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Application of ^{99}Mo/^{99m}Tc alumina generator in the labeling of metoprolol for diagnostic purposes

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Labeling of metoprolol by technetium-99m in pertechnetate form ($^{99m}TcO_4^-$) eluted from a ^{99}Mo/^{99m}Tc alumina generator in the presence of stannous chloride dihydrate was carried out via chelation reaction. The reaction parameters that affect the labeling yield such as metoprolol concentration, stannous chloride dihydrate concentration, reaction temperature, and pH of the reaction mixture were studied to optimize the labeling conditions. Using 1 GBq $^{99m}TcO_4^-$, 500 μg metoprolol as substrate dissolved in 500 μL phosphate buffer at pH 9 and 50 μL of stannous chloride as reducing agent (1 mg/mL) at 25°C for 30 min reaction time, a maximum radiochemical yield of ^{99m}Tc-metoprolol (92%) was obtained. ^{99m}Tc-metoprolol was characterized by thin layer chromatography (TLC) and by high pressure liquid chromatography (HPLC). The specific activity of ^{99m}Tc-metoprolol obtained was 888 MBq/1.88 mmol. The biological distribution in normal mice showed that ^{99m}Tc-metoprolol is rapidly concentrated after injection in the heart, which indicates its suitability for heart imaging.

Keywords: metoprolol; labeling; technetium-99m; ^{99}Mo/^{99m}Tc alumina generator

Introduction

The ^{99}Mo/^{99m}Tc generator was introduced for clinical application.[1] The vital role of ^{99m}Tc in the field of diagnostic nuclear medicine is well established.[2–7] The evolution of diagnostic nuclear medicine can be principally attributed to the existence and chemical adaptability of ^{99m}Tc, the ideal radiotracer, which is used predominantly in one form or another in nuclear medicine. The nuclear properties of ^{99m}Tc include its 140 keV gamma photon emission with 89% abundance, which is ideal for imaging with gamma cameras in nuclear medicine, its half-life of 6 h, which is suitable for preparing the radiopharmaceutical, performing its quality control, and injecting into the patient for imaging studies, and it is short enough to minimize the absorbed radiation dose. Rapid growth in this field in the last few decades is attributable, apart from its ideal radionuclidic characteristics, to the conception and development of the labeling process for novel ligands.

The highest oxidation state (VII) of technetium is occupied by a pertechnetate anion (TcO_4^-), which is eluted from the ^{99}Mo/^{99m}Tc alumina generator. The chemical reactivity of the pertechnetate anion is negligible; it does not bind directly to any ligand. Thus, reduction to lower oxidation states in the presence of a suitable ligand is a prerequisite for the synthesis of ^{99m}Tc-labeled molecules. During reduction, the ligand stabilizes the lower oxidation state. The so-called coordination complexes of technetium are formed by means of bonds between technetium acting as Lewis acid and atoms or functional groups acting as Lewis bases (they donate electron pairs). The pertechnetate in acid medium (pH 2.5) is reduced to a lower oxidation state by using $SnCl_2$ as a commonly used reducing agent and in the presence of ligands[8]; for example, dimethyl succinic acid (DMSA), the coordination characteristics of the ^{99m}Tc(III)-DMSA complex is used for renal scintigraphy,[9] while at elevated pH (pH 7.5–8), a ^{99m}Tc-DMSA complex coordinated as a Tc(V) oxocore[10] was accumulated in the skeleton,[11] so the reduction at high pH usually does not release all oxygen atoms, leading to complexes in which a TcO^{3+} core exists.[12]

Metoprolol is a beta-adrenergic blocking agent,[13] blocking the action of the sympathetic nervous system,[14] a portion of the involuntary nervous system, proved its importance in medicine as a drug for high blood pressure and treatment of chest pain (angina pectoris) related to coronary artery disease. It is also useful in slowing and regulating certain types of abnormally rapid heart rates. Other uses for metoprolol include the prevention of migraine headaches and the treatment of certain types of tumors.[15] On the other hand, it represents a novel ligand for labeling by technetium-99m to study its importance in nuclear medicine especially for diagnostic purposes.

The present work deals with the labeling of metoprolol by ^{99m}Tc and the factors that affect the labeling yield were investigated. The labeled compound was separated by HPLC and the biodistribution study in normal mice was performed.

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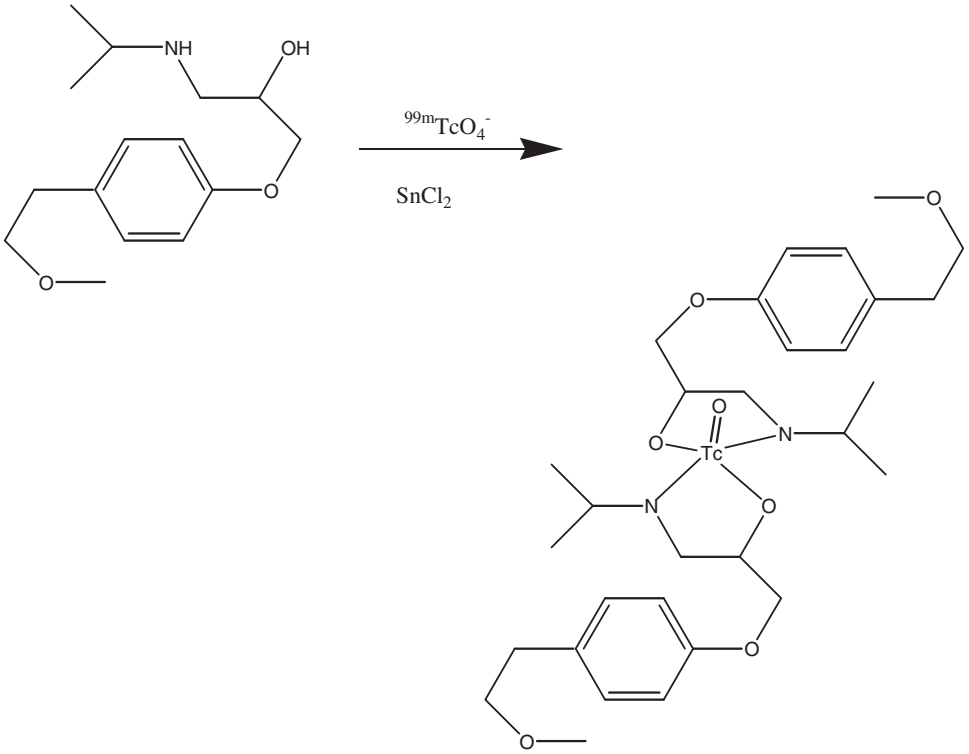

Scheme 1. The presumbale structure of ^{99m}Tc-metoprolol.

The presumable structure of ^{99m}Tc-metoprolol via reaction of metoprolol with $^{99m}TcO_4^-$ in the presence of stannous chloride dihydrate at pH 9 at room temperature is shown in Scheme 1, where ^{99m}Tc forms a complex with two molecules of metoprolol.

Results and discussion

Quality control on the eluted technetium-99m

Radiochemical purity of the ^{99m}Tc eluates was studied by the ascending paper chromatography method. Figure 1 shows a radiochromatogram of the ^{99m}Tc eluate obtained from the spent ^{99}Mo/^{99m}Tc alumina generator (~1.8 GBq) by passing 10 mL 0.9% NaCl solution through the column at a flow rate of 0.5 mL/min at 25°C. Figure 1 shows one R_f value of ~0.67 corresponding to the pertechnetate, $^{99m}TcO_4^-$, species. Radiochemical purity of the ^{99m}Tc eluted from the alumina column was found to be 97.6 % as $^{99m}TcO_4^-$. The pH value of the ^{99m}Tc eluates was measured using a pH meter and was always found to be in the neutral range that is physiologically acceptable.[16]

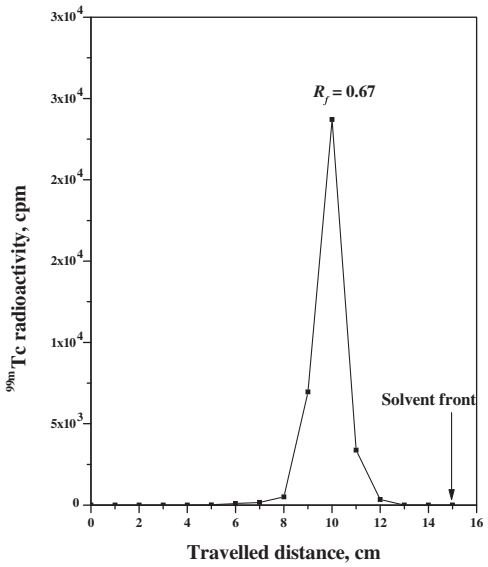

Figure 1. Radiochromatogram of the ^{99m}Tc eluate from 3 g Alumina column (1 cm i.d.) loaded with ^{99}Mo and eluted with 10 ml 0.9% NaCl solution at flow rate of 0.5 ml/min.

Labeling of metoprolol by technetium-99m

Effect of metoprolol amount

The radiochemical yield of ^{99m}Tc-metoprolol, as a function of metoprolol concentration in the presence of stannous chloride dihydrate as a reducing agent, was studied as shown in Figure 2. The results clarify that the radiochemical yield of ^{99m}Tc-metoprolol increased from 85 to 92% by increasing the amounts of metoprolol from 100 to 500 μg. The amount of metoprolol higher than 500 μg has no effect on the labeling yield. This may be attributed to the fact that the ligand amount of metoprolol at 100 μg is insufficient to shift completely the complex formation equilibrium towards the final complex (Tc/L = 1/2), while 500 μg can shift it with higher efficiency. Increase in the amount of metoprolol above 500 μg does not modify substantially the yields.

Effect of stannous chloride dihydrate amount

For contributing most of technetium-99m to increase the labeling yield of radiophamaceuticals, $SnCl_2.2H_2O$ remained the best

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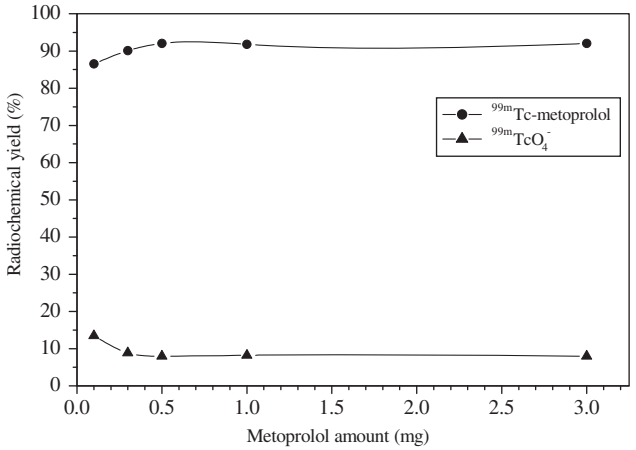

Figure 2. Variation of the radiochemical yield of ^{99m}Tc-metoprolol as a function of metoprolol concentration [10 μL (10 MBq) TcO_4^- + 500 μL (x μg) metoprolol in phosphate buffer + 50 μL (50 μg) stannous chloride] at 25°C, pH 9 and 30 min reaction time.

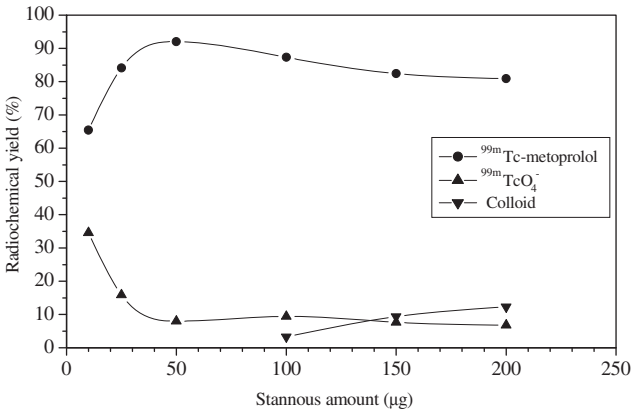

Figure 3. Variation of the radiochemical yield of ^{99m}Tc-metoprolol as a function of stannous concentration [10 μL (10 MBq) TcO_4^- + 50 μL (500 μg) metoprolol in phosphate buffer + 50 μL (× μg) stannous chloride] at 25°C, pH 9 and 30 min reaction time.

reducing agent for reduction of ^{99m}Tc from (VII) to lower valence state, which facilitates its chelation by compounds of diagnostic importance. The influence of stannous chloride amount on the labeling process was studied as shown in Figure 3. The experiment was carried out by adding different volumes of nitrogen purged stannous chloride dihydrate solution to the solution of metoprolol and pertechnetate in closed penicillin vial (10 mL) kept under positive nitrogen gas pressure. The results clarify that the labeling yield increased from 65 to 92% by increasing the amount of stannous chloride ($SnCl_2.2H_2O$) from 10 to 50 μg. By increasing the stannous chloride amount more than 50 μg, the labeling yield decreased. This may be due to the fact that most of the ligand molecules were consumed in the formation of complexes, so the pertechnetate is reduced to insoluble technetium (IV) $TcO_2.xH_2O$ in the absence of ligand[17] or due to the fact that the excess amount of stannous chloride leads to the formation of stannous hydroxide colloid $Sn(OH)_3^-$ in basic medium[18] as the very high Sn(II) concentration increases the reduction reaction rate to colloid formation so that it becomes more competitive with respect to the complexation reaction thus decreasing the labeling yields. Most of the radiochemical impurities found are colloids equal to 12.3%.

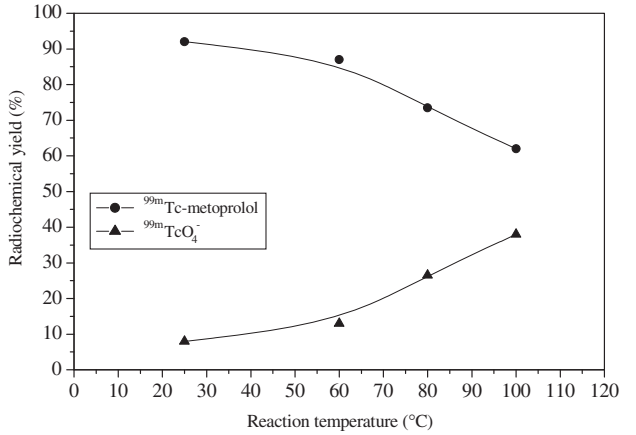

Figure 4. Variation of the radiochemical yield of ^{99m}Tc-metoprolol as a function of reaction temerature [10 μL (10 MBq) TcO_4^- + 50 μL (500 μg) metoprolol in phosphate buffer + 50 μL (50 μg) stannous chloride] at x°C, pH 9 and 30 min reaction time.

Table 1. Effect of the reaction time on the radiochemical yield of ^{99m}Tc- metoprolol at 25°C

Reaction time (min)	Radiochemical yield	
	^{99m}Tc-metoprolol	$^{99m}TcO4^-$
5	43	57
10	55	45
20	76	24
30	92	8
60	91.8	8.2
120	92	8

Effect of reaction temperature

The labeling of metoprolol by technetium-99m was carried out by studying the effect of reaction temperature (25–100°C) in the presence of stannous chloride dihydrate as reducing agent at pH 9 within 30 min reaction time. The results are shown in Figure 4. The reaction temperature is a significant factor that has a harmful effect on the labeling yield, where the maximum radiochemical yield of ^{99m}Tc-metoprolol was obtained at room temperature (25°C) and gradually decreased from 92 to 62% by raising the reaction temperature from 25 to 100°C. This can be related to the increasing rate of side decomposition reactions.

Effect of reaction time

The radiochemical yield of ^{99m}Tc-metoprolol was studied at different reaction times (5–120 min) in the presence of stannous chloride dihydrate as a reducing agent at pH 9 and 25°C reaction temperature as shown in Table 1. It is clear that the labeling yield increased from 43 to 92% by increasing the reaction time from 5 to 30 min. The radiochemical yield reaches the saturation value and is not affected by increasing the reaction time above 30 min.

Effect of pH of the reaction mixture

The data presented in Table 2 reflect the results obtained from the labeling of metoprolol with technetium-99m at different pH values. The results confirm the influence of pH of the reaction

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mixture on the radiochemical yield of ^{99m}Tc-metoprolol. The percentage of ^{99m}Tc-metoprolol increased gradually with increasing the pH up to 9 to give a labeling yield of 92% at 25°C within 30 min. By increasing the pH of the reaction medium above pH 9 the yield of ^{99m}Tc- metoprolol slightly decreased and reached 87% at pH 11. At low pH (pH 2.5), the low values of the labeling yield may be attributed to the formation of unstable ^{99m}Tc-metoprolate complexes, which decompose after destroying the reductive medium. At high pH (pH 9), the labeling yield increased to 92%, which may be attributed to the deprotonation of the metoprolol that is surely present at high pH values and increased the stability of $TcO(V)(Metoprolate)_2$ complex. Higher OH^- concentration could be responsible for the partial hydrolysis of the complex and oxidation of Tc(V) to pertechnetate.

In vitro *stability of ^{99m}Tc-metoprolol*

The stability of ^{99m}Tc-metoprolol was studied in order to determine the suitable time for injection to avoid the formation of the undesired products that result from the radiolysis of the labeled compound. These undesired radioactive products may be accumulated in non-target organs. Table 3 clarifies the stability of ^{99m}Tc-metoprolol. The results show that ^{99m}Tc-metoprolol is stable up to 12 h.

Table 2. Effect of pH of the reaction medium on the radiochemical yield of ^{99m}Tc-metoprolol

pH value	^{99m}Tc-metoprolol (%)	$^{99m}TcO_4^-$ (%)
2	45.5 ± 0.2	54.5 ± 3.2
4	79.3 ± 0.5	20.7 ± 2.2
6	89.4 ± 0.8	10.6 ± 0.2
9	92 ± 1.0	8.0 ± 1.6
11	87 ± 1.3	13.0 ± 1.4

Table 3. Stability of ^{99m}Tc-metoprolol

Time (h)	Percentage purity (%)
1	91.8
2	92.0
4	91.9
6	92.4
12	91.3

Biodistribution of ^{99m}Tc-metoprolol

In vivo biodistribution studies were performed using four groups of albino mice each group contains six mice. Each animal was injected in the tail vein with 0.2 mL solution containing 40 MBq of ^{99m}Tc-metoprolol. The mice were kept in metabolic cages for the required time. Each group was sacrificed by cervical dislocation at the recommended time (15 min, 1, 12 or 24 h) after injection. Organs or tissues of interest were removed, washed with saline, weighted and counted. Correction was made for background radiation and physical decay during the experiment. The weights of blood, bone and muscles were assumed to be 7, 10 and 40% of the total body weight, respectively.

Blood was the site of the greatest uptake of ^{99m}Tc-metoprolol at 15 min post-intravenous injection. At that time, heart and lung were the organs of great uptake compared with other organs. This may be attributed to the fact that they are rich with beta receptors.[14] Also the rapid uptake of ^{99m}Tc-metoprolol in kidney may indicate that excretion will be done in urine, this means that ^{99m}Tc-metoprolol is hydrophilic agent, like atenolol, which are excreted unchanged by the kidney.[19] Rapid decline of ^{99m}Tc-metoprolol uptake in blood, while slowly in heart and lung was observed after 1 h post-injection. Organs like kidney, stomach, bone and muscle showed significant increase in ^{99m}Tc-metoprolol uptake at 1 h compared with its uptake at 15 min post-injection. At 12 and 24 h post-injection, the majority of organs showed significant decrease in ^{99m}Tc-metoprolol uptake. These results revealed that ^{99m}Tc metoprolol is rapidly concentrated after injection in the heart and this reflects the possibility of imaging the heart using this labeled compound as shown in Table 4.

Experimental

Materials

Metoprolol was kindly presented from the Egyptian International Pharmaceutical Industries Company (EIPICO), Egypt.

Table 4. Biodistribution of ^{99m}Tc-metoprolol in normal mice

	% ^{99m}Tc-metoprolol/gram organ Time post injection			
Organs & Body fluids	15 min	1 h	12 h	24 h
Blood	27.5 ± 1.10	14.1 ± 0.4	4.1 ± 0.1	2.2 ± 0.15
Bone	3.00 ± 0.15	5.3 ± 0.15	2.4 ± 0.15	1.8 ± 0.17
Muscle	3.25 ± 0.09	4.4 ± 0.02	1.1 ± 0.01	0.7 ± 0.04
Liver	6.70 ± 0.25	6.4 ± 0.2	1.6 ± 0.06	1.1 ± 0.07
Lung	14.50 ± 0.10	11.6 ± 0.04	4. 0 ± 0.1	2 .5 ± 0.1
Heart	22.00 ± 0.30	17.4 ± 0.40	5.4 ± 0.1	2.4 ± 0.12
Stomach	4.50 ± 0.10	7.4 ± 0.9	8.1 ± 0.6	5.0 ± 0.5
Intestine	3.20 ± 0.15	6.7 ± 0.07	5.40 ± 0.1	3.90 ± 0.2
Kidney	8.10 ± 0.40	15.4 ± 0.1	6.01 ± 0.1	1.2 ± 0.06
Spleen	2.50 ± 0.10	1.5 ± 0.01	0.5 ± 0.01	0.4 ± 0.0
Urine	4.00 ± 0.02	10 ± 0.04	60.1 ± 0.06	78.2 ± 0.05

Values represent mean ± SEM, $n = 6$.

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All chemicals used in the present work were of analytical grade.

Elution of the ^{99}Mo/^{99m}Tc alumina generator

No carrier added ^{99m}Tc solution was obtained by elution of a spent 'Mon Tek' ^{99}Mo/^{99m}Tc alumina generator by washing with 10 ml of 0.9% NaCl solution. The eluted ^{99m}Tc solution was directly analyzed to investigate the radiochemical purity and radionuclidic purity before its use.

Quality control on the eluted ^{99m}Tc

Radionuclidic purity

The radioactivity of ^{99}Mo/^{99m}Tc radionuclides was identified and determined using a HPGe detector of efficiency 25% (CANBERRA), high voltage power supply model CANBERRA 3106D, spectroscopy amplifier coupled to multichannel analyzer, and a gamma-vision software used for analyzing the measured gamma ray spectra at 140.5, 181.1, 740 and 778 keV gamma-ray energy peaks. The gross gamma radioactivity was measured using a counter (Nucleus Model 2010) connected with a well type NaI (Tl) crystal.

Radiochemical purity

Radiochemical purity of the ^{99m}Tc eluates was determined by the ascending paper chromatography method using a strip of 'Whatman No. 1' paper chromatography (30 cm long and 5 cm wide) and a solution of 85% methanol as the developing solvent.

Labeling of metoprolol by technetium-99m

A specific amount of metoprolol (500 μg) dissolved in 500 μL phosphate buffer at pH 9, 50 μL of freshly prepared deoxygenated aqueous solution of stannous chloride dihydrate (1 mg/mL; 4.4 mM) and sodium pertechnetate (1–1.5 GBq) were introduced and mixed in sterile and under positive nitrogen gas pressure glass vial, closed with a rubber stopper and an aluminum cap. The mixture was agitated in a vortex mixer and left to react at room temperature (25°C) for 30 min. The factors that affect the labeling yield like metoprolol amount (100–3000 μg; 0.75–22.5 mM), stannous chloride amount (10–200 μL of 1 mg/mL), reaction temperature (25–100°C), reaction time (5–120 min) and pH of the reaction mixture (2–11) were studied to optimize the reaction conditions.

Quality control on the ^{99m}Tc-metoprolol

Radiochemical yield and purity

The radiochemical yield and purity were determined by thin layer chromatography (TLC) and high performance liquid chromatography (HPLC).

TLC analysis

The radiochemical yield of ^{99m}Tc-metoprolol complex was determined according to the following:

(1) The percentage of reduced hydrolyzed technetium-99m ($RH^{99m}TC$) and stannous hydroxide colloids were determined by filtration of the reaction mixture through 0.22 μm millipore filter by using a suitable pressure and according to the following equation:

$$\% \text{ colloids} = \frac{\text{Activity before filtration} - \text{Activity after filtration}}{\text{Total activity}} \text{X100}$$

(2) TLC-SG sheets were marked 2 cm from the base and lined into fragments 1 cm each up to 14 cm using non-pointed pencil. A spot (5 μL) from the reaction mixture obtained after 0.22 μm millipore filtration was applied using micropipette, and then the sheet was developed in an ascending manner in a closed jar containing the developing solvent of methyl ethyl ketone (MEK) or 0.9% NaCl. The sheets after complete development were removed, dried, and cut into strips, each strip is 1 cm width, and then the strips were counted in a well type ã-counter. Free $^{99m}TcO_4^-$ moves with the solvent front ($R_F = 1$), while ^{99m}Tc-metoprolol complex remains at the origin ($R_F = 0$). The percent labeling yield was calculated as follows:

$$\% \text{ Free pertechnetate} = \frac{\text{activity of pertechnetate}}{\text{Total activity}} \text{X100}$$

$$\% \text{ Radiochemical yield} = 100 - (\% \text{ colloid} + \% \text{ free}^{99m}TcO^{-}4)$$

HPLC analysis

The radiochemical purity of ^{99m}Tc-metoprolol was determined by direct injection of 5–10 μl, of the reaction mixture at the optimum conditions for obtaining the highest radiochemical yield, into HPLC with stationary phase comprising a reversed phase Nucleosil phenyl column (250 mm × 4.6 mm, 5 μm) using methanol: H_2O (70: 30 v/v) as a mobile phase with a flow rate of 1 mL/min. The labeled compound was collected by using a fraction collector and its activity was counted by using a well type NaI (Tl) crystal connected with single channel analyzer. The free pertechnetate was separated at retention time 2 min and metoprolol at 4.5 min, while the labeled compound (^{99m}Tc-metoprolol) at 6.5 min as shown in Figure 5.

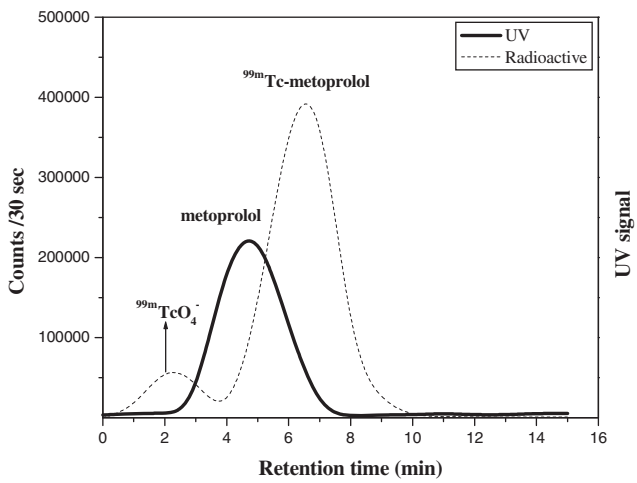

Figure 5. High performance liquid chromatography elution profile of metoprolol, separated on reversed phase column nucleosil (250 mm × 4.6 mm, 5 μm) at a flow rate of 1 mL/min.

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Methodology

Animals

Male Swiss Albino mice weighing 20–25 gm were used. The animals were kept at constant environmental and nutritional conditions throughout the experimental period and kept at room temperature (25 ± 2)°C with a 12 h on/off light schedule.

Conclusion

The pH has a vital role in the expected mechanism for the labeling of metoprolol in the presence of stannous chloride as reducing agent, where at relatively high pH (pH 9), stannous chloride could reduce ^{99m}Tc(VII) into ^{99m}Tc(V), which facilitates its introduction in the oxocore form into the cheleator (metoprolol) to form the expected complex to reach the maximum yield (92%) at 25°C and 30 min reaction time, while at low pH, low labeling yield was obtained. The labeled compound was injected in normal mice for studying the biological distribution that clarifies the utility of ^{99m}Tc-metoprolol for heart imaging.

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