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Chromatographic Separation and Utilization of labeled ^{99m}Tc-Valsartan for Cardiac Imaging

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Abstract: *A procedure was developed for preparing high radiochemical purity ^{99m}Tc-valsartan with yield of 98 %. The complex was prepared by mixing of valsartan with SnCl2.2H2O solution and the pH of the mixture was adjusted to 8 then mixed with a freshly eluted $^{99m}TcO_4^-$ (~ 400MBq), shacked at room temperature for 30 min. The radiochemical yield and purity of the labeled product were determined individually by HPLC, paper chromatography and paper electrophoresis. Biodistribution studies were carried out in normal Albino Swiss mice at different time intervals after administration of ^{99m}Tc-valsartan. The labeled compound cleared from the systematic circulation within 2 h after administration, and the majority of organs showed significant decrease in the uptake of ^{99m}Tc-valsartan. The heart uptake of ^{99m}Tc- valsartan was sufficiently high for using this agent as myocardial imaging agent.*

Key Words: *^{99m}Tc- valsartan / Heart / Losartan /Chromatographic /Analysis / Biodistribution.*

I. Introduction

Valsartan is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including the class to which this drug principally belongs. There are no controlled trials in hypertensive patients demonstrating risk reduction with Diovan. Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Valsartan is chemically N-(1-Oxopentyl)-N-[[2'-(1H-tetrazol- 5-yl) [1, 1'-biphenyl]-4-yl] methyl]-L-valine Fig. 1[1-2] .Valsartan is potent Angiotensin II receptor blocker. It is mainly used as anti-hypertensive drug. [3-4].

Technetium-99m (^{99m}Tc) is one of the most desirable radionuclides for external imaging in diagnostic nuclear medicine, due to the emission of gamma ray of optimal energy (140 keV), a suitable half-life (6 h), and availability from ^{99}Mo-^{99m}Tc generator systems. In addition, development of ^{99m}Tc radiopharmaceuticals for tumor imaging paves the way for therapeutic radiopharmaceuticals with high energy beta emitters ^{186}Re and ^{188}Re because of similar chemical properties between technetium and rhenium.

The present study was mainly oriented to develop a simple method for ^{99m}Tc labeling of valsartan. The influence exerted on the reaction rate such as hydrogen ion concentration, substrate and reducing agent amounts, and reaction time have been examined to ensure high radiochemical yield of pure ^{99m}Tc- valsartan.

II. Experimental

2.1 Materials.

Valsartan was gift from Sigma Company for Pharmaceutics. All other chemicals were purchased from Merck and they were reactive grade. The water used is purged with nitrogen gas to give deoxygenated bidistilled water.

2.2 Apparatus.

Well-type γ-scintillation counter: Scalar Ratemeter SR7 (Nuclear Enterprises Ltd., USA); pH meter: model 601 A digital ion analyzer (Orion Research, USA); ionization chamber: model CRC-15R (Capintec, USA); precision electronic balance: model HA 120 (MAD Company Ltd., Japan); stirring hot plate: model 210 T Thrmix (Fisher, USA); electrophoresis apparatus: E.C. Corporation (USA)

2.3 Labeling Method of Valsartan.

Accurately weighed 2 mg valsartan was dissolved ethanol and transferred to an evacuated penicillin vial. Exactly 50µg SnCl2.2H2O solution was added and the pH of the mixture was adjusted to 8 using 0.1N NaOH, then the volume of the mixture was adjusted to one ml by N_2-purged distilled water. One ml of freshly

eluted $^{99m}TcO4^-$ (~ 400MBq) was added to the above mixture. The reaction mixture was vigorously shaken and allowed to react at room temperature for 30 min to complete the reaction [5, 6].

This experiment was conducted to study the different factors that affect the labeling yield such as tin content as (SnCl2.2H2O), substrate content, pH of the reaction medium, and reaction time. For labeling process, trials were performed for each factor under investigations to obtain the optimum value. The experiment was repeated with all factors kept at optimum values except the factor under study, till the overall optimal conditions are achieved [7].

2.4 Separation methods and recovery of 99mTc- valsartan complex.

2.4.1 Paper Chromatography

Radiochemical yield of 99mTc- valsartan was checked by paper chromatographic method in which, the reaction product was spotted on ascending paper chromatography strips (10×1.5 cm). Free 99mTcO4- in the preparation was determined using acetone as the mobile phase. Reduced hydrolyzed technetium was determined by using ethanol: water: ammonium hydroxide mixture (2:5:1) or 5N NaOH as the mobile phase.

After complete development, the strips were dried then cut into 0.5cm pieces and counted in a well-type γ-scintillation counter. The radiochemical purity was determined by subtracting the sum of the percent of reduced hydrolyzed technetium and free pertechnetate from 100 %. The radiochemical yield is the mean value of five experiments.

2.4.2 Electrophoresis Conditions

Electrophoresis was done with EC-3000 p-series programmable (E.C.apparatus corporation) power and chamber supply units using cellulose acetate strips. The strips were moistened with 0,05 M phosphate buffer pH 7.2±0.2 then introduced in the chamber. 99mTc- valsartan was passed through a Millipore filter (0.22 μm) to separate colloids, if present .Samples (5μl) were applied at a distance of 10 cm from the cathode. The radioactivity values were evaluated at the applied voltages 300 V and standing time, one and half hours. Developed strips were dried and cut into1 cm segments and counted by a well-type NaI scintillation counter. The radiochemical yield was calculated as the ratio of the radioactivity of the labeled product to the total radioactivity.

2.4.3 HPLC analysis

HPLC analysis of valsartan solution was done by injection of 10□ l from the reaction mixture into the column (RP-18-250 mmx4.6 mm, 5□ m, LiChrosorb) built in HPLC Shimadzu model which consists of pumps LC-9A, Rheohydron injector and UV spectrophotometer detector (SPD-6A) adjusted to the 225 nm wavelength. The column was eluted with a mobile phase phosphate buffer (1%): acetonitrile (40:60 v/v, pH 3.2), as at flow rate 1.0 ml/min . Fractions of 1ml were collected separately using a fraction collector up to 15 ml and counted in a well-type-□-scintillation counter. [8].

2.5 Stability of ^{99m}Tc- valsartan

The stability of 99mTc- valsartan was studied in vitro by mixing 1.8ml of normal human serum and 0.2ml of 99mTc- valsartan and incubated at 37°C for 24 hrs. Exactly 0.2 ml aliquots were withdrawn during the incubation at different time intervals up to 24 hrs and subjected to paper chromatography for determination of the percent of 99mTc- valsartan, reduced hydrolyzed technetium and free pertechnetate.

2.6 Animal studies

The study was approved by the animal ethics committee, Labeled Compound Department, and was in accordance with the guidelines set out by the Egyptian Atomic Energy Authority. For the infection model the animals, Swiss Albino mice (25-30 gm), were intravenously injected with 100 μl (100–150 MBq) of sterile 99mTc- valsartan, adjusted to physiological pH via the tail vein and kept alive in metabolic cage for different intervals of time under normal conditions. For quantitative determination of organ distribution, five mice were used for each experiment and the mice were sacrificed at different time post-injection. Samples of fresh blood, bone and muscle were collected in pre-weighed vials and counted. The different organs were removed, counted and compared to a standard solution of the labeled valsartan. The average percent values of the administrated dose/organ were calculated. Blood, bone and muscles were assumed to be 7, 10 and 40 %, respectively, of the total body weight [9]. Corrections were made for background radiation and physical decay during experiment. Differences in the data were evaluated with the Student t test. Results for P using the 2-tailed test are reported and all the results are given as mean ± SEM. The level of significance was set at $P< 0.05$.

III. Results and Discussion

3.1 Separation Performance.

In paper chromatographic method, free $^{99m}TcO_4^-$ moved with the solvent front (Rf =1), while ^{99m}Tc-valsartan and reduced hydrolyzed technetium remained at the point of spotting. After elution reduced hydrolyzed technetium remains at the origin (Rf = 0) while other species migrate with the solvent front (Rf =1).

The paper electrophoresis pattern revealed that ^{99m}Tc- valsartan complex moved towards the anode, indicating that valsartan has partially negative charge by lone pairs of nitrogen atoms while $^{99m}TcO_4^-$ moved sharply toward the anode, suggesting that it has completely ionized negative charge.

HPLC chromatogram was presented in Fig. 2 and shows two peaks, one at fraction No. 3, which corresponds to $^{99m}TcO_4^-$ **,** while the second peak was collected at fraction No. 6.4 for ^{99m}Tc- valsartan which was found to coincide with the UV signal.

3.2 Factors Affecting the Labeling Yield.

3.2.1 Effect of $SnCl_2.2H_2O$ concentration.

As shown in Fig. 3, the radiochemical yield is highly dependent on the amount of SnCl2.2H2O present in the reaction mixture. At 25 µg SnCl2.2H2O, the labeling yield of 99mTc- valsartan was 77.5 % due to the fact that SnCl2.2H2O concentration was insufficient to reduce all pertechnetate so the percentage of 99mTcO4- was relatively high (19.0 %).The labeling yield significantly increased by increasing the amount of SnCl2.2H2O from 25 to 50 µg (optimum content), at which a maximum labeling yield of 98 % was obtained. By increasing the amount of SnCl2.2H2O above the optimum concentration value, the labeling yield decreased again because the excess SnCl2.2H2O was converted to colloid (51.2 % at 200 µg SnCl2.2H2O) [10-12].

3.2.2 Effect of valsartan amount

As shown in Fig.4 ,the labeling yield of ^{99m}Tc- valsartan complex was 70.0 % at 1 mg valsartan and increased with increasing the amount of valsartan till reaching the maximum value of 98 % at 2 mg .The formed complex remained stable with increasing the amount of valsartan up to10 mg. So the optimum amount of valsartan was kept at 2 mg [13, 14].

2.2.3 Effect of pH of the reaction mixture

The results in Fig. 5 demonstrated that at pH 4 the labeling yield of ^{99m}Tc- valsartan complex was relatively low reaching to 60.0 % .The yield increased with increasing the pH of the reaction mixture where at pH 8 gave the maximum labeling yield of 98 %. By increasing the pH greater than 8, the labeling yield decreased again till it became 45.8 % at pH 10 where colloid material becomes the main impurity (40.5 % at pH 10). After pH 10 more colloidal solutions are formed [15].

2.2.4 Effect of reaction time

Figure 6 describes the effect of reaction time on the radiochemical purity of ^{99m}Tc- valsartan complex. At 1 min post labeling, the yield was relatively moderate reached to 86.0 % which increased with time till reaching to its maximum value of 98 % at 30 min. The yield remains stable at 98.2 % for a time up to 2 hrs [16].

3.3. Stability Test

As shown in Figure 7, in-vitro stability of ^{99m}Tc- valsartan was studied in order to determine the suitable time for injection to avoid the formation of the undesired products that result from the decomposition of the complex. These undesired radioactive products might be accumulated in non-target organs. The results of stability test showed that the ^{99m}Tc- valsartan is stable for 24 hours at 37^{o}C resulted in a small release of radioactivity (n = 5 experiments) from the ^{99m}Tc- valsartan. The results was determined by paper chromatography which showed that the stability decreased from 98 to 92.0% [17**].**

3.4. Biodistribution of ^{99m}Tc- valsartan in normal mice.

Biodistribution experiments showed that ^{99m}Tc– valsartan was distributed rapidly in blood, heart, kidneys, liver and intestine at 15 min post injection. After 1 h, the ^{99m}Tc-valsartan uptake significantly decreased in blood, kidneys and intestine (Table 1). The heart uptake was 9.1, 11.2, and 5.9 % ID/g at 15 min, 30 min, and 1 h, respectively. This uptake may be useful for radioimaging of the heart. Thus, this procedure for ^{99m}Tc labeling of valsartan at room temperature (25 ± 1°C) in reasonable time (30 min) using $SnCl_2 \cdot 2H_2O$ as a reducing agent at pH 8 has been successively examined with high yield reached to 98 %. The biodistribution of labeled valsartan in normal mice reflects the rapid heart uptake which is higher than that of ^{99m}Tc–losrtan (Tables 2) [18-22] which have maximum heart uptake of (8.2 % at 15 min) .The uptake percent of ^{99m}Tc–valsartan is sufficient for myocardial imaging.

Table(1): Biodistribution of ^{99m}Tc– valsartan in normal mice.

Organs &body fluids	Percent I.D./gram organ Time post injection			
	15 min	**1/2 hr**	**1 hr**	**2 hr**
Blood	14.9 ±0.19	11.8 ± 0.80	5.8 ± 0.29	2.7 ± 0.44
Bone	1.9 ± 0.78	2.7 ± 0.64	2.8± 0.19	1.8 ± 0.09
Muscle	0.87 ± 0.01	1.2 ± 0.02	1.3 ± 0.13	1.15± 0.11
Liver	4.9 ± 0.18	9.7 ± 0.17	6.1 ±0.48	2.8 ± 0.39
Lung	3.5 ± 0.16	2.18 ± 0.33	2.21 ± 0.31	1.9 ± 0.02
Heart	9.1 ± 0.12	11.2 ± 0.27	5.9 ± 0.32	2.4 ± 0.41
Stomach	2.8 ± 0.29	2.9 ± 0.16	1.5 ± 0.16	0.9 ± 0.01
Intestine	4.1 ± 0.17	5.8 ± 0.28	2.3 ± 0.13	1.4± 0.12
Kidney	8.3 ± 0.20	13.4 ± 0.39	5.9 ± 0.23	3.1 ± 0.13
Spleen	1.2± 0.02	1.5 ± 0.13	1.0 ± 0.11	1.3 ± 0.20

Mean ± SD (mean of five experiments).

Table (2): Biodistribution of ^{99m}Tc--losartan in normal mice.

Organs &body fluids	Percent I.D./gram organ Time post injection			
	15 min	**1/2 hr**	**1 hr**	**2 hr**
Blood	12.2 ±1.10	11.6 ± 0.20*	7.2 ± 0.04*	3.7 ± 0.30*
Bone	2.0 ± 0.05	3.2 ± 0.10*	2.3 ± 0.10*	2.2 ± 0.2
Muscle	0.5 ± 0.01	1.5 ± 0.02*	1.3 ± 0.10	0.7 ± 0.02*
Liver	5.1 ± 0.05	6.5 ± 0.15*	3.5 ± 0.06*	2.0 ± 0.02*
Lung	4.3 ± 0.10	6.5 ± 0.12*	3.2 ± 0.20*	2.1 ± 0.01*
Heart	8.2 ± 0.80	6.9 ± 0.30*	5.2 ± 0.01*	1.8 ± 0.04*
Stomach	5.2 ± 0.90	7.2 ± 0.60	7.6 ± 0.16*	7.7 ± 0.2
Intestine	5.4 ± 0.50	7.2 ± 0.30*	3.1 ± 0.10*	1.9 ± 0.03*
Kidney	6.9 ± 0.40	9.0 ± 0.600	4.1 ± 0.30*	2.1 ± 0.06*
Spleen	1.7 ± 0.02	3.1 ± 0.14*	3.0 ± 0.16	1.1 ± 0.20*

Mean ± SD (mean of 10 experiments).
*significantly different from the previous value of each organ using unpaired Student's t-test ($P<0.05$).

IV. Conclusion

Valsartan can be labeled easily with ^{99m}Tc using 50 µg stannous chloride ($SnCl_2.2H_2O$) as a reducing agent and 2 mg valsartan at pH 8 for 30 min at room temperature to give ^{99m}Tc- valsartan complex with a radiochemical yield of 98 %. Biodistribution studies showed that, the uptake of ^{99m}Tc- valsartan in the heart (11.2 % ±0.20) at 30 min post injection is higher than that of ^{99m}Tc–losrtan (8.2 % ±0.80) at 15 min post injection. Furthermore, ^{99m}Tc- valsartan could be considered as a novel radiopharmaceutical for heart imaging.

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List of Fig.

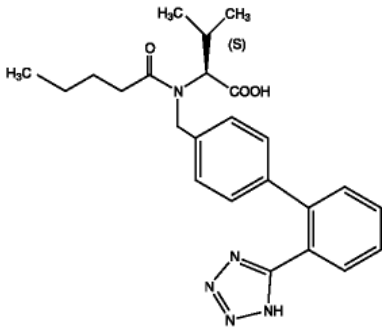

Figure 1. Chemical structure of valsartan ((S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol- 5-yl) - biphenyl-4- methyl] amine)

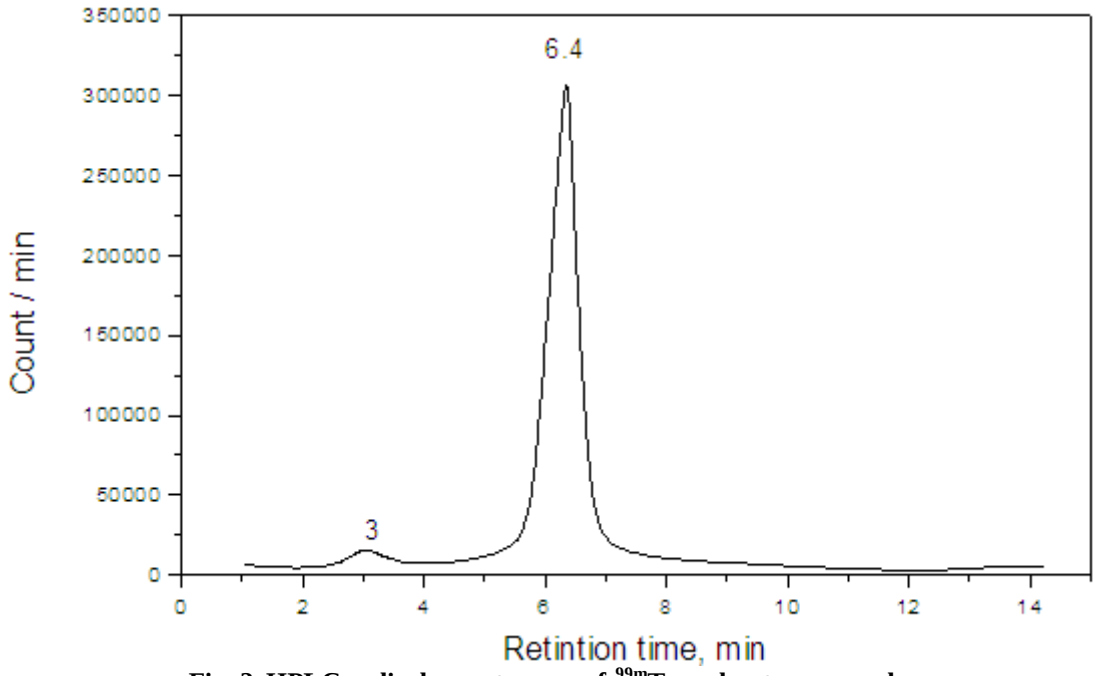

Fig. 2. HPLC radiochromatogram of ^{99m}Tc- valsartan , complex

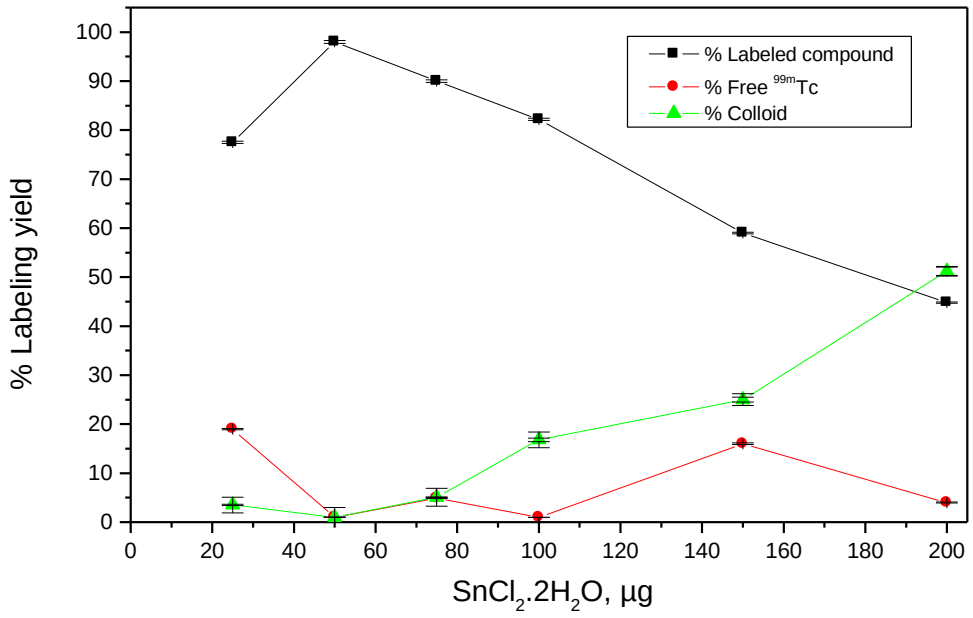

Fig. 3. Effect of Sn (II) content on the labeling yield of ^{99m}Tc- valsartan, complex. Conditions: 2mg valsartan, 25-200 µg Sn (II), pH 8 and 30 min.reaction time, n=3

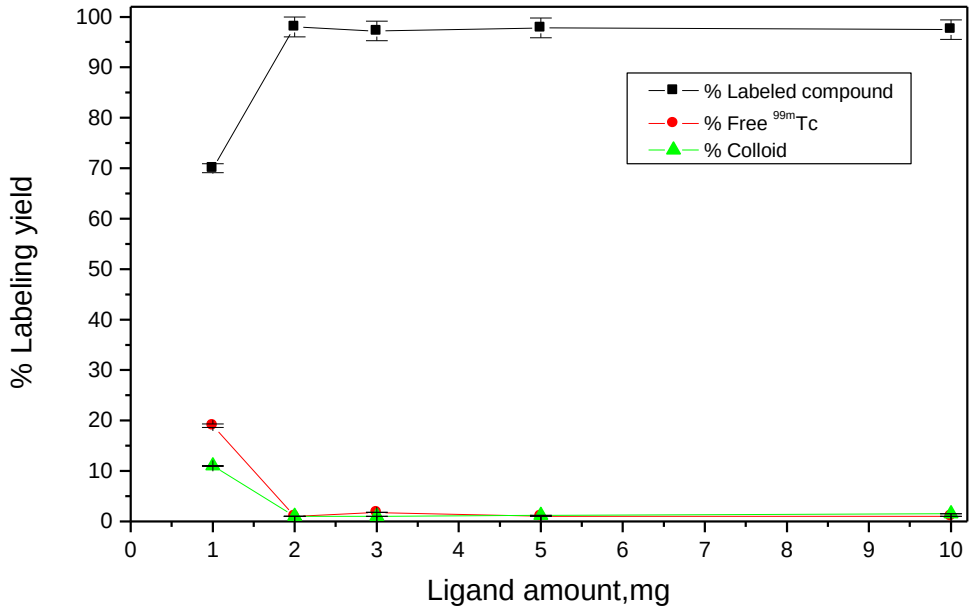

Fig.4. Effect of valsartan concentration on the labeling yield of ^{99m}Tc- valsartan complex. Conditions: 1-10 mg of valsartan**, 50 µg Sn (II), pH 8 and 30 min.reaction time, n=3**

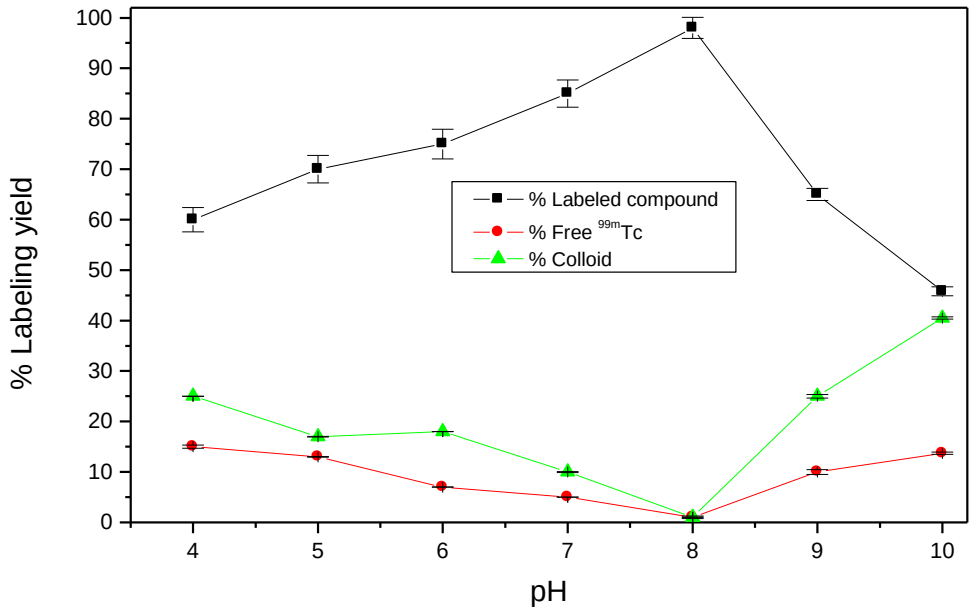

Fig. 5. Effect of pH on the labeling yield of ^{99m}Tc- valsartan complex. Conditions: 2 mg valsartan, 50 µg Sn (II), pH 4-10 and 30 min.reaction time, n=3

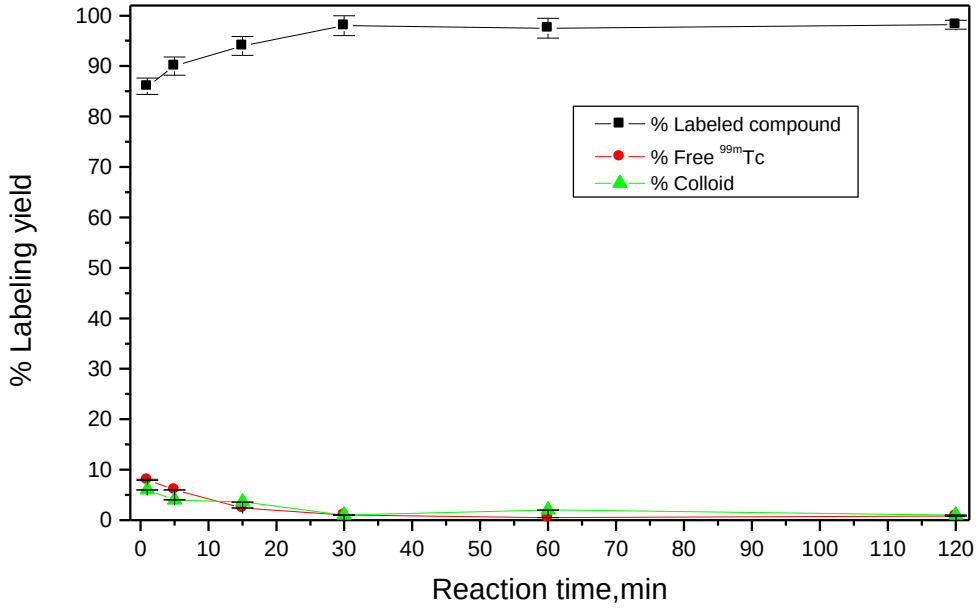

Fig.6: Effect of reaction time on the labeling yield of ^{99m}Tc - valsartan complex. Conditions: 2 mg valsartan, 50µg Sn(II), pH= 8, the 1-120 min. reaction time, n=3

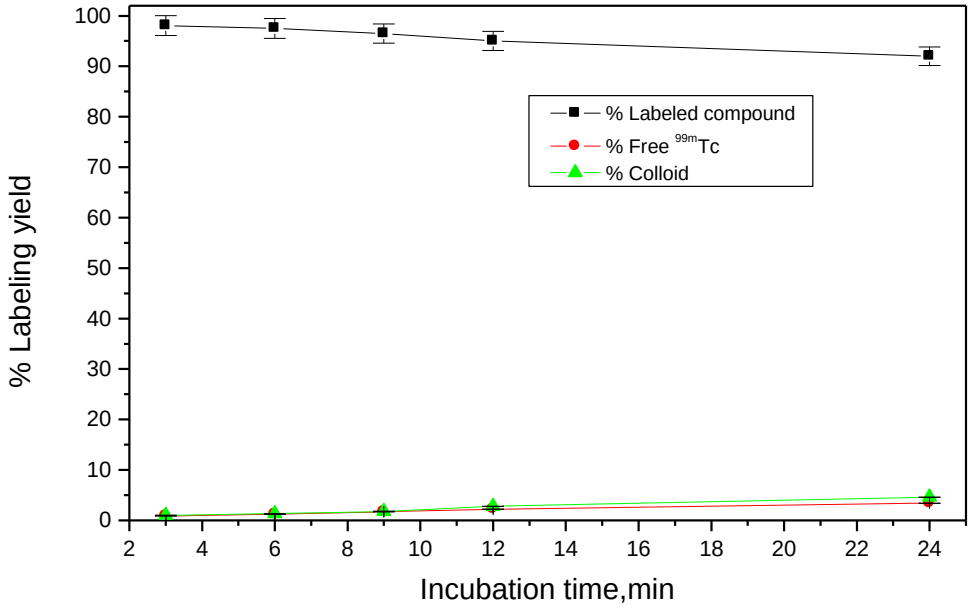

Fig. 7. In vitro stability of ^{99m}Tc- valsartan in normal serum at optimum conditions

List of Tables:
Table(1): Biodistribution of ^{99m}Tc– valsartan in normal mice.
Table (2): Biodistribution of ^{99m}Tc--losartan in normal mice.

Table(1): Biodistribution of ^{99m}Tc– valsartan in normal mice.

Organs &body fluids	Percent I.D./gram organ Time post injection			
	15 min	1/2 hr	1 hr	2 hr
Blood	14.9 ±0.19	11.8 ± 0.80	5.8 ± 0.29	2.7 ± 0.44
Bone	1.9 ± 0.78	2.7 ± 0.64	2.8± 0.19	1.8 ± 0.09
Muscle	0.87 ± 0.01	1.2 ± 0.02	1.3 ± 0.13	1.15± 0.11
Liver	4.9 ± 0.18	9.7 ± 0.17	6.1 ±0.48	2.8 ± 0.39
Lung	3.5 ± 0.16	2.18 ± 0.33	2.21 ± 0.31	1.9 ± 0.02
Heart	9.1 ± 0.12	11.2 ± 0.27	5.9 ± 0.32	2.4 ± 0.41
Stomach	2.8 ± 0.29	2.9 ± 0.16	1.5 ± 0.16	0.9 ± 0.01
Intestine	4.1 ± 0.17	5.8 ± 0.28	2.3 ± 0.13	1.4± 0.12
Kidney	8.3 ± 0.20	13.4 ± 0.39	5.9 ± 0.23	3.1 ± 0.13
Spleen	1.2± 0.02	1.5 ± 0.13	1.0 ± 0.11	1.3 ± 0.20

Mean ± SD (mean of five experiments).

Table (2): Biodistribution of ^{99m}Tc--losartan in normal mice.

Organs &body fluids	Percent I.D./gram organ Time post injection			
	15 min	1/2 hr	1 hr	2 hr
Blood	12.2 ±1.10	11.6 ± 0.20*	7.2 ± 0.04*	3.7 ± 0.30*
Bone	2.0 ± 0.05	3.2 ± 0.10*	2.3 ± 0.10*	2.2 ± 0.2
Muscle	0.5 ± 0.01	1.5 ± 0.02*	1.3 ± 0.10	0.7 ± 0.02*
Liver	5.1 ± 0.05	6.5 ± 0.15*	3.5 ± 0.06*	2.0 ± 0.02*
Lung	4.3 ± 0.10	6.5 ± 0.12*	3.2 ± 0.20*	2.1 ± 0.01*
Heart	8.2 ± 0.80	6.9 ± 0.30*	5.2 ± 0.01*	1.8 ± 0.04*
Stomach	5.2 ± 0.90	7.2 ± 0.60	7.6 ± 0.16*	7.7 ± 0.2
Intestine	5.4 ± 0.50	7.2 ± 0.30*	3.1 ± 0.10*	1.9 ± 0.03*
Kidney	6.9 ± 0.40	9.0 ± 0.600	4.1 ± 0.30*	2.1 ± 0.06*
Spleen	1.7 ± 0.02	3.1 ± 0.14*	3.0 ± 0.16	1.1 ± 0.20*

Mean ± SD (mean of 10 experiments).
*significantly different from the previous value of each organ using unpaired Student's t-test (P<0.05).