TcO_4^-$ and evaluating RCP

The various ^{99m}Tc-cold kits starting from methylene diphosphonic acid (MDP), diethylenetriaminepentaacetic acid (DTPA), dimercapto-succinic acid-III (DMSA-III), dimercapto-succinic acid-V (DMSA-V), ethylene dicysteine (EC), L,L-ethyl cysteinate dimer (ECD), sodium glucoheptonate(GHA), N-[2,4,6-trimethyl-3 bromo-acetanilid], iminodiacetic acid (mebrofenin), phytate, sulfur colloid (SC) along with fourth generation cold kits viz. methoxy-isobutylisonitrile (MIBI), hydrazinonicotinamide-Tyr3-octreotide (Hynic-Toc), human serum albumin-nanocolloid (HSA-NC), 2 [N,N0-bis(2-mercaptoethyl)ethylenediaminomethyl]- 3 -(4-chlorophenyl) tropane) (TRODAT-1) and Ubiquicidin(29-41) {UBI(29-41)} were labeled with $^{99m}TcO_4^-$ extracted from autosolex generator as per the standard published protocol [3]. The RCP for each of these ^{99m}Tc-RP was determined either by rapid TLC or PC using specific mobile phases viz. acetone, saline, MEK, acetonitrile/water, sodium citrate buffer (0.1N), chloroform/tetrahydrofuran and ethanol/chloroform/toluene/0.01N ammonium acetate buffer prior to release for injection in patients. The pH was also checked for each of these products using narrow range universal pH strips.

Measurement of leakage Radiation Dose during operation of Autosolex Generator

During extraction of $^{99m}TcO_4^-$ from LSA $^{99}MoO_4^{2-}$, the radiation field was measured with calibrated plastic scintillator detector based survey meter having detection range from 50 nSv/h to 10 Sv/h (energy range of 15 keV to 10 MeV) with sensitivity of 70 cps/μSv/h for ^{137}Cs source.

Scintigraphic imaging in patients

Required dose of different ^{99m}Tc-cold kits labeled with $^{99m}TcO_4^-$ extracted from autosolex generator were administered in patients (adults and infants) and scintigraphic imaging were performed using dual head gamma camera as per standard procedures followed at our center.

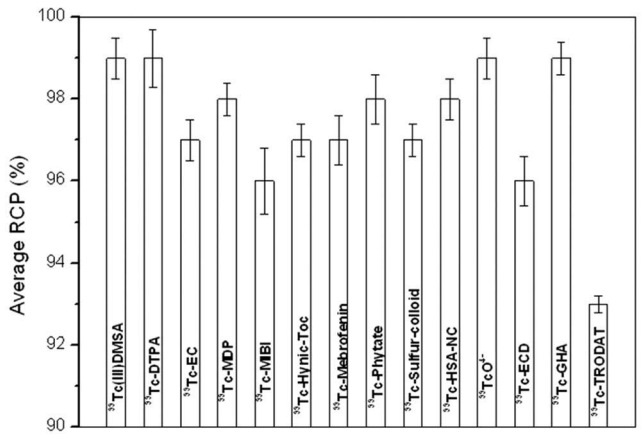

Figure 2. Labeling efficiency (Average radiochemical purity in %) of different TCKs labeled with $^{99m}TcO_4^-$

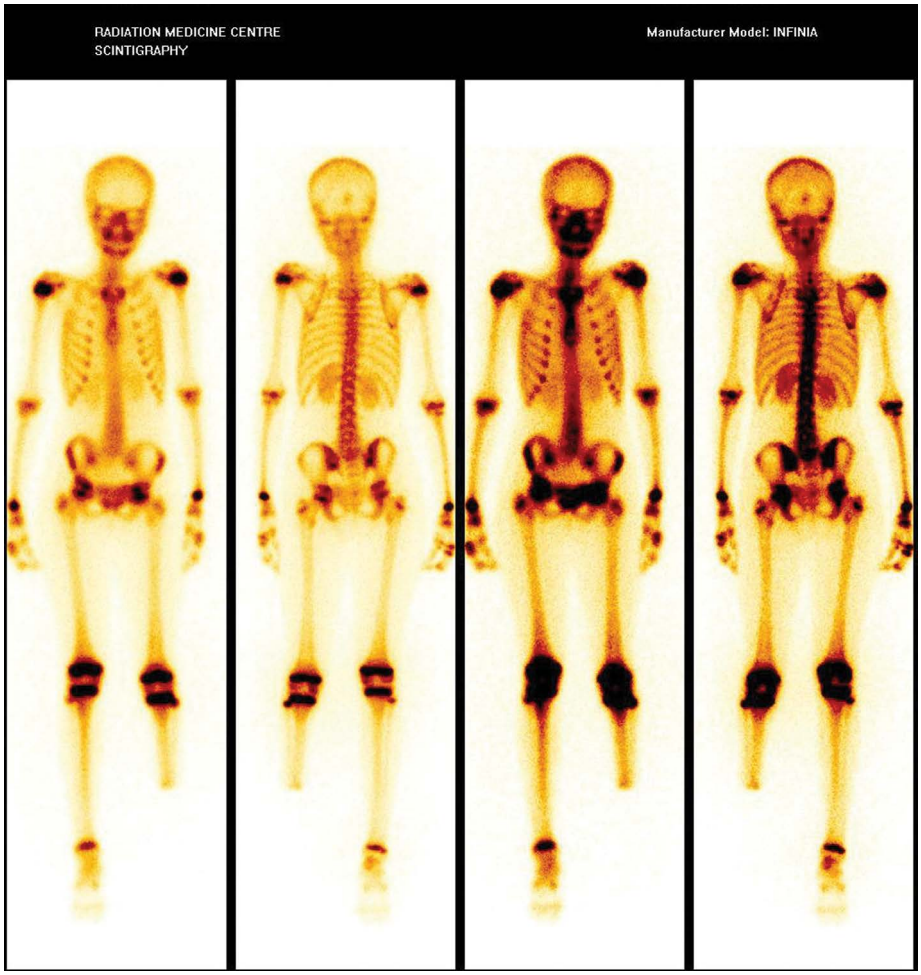

Figure 3A. Patient with osteosarcoma after surgical treatment, injected with 6–10 mCi of ^{99m}Tc-MDP labeled with autosolex's $^{99m}TcO_4^-$. Underwent static scan for 10 minutes

Results

$^{99m}TcO_4^-$ Extraction Efficiency

$^{99m}TcO_4^-$ is extracted from autosolex generator using three different batch size of LSA $^{99}MoO_4^{2-}$ 200 mCi (n = 7), 500 mCi (n = 28) and 750 mCi (n = 3). $^{99m}TcO_4^-$ average extraction yield without decay correction were found in the range of 81 ± 1.0%, 81 ± 1% and 84 ± 1% for 200 mCi, 500 mCi and 750 mCi of $^{99}MoO_4^{2-}$ respectively. Extracted $^{99m}TcO_4^-$ is reconstituted with varying volume of sterile pyrogen free saline ranging from 1.5 to 9.0 mL in order to maintain RAC in the range of 40–60 mCi/mL.

Functionality study of Conductivity Detector used for Separation of Aqueous and Organic Phase with respect to various concentrations of NaOH concentration

In autosolex generator, the separation of aqueous ($^{99}MoO_4^{2-}$ in NaOH solution) and organic phase ($^{99m}TcO_4^-$ in MEK) based on difference of conductance between aqueous and organic phase. The smooth operation of conductivity detector depends on concentration of sodium hydroxide in LSA $^{99}MoO_4^{2-}$ solution. The optimized functioning of conductivity detector for good separation was observed between 4N - 5N concentration of LSA $^{99}MoO_4^{2-}$ solution. The 27.5 GBq (750 mCi) of LSA $^{99}MoO_4^{2-}$ were obtained in 24–25 mL.

In a typical production, 12–14 GBq of LSA $^{99}MoO_4^{2-}$ were obtained in ~ 300 mL. In such cases 40–45 gm of $^{98}MoO_3$ and 25–30 gm of NaOH were dissolved in 300 mL volume of water. Typically in reaction (MoO_3 + 2NaOH Na_2MoO_4 + H_2O), 20–25 gm of NaOH is consumed, whereas excess 4–5 gm of NaOH was left in the LSA $^{99}MoO_4^{2-}$ solution. Hence the strength of resultant stock LSA $^{99}MoO_4^{2-}$ solution falls to 0.4–0.5N. This concentration of LSA $^{99}MoO_4^{2-}$ was not sufficient for proper functioning of conductivity detector. The 4–5N strength of LSA $^{99}MoO_4^{2-}$ was achieved by addition of 10–15 mL of 10N NaOH.

However, it has also been observed that if > 10N NaOH solution is added in the stock LSA $^{99}MoO_4^{2-}$ solution, a precipitate occurs in the stock LSA $^{99}MoO_4^{2-}$ solution which blocks the 1/16" (OD) Tefzel® tubing connected to conductivity detector used in autosolex generator.

Advantages of Using Spectroscopy Grade MEK Over Analytical Reagent Grade

We evaluated the extraction of $^{99m}TcO_4^-$ using spectroscopy grade (water content < 0.05%) and analytical reagent grade MEK (water content > 0.2%). Upon evaporation of MEK at 80°C and further reconstitution with physiological saline, we observed the resultant $^{99m}TcO_4^-$ was colorless on using spectroscopy grade

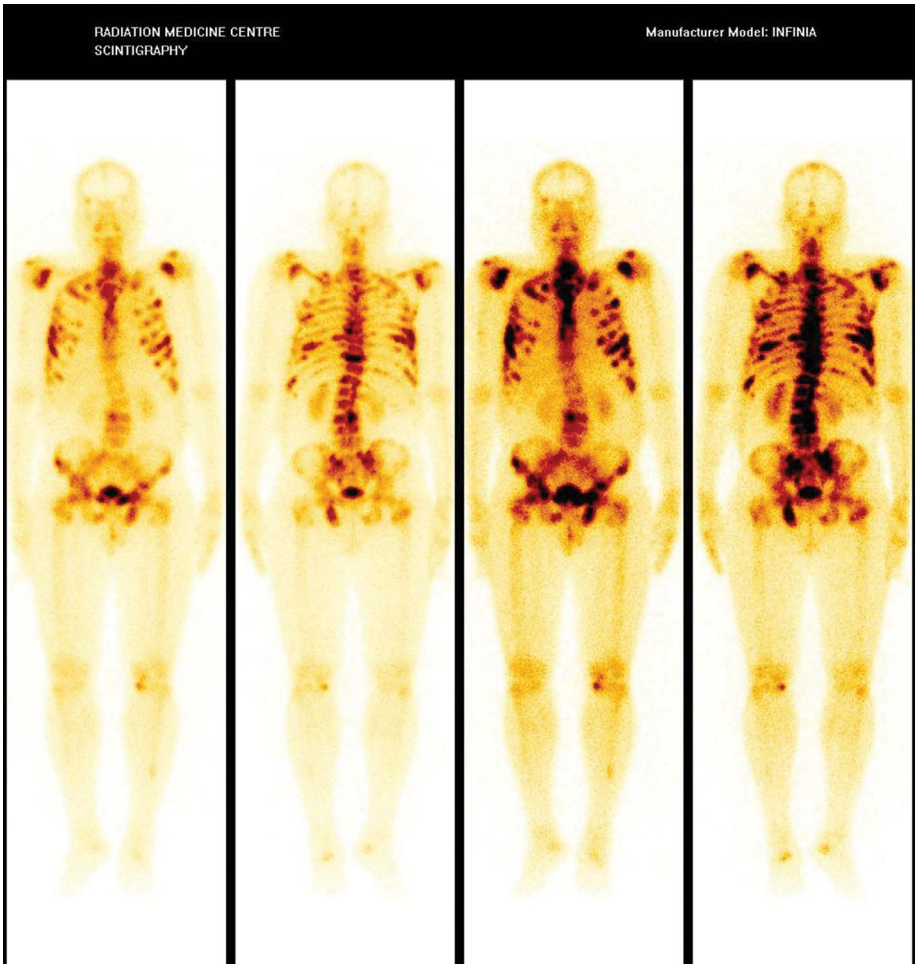

Figure 3B. Prostrate cancer patient with multiple metastases in ribs and pelvis underwent static scan for 20 minutes after injection of 15–20 mCi of same ^{99m}Tc-MDP

MEK, while brownish color on using analytical reagent grade MEK. This brownish color of $^{99m}TcO_4^-$ was due to the thermal decomposition of analytical reagent grade MEK containing > 0.2% water, which leads to the formation of MEK dimer and hydrazone derivatives [14].

Radiochemical, Radionuclide, Chemical, and Biological purity of extracted $^{99m}TcO_4^-$

Ninety seven batches of $^{99m}TcO_4^-$ were produced using autosolex at our hospital radiopharmacy. All batches of $^{99m}TcO_4^-$ (n = 97) was clear and colorless with RCP > 98%, pH between 5.0–6.5, and ^{99}Mo breakthrough was within permissible level of < 0.15% (0.026–0.001%). Mo and Al levels were <10 μg/mL, whereas MEK levels were < 0.1% (v/v). A single peak of 140 keV corresponding to ^{99m}Tc is observed in the extracted $^{99m}TcO_4^-$. All the extracted batches, complies sterility test and EL < 5 EU/mL (n = 97). Total $^{99m}TcO_4^-$ production batches and its QC data (physico-chemical) are given in Table 1.

Labeling Efficiency with different ^{99m}Tc- cold kits

Of the 97 batches of $^{99m}TcO_4^-$ extracted, Seven were used for evaluating the $^{99m}TcO_4^-$ and 90 batches were used for labeling of various ^{99m}Tc-cold kits, out of which a total of 45 extracted batches of $^{99m}TcO_4^-$ were labeled with different ^{99m}Tc-cold kits for oncological and non-oncological investigations (scintigraphic imaging) in patients. RCP of all these ^{99m}Tc-RP was > 95% except for ^{99m}Tc-TRODAT whose RCP is > 90%. RCP was determined by in house developed rapid TLC or PC method for all the ^{99m}Tc-RP at our hospital radiopharmacy center. This type of rapid TLC or PC could be performed without much decay of the ^{99m}Tc-RP at the hospital radiopharmacy prior to injection in patients, which ensures that the product complies with the regulatory norms. In each extraction, $^{99m}TcO_4^-$ is reconstituted with varying volume of sterile pyrogen free saline ranging from 1.5 to 9.0 mL and see if the average extraction yield of extraction was varying with radioactive concentration (RAC).

Use of ^{99m}Tc-radiopharmaceuticals for scintigraphic imaging of patients

We have labeled ^{99m}Tc-MDP (n = 07), ^{99m}Tc-DTPA (n = 13), ^{99m}Tc(III)DMSA (n = 19), ^{99m}Tc-EC (n = 05), ^{99m}Tc-MIBI (n = 22), ^{99m}Tc-Hynic-Toc (n = 05), ^{99m}Tc-mebrofenin (n = 02), ^{99m}Tc-phytate (n = 02), ^{99m}Tc-sulfur-colloid (n = 01) and ^{99m}Tc-HSA-NC (n = 03) ^{99m}Tc-UBI(29-41) (n = 01) using $^{99m}TcO_4^-$ extracted from autosolex generator. All these ^{99m}Tc-RPs were used in scintigraphic imaging of patients at our center. Table 2 represents total number of patients who undergone scintigraphic imaging using each of these ^{99m}Tc-RPs.

Table 2. Summary of various ^{99m}Tc-labeled radiopharmaceuticals used in scintigraphic imaging studies

^{99m}Tc-labeled radiopharmaceuticals	Number of batches labeled or used	Number of patients undergone scan	Purpose of study or scan
^{99m}Tc(III)DMSA	22	30	Kidney
^{99m}Tc-DTPA	16	79	Glomerular filtration rate (GFR)
^{99m}Tc-EC	09	26	Effective renal plasma flow (ERPF)
^{99m}Tc-MDP	15	26	Bone
^{99m}Tc-MIBI	26	155	Myocardial perfusion
	03	03	Parathyroid
^{99m}Tc-Hynic-Toc	10	22	Neuroendocrine tumors (NET)
^{99m}Tc-Mebrofenin	05	02	Hepatobiliary function
^{99m}Tc-Phytate	06	02	Liver
^{99m}Tc-sulfur colloid	05	01	Reticulo-endothelial system (RES)
^{99m}Tc-HSA-NC	09	03	Lymph nodes
^{99m}Tc-TcO_4^-	03	04	Thyroid
^{99m}Tc-ECD	04	–	Brain perfusion
^{99m}Tc-GHA	07	–	Kidney
^{99m}Tc-TRODAT	03	–	Parkinson's diseases
^{99m}Tc-UBI (29-41)	04	01	Bacterial infection

Table 1. Summary of physico-chemical evaluation of various batches of extracted $^{99m}TcO_4^-$ from LSA $^{99}MoO_4^{2-}$

Sr No.	99MoO42-: Total No. of batches and radio-activity handled (Ci)	99mTcO4-: Total No. of batches extracted	Avg pH	Avg EY* (%)	Avg 99Mo-BT# (μCi/mCi)	Avg RAC$ (mCi / mL)	Avg RCP@ (%)
1	01 (0.2)	04	6.0	78.75 ± 0.95 (78–80)	0.0075 ± 0.0042 (0.003–0.013)	60 ± 0.81 (59–61)	99.42 ± 0.17 (99.5–99.9)
2	02 (0.2)	05	6.0	77.6 ± 0.89 (77–79)	0.0086 ± 0.0056 (0.003–0.018)	55.6 ± 0.89 (55–57)	99.72 ± 0.16 (99.5–99.9)
3	01 (0.2)	02	6.0	84 ± 0.0	0.0075 ± 0.0021 (0.006–0.009)	47.5 ± 0.70 (47–48)	99.75 ± 0.07 (99.7–99.8)
4	01 (0.2)	04	6.0	76.25 ± 0.95 (75–77)	0.0132 ± 0.0064 (0.004–0.019)	47 ± 0.81 (46–48)	99.6 ± 0.08 (99.5–99.7)
5	02 (0.2)	09	6.0	88.88 ± 1.16 (87–90)	0.0044 ± 0.0024 (0.002–0.008)	58.33 ± 1.11 (57–60)	99.53 ± 0.21 (99.2–99.8)
	01 (0.5)	05	6.1 ± 0.22 (6–6.5)	89.4 ± 1.14 (89–91)	0.0176 ± 0.0104 (0.002–0.026)	58 ± 1.22 (56–59)	99.62 ± 0.17 (99.4–99.8)
6	04 (0.5)	11	5.9 ± 0.15 (5.5–6.0)	88 ± 1.78 (85–91)	0.0064 ± 0.0030 (0.002–0.01)	46.81 ± 1.77 (45–50)	99.4 ± 0.38 (98.8–99.9)
7	04 (0.5)	18	5.94 ± 0.16 (5.5–6.0)	89.05 ± 1.16 (87–91)	0.0027 ± 0.0013 (0.002–0.006)	58.05 ± 1.43 (55–61)	99.47 ± 0.34 (98.8–99.9)
8	03 (0.5)	13	5.73 ± 0.33 (5–6)	85 ± 1.41 (82–87)	0.0030 ± 0.0019 (0.001–0.006)	58 ± 1.47 (56–60)	99.44 ± 0.38 (98.8–99.9)
9	04 (0.5)	12	5.70 ± 0.33 (5.5–6.0)	88 ± 1.04 (87–90)	0.0052 ± 0.0031 (0.001–0.01)	59.16 ± 1.19 (56–60)	99.39 ± 0.33 (98.6–99.8)
10	02 (0.75)	07	5.5 ± 0.28 (5.5–6.0)	89.14 ± 1.06 (88–90)	0.0035 ± 0.0021 (0.002–0.008)	63.42 ± 1.13 (62–65)	99.08 ± 0.42 (98.6–99.6)
11	01 (0.75)	03	6.0	89.33 ± 1.15 (88–90)	0.0036 ± 0.0025 (0.001–0.006)	59.33 ± 1.15 (58–60)	99.4 ± 0.2 (99.2–99.6)
12	02 (0.5)	01	6.0	87	0.006	56	99.3
13	01 (0.5)	01	6.0	84	0.009	59	99.7
14	02 (0.5)	02	5.5	84.5 ± 0.70 (84–85)	0.0015 ± 0.0007 (0.001–0.002)	60 ± 0.0	99.4 ± 0.28

*EY — extraction yield, # 99Mo-BT — 99Mo breakthrough, $ RAC — Radioactive concentration, @RCP — radiochemical purity. All the extracted batches of 99mTcO4- were clear and colorless, RNP: 140 keV (peak), EL: < 5 EU/ml, Sterility test: complies, Mo and Al levels: < 10 μg/ml and MEK levels: < 0.1%

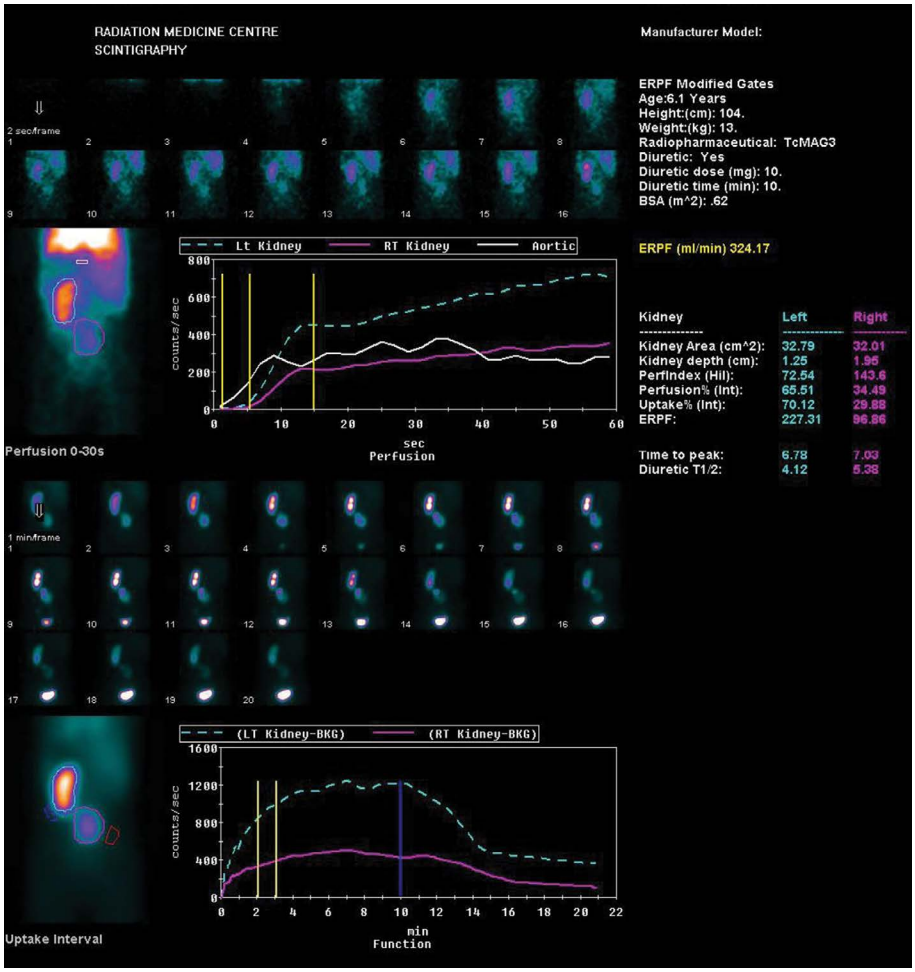

Figure 4A. Patient injected with 3–5 mCi of ^{99m}Tc-EC labeled with $^{99m}TcO_4^-$ from autosolex generator, who undergone dynamic scan for 20 minutes, having **right ectopic kidney**

Scintigraphic image of patients administered with ^{99m}Tc-MDP, ^{99m}Tc-EC, ^{99m}Tc-Hynic-Toc and ^{99m}Tc-MIBI

^{99m}Tc-MDP

Two hours post injection bone scan of 10 minutes for post operated osteosarcoma of left tibia patient administered with 6–10 mCi of ^{99m}Tc-MDP shows good uptake in bone with increased uptake in joints since the patient is below 10 years of age (Figure 3A). Another patient with prostate cancer injected with 15–20 mCi of same ^{99m}Tc-MDP scanned for 20 minutes showed multiple metastases in vertebral column, ribs and pelvis (Figure 3B). However, normal clearance of radiotracer were observed from kidneys in both cases.

^{99m}Tc-EC

20 minutes dynamic scan of patient with erratic abdomen pain and right ectopic kidney administered with 3–5 mCi of ^{99m}Tc-EC shows preserved function with adequate clearance post Lasix {furosemide?} from left kidney and normal function of right kidney (Figure 4A). Another neuro-endocrine tumor (NET) patient post peptide receptor radionuclide therapy (PRRT) injected with 3–5 mCi of ^{99m}Tc-EC underwent dynamic scan for 20 minutes shows normal effective renal plasma flow (ERPF) (Figure 4B) with normal clearance from kidney.

^{99m}Tc-Hynic-Toc

15–20 mCi of ^{99m}Tc-Hynic-Toc administered in patient with primary NET before undergoing PRRT scanned for 20 minutes shows excellent uptake in liver (Figure 5A).Another patient having NET with multiple bone metastases injected with 15–20 mCi of same ^{99m}Tc-Hynic-Toc, on scanning for 20 minutes shows focal uptake in skull, humerus, dorsal vertebrae and femur. These are the sites of somatostatin (SSTR) positive metastases (Figure 5B). The circulating background levels were minimum in both the patients, whereas clearance from kidneys in both cases was normal without any label breakdown of radiotracers.

^{99m}Tc-MIBI

A dose of 8–12 mCi ^{99m}Tc-MIBI administered in a patient with known case of ischemic heart disease (IHD) with intermittent chest pain. The rest and stress scan for 15 minutes showed normal uptake in the myocardium without any perfusion defects. Normal excretion was observed from liver through hepatobiliary system (Figure 6A). Another rest scan for 15 minutes of patient administered with 8–12 mCi of same ^{99m}Tc-MIBI suffering from coronary artery disease (CAD) and poor effort tolerance with chest pain shows left ventricular

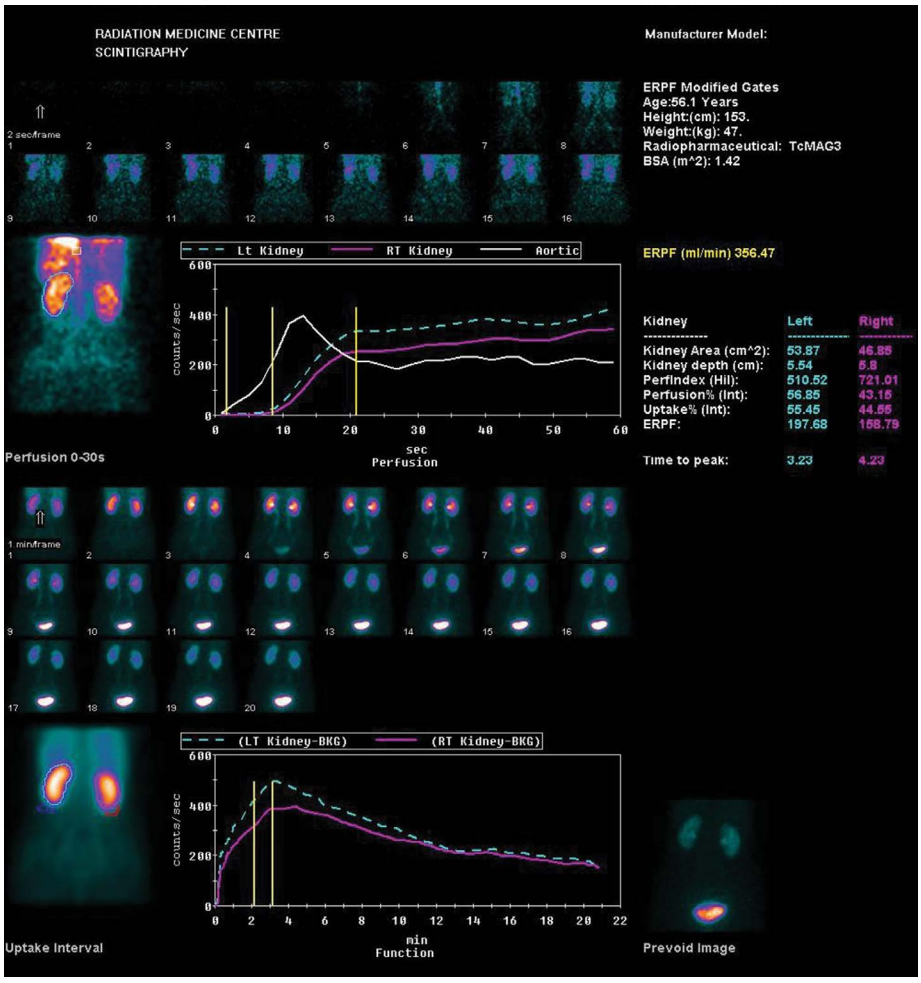

Figure 4B. Post-PRRT, NET patient underwent dynamic scan for 20 minutes after administration of 3–5 mCi of same ^{99m}Tc-EC

cavity dilatation and abnormal perfusion in anterior, inferior and apical segments with left ventricular ejection fraction (Figure 6B).

Radiation exposure while operating Autosolex Generator

Maximum radiation field while loading LSA $^{99}MoO_4^{2-}$ is 35–45 μSv/h. Average radiation fields of 26–200 μSv/h were observed at 10 cm and 0.5–2 μSv/h at 1 m distance respectively on handling 0.2–0.75 Ci of LSA $^{99}MoO_4^{2-}$ for extracting $^{99m}TcO_4^-$ using autosolex generator. Individual radiopharmacist received radiation dose in the range of 10 to 20 μSv during automated operation of autosolex generator. The radiation exposure (μSv/GBq) during extraction of $^{99m}TcO_4^-$ during both solvent extraction process (manual and automated) utilizing 0.5 Ci of LSA $^{99}MoO_4^{2-}$ is shown in Figure 7.

Discussion

Self-shielded autosolex generator with capacity of extracting 400 mCi of pharmaceutical grade $^{99m}TcO_4^-$ till 6th day of the week fits the requirement of a typical hospital radiopharmacy center and has satisfactorily proved its radiological and pharmacological safety. Additionally, its compact design (43 cm L x 28 cm D x 41 cm H, weight: 150 kg) allows it to be housed in commercially available standard negative pressure fume hood occupying a small area of 0.88 sq. m as shown in Figure 8. Our autosolex generator is a masterpiece advancement in technology for solvent extraction for eminently suitable for use in hospital radiopharmacy center compare to earlier reported semi-automated solvent extraction system utilizing MEK (extracting up to 8 Ci of $^{99m}TcO_4^-$) [18, 19]. The latter is more suitable for centralized radiopharmacy center rather than hospital based radiopharmacy settings. Performance and design of this self-shielded autosolex generator [2] meets the radiation protection criteria guidelines in hospital radiopharmacy (RPCHR) set up [21]. Additionally, solvent extractor vessel and ^{99}Mo stock vials are housed in respective 300 mm and 220 mm thick lead pots respectively which in turn are kept inside the 15 mm lead walls of the autosolex generator. Overall shielding maintain an average external radiation dose limit of 0.5–2.0 μSv/h at 1 m distance on handling 7.4–27.5 GBq of LSA $^{99}MoO_4^{2-}$ during uninterrupted automated extraction of $^{99m}TcO_4^-$ using autosolex generator. This is a perfect technological example of radiological safety meeting RPCHR guidelines [21].

Autosolex generator separates aqueous (NaOH solution containing $^{99}MoO_4^{2-}$) and organic (MEK containing $^{99m}TcO_4^-$) phase based on the difference in conductivity of the aqueous and

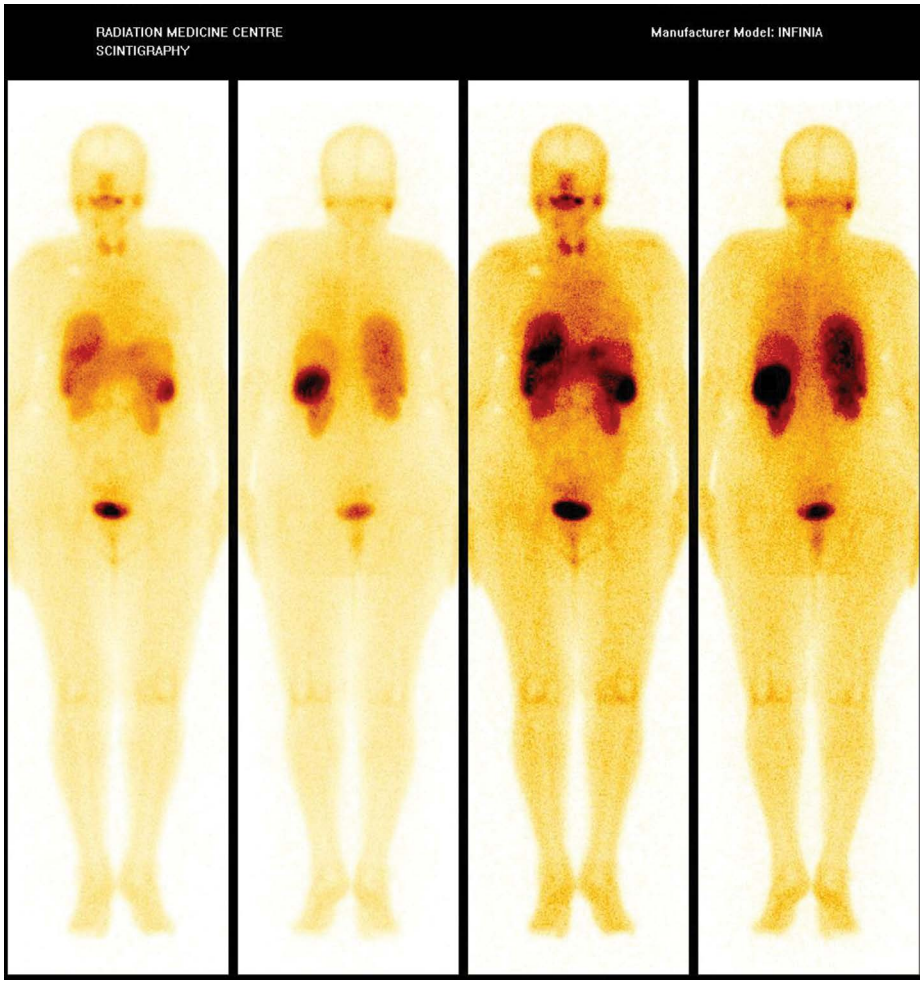

Figure 5A. Primary NET patient administered 15–20 mCi of ^{99m}Tc-Hynic-Toc labeled from autosolex's $^{99m}TcO_4^-$. Whole body static scan performed for 20 minutes

organic phase. The ^{99}Mo content (breakthrough) in extracted $^{99m}TcO_4^-$is less than 0.026% (n = 97). The $^{99m}TcO_4^-$ passed all the QC tests as specified in IP 2014 monograph [4]. MEK detection was carried out by Iodoform test and gas chromatography. Elemental molybdenum and alumina content were detected by colorimetric spot test. Pharmacopeia grade sodium pertechnetate extracted using autosolex generator were clear and colorless (n = 97) with pH between 5.0 and 6.5 (n = 97). Before each daily operation, automated sanitization of MEK evaporation flask, Tefzel® tubing and solenoid valves connected to the saline port for reconstitution of $^{99m}TcO_4^-$ and tubing for final collection of $^{99m}TcO_4^-$ were done with ethanol (70%) followed by saline makes the autosolex generator to meet current good radiopharmacy practice (cGRPP) regulations [15]. Additionally at the end of each week automated clean-disinfect cycle of $^{99}MoO_4^{2-}$ stock vial, extractor, conductivity detector, Tefzel® tubing and solenoid valves with 0.1N HCl, acetone, sterile water make the autosolex generator to meet good laboratory practice (GLP) standards [15, 16]. Autosolex generator can be used for $^{99m}TcO_4^-$ extraction without changing any Tefzel/Tygon/Teflon tubing, solenoid valves and PEEK adapters/connectors until and unless any one of these found defective for at least six month. This makes the autosolex generator cost effective compare to automated radiochemistry module using disposable kits for separation and purification of $^{99m}TcO_4^-$ produced via ^{100}Mo(p,2n)^{99m}Tc [9, 17]. In each extraction, $^{99m}TcO_4^-$ is reconstituted with varying volume of sterile pyrogen free saline ranging from 1.5 to 9.0 mL and see if the average extraction yield of extraction was varying with radioactive concentration (RAC). In each extraction, volumes of spectroscopy grade MEK used for mixing in solvent extractor vessel varied from 15 to 30 mL. This parameter was changed to see if the average extraction yield and average ^{99}Mo breakthrough of extracted $^{99m}TcO_4^-$ was varying or not. Even we have evaluated if the content of MEK in the extracted $^{99m}TcO_4^-$ is varying. In present study we have also extracted $^{99m}TcO_4^-$ from 27.5 GBq (750 mCi) of LSA $Na_2{}^{99}MoO_4$ in 24–25 mL volume, which was not reported earlier [2].

The radiolabeling of the fourth generation ^{99m}Tc radiopharmaceuticals cold kits is sensitive to the quality of ^{99m}Tc-pertechnetate, moreover, we have used low specific activity (LSA) ^{99}Mo-SodiumMolybdate ($^{99}MoO_4^{2-}$) and separation was based on methyl ethyl ketone (MEK) – solvent extraction technique. In this context it is to note that a limited number of ^{99m}Tc radiopharmaceuticals cold kits radiolabeling were reported earlier [2]. The extracted ^{99m}Tc-Sodium Pertechnetate ($^{99m}TcO_4^-$) was used in labelling of various fourth generation ^{99m}Tc radiopharmaceuticals cold kits viz. ^{99m}Tc-ethylene dicysteine (^{99m}Tc-EC), ^{99m}Tc-L,L-ethyl cysteinate dimer (^{99m}Tc-ECD),^{99m}Tc-methoxyisobutyliso nitrile(^{99m}Tc-MIBI), ^{99m}Tc-hydrazinonicotinamide-Tyr3-octreotide(^{99m}Tc-

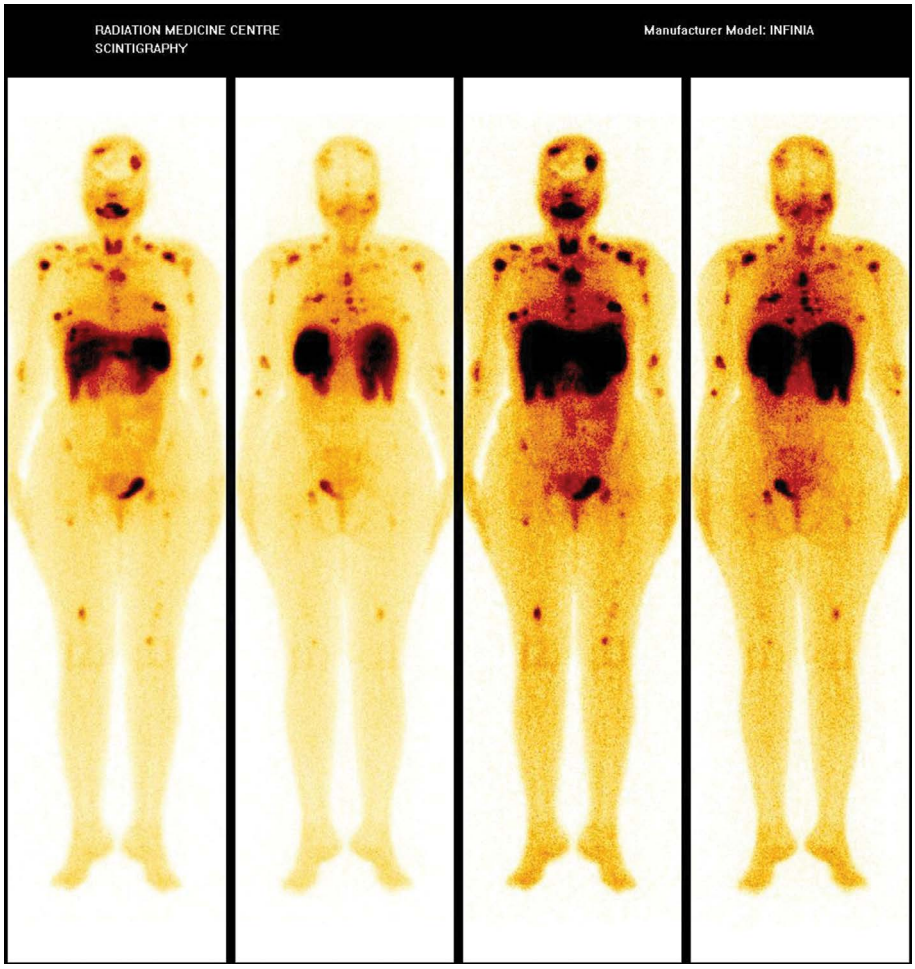

Figure 5B. Multiple bone metastases in a NET patient administered 15–20 mCi of same ^{99m}Tc-Hynic-TOC. Whole body images were acquired after 20-minute static scan

Hynic-Toc), ^{99m}Tc-human serum albumin-nanocolloid (^{99m}Tc-HSA-NC), ^{99m}Tc-2 [N,N0-bis(2-mercaptoethyl)ethylenediaminomethyl]- 3 -(4-chlorophenyl)tropane) (^{99m}Tc-TRODAT-1) and ^{99m}Tc-ubiquicidin [29–41] {^{99m}Tc-UBI [29–41]} and quality of these radiopharmaceuticals was found to be satisfactory for clinical studies. In the present study we have shown the scintigraphic image of patients with varied clinical conditions using fourth generation ^{99m}Tc-radiopharmaceuticals (^{99m}Tc-RP) viz. ^{99m}Tc-MDP, ^{99m}Tc-EC, ^{99m}Tc-Hynic-Toc and ^{99m}Tc-MIBI as these results were not reported earlier (2). These ^{99m}Tc-RPs were formulated using $^{99m}TcO_4^-$ extracted from autosolex generator.

Clinical Evaluation – Scintigraphic image of patients administered with ^{99m}Tc-MDP, ^{99m}Tc-EC, ^{99m}Tc-Hynic-Toc and ^{99m}Tc-MIBI

The clinical utility of a radiopharmaceuticals would give optimal imaging study helpful in understanding the underlying physiology of the diseases.

^{99m}Tc-MDP

The images (3A and 3B) given are representative images from among the scans performed with ^{99m}Tc-MDP formulated using $^{99m}TcO_4^-$ from autosolex generator.

These two patients were referred to our center for a bone scan procedure. The patients were injected with approximately 15–20 mCi ^{99m}Tc-MDP. The images were obtained 2–3 hours post injection as per SNM guidelines. The image (3A) shows the bone scan of a 13 year old child who was operated for osteosarcoma of the left tibia. The scan shows no abnormal tracer concentrations in the stomach or thyroid signifying no label breakdown or free pertechnetate. There is no liver uptake showing no colloidal complex formations in the labeled product. The scan shows optimal bone uptake in the axial and appendicular skeleton. The increased uptake in the joints is due to the increased osteoblastic activity due to new bone formation (growing bone ends) in pediatric age group. The scan showed normal kidney uptake and normal background noise rate clearance showing good signal to noise ratio. The image (3B) shows the bone scan of a 60 year old patient suffering from prostatic carcinoma. Other than absence of stomach, thyroid and liver uptake, the scan showed multiple sites of linear uptake in the bones of the vertebral column, pelvis and rib cage which are due to the metastases from the prostatic primary. The background clearance and a good signal to noise ratio makes the ^{99m}Tc-MDP formulated using $^{99m}TcO_4^-$ from autosolex generator equivalent to ^{99m}Tc-MDP formulated using $^{99m}TcO_4^-$ from column generator.

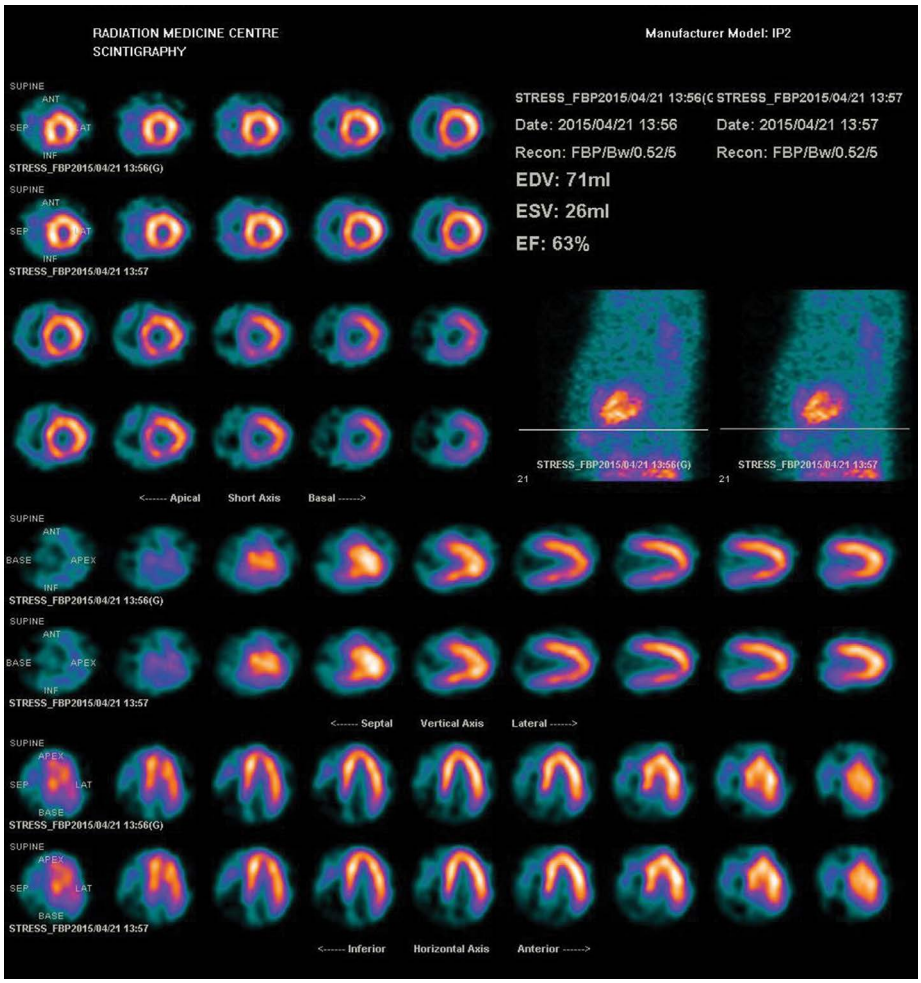

Figure 6A. Ischemic Heart Disease patient administered with 8–12 mCi of ^{99m}Tc-MIBI labeled with $^{99m}TcO_4^-$ from autosolex. Image acquired after 15 minutes of **scan_{scanning}.**

^{99m}Tc-EC

The radiolabeling of ^{99m}Tc-EC was performed using $^{99m}TcO_4^-$ produced from the autosolex generator. EC renogram study was done for patients from that two representative images (4A and 4B) were described. These images show no stomach activity proving no label breakdown and no prolonged retention of the tracer in the liver ruling out any colloidal complex formation. The image (4A) was from a patient suffering from abdominal pain and a sonography showing abnormal position of the kidneys referred for functional evaluation of kidney status. 20 minutes dynamic scan of patient administered with 3–5 mCi of ^{99m}Tc-EC showed ectopic right kidney with preserved function with adequate clearance post Lasix {furosemide?} from left kidney and normal function of right kidney. The time of aortic transit of the tracer to the kidney, the kidney uptake as compared to the background and the transit of the tracer from the bladder with the bladder filling time seemed to be normal. The clearance curves shows delayed clearance of the tracer. Another image (4B) was from a patient undergoing peptide receptor radionuclide therapy (PRRT) treatment for neuro-endocrine tumor (NET). 3–5 mCi of ^{99m}Tc-EC was injected and dynamic scan done for 20 minutes shows normal effective renal plasma flow (ERPF) with normal clearance from kidney with good signal to noise ratio.

^{99m}Tc-Hynic-Toc

The patients scanned with ^{99m}Tc-Hynic-Toc, which were prepared using $^{99m}TcO_4^-$ eluted from autosolex generator showed comparable tracer kinetics with uptake in the liver, spleen, thyroid, salivary glands and kidneys. These were patients with NET planned for PRRT therapy. The image (5A) showed no uptake in stomach ruling out technetium breakdown. The image shows no abnormal uptake suggesting no somatostatin expression. The image (5B) was from a patient with multiple somatostatin positive metastases in the skull, clavicle, femur, humerus, dorsal vertebrae. There was good signal to noise ratio and no increased background therefore making it comparable to ^{99m}Tc-Hynic-Toc prepared using $^{99m}TcO_4^-$ from column generator. The circulating background levels were minimum in both the patients.

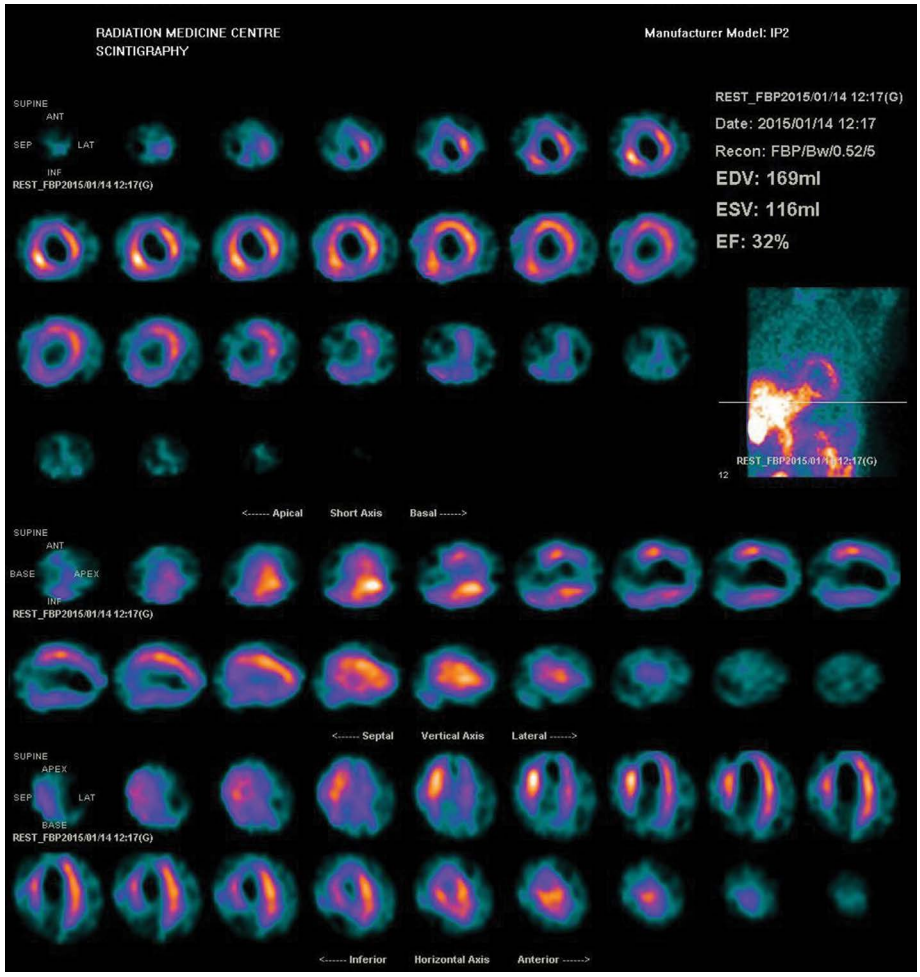

Figure 6B. Coronary Artery Disease patient scanned for 15 minutes after administration of 8–12 mCi of same ^{99m}Tc-MIBI.

^{99m}Tc-MIBI

^{99m}Tc-MIBI prepared using $^{99m}TcO_4^-$ obtained from autosolex generator showed similar tracer kinetics like that of pertechnetate obtained from the column generator. There was no uptake in the stomach ruling out label breakdown. After one hour of injection it showed optimal tracer in the myocardium. The ^{99m}Tc-MIBI showed normal uptake in the hepatocyte with normal hepatobiliary clearance of the tracer. The liver, gall bladder and intestine along with the cardiac {cardiac tissues? / heart? } showed normal uptake of the tracer. A dose of 8–12 mCi ^{99m}Tc-MIBI administered in a patient (6A) with known case of ischemic heart disease (IHD) with intermittent chest pain. The rest and stress scan acquired for 15 and 60 minutes after tracer administration showed normal uptake in the myocardium without any perfusion defects. Another rest scan of patient (6B) administered with 8–12 mCi of same ^{99m}Tc-MIBI suffering from coronary artery disease (CAD) and poor effort tolerance with chest pain shows left ventricular cavity dilatation and abnormal perfusion in anterior, inferior and apical segments with abnormal left ventricular ejection fraction and derailed values of end diastolic and end systolic volumes.

The proper uptake of these ^{99m}Tc-RP in the targeted organs proves the clinical efficacy of the $^{99m}TcO_4^-$ extracted from autosolex generator. Clinically acceptable good scintigraphic images of 355 patients [20] in our nuclear medicine center using various ^{99m}Tc-RP labeled with $^{99m}TcO_4^-$ extracted from autosolex generator proves that the $^{99m}TcO_4^-$ produced fulfils the radiopharmaceutical requirement.

Conclusions

Autosolex Generator utilizing 7.4–27.5 GBq of LSA $^{99}MoO_4^{2-}$ is a reliable and cost effective alternate technological solution during non-availability of ^{99}Mo/^{99m}Tc-Alumina-Column Generator utilizing HSA $^{99}MoO_4^{2-}$ for preparation of pharmaceutical grade $^{99m}TcO_4^-$ for preparation of a wide range of ^{99m}Tc-radipharmaceutical.

Acknowledgments

The authors gratefully acknowledge Shri K. N. Vyas, Chairman, Atomic Energy Commission, and Director, BARC, Mumbai, India,

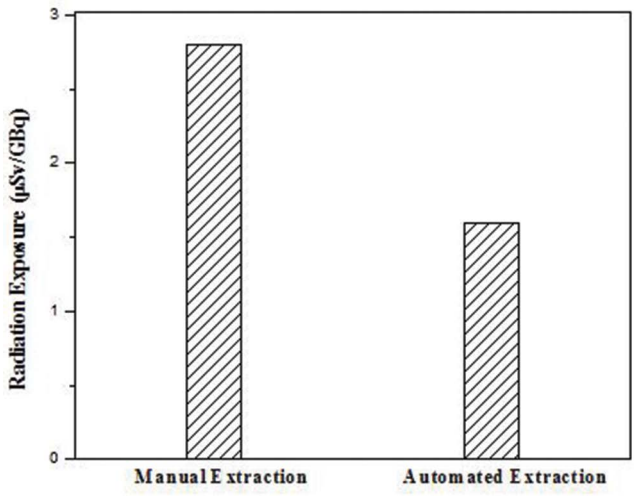

Figure 7. Radiation exposure (μSv/GBq) during manual and automated solvent extraction (using autosolex generator) of $^{99m}TcO_4^-$ from 0.5 Ci of LSA $^{99}MoO_4^{2-}$

Figure 8. Autosolex Generator occupying 0.88 sq. m area inside fume hood

Shri G. Ganesh, Chief Executive, BRIT, Mumbai, India and Shri Amitava Roy, Director, Variable Energy Cyclotron Center (VECC), Kolkata, India, for their keen interest and support in this project.

References

1. Le V. TcGenerator Development: Up-to-DateTcRecovery Technologies for Increasing the Effectiveness ofMoUtilisation. Science and Technology of Nuclear Installations. 2014; 2014: 1–41, doi: 10.1155/2014/345252.
2. Chattopadhyay S, Barua L, Das S, et al. Pharmaceutical grade sodium [99mTc] pertechnetate from low specific activity 99Mo using an automated 99Mo/99mTc-TCM-autosolex generator. Journal of Radioanalytical and Nuclear Chemistry. 2014; 302(2): 781–790, doi: 10.1007/s10967-014-3211-1.
3. Ramamoorthy N, Shivarudrappa V, Bhelose AA, et al. Radiopharmaceuticals and Hospital Radiopharmacy Practices- Manual for Accreditation/ Certification of Hospital Radiopharmacist. BRIT Report. BRIT. Mumbai 2000: 61–82.
4. Monographs on Sodium Pertechnetate (99mTc) Injection (Non fission). Indian Pharmacopoeia Commission. www.ipc.gov.in (31.10.2014).
5. Tanase M, Tatenuma K, Ishikawa K, et al. A 99mTc generator using a new inorganic polymer adsorbent for (n,) 99Mo. Applied Radiation and Isotopes. 1997; 48(5): 607–611, doi: 10.1016/s0969-8043(96)00320-x.
6. Chakravarty R, Ram R, Dash A, et al. Preparation of clinical-scale 99Mo/99mTc column generator using neutron activated low specific activity 99Mo and nanocrystalline -Al2O3 as column matrix. Nucl Med Biol. 2012; 39(7): 916–922, doi: 10.1016/j.nucmedbio.2012.03.010, indexed in Pubmed: 22632898.
7. Chakravarty R, Shukla R, Gandhi S, et al. Polymer embedded nanocrystalline titania sorbent for 99Mo-99mTc generator. J Nanosci Nanotechnol. 2008; 8(9): 4447–4452, doi: 10.1166/jnn.2008.280, indexed in Pubmed: 19049039.
8. Chakravarty R, Shukla R, Ram R, et al. Practicality of Tetragonal Nano-Zirconia as a Prospective Sorbent in the Preparation of 99Mo/99mTc Generator for Biomedical Applications. Chromatographia. 2010; 72(9-10): 875–884, doi: 10.1365/s10337-010-1754-z.
9. Bénard F, Buckley KR, Ruth TJ, et al. Implementation of Multi-Curie Production of (99m)Tc by Conventional Medical Cyclotrons. J Nucl Med. 2014; 55(6): 1017–1022, doi: 10.2967/jnumed.113.133413, indexed in Pubmed: 24722529.
10. Sarkar SK, Kothalkar C, Naskar P, et al. Indigenous technology development and standardization of the process for obtaining ready to use sterile sodium pertechnetate-Tc-99m solution from Geltech generator. Indian J Nucl Med. 2013; 28(2): 70–74, doi: 10.4103/0972-3919.118226, indexed in Pubmed: 24163509.
11. Evans JV, Moore PW, Shying ME, et al. Zirconium molybdate gel as a generator for technetium-99m--I. The concept and its evaluation. Int J Rad Appl Instrum A. 1987; 38(1): 19–23, doi: 10.1016/0883-2889(87)90230-9, indexed in Pubmed: 3030964.
12. Boyd RE. The gel generator: a viable alternative source of 99mTc for nuclear medicine. Applied Radiation and Isotopes. 1997; 48(8): 1027–1033, doi: 10.1016/s0969-8043(96)00298-9.
13. Saraswathy P, Sarkar SK, Ramamoorthy N, et al. 99mTc Gel Generators Based on Zirconium Molybdate-99Mo: II. Evaluation of Preparation and Performance. Radiochimica Acta. 1998; 83(2), doi: 10.1524/ract.1998.83.2.103.
14. Mohammad R, Moore DE, Maddalena DJ, et al. Studies on 99mTc-Pertechnetate from the MEK solvent extraction generator. AAEC (E)/589. 1984: 1–17.
15. Elsinga P, Todde S, Penuelas I, et al. Guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals. European Journal of Nuclear Medicine and Molecular Imaging. 2010; 37(5): 1049–1062, doi: 10.1007/s00259-010-1407-3.
16. Verbruggen A, Coenen HH, Deverre JR, et al. Guideline to regulations for radiopharmaceuticals in early phase clinical trials in the EU. Eur J Nucl Med Mol Imaging. 2008; 35(11): 2144–2151, doi: 10.1007/s00259-008-0853-7, indexed in Pubmed: 18690437.
17. Bénard F, Zeisler SK, Vuckovic M, et al. Cross-linked polyethylene glycol beads to separate 99mTc-pertechnetate from low-specific-activity molybdenum. J Nucl Med. 2014; 55(11): 1910–1914, doi: 10.2967/jnumed.114.143834, indexed in Pubmed: 25332438.
18. Kuznetsov AA, Kudrin A, Kodina GE, et al. Semi-Automatic 99mTc solvent extraction system. 7th International Symposium on Technetium and Rhenium – Science and Utilization – (Meeting Abstract). 2011: 158.
19. Semi-automatic 99mTc solvent extraction system. http://www.rcrusia.com.ar/espanol/cooperacion/pub4.pdf.
20. Mitra A, Chandak A, Lad S, et al. Operational and clinical evaluation of 99Mo/99mTc-TCM-autosolex generator at hospital radiopharmacy center (Meeting Abstract). Indian J Nucl Med. 2016; 31: S29.
21. Manual on Radiation protection in Hospitals and in General Practice; 4: Nuclear medicine. http://www-ns.iaea.org/downloads/rw/ppss/iaporp/iaporp09.do.