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Radiosynthesis and biological evolution of $^{99m}Tc(CO)_3$–sitafloxacin dithiocarbamate complex: a promising *Staphylococcus aureus* infection radiotracer

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Abstract Radio-complexation of sitafloxacin dithiocarbamate (SFDE) with technetium-99m (^{99m}Tc) using $[^{99m}Tc(OH_2)_3(CO)_3]^+$ precursor was investigated and compared with the ^{99m}Tc labeled SFDE prepared through ^{99m}TcN core. The $^{99m}Tc(CO)_3$–SFDE radiocomlpex was assessed in terms of radiochemical purity (RCP), eternalness in serum, in vitro binding with *Staphylococcus aureus* (*S. aureus*) and biodistribution in artificially *Staphylococcus aureus* infected rats (SAIR). The feasibility of the $^{99m}Tc(CO)_3$–SFDE radiocomplex as a suitable *S. aureus* infection radiotracer was evaluated in SAIR. The complex showed maximum RCP of 98.45 ± 0.21% in saline and was remained tagged more than 90% up to 4 h. The complex was found stable in serum and after 16 h only 17.95% de-tagged radio-fractions was observed. Similar saturated in vitro binding behaviour was observed for both the radiocomplexes ($^{99m}Tc(CO)_3$–SFDE and ^{99m}TcN–SFDE) with living *S. aureus*. Both the radiocomplexes showed almost similar in vivo biodistribution in SAIR. Significantly higher but similar infected to normal muscle ratio was observed for both the radiocomplexes in SAIR. The results of radiochemical purity (RCP), eternalness in serum, in vitro binding and in vivo biodistribution in SAIR posed the $^{99m}Tc(CO)_3$–SFDE radiocomplex as suitable *S. aureus* infection radiotracer.

Keywords Sitafloxacin dithiocarbamate · $[^{99m}Tc\ (OH_2)_3(CO)_3]^+$ · ^{99m}TcN core · *S. aureus*

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Introduction

A number of techniques are available to diagnose in vivo suspected infection, like Nuclear Medicine Scintigraphy (NMS), Ultrasonography (US), Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) [1]. However selection of the right technique is always a big problem for the clinicians with special reference to the fever of unknown origin [2].

The MRI, CT and US have been found sensitive techniques in imaging infection but the specificity and after treatment monitoring failure limits their use [3, 4]. In the last two decades, the NMS tenders substantial expectation after the development of the promising specific infection radiotracers [5–12]. Recently, we have reported technetium-99m (^{99m}Tc) labeled antibiotics and evaluated their efficacy as radiotracers [13–18]. High RCP values in saline, stability in serum, in vitro bacterial uptake, promising biodistribution, high target to non-target ratio and specific imaging results support our effort for the development of infection radiotracers.

The role of $(TcO)^{3+}$ core in the development of newer and better ^{99m}Tc radiopharmaceuticals intended for various imaging and therapy is very vital. The $[^{99m}Tc(CO)_3(H_2O)_3]^+$ organometallic water stable precursor have explored new ways for the development of promising diagnostic and therapeutic agents. Using the $[^{99m}Tc(CO)_3(H_2O)_3]^+$ as the staring material escorted, to

form promising newer radiopharmaceuticals, have re-energized the research in the nuclear medicine technology [19–23].

In the current investigation the radiolabeling of sitafloxacin dithocarbamate (SFDE) (Fig. 1b) with ^{99m}Tc is reported using the $[^{99m}Tc(OH_2)_3(CO)_3]^+$ precursor. The RCP values, stability in serum, in vitro bacterial uptake and biodistribution were determined and compared with ^{99m}Tc labeled SFDE complex prepared through ^{99m}TcN core.

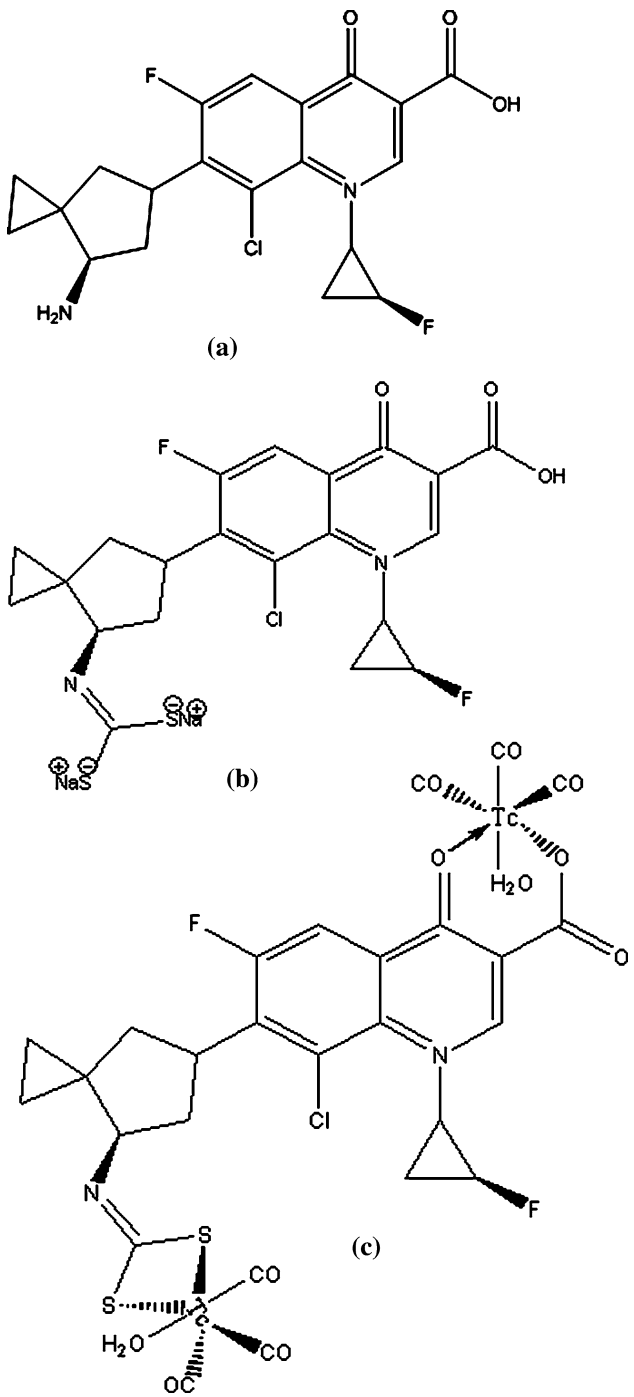

Fig. 1 **a** Chemical structure of Sitafloxacin, **b** Sitafloxacin dithiocarbamate (S FDE), **c** Proposed structure of the ^{99m}Tc $(CO)_3$–SFDE radiocomplex

Experimental

Materials

Sitafloxacin (STF) (Daiichi Sanko, Japan), succinic dihydrazide (SDH), propylenediamine tetra acetic acid (PDTA) (Aldrich, USA) and all the other chemicals and solvents of analytical grade (Sigma)., RP-HPLC (Shimadzu, Japan), well counter, scalar count rate meter (Ludlum, USA), Dose calibrator (Capintech USA) and the Gamma camera (GEADE Nuclearmedizine system, Germany).

Method

Sitafloxacin dithocarbamate (SFDE) preparation

Sitafloxacin dithocarbamate (GXND) was prepared using the reported method [18]. Briefly, Sitafloxacin (STF) (3.625 g) was mixed with 1.2 g of sodium hydroxide and dissolved in 11 mL of 40% tetrahydrofuran (THF) followed by continuous shaking in ice-bath for 10 min. Thereafter, 1 mL of carbon disulfide (CS_2) was added followed by 8 h continuous shaking in an ice-bath. The final product (SFDE) was recovered and characterized.

Preparation of the ^{99m}Tc$(CO)_3$–SFDE complex

$Na^{99m}TcO_4^-$, 0.5 mL (1–2 mCi) freshly eluted was injected to the kit (Isolink) and incubated for 15 min followed by addition of 0.1 mol/L HCL. Thereafter 2 mg of SFDE in water was added and incubated for 15 min.

Partition coefficient of the ^{99m}Tc$(CO)_3$–SFDE complex

The ^{99m}Tc$(CO)_3$–SFDE complex was mixed with octanol and phosphate buffer in equal volume and vortexed at room temperature for 2 min. Thereafter, the mixture was centrifuged at 5000 rpm/min for 10 min. Aliquot, 0.1 mL was obtained at different intervals and counted for activity using well counter interface with scalar count rate meter. The partition coefficient was determined using the following formula.

$$P = \frac{(\text{Counts per min in octanol} - \text{counts per min in background})}{(\text{Counts per min in octanol} - \text{counts per min in background})}$$

The same process was repeated for the ^{99m}TcN–SFDE and ^{99m}Tc–STF radiocomplexes for comparison.

RP-HPLC Characterization of the $^{99m}Tc(CO)_3$–SFDE radiocomplex

RP-HPLC chromatography was used to characterized the $^{99m}Tc(CO)_3$–SFDE radiocomplex using SCL-10 AVP shimadzu system fitted with SDP-10 AVP UV detector operating at 254 nm, Packard 500 TR series flow scintillation analyzer, binary pump, and online degasser. The $^{99m}Tc(CO)_3$–SFDE radiocomplex, 10 µL was introduced to the main unit of the SCL-10 AVP shimadzu system through the C-18 column (4.6 × 150 mm). Water:ethanol was used as a mobile phase, with a flow rate of 1 mL/min for 15 min (0–3 min (100%: W), 3–5 min (100–75% W), 5–8 min (75–66% W), 8–10 (34–100 M), 10–13 (100% M) and 13–15 (100% M to 100% W)). The fractions collected at 1–15 min were counted for activity using well counter interface with scalar count rate meter. The RCP values of the $^{99m}Tc(CO)_3$–SFDE radiocomplex was compared with the ^{99m}TcN–SFDE radiocomlpex.

Serum stability

The in vitro immovability of the $^{99m}Tc(CO)_3$–SFDE radiocomplex in serum was investigated using TLC. The radiocomplex, 0.2 mL was incubated at 37 °C with 1.8 mL serum. Thereafter, aliquots obtained at 2, 4, 6, 8, 10, 12 14 and 16 h of incubation were spotted on the polyamide strip and developed in saline and CH_2Cl_2:CH_3OH (9:1) (v/v). The developed polyamide strips were counted for activity using well counter interface with scalar count rate meter. The in vitro serum stability profile of the $^{99m}Tc(CO)_3$–SFDE was compared with the ^{99m}TcN–SFDE radiocomplex.

In vitro binding with pathogens

In vitro binding of *S. aureus* was assessed by using the reported method [24]. Briefly, $^{99m}Tc(CO)_3$–SFDE radiocomplex, 10 MBq was transferred to a flask holding 0.1 mL sodium phosphate buffer (Na-PB). Subsequently, 0.8 mL (50%, v/v) 0.01 M acetic acid containing approximately 1×10^8 colony forming units (CFU) of *S. aureus* was added. Thereafter, at 4 °C the preparations were incubated for 1 h and the pH 5 was adjusted. The mixture was centrifuged for 10 min (2000 rpm) followed by removal of the supernatant. The pellets were resuspended in Na-BP (2 mL) and re-centrifuged for 10 min with the same spin speed. The activity uptake in pellets was estimated using well counter interface with scalar count rate meter. The in vitro bacterial binding of the $^{99m}Tc(CO)_3$–SFDE was compared with the ^{99m}TcN–SFDE radiocomplex.

Biodistribution

Twelve male Sprague–Dawley rats (weight, 180–220 g) were randomly selected and divided into two groups (A and B) in each of the group six rats were injected with 0.2 mL sterile turpentine oil intramuscularly (I.M.) to the left thigh. Approximately, 1×10^8 CFU of living *S. aureus* in 0.2 mL normal saline was injected to the left thigh of the rats of the group A and a similar amount of heat killed *S. aureus* to the group B rats. After 24 h, 0.5 mCi (0.5 mL) of the $^{99m}Tc(CO)_3$–SFDE was administered to all the rats, separately and then exterminated in accordance with the Nuclear Medicine Research Laboratory University of Peshawar rules and regulations. The absorbed dose (%) per gram (each) in blood, liver, spleen, stomach, intestine, kidney, infected muscle, inflamed and normal muscle was calculated using well counter interface with scalar count rate meter. The biodistribution profile of the $^{99m}Tc(CO)_3$–SFDE radiocomplex was compared with the ^{99m}TcN–SFDE radiocomplex.

Result and discussion

Chemistry of the $^{99m}Tc(CO)_3$–SFDE radiocomplex

Sitafloxacin (Fig. 1a) was converted to its dithiocarbamate (Fig. 1b) which was radiolabeled with ^{99m}Tc using $[^{99m}Tc(OH_2)_3(CO)_3]^+$ precursor giving the proposed structure (Fig. 1c) having a tetrahedral bipyramidal geometry and stoichiometry of Lig:$Tc(CO)_3$ as 1:2 [25].

The two sulfur atoms of the bidentate SFDE under substitution reaction with an intermediate $[^{99m}TcN]^{2+}$core yield ^{99m}TcN–SFDE radiocomplex while in the *fac*-$[^{99m}Tc(CO)_3(H_2O)_3]^+$ precursor readily displaced H_2O to give the $^{99m}Tc(CO)_3$–SFDE radiocomplex.

Participation coefficient of the $^{99m}Tc(CO)_3$–SFDE radiocomplex

The value of participation coefficient determined for the $^{99m}Tc(CO)_3$–SFDE, ^{99m}Tc–STF and ^{99m}TcN–SFDE radiocomplexes were 0.47 ± 0.02, -1.06 ± 0.05 and

1.12 ± 0.01, respectively. The participation coefficient values of the ^{99m}Tc(CO)$_3$–SFDE was decreased than ^{99m}TcN–SFDE and increased then ^{99m}Tc–STF radiocomplex. The values of the participation coefficient for the ^{99m}Tc(CO)$_3$–SFDE and ^{99m}TcN–SFDE radiocomplexes suggest that both are lipophilic and the ^{99m}Tc–STF are hydrophilic.

HPLC characterization of the ^{99m}Tc(CO)$_3$–SFDE radiocomplex

The HPLC radio-chromatogram of the ^{99m}Tc(CO)$_3$–SFDE radiocomplex (Fig. 2) demonstrated two peaks with the retention times (RT) of 2.1 and 8.2 min. The peak at 8.2 min represents the yield of ^{99m}Tc(CO)$_3$–SFDE radiocomplex. However, the RT observed for the SFDE radiocomplex prepared through [^{99m}TcN]$^{2+}$ core using the same parameters were 3.2 and 10.5 min. The activity peak observed at 10.5 min represents the ^{99m}TcN–SFDE radiocomplex.

The ^{99m}Tc(CO)$_3$–SFDE radiocomplex showed stable radiochemical profile in saline at different intervals after reconstitution as shown in Fig. 3. The maximum RCP value observed for the ^{99m}Tc(CO)$_3$–SFDE radiocomplex was 98.45 ± 0.21% at 30 min after reconstitution and showed more than 90% stability up to 4 h. No significant change was observed between the RCP values of the ^{99m}Tc(CO)$_3$–SFDE and ^{99m}TcN–SFDE radiocomplexes.

In vitro stability of the ^{99m}Tc(CO)$_3$–SFDE radiocomplex in serum

A comparative in vitro stability profile of the ^{99m}Tc(CO)$_3$–SFDE and ^{99m}TcN–SFDE radiocomplexes is shown in Fig. 4. Similar stable in vitro profile in serum at 37 °C was observed for the ^{99m}Tc(CO)$_3$–SFDE radiocomplex up to 4 h and insignificantly the stability went down to 80.50 ± 0.29% up to 16 h after reconstitution.

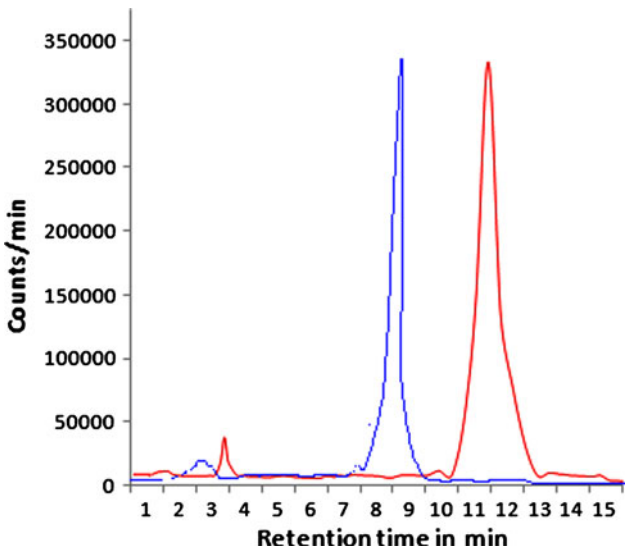

Fig. 2 HPLC radio-chromatogram of the ^{99m}Tc(CO)$_3$–SFDE radiocomplex

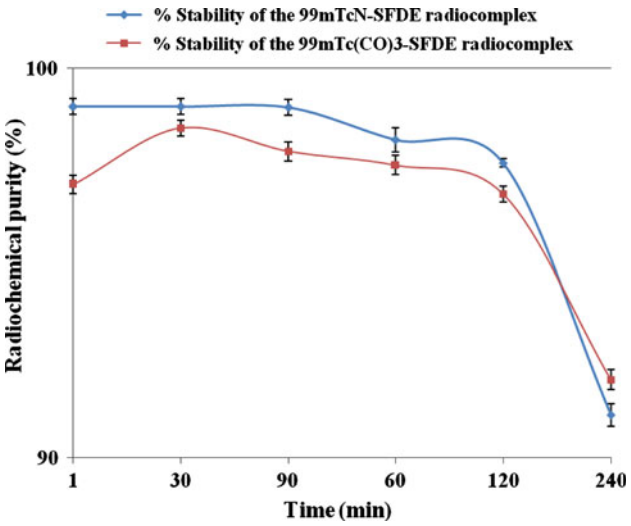

Fig. 3 Comparative radiochemical stability of the ^{99m}Tc(CO)$_3$–SFDE and ^{99m}TcN–SFDE radiocomplexes in saline

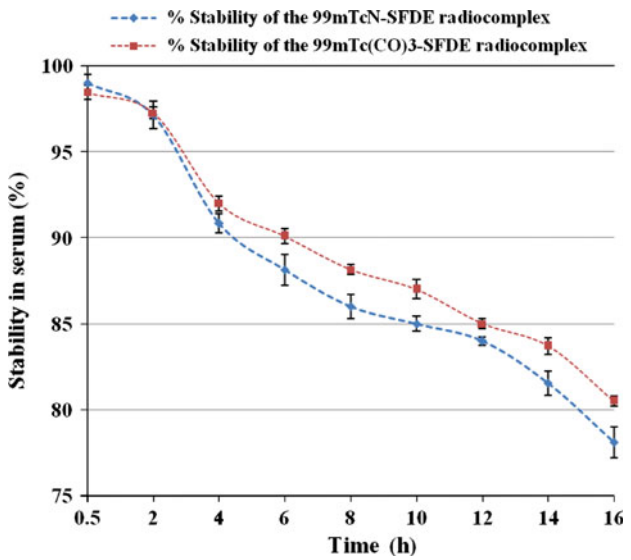

Fig. 4 Comparative in vitro stability of the ^{99m}Tc(CO)$_3$–SFDE and ^{99m}TcN–SFDE radiocomplexes in serum at 37 °C

In vitro pathogenic uptake

The ^{99m}Tc(CO)$_3$–SFDE radiocomplex showed saturated in vitro binding with living *S. aureus* like ^{99m}TcN–SFDE radiocomplex. A comparative in vitro binding affinity of the ^{99m}Tc(CO)$_3$–SFDE and ^{99m}TcN–SFDE radiocomplex is given in Fig. 5.

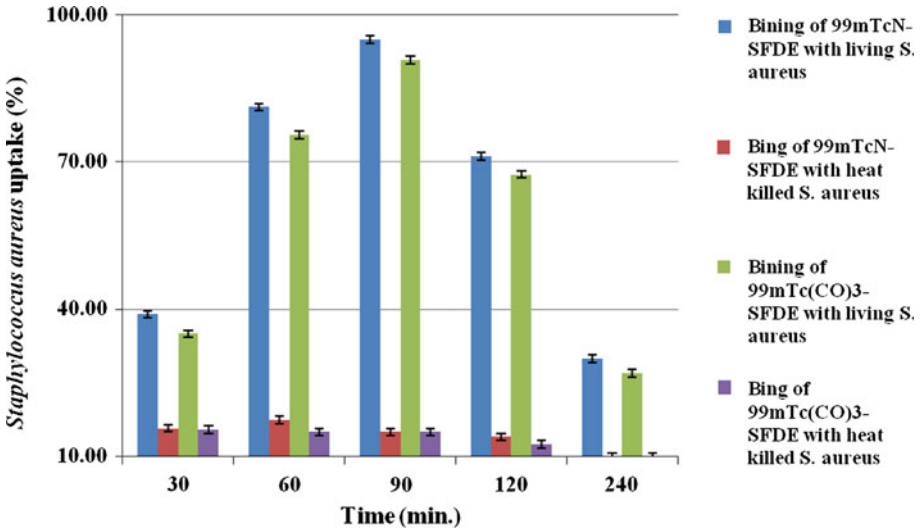

Fig. 5 Comparative in vitro binding profile the $^{99m}Tc(CO)_3$–SFDE and ^{99m}TcN–SFDE radiocomplexes with *Staphylococcus aureus* at different interval

Biodistribution

The in vivo biodistribution of the $^{99m}Tc(CO)_3$–SFDE radiocomplex in rats of group A and B is given in Table 1. It was observed that the amount of the $^{99m}Tc(CO)_3$–SFDE radiocomplex in blood of the group A and B rats went down with time. The radiocomplex showed almost similar blood activity profile in all the infected rats irrespective of the live or heat killed pathogen. The uptake of the $^{99m}Tc(CO)_3$–SFDE radiocomplex in group A showed significantly higher amount in the infected muscle as compared to the inflamed and normal muscle. In case of group B rats almost similar uptake was observed in infected, inflamed and normal muscle. The uptake of the radiocomplex in case of group A (live *S. aureus* infected rats) was approximately 6 time higher in the infected muscle as compared with the inflamed and normal while in the heat killed (group B) no significant difference was observed. The activity significantly decreased in liver and spleen and increased in kidney with time in infected rats of group A and B. The appearance of activity of the $^{99m}Tc(CO)_3$–SFDE radiocomplex in urinary system and disappearance from circulatory system confirmed the normal route of excretion.

The infected to normal muscle uptake ratio of the $^{99m}Tc(CO)_3$–SFDE and ^{99m}TcN–SFDE radiocomplexes in SAIR are given in Figure 6. Both the radiocomplexes showed almost similar uptake patron. Significantly, higher up take was observed in infected muscle as compared to inflamed and normal muscle.

Conclusion

In the current investigation the feasibility of the sitafloxacin dithiocarbamate (SFDE) radiolabeling with ^{99m}Tc using $[^{99m}Tc(OH_2)_3(CO)_3]^+$ precursor and biological evaluation in artificially infected *Staphylococcus aureus*

Table 1 Biodistribution of the $^{99m}Tc(C)O)_3$–SFDE radiocomplex in artificially *Staphylococcus aureus* (live and heat killed) infected rats at different intervals of I.V. injection (mean ± SD)

Organs of the *S. aureus* infected rats (gm)	In vivo distribution of $^{99m}Tc(C)O)_3$–SFDE radiocomplex							
	Living *S. aureus* infected rats				Heat killed *S. aureus* infected rats			
	30	60	90	120	30	60	90	120
Infected muscle	5.50 ± 0.16	12.00 ± 0.14	15.25 ± 0.12	14.50 ± 0.15	3.50 ± 0.15	3.25 ± 0.17	3.10 ± 0.0.12	3.00 ± 0.16
Inflamed muscle	3.50 ± 0.14	3.50 ± 0.10	3.25 ± 0.0.15	3.00 ± 0.20	3.50 ± 0.16	3.50 ± 0.14	3.25 ± 0.0.12	3.00 ± 0.12
Normal muscle	2.50 ± 0.15	2.50 ± 0.12	2.50 ± 0.14	2.50 ± 0.11	2.50 ± 0.10	2.50 ± 0.09	2.50 ± 0.14	2.50 ± 0.18
Blood	21.50 ± 0.16	8.00 ± 0.10	7.10 ± 0.14	2.5.00 ± 0.20	21.00 ± 0.18	7.50 ± 0.12	6.85 ± 0.16	3.00 ± 0.10
Liver	18.00 ± 0.11	10.50 ± 0.14	7.50 ± 0.20	4.50 ± 0.14	18.50 ± 0.15	11.00 ± 0.12	8.10 ± 0.15	5.00 ± 0.18
Spleen	9.25 ± 0.15	7.00 ± 0.20	4.50 ± 0.11	3.25 ± 0.10	8.50 ± 0.10	6.75 ± 0.12	5.00 ± 0.16	3.00 ± 0.11
Kidney	12.50 ± 0.20	19.15 ± 0.11	22.25 ± 0.12	24.00 ± 0.14	12.00 ± 0.18	20.50 ± 0.14	22.15 ± 0.16	23.50 ± 0.10
Stomach and intestines	9.50 ± 0.12	8.25 ± 0.18	7.20 ± 0.11	3.00 ± 0.14	10.00 ± 0.10	9.50 ± 0.18	6.00 ± 0.12	3.25 ± 0.12

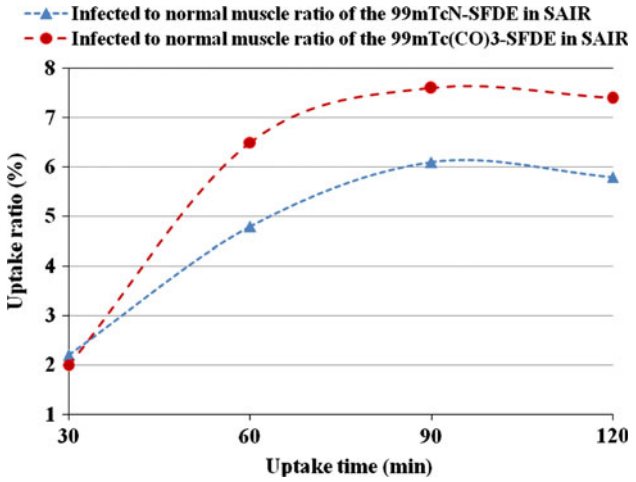

Fig. 6 Ratios of the $^{99m}Tc(CO)_3$–SFDE and ^{99m}TcN–SFDE radiocomplexes uptake in the infected and normal muscles of SAIR at different intervals

rats was assessed to verify the achievability of the $^{99m}Tc(CO)_3$–SFDE radiocomplex as a potential *Staphylococcus aureus* in vivo infection radiotracer. The high radiochemical stability in saline, supercilious in vitro serum immovability, targeted biodistribution profile and desired target to non-target (infected to inflamed muscle) ratio we recommend the $^{99m}Tc(CO)_3$–SFDE radiocomplex as a radiotracer for in vivo localization of *Staphylococcus aureus* infection in human.

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