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Preliminary Assessment of ^{99m}Tc-Salmeterol Xinafoate as a Potential Bone Imaging Agent

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Abstract: Sameterol xinafoate is a selective β2-adrenoceptor agonist used in the treatment of some lung diseases and play a vital role in the regulation of bone mass and bone turnover. ^{99m}Tc-salmeterol was formulated for the development of a novel potential diagnostic bone imaging agent with excellent biological properties. Factors influencing the labeling yield such as salmeterol xinafoate amount, pH of the reaction medium, reducing agent amount and the reaction time were studied in details. ^{99m}Tc-salmeterol was obtained with a high radiochemical yield of 94.6±0.5% and *in vitro* stability of 6 h when 0.5 mg of salmeterol was mixed with 10 mg $NaBH_4$ at pH 9 and a reaction time 30 min. The biological distribution showed that ^{99m}Tc-salmeterol was highly concentrated in the bone (36.5 ± 2%ID/organ) at 30 min post injection. The bone uptake of ^{99m}Tc-salmeterol was remained high (29.3 ± 2ID/organ) for a time up to 2h post injection. The results revealed that ^{99m}Tc-salmeterol could solve the ^{99m}Tc-phosphonate drawbacks and could be used as a bone imaging agent.

Keywords: Biodistribution, Bone, Imaging, Salmeterol xinafoate, Technetium-99m.

INTRODUCTION

Radionuclide bone imaging is one of the most useful clinical methods for assessing different bone diseases in the whole body and characterized by its high sensitivity and relatively low specificity [1 - 3]. In the last decades, the use of compounds labeled with radioactive isotopes for the skeletal imaging in the medical field has great interest. This nuclear medicine technique can detect cancerous cells, evaluate fractures in the bones and monitor other bone conditions such as infections, arthritis. Also it can detect cancer that has metastasized to the bone from different primary sites, such as the breast, prostate or lungs. It may also be used to evaluate the bone health before treatment [4 - 6].

Several ^{99m}Tc-labeled bone-imaging agents, ^{18F}-labeled NaF and ^{68}Ga-labeled compounds were widely used for skeletal scintigraphy [7 - 10].

Methylene diphosphonate (MDP) and hydroxy-methylene diphosphonate (HMDP) were labeled easily with technetium-99m to be widely used as radiopharmaceuticals for bone imaging [11 - 13]. The most drawbacks of these commercially available skeletal imaging agents were an interval of 2– 6 h is needed between the injection and bone imaging [14]. Decreasing the interval time of patient examination would decrease the burden on both the patients and the medical staff, the total length of the examination and the dose of radiation absorbed.

For a good imaging at an earlier time post injection, a radiopharmaceutical with a higher bone uptake is required [15]. Consequently the nature of the organic compounds (pharmaceuticals) is an important factor that determines the advantages of the radiopharmaceuticals for the skeletal imaging [14, 16]. Thus, the choice of the most adequate

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pharmaceutical for bone targeting must depend on not only the complex formation properties (high labeling yield and stability), but also its biological properties (high bone uptake, *in vivo* stability and short time interval required for imaging). On the other hand, the pharmacological modulators of β-adrenoceptors play a vital role in the bone mineral density and fracture risk [17]. Some studies reported that the β2-adrenoceptor agonists influence bone resorption by regulating the expression of RANK-L (receptor activator of nuclear factor kβ ligand) on osteoclast [17 - 19]. Other studies showed that the β-adrenoceptor antagonists inhibit bone resorption [20, 21]. Depending on these findings, it was found the modulators of β-adrenoceptors play an important pharmacological efficacy in the regulation of bone mass and bone turnover. Also, salmeterol xinafoate has been developed as a selective β2-adrenoceptor agonist having the desired pharmacological profile of a long-acting bronchodilator [22 - 25].

For the purpose of developing new bone imaging agent with excellent biological properties, a new non-phosphonate β2-agonist compound (salmeterol xinafoate) (Fig. **1**) was labeled with technetium-99m and its biological properties was investigated.

The aim of this study is assessing efficiently the performance labeling yield of salmeterol xinafoate with technetium-99m efficiently and studying the factors affecting the labeling yield in details. Moreover, this study revealed the biodistribution of ^{99m}Tc-salmeterol xinfoate and evaluated it as a useful radiotracer used for *in-vivo* bone imaging.

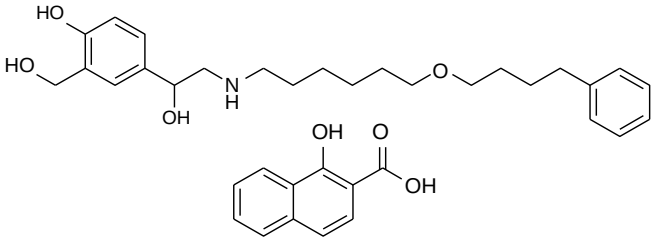

Fig. (1). Salmeterol xinfoate.

EXPERIMENTAL

All of the chemical reagents were of analytical reagent grade and bidistilled water was used for solution preparation. Salmeterol xinafoate was obtained as a gift from King Saud University. Albino Swiss mice, each of 20–25 g were used for the biological distribution study. A NaI(Tl) γ-ray scintillation counter (Scaler Ratemeter SR7, Nuclear Enterprises, Edinburgh, UK) was used for the measurement of γ-ray radioactivity.

Preparation of ^{99m}Tc-Salmeterol Xinafoate Complex

Labeling Procedure

Exactly 0.5 mg of salmeterol xinafoate dissolved in ethanol (1mL) was separately transferred to penicillin vials. Exactly 10 mg of $NaBH_4$ was added to each vial along with different amounts of NaOH (0.1 N) or HCl (0.1 N) to adjust the pH value in a range of 3-12. Then, freshly eluted $^{99m}TcO_4^-$ (400 MBq) (1mL) was added to each vial. The reaction mixtures were left at room temperature for 30 min. The same procedure was repeated with varying $NaBH_4$ amounts (2-20 mg), varying salmeterol amounts (0.1-1 mg) at different reaction times (1-360 min).

Radiochemical Yield of ^{99m}Tc-Salmeterol Xinafoate Complex

The labeling yield percent of the labeled ^{99m}Tc-salmeterol xinafoate complex was determined using the ascending paper chromatographic technique. Strips of Whatman No.1 paper chromatography (Whatman International Ltd, Maidstone, Kent, UK) of 13 cm long and 0.5 cm wide were marked at a distance of 2 cm from the lower end and lined into sections, 1 cm each up to 10 cm. A spot from ^{99m}Tc-salmeterol xinafoate complex solution was applied using hypodermic syringe and then the strip was developed in an ascending manner in a closed jar. The used developing solvent was acetone. After complete development, the strip was dried and cut into fragments, 1 cm each. Then the sections were assayed in a NaI(Tl) γ-ray scintillation counter.

In Vitro Stability of ^{99m}Tc-Salmeterol Complex

The *In vitro* stability of ^{99m}Tc-salmeterol xinafoate complex was investigated as a function of time up to 6 h after labeling.

Biodistribution Studies in Animals

Experiments were performed using the procedure that was approved by the animal ethics committee and was in accordance with the guidelines set out by the Egyptian Atomic Energy Authority. Male Albino Swiss mice weighing 20-25 g were used. The biodistribution of the ^{99m}Tc-salmeterol xinafoate complex was evaluated in male Albino Swiss mice (body mass 25-30 g). For the quantitative determination of organ distribution, five mice were used for each experiment and 0.1 mL of about 18 MBq of ^{99m}Tc-salmeterol solution was injected into the tail vein of mice. Then the mice were anesthetized and blood was obtained by cardiac puncture. Samples of fresh blood, bone and muscle were collected in pre-weighed vials and counted. The different organs were removed, counted and compared with a standard solution of the labeled salmeterol. 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 [26]. Corrections were made for the background radiation and the physical decay during the experiment [27].

RESULTS AND DISCUSSION

Radiolabeling of ^{99m}Tc-Salmeterol Xinafoate Complex

Using the ascending paper chromatographic technique, the radiochemical purity of the formed ^{99m}Tc-salmeterol xinafoate complex was checked by using acetone as a developing solvent where free ^{99m} TcO_4^- was moved with the solvent front (R_f = 1), while^{99m}Tc-salmeterol xinafoate complex remained at the point of spotting. The radiochemical yield is the mean value of three experiments.

Effect of Ligand Concentration

As shown in Fig. (**2**), the labeling yield of ^{99m}Tc-Salmeterol xinafoate complex was low (62.8%) at 0.1 mg salmeterol because the amount of salmeterol is not enough to form complex with all of the reduced technetium-99m [28] and the yield was increased with increasing the amount of salmeterol till reaching the maximum value of 94.6% at 0.5 mg. The amount of salmeterol at 0.5 mg was sufficient enough to form ^{99m}Tc-salmeterol xinafoate complex with a high labeling yield. The labeling efficiency remained stable even with increasing the amount of salmeterol xinafoate above 0.5 mg.

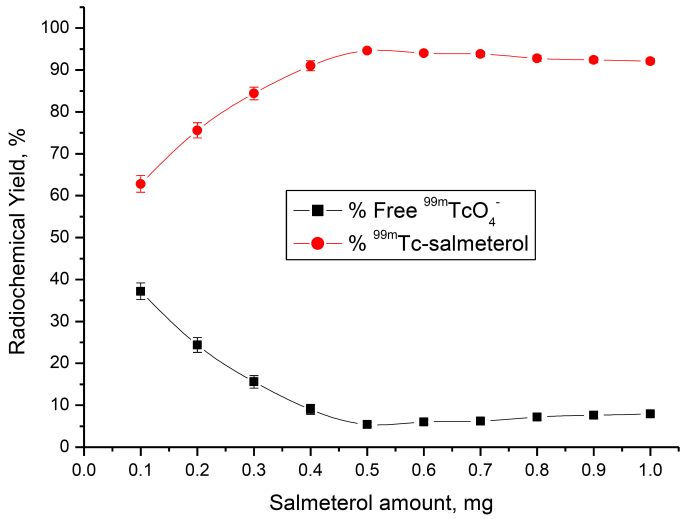

Fig. (2). Radiochemical yield of ^{99m}Tc-salmeterol xinafoate as a function of salmeterol xinafoate amount. Reaction conditions: Xmg salmeterol xinafoate, 10 mg of $NaBH_4$, pH 9, 1 mL(~400 MBq) of $^{99m}TcO_4$– solution, room temperature, 30 min.

Effect of $NaBH_4$ Concentration

The effect of $NaBH_4$ amount was summarized in Fig. (**3**). The data showed that the radiochemical yield was dependent on the amount of $NaBH_4$ present in the reaction mixture. At $NaBH_4$ of 2 mg, the labeling yield of ^{99m}Tc-salmeterol xinafoate was 45.3% because $NaBH_4$ concentration was insufficient to reduce all pertechnetate so the

percentage of $^{99m}TcO_4^-$ was relatively high (54.7%). The labeling yield was significantly increased by increasing the amount of $NaBH_4$ where the maximum labeling yield of 94.6% was obtained at 10 mg $NaBH_4$. By increasing the amount of $NaBH_4$ above the optimum concentration value, the labeling yield decreased again (85% at 20 mg $NaBH_4$).

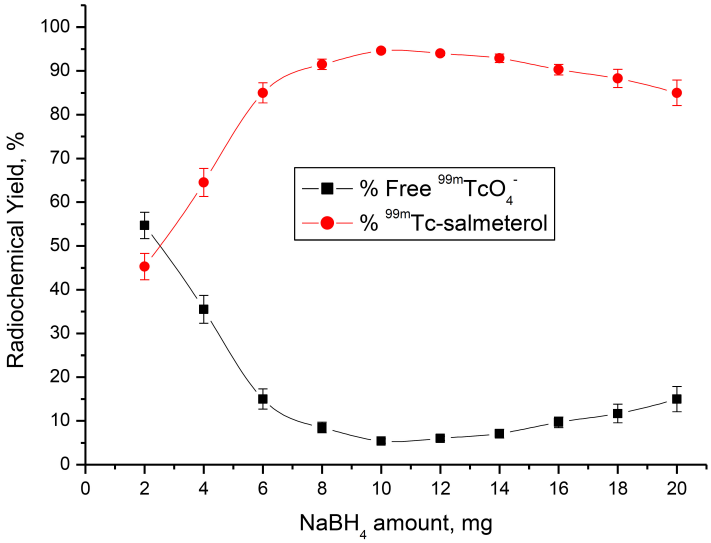

Fig. (3). Radiochemical yield of ^{99m}Tc-salmeterol xinafoate as a function of $NaBH_4$ amount. Reaction conditions: 0.5 mg salmeterol xinafoate, X mg of $NaBH_4$, pH 9, 1 mL(~400 MBq) of $^{99m}TcO_4$–solution, room temperature, 30 min.

Effect of pH

Radiochemical yield of ^{99m}Tc-salmeterol xinafoate complex was affected by changes in the pH values as graphically illustrated in Fig. (**4**). The maximum yield was obtained at pH 9. At pH 3, the radiochemical yield was low (8.9%) compared to 94.6% at pH 9. At pH 12, the labeling yield of ^{99m}Tc-salmeterol complex was relatively low and equal to 89.5%.

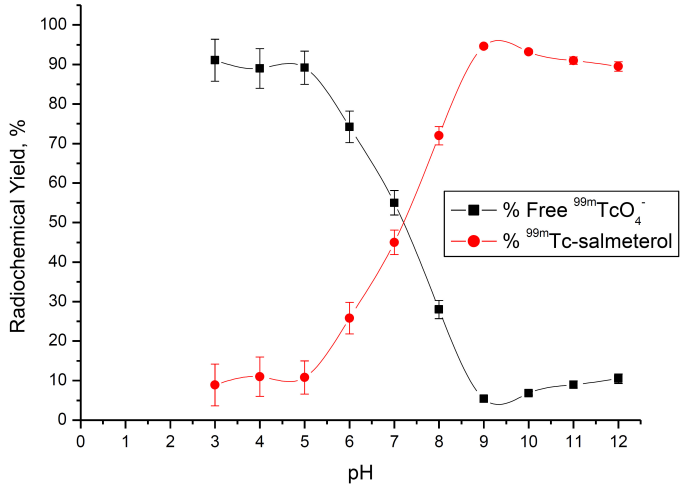

Fig. (4). Radiochemical yield of ^{99m}Tc-salmeterol xinafoate as a function of pH amount. Reaction conditions: 0.5 mg salmeterol xinafoate, 10 mg of $NaBH_4$, pH = X, 1 mL(~400 MBq) of $^{99m}TcO_4$– solution, room temperature, 30 min.

Effect of Reaction Time

Fig. (**5**) describes the labeling yield of ^{99m}Tc-salmeterol xinafoate complex at different reaction times. At 5 min reaction time, the percentage of ^{99m}Tc-salmeterol complex was relatively small and equal to 85%, this may be because the time required for the reaction between the reduced ^{99m}Tc and salmeterol xinafoate was not enough to give the

maximum labeling yield. The labeling yield increased with time till reaching its maximum value of 94.6% at 30 min. So, 30 min is the optimum reaction time required to obtain the maximum labeling yield.

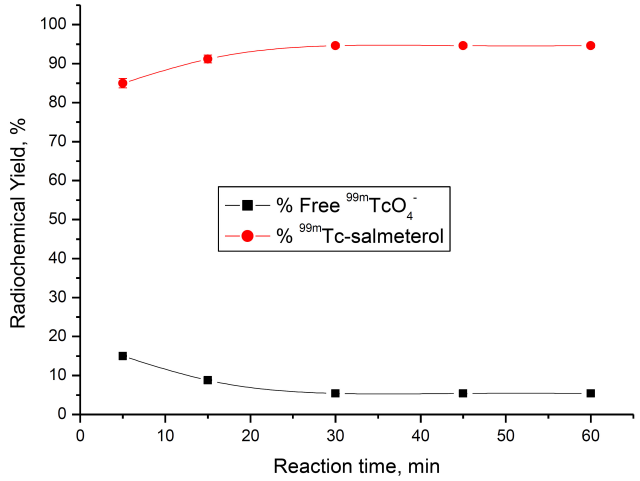

Fig. (5). Radiochemical yield of ^{99m}Tc-salmeterol xinfoate as a function of the reaction time. Reaction conditions: 0.5 mg salmeterol,10 mg of $NaBH_4$, pH = 9, 1 mL(~400 MBq) of $^{99m}TcO_4$– solution, room temperature, X min reaction time.

In Vitro Stability

The stability of ^{99m}Tc-salmeterol xinafoate 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 the non-target organs [29]. The results showed that ^{99m}Tc-salmeterol complex is stable at ~94% up to 6 h, as shown in Fig. (**6**).

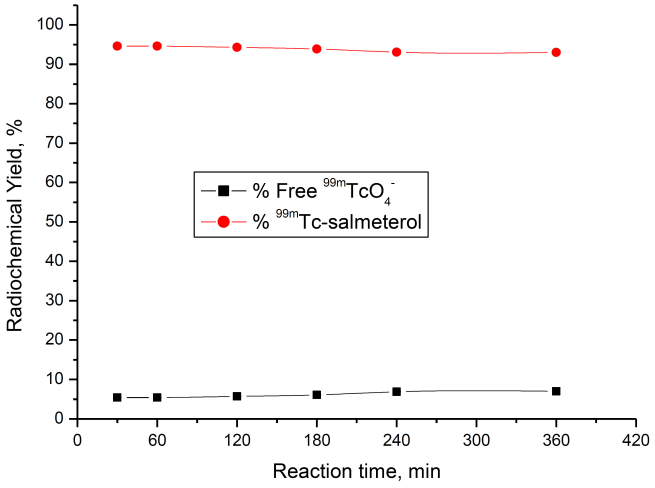

Fig. (6). Radiochemical yield of ^{99m}Tc-salmeterol as a function of the reaction time. Reaction conditions: 0.5 mg salmeterol,10 mg of NaBH4, pH = 9, 1 mL(~400 MBq) of $^{99m}TcO_4$– solution, room temperature, X min reaction time.

Biological Distribution Study

Table **1** shows the biodistribution of ^{99m}Tc-salmeterol xinafoate complex in different body organs and fluids in mice at different time intervals after intravenous administration of ^{99m}Tc-salmeterol xinafoate complex. The washout of the radioactivity from the body was through both urinary and hepatobiliary pathways where the activity in urine and intestine were about 23 and 14 % at 2 h post injection.

The bone uptake started high and equal to ~ 36.5 % at 30 min then the activity remained relatively high at this level (36.5 - 29 %) up to 2 h post injection. So, excellent skeletal uptake can be obtained faster with ^{99m}Tc-salmeterol than

with other commercially available radio pharmaceuticals used for skeletal imaging [14]. So, ^{99m}Tc-salmeterol could be used to scan the skeletal body bones faster than the other radio pharmaceuticals with low expose of the patients and the operating staff to a high radiation dose.

Table 1. Biological distribution of ^{99m}Tc-salmeterol xinafoate complex in mice as a function of time.

Organs and body fluids	% Injected dose/organ and body fluid at different times post injection (min)				
	5	30	60	120	240
Bone	16.2 ± 1.1	36.5 ± 3.6	33.85 ± 3.6	29.3 ± 1.9	25.1±2.3
Muscles	14.25 ± 0.9	8.05 ± 0.5	4.56 ± 0.2	2.24 ± 0.1	2.11±0.1
Kidneys	6.38 ± 0.2	7.23± 0.6	8.67 ± 0.6	10.2 ± 0.8	11.23±0.0
Blood	22.76 ± 1.9	13.75± 1.1	6.48 ± 0.1	2.85 ± 0.1	0.62±0.0
Intestine	5.5 ± 0.02	5.55± 0.2	10.65 ± 0.9	14.93±0.7	16.1±1.0
Liver	5.47± 0.3	5.83± 0.3	6.31 ± 0.2	9.17±0.3	11.09±0.2
Stomach	2.34 ± 0.1	2.52± 0.1	6.39 ± 0.1	6.45±0.3	7.43±0.5
Lungs	5.78 ± 0.3	3.92± 0.2	2.72 ± 0.1	1.02±0.0	0.8±0.1
Spleen	3.85 ± 0.2	0.63± 0.0	0.36 ± 0.0	0.23±0.0	0.20±0.0
Heart	2.05 ± 0.0	0.63± 0.0	0.46 ± 0.0	0.19 ±0.0	0.06±0.0
Urine	14.36 ± 0.5	15.18± 1.3	19.01 ± 1.1	23.35±1.3	25.07±1.3

CONCLUSION

^{99m}Tc-salmeterol xinafoate complex is a novel non phosphonate radiopharmaceutical. It was achieved by using 0.5 mg salmeterol, 10 mg $NaBH_4$, at pH 9 and 30 min reaction time. Biological distribution of ^{99m}Tc-salmeterol in Albino Swiss mice revealed that ^{99m}Tc-salmeterol was rapidly accumulated in the bone with a higher uptake of 36.5% at 30 min post injection than the other commercially available radiopharmaceuticals for bone imaging. The bone uptake was remained high for a time up to 2 h (29%) sufficient for imaging without expose the patient and the medical staff to a high radiation dose. So, ^{99m}Tc-salmeterol xinafoate complex could be used for bone imaging and solve the drawbacks of the other commercially available ^{99m}Tc-phosphonate derivatives.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared None.

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