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RADIOCOMPLEXATION, CHROMATOGRAPHIC SEPARATION AND BIOEVALUATION OF [^{99m}Tc]DITHIOCARBAMATE OF PROCAINAMIDE AS SELECTIVE LABELED COMPOUND FOR MYOCARDIAL PERFUSION IMAGING

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Cardiac imaging is one of the most important tools for diagnosing many diseases related to the heart. This work was devoted to developing this method using experiments on mice. The formation of a complex of [^{99m}Tc]dithiocarbamate of procainamide under optimum conditions of reaction temperature (37°C), reaction time (30 min), pH of the reaction mixture (8), amount of substrate (100 μg), amount of reducing agent tin(II) (content, 50 μg), and stability in rat serum (8 h) was achieved using radioactive Tc-99m (300 – 500 MBq) to give high labeling yield (98.5%) and radiochemical purity. Procainamide works through sodium channel blocker. Normal mice were used in biodistribution investigations. High absorption uptake of the [^{99m}Tc]dithiocarbamate of procainamide complex was found to be 33.47± 0.83% injected dose/g organ (ID/g) as observed in mice for up to 5 min, which demonstrated its usefulness as a radiotracer for heart imaging.

Keywords: complex, [^{99m}Tc]dithiocarbamate of procainamide; procainamide; bioevalution; sodium channel blocker; heart imaging.

1. INTRODUCTION

Procainamide (PA) has been medically selected due to its association with sodium channel blocker as an effective anti-arrhythmic agent used in the treatment of many diseases related to the heart [1 – 6]. According to reports, a lot of radiotracers have been used for heart imaging [7 – 20]. However, there is a critical point to consider regarding the concentration of reported radiotracers in lungs and heart together in addition, with blood and liver as well through $\hat{a}_1$-receptors. To minimize the drawbacks, procainamide was selected as a new drug that can be used in heart imaging through sodium channel blocker instead of the other receptors that were studied previously. Because procainamide as the drug has a high affinity for specific heart receptors such as sodium channel blocker, it can be employed as possible marker in heart imaging.

[^{99m}Tc] nitrido complexes are regarded as important radiotracers playing an essential role in radiocomplexation and diagnostic procedures in nuclear medicine. In some respects, including chemical and biological properties, the [^{99m}Tc]nitrido core outperforms the [^{99m}Tc]oxo core. Because the nitrido ($N^{?3}$) ligand is a powerful π-electron donor, it can stabilize its [^{99m}Tc]nitrido core, making these labeled compounds pyrogen free [21 – 36]. Although procainamide as the drug was initially labeled with Tc-99m, however, the heart uptake of ^{99m}Tc-procainamide was not large: 16.7 ± 0.8% ID/g at 5 min post-injection (p.i.). In addition, this radiotracer does not possess *in-vivo* stability (high stomach uptake of 10.5 ± 0.5% ID/g at 120 min p.i. [20]. Therefore, we need to make further modifications of this compound to improve its heart uptake and reduce the unwanted accumulation in other tissues and/or organs such as stomach.

The goal of this work was to prepare a dithiocarbamate of procainamide (Fig. 1) and then label it with [^{99m}Tc]nitrido core to give [^{99m}Tc]dithiocarbamate of procainamide complex (Fig. 2). In a biodistribution investigation, Swiss Albino mice model were used to evaluate the amount of this labeled compound, [^{99m}Tc]dithiocarbamate of procainamide com-

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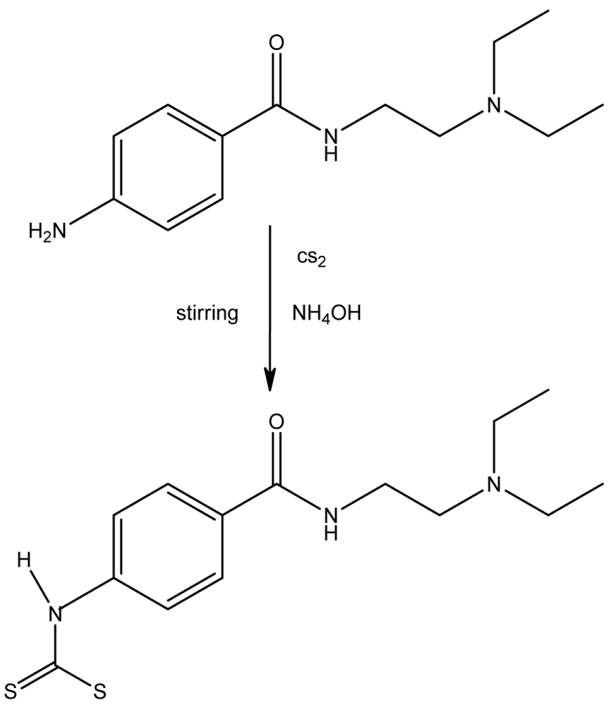

Fig. 1. Schematic representation of synthesis of dithiocarbamate of procainamide.

plex, in its target organ (heart) through sodium channel blocker.

2. EXPERIMENTAL

2.1. Chromatography

Procainamide, succinicdihydrazide, propylenediaminetetraacetic acid (PDTA), aqueous ammonia solution, and carbon disulfide were purchased from Sigma-Aldrich, St. Louis, MO, USA. Unless otherwise specified, all chemicals were of analytical or clinical grade and were used directly without further purification. Elemental analyses were performed at the National Research Centre's Micro Analytical Center (Cairo, Egypt) using an ELEMENTAR Vario EL instrument from Germany. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. The ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury VXR-350 MHz spectrometer using samples dissolved in deuterated chloroform ($CDCl_3$) or dimethylsulphoxide (DMSO-d_6), and the chemical shifts were measured as δ (ppm) down field from tetramethylsilane (TMS) as an internal standard. A well-type NaI scintillation γ-Counter Model Scalar Ratemeter SR7 (Nuclear Enterprises Ltd., USA) was used for radioactive measurement.

The radiotracer, [^{99m}Tc]dithiocarbamate of procainamide complex, was purified by high performance liquid chromatography (Shimadzu HPLC) equipped with a UV detector SpD-6A, a reversed phase Waters symmetry C_{18} (10 µm, 250 × 4.6 mm) column (Waters Corporation, Milford, MA, USA), a Lischrosorb column. RP-HPLC analysis was performed using isocratic elution of pH 5.5 (1% acetic acid): methanol (76:24, v/v) were used as a mobile phase at a flow

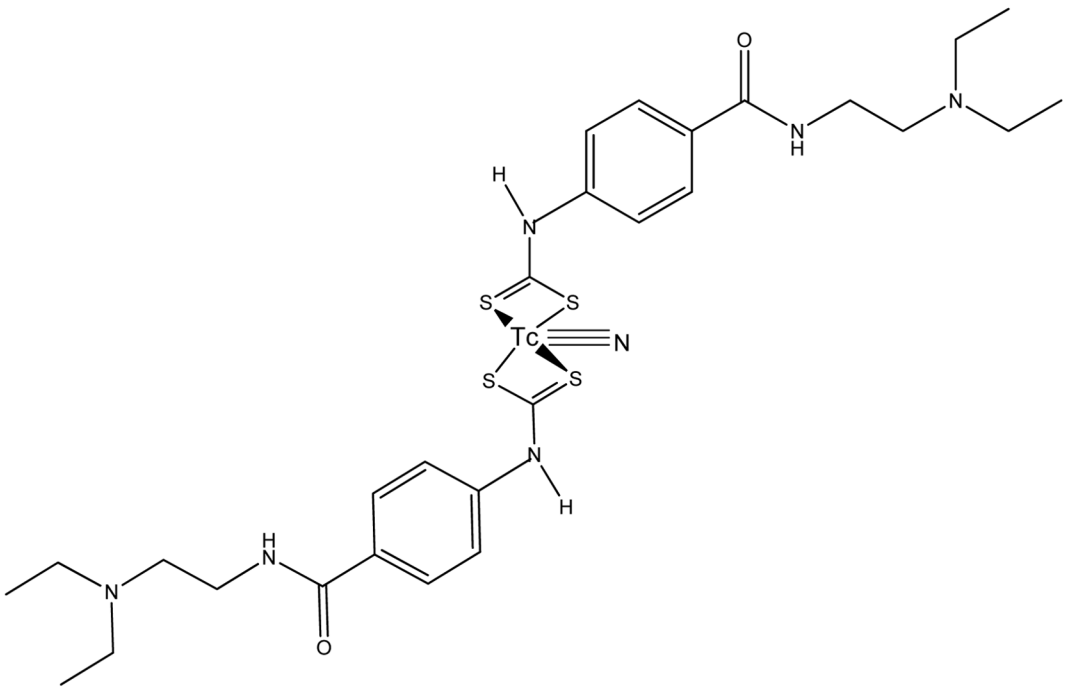

Fig. 2. Structure of [^{99m}Tc]dithiocarbamate of procainamide complex.

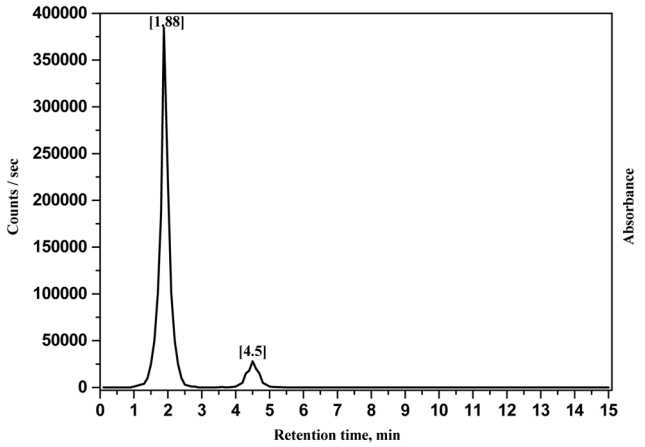

Fig. 3. HPLC paattern of [^{99m}Tc]nitride core > 99%, t_R =1.88 min. (mean yield % ± SD, *n* = 3).

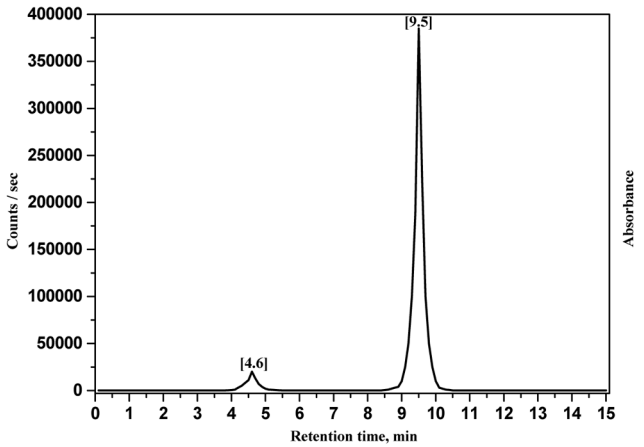

Fig. 4. HPLC pattern of [^{99m}Tc]dithiocarbamate of procainamide complex > 98%, (mean yield % ± SD, *n* = 3).

rate of 0.20 mL min^{-1}. The flow rate was set at 0.20 mL/min with the detection wavelength of 280 nm [37]. The radiotracer, [^{99m}Tc]dithiocarbamate of procainamide complex, was collected with a fraction collector and its activity was measured with a well type NaI (Tl) crystal connected to a single channel analyzer (BLC-20, BUCK Scientific). In addition, the [^{99m}Tc]nitrido core was determined using a reaction through the HPLC column of RP-18 (Lichrosorb, 5 µm, 150 mm × 4.6 mm) using the gradient elution of water (solvent A) and acetonitrile (solvent B) injected through this column. Starting with 100% A/0% B with a linear gradient to 0% A/100% B from 0 to 30 min. The flow rate was adjusted to 1.0 mL/min [30].

Thin layer chromatography (TLC) aluminum sheets (20 × 25 cm) SG-60 F_{254} were supplied by Merck. The [^{99m}Tc]nitrido core was detected using TLC sheets were marked 2 cm from the base and lined into fragments 1 cm each up to 14 cm using a combination of two different solvent systems of normal saline 0.9% and methanol: chloroform (1:9 v/v). A spot (5 µL) from the reaction mixture was applied with a micropipette, and then the strip was developed in an ascending manner in a closed jar filled with N_2 gas to prevent the oxidation of the labeled spot. The strip was developed using the eluting solvent system, dried, cut into 1 cm segments, and the radioactivity associated with each segment was measured using a well-type NaI(Tl) detector. The colloidal impurities were separated by filtration of the reaction mixture through 0.22 µm Millipore filter at a suitable pressure [38 – 44].

2.2 Synthesis of Dithiocarbamate of Pprocainamide

This synthesis was carried out by adding 0.5 mL of carbon disulfide solution in ethanol (1:4 v/v) to a pre-cooled solution of procainamide (5 mg, 21.25 µmol) in aqueous ammonia (2 mL) at 0°C with stirring. The resulting mixture was stirred nightly at room temperature. After the reaction was completed, the dithiocarbamate procainamide product was given using a vacuum process to eliminate the solution [45 – 50]. It was then re-crystallized from the solvents and characterized by ^{1}H NMR, ^{13}C NMR, mass spectrometry, and elemental analysis. The yield of dithiocarbamate procainamide was 56%, and the melting point was (177 – 179°C).

2.3 Characterization of Dithiocarbamate Procainamide

Mass spectrometry and elemental analysis confirmed the synthesis of dithiocarbamate procainamide with formula $C_{14}H_{20}N_3OS_2$ and a molecular ion peak at m/z 278.44 [M-S]. The obtained results of elemental analysis were C 54.15; H 6.47; and N 13.56%, which were in good agreement with the calculated elemental analysis as C 54.14; H 6.44; and N 13.53%. The ^{1}H-NMR (d^6-DMSO, 350 MHz) showed peaks at: δ 8.45 (dd, 2H, aromatic C–CH, J = 5.4,2.7Hz), δ 8.11 at (dd, 2H, aromatic C–CH, J = 5.4,2.7 Hz), 2.49 (m, 4H, -$\underline{CH_2}CH_3$), 1.08 (t, 6H, -$CH_2\underline{CH_3}$), 2.59 (t, 2H, -$\underline{CH_2}N$), 3.62 (t, 2H, -$\underline{CH_2}NH$-), 8.07 (s, 1H, $\underline{NH}$), 8.59 (s, 1H, $\underline{NH}$-CS_2). The ^{13}C NMR (DMSO-d6) spectrum showed the presence of 12 carbon resonances in the molecule at δ (ppm) 14.22, 14.22, 38.11, 49.81, 49.81, 55.62, 128.18, 128.18,130.12, 130.12, 132.49, 144.35, 169.24, and 202.91.

2.4 Synthesis of Technetium-99m Nitride Core

It was synthesized using 50 µL (50 µg) of $SnCl_2{\cdot}2H_2O$ in aqueous HCl, adding 5 mg of succinicdihydrazide and 5 mg of propylenediaminetetraacetic acid (PDTA), sodium dihydrogen phosphate (0.5 mg) and disodium hydrogen phosphate (5.8 mg). The mixture was then kept at ambient temperature for 30 min after the addition of 1 mL of pertechnetate (38 MBq, 1 mCi) [21 – 30]**.** As a result, the reaction mixture yielded a technetium-99m nitride core, which was characterized using TLC and HPLC (Fig. 3).

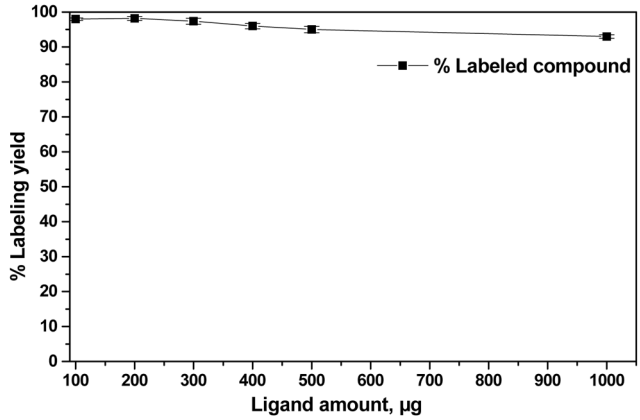

Fig. 5. Effect of dithiocarbamate of procainamide amount on the radiochemical yield % of [^{99m}Tc]dithiocarbamate of procainamide complex. Conditions: 100 – 1000 µg of procainamide, 50 µg Sn(II), pH 8, and 30 min. reaction time, (mean yield % ± SD, n = 3).

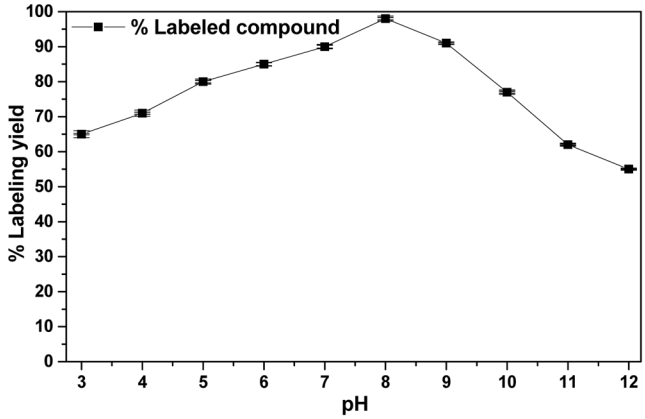

Fig. 6. Effect of pH on the radiochemical yield % of [^{99m}Tc]dithiocarbamate of procainamide complex. Conditions: 100 µg of procainamide, 50 µg Sn(II), pH 3 – 12, and 30 min. reaction time (mean yield % ± SD, n = 3).

2.5 Factors Affecting the Radiochemical Yield

Many parameters, including substrate concentration, procainamide (100 – 1000 µg), reaction mixture pH (3 – 12) and reaction time (1 – 60 min) were considered based on previous reports [21 – 23]. To achieve the best results (high percent of radiochemical yield), each of the investigated factors of the labeling process was further optimized using the trials and errors method. The experiment was repeated until the optimal conditions were attained, with all factors kept at optimum altering except the factor under study, till the optimization process were performed.

2.6. Preparation of Radiotracer as [^{99m}Tc]dithiocarbamate of Procainamide Complex

Kit sterilization for the preparation of [^{99m}Tc]dithiocarbamate of procainamide complex injection is a multidose reaction vial which contains the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce this complex injection for diagnostic use by intravenous injection. Each 10 mL vial contains 0.5 mL solution of freshly prepared technetium-99m nitride core (18 – 25 MBq) with 100 µg of procainamide dissolved in ethanol (1 mL,1mg:1mL), 50 µg (50 µL) maximum total tin as stannous chloride dihydrate; pH is adjusted to 8 prior to lyophilization and 30 min reaction time. The product was vortexed vigorously and then kept at ambient temperature, without bacteriostatic preservatives, sealed under nitrogen. The radiochemical purity of the complex was detected using RP-HPLC as shown in Fig. 4. The chemical structure is in good agreement with previously published works [21 – 23].

2.7. Stability Testing

This test was performed by adding 0.1 mL of radiotracer, [^{99m}Tc]dithiocarbamate of procainamide complex, to 1.9 mL freshly prepared rat serum. The procedure was carried out by allowing the radiotracer to stand at room temperature for 24 hours. To determine the yield of [^{99m}Tc]dithiocarbamate of procainamide complex, about 50 µL aliquots were taken from the total mixture and analyzed by HPLC to detect the radiochemical complex using a perfect γ-scintillation counter [51 – 56].

2.8. Biodistribution Study

The biodistribution process of the radiotracer, [^{99m}Tc]dithiocarbamate of procainamide complex was performed using six groups (5 mice for each group to give 30 mice in total for whole study, n = 5), were intravenously injected with 0.2 mL (200 – 420 KBq) of [^{99m}Tc]dithiocarbamate of procainamide complex via the tail vein (after purifying by HPLC). Animals were sacrificed at various time points after injection (5, 15, 30, and 60 min, 2 h and 3 h). All organs were isolated and the biodistribution of [^{99m}Tc]dithiocarbamate of procainamide complex in these organs was examined in comparison to a standard solution of the labeled substrate [57 – 99]. The Student's t-test was used to assess data differences. Results of the 2-tailed test for P are reported and all findings are expressed as mean ± SEM. The level of significance was set at $P < 0.05$.

2.9. Blocking Study

Various concentrations of unlabeled procainamide ranging from 0 to 1000 µg were used. Unlabeled procainamide was injected into the mice 5 min before the administration of the radiotracer, [^{99m}Tc]dithiocarbamate of procainamide complex, and the percent of cardiac uptake was assessed 5 min p.i. of the [^{99m}Tc]dithiocarbamate of procainamide complex (n = 5) [21 – 23].

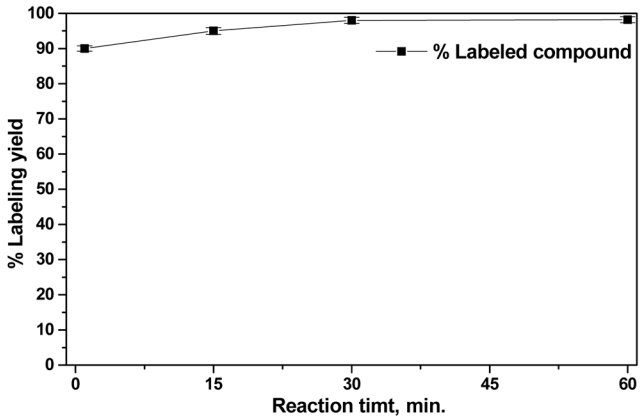

Fig. 7. Effect of reaction time on the radiochemical yield % of [^{99m}Tc]dithiocarbamate of procainamide complex. Conditions: 100 μg of procainamide, 50 μg Sn(II), pH 8, and 1 – 60 min reaction time (mean yield % ± SD, *n* = 3).

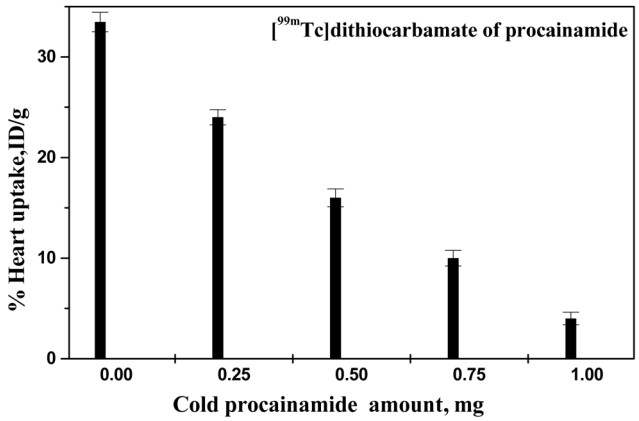

Fig. 8. [^{99m}Tc]dithiocarbamate of procainamide complex inhibition heart uptake in normal male Swiss Albino mice at 5 min p.i. (%ID/g ± SD, *n* = 5).

3. RESULTS AND DISCUSSION

3.1 Evaluation of Percentage Radiotracer and the Purity of Labeled Compound [^{99m}Tc]dithiocarbamate of Procainamide Complex

The most of colloid impurities such as ^{99m}Tc -tin-colloid, technetium dihydroxide, stannous dihydroxide, or technetium tetrahydroxide were eliminated using a 0.22 μm Millipore filter. There are four main species, [^{99m}Tc]nitride core, [^{99m}Tc]dithiocarbamate of procainamide complex, [$^{99m}TcO_4$]$^-$ and the rest colloid ($^{99m}TcO_2 \cdot nH_2O$) radiochemical yield % were estimated using the TLC method described in earlier reports [21 – 23]. In the first mobile phase (saline), free pertechnetate, colloid (if any, $^{99m}TcO_2 \cdot nH_2O$) and the complex ([^{99m}Tc]dithiocarbamate of procainamide complex) remained at the origin, Rf 0 – 0.1 but the intermediate core ([^{99m}Tc]nitride core) emigrated at the front, Rf 0.7 – 0.1. In the second mobile phase (methanol: chloroform,1:9 v/v), the complex ([^{99m}Tc]dithiocarbamate of procainamide complex) emigrated at the front, Rf 0.9 – 0.1, but the free pertechnetate, ([$^{99m}TcO_4$]$^-$), colloid, if any ($^{99m}TcO_2 \cdot nH_2O$) and intermediate core ([^{99m}Tc]nitride core) remained at the origin, Rf 0 – 0.1. Additionally, the purity of the radiotracer, [^{99m}Tc]dithiocarbamate of procainamide complex and its core was also confirmed by HPLC data [100 – 106]. The purity of the core intermediate ([^{99m}Tc]technetium-nitride core) was more than 99% at Rt value of 1.88 min, whereas the Rt value of free pertechnetate was 4.5 min (Fig. 3). On the other hand, the R_t value of [^{99m}Tc]dithiocarbamate of procainamide complex and the free pertechnetate were 9.5 and 4.6 min, respectively (Fig. 4).

3.2. Reaction Optimization

Parameters affecting the labeling process were completely optimized to provide the maximum radiolabeling yield at ambient temperature. As shown in Fig. 5, the high radiolabeling yield of the complex (98.5%) was observed with substrate concentrations of 100 μg of procainamide and 7.6 MBq of [^{99m}Tc]nitride core considering the rest of factors were kept constant [31 – 33]. Furthermore, pH of the reaction mixture was regarded as a crucial parameter in the radiolabeling process and pH 8 was found to be optimum for this process (Fig. 6), potentially through improving the stability of the [^{99m}Tc]dithiocarbamate of procainamide complex. The effective reaction time (Fig. 7) was also verified and investigated. In which the period of 30 min yielded a maximum radiolabeling yield of 98.5% without being noticeably improved by raising the response time above the optimum (30 min). Additionally, the radiolabeling yield was greatly increased up to a maximum of 50 μg of tin(II) content (optimum content) to produce 98.5%. Excess tin(II) content greater than 50 μg may lead to the formation of an undesirable colloid. Ultimately, the in vitro stability of [^{99m}Tc]dithiocarbamate of procainamide complex was investigated in rat serum. The radiotracer, [^{99m}Tc]dithiocarbamate of procainamide complex, was shown to be stable for 8 h with no discernible alteration. After 12 h, the purity reached 96%, and then dropped to 95% after 24 h [21 – 23].

3.3. Study of Sodium Channel Blocking

Procainamide (250 – 1000 μg) was utilized to pre-dose animals with unlabeled procainamide 5 min before the injection of labeled [^{99m}Tc]dithiocarbamate of procainamide complex, which reduced heart uptake from 33.47 to 5% ID/g organ at 5 min p.i.. The thermally tagged molecule, [^{99m}Tc]dithiocarbamate of procainamide complex, binds specifically with sodium channel blocker in the heart. As a consequence

of this research, [^{99m}Tc]dithiocarbamate of procainamide complex can be successfully used for imaging sodium channel blocker in mice (Fig. 8).

3.4. Biodistribution Study

Table 1 shows the biodistribution of [^{99m}Tc]dithiocarbamate of procainamide complex in various organs and fluids of normal mice. All radioactivity levels are expressed as an average percent-injected dose per organ tissue (% ID/g organ ± S.D). The kidneys' uptake was found to be 25.12% at 60 min and reduced to 6.42% at 3 h p.i. [39, 40]. In addition, the liver uptake was found to be 8.12% at 60 min and reduced to 3.12% at 3 h p.i.. Therefore the labeled compound, [^{99m}Tc]dithiocarbamate of procainamide complex, was excreted mainly through hepatobiliary and urinary pathways [41 – 43]. The radiotracer, [^{99m}Tc]dithiocarbamate of procainamide complex, is distributed rapidly in most organs (blood, heart, lungs, liver, intestine, kidneys, heart, stomach, etc.) at 5 min p.i.. The uptake of heart was 33.47% at 5 min p.i. and remained high to 25.11% at 30 min p.i. and reduced to 4.27% at 3 h p.i., which was higher compared to ^{99m}Tc-procainamide [20] and represented overcoming of the first defect. In addition, the stomach absorption of [^{99m}Tc]dithiocarbamate of procainamide complex was 1.19% at 5 min p.i. and remained low during 3 h p.i., to give 0.95% p.i., which indicates that [^{99m}Tc]dithiocarbamate of procainamide complex is more in vivo stability than ^{99m}Tc-procainamide [20] which had stomach absorption of 10.5 ± 0.5% ID/g at 120 min p.i., which represented overcoming of the second defect. The heart-to-liver ratios of [^{99m}Tc]dithiocarbamate of procainamide complex was 8.12, 5.56, 4.05, 1.19, 1.39 and 1.37% at 5, 15, 30, 60, 120 and 180 min p.i., respectively. Additionally, the heart-to-lungs ratios of [^{99m}Tc]dithiocarbamate of procainamide complex was 9.90, 12.41, 13.22, 6.64, 5.98, and 3.85% at 5, 15, 30, 60, 120 and 180 min p.i; respectively. In comparison with ^{99m}Tc-procainamide [20] radiotracer, it was found that our radiotracer, [^{99m}Tc]dithiocarbamate of procainamide complex had higher ratios of heart-to-liver and heart-to-lungs ratios as reported for the first 30 min. Firstly, the heart-to-liver ratio of ^{99m}Tc-procainamide gave 2.98, 2.60, 2.40, 2.06, 0.95, and 0.49% at 5, 10, 15, 30, 60, and 120 min p.i., respectively. Secondly, the heart-to-lungs ratio of ^{99m}Tc-procainamide gave 4.63, 4.81, 5.13, 6.38, 5.40, and 3.62% at 5, 10, 15, 30, 60, and 120 min p.i., respectively. This comparison suggested that the proposed complex [^{99m}Tc]dithiocarbamate of procainamide is superior to ^{99m}Tc-procainamide [20] complex in heart-to-liver and -lungs ratios. According to the findings of this investigation, the labeled compound, [^{99m}Tc]dithiocarbamate of procainamide complex, has a higher % ID/g organ ± S. D value than other materials [7 – 9].

4. CONCLUSION

The labeled molecule, [^{99m}Tc]dithiocarbamate of procainamide complex, has been improved for production in high yield to achieve optimum radiolabeling purity (98.5%) and higher stability in rat serum. According to biodistribution experiments in mice, the radiotracer, [^{99m}Tc]dithio-

TABLE 1. Biodistribution of [^{99m}Tc]dithiocarbamate of Procainamide Complex (Mean ± SD, n = 5) in Normal Mice at Various Time Points

Organs	% I. D./g at various times post injection					
	5 min	15 min	30 min	60 min	120 min	180 min
Blood	11.19 ± 0.18	6.39 ± 0.18	4.15 ± 0.33	3.27 ± 0.27	1.15 ± 0.06	0.98 ± 0.04
Bone	1.16 ± 0.05	1.15 ± 0.03	1.12 ± 0.08	1.11 ± 0.06	0.99 ± 0.02	0.90 ± 0.00
Muscle	2.99 ± 0.28	3.11 ± 0.07	3.88 ± 0.17	4.15 ± 0.13	2.48 ± 0.12	1.11 ± 0.13
Brain	1.22 ± 0.09	1.18 ±0.29	1.12 ± 0.17	1.11 ± 0.08	0.92 ± 0.00	0.85 ± 0.00
Lungs	3.38 ± 0.16	2.19 ± 0.41	1.90 ± 0.12	1.46 ± 0.12	1.19 ± 0.18	1.11 ± 0.22
Heart	33.47 ± 0.83	27.15 ± 0.73	25.11 ± 0.62	9.69 ± 0.39	7.12 ± 0.44	4.27 ± 0.28
Liver	4.12 ± 0.76	4.88 ± 0.29	6.20 ± 0.13	8.12 ± 0.82	5.11 ± 0.76	3.12 ± 0. 82
Kidneys	3.26 ± 0.22	9.63 ± 0.52	16.88 ± 0.51	25.12 ± 0.19	17.39 ± 0.82	6.42 ± 0.91
Spleen	1.19 ± 0.08	1.17 ± 0.06	1.10 ± 0.05	1.00 ± 0.04	0.98 ± 0.00	0.90 ± 0.00
Intestine	3.61 ± 0.33	3.98 ± 0.15	5.11 ± 0.11	6.17 ± 0.72	5.10 ± 0.12	3.15 ± 0.29
Stomach	1.19 ± 0.09	1.17 ± 0.07	1.11 ± 0.08	1.00 ± 0.05	0.98 ± 0.00	0.95 ± 0.00
Heart/Blood	2.88 ± 0.05	4.25 ± 0.08	6.10 ± 0.11	2.96 ± 0.12	6.19 ± 0.17	4.36 ± 0.18
Heart/Lungs	9.90 ± 0.32	12.41 ± 0.42	13.22 ± 0.52	6.64 ± 0.72	5.98 ± 0.24	3.85 ± 0.36
Heart/ Liver	8.12 ± 0.43	5.56 ± 0.29	4.05 ± 0.22	1.19±0.02	1.39 ± 0.10	1.37 ± 0.08

Mean ± SD (mean of five experiments)

carbamate of procainamide complex, has a high heart absorption of 33.47 % ID/g at 5 min p.i. and continues to be high for the next 30 min, giving 25.11%. This ID/organ value is greater than that of newly found agent of ^{99m}Tc-procainamide [20]. Therefore, the radiotracer [^{99m}Tc]dithiocarbamate of procainamide complex might be considered a new possible selective radiotracer for preclinical diagnostic studies and procainamide labeled with ^{99m}Tc combined with SPECT can be used.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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