

A Study on Labeling of Bioactive Molecules Using $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$ Precursor

*, , , , , , , *

150

220

가(+1)

$(^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+)$ (in vitro) , $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$ (in vivo) , $^{99m}\text{TcCO}_4^-$ NaBH₄ (in
 vitro) (1 atm), CO 가 , 98%
 , 8 , $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$ ^{99m}Tc -
 $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$, ^{99m}Tc - $^{99m}\text{TcCO}_4^-$, $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$
 , 가

Abstract

To radiolable bioactive molecules, we synthesized ^{99m}Tc precursor, $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$ with a low oxidation state (). We evaluated the characteristics of bioactive molecules labeled with precursor using in vitro and in vivo study. The $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$ was synthesized by low pressure carbonylation (1 atm CO) of $^{99m}\text{TcCO}_4^-$ in the presence of NaBH₄ with high labeling yield(>98%) and stability up to 8 hrs. A prepared $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$ was reacted with common ligands for ^{99m}Tc labeling and amino acids to investigate labeling property of $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$. And we also assessed the biodistribution property of $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$ -complexes in rabbit. ^{99m}Tc -tricarbonyl complexes with ligands for ^{99m}Tc labeling was also easily prepared and the properties of biodistribution differ between ^{99m}Tc -tricarbonyl labeling group and ^{99m}Tc labeling one. From these results, we concluded that $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$ and ^{99m}Tc -tricarbonyl complex is a potential precursor for the development of radiopharmaceuticals, especially for labeling of biomolecules.

^{99m}Tc 140 keV

6.02

^{99}Mo - ^{99m}Tc

가

^{99m}Tc

^{99m}Tc

30

^{99m}Tc

9,10)

가

N, S

()

N_2S_2 ()

), N_3S_1 (

)

$^{186/188}\text{Re}/^{99m}\text{Tc}$

^{99m}Tc

Tc()

Tc()

^{99m}Tc

Tc()

Tc()

가

Roser Alberto

()가

^{99m}Tc -

1-5)

$^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$

$^{99m}\text{TcO}_4^-$

1 CO 가

1).

$^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$

가

2).

^{99m}Tc -

$^{123/131}\text{I}$ -orthoiodohippuran (OIH)

^{99m}Tc -

mercaptoacetyl triglycine (MAG_3)

13,14)

NaBH_4

$^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$

^{99m}Tc -

CO gas (99.5%) 가 (Seoul, Korea)

$^{99m}\text{TcO}_4^-$

L-alanine, glycine, triglycine, glycine methyl ester, methionine, tryptopane, histidine, glutathion Fluka (Buchs, Switzerland) SIGMA chemical co.,(St. Louis, USA)

Ethylcysteinate dimer (ECD), MIBI, mercaptoacetyl triglycine(MAG₃), hexamethylpropyleneamine oxime (HMPAO), diisopropyliminodiacetic acid (DISIDA), diethylenetriaminetetraacetic acid (DTPA), methylenediphosphonate (MDP), metaiodobenzylguanidine (MIBG) Amersham (UK), Dupont (USA) or KAERI (Korea)

$^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$

$^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$ Alberto 1). 10 ml Na_2CO_3 (8 mg, 0.076 mmol) NaBH_4 (10 mg, 0.26 mmol) CO 가 30

37 GBq [$\text{Na}^{99m}\text{TcO}_4$] 6 ml 10ml

가 75 30 가 CO 가 가

0.6 ml phosphate (1M, pH 7.4) 가 0.05 M tetraethylammoniumphosphate (TEAP) 100% methanol (HPLC) , 8

$^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^-$

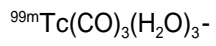
$^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$ ^{99m}Tc $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$ 1 ml 0.2 ml 가 , 75 30 가

가 HPLC HPLC 2 Waters 501 pumps, μ Bondapak C-18 (3.9 x 300 mm, Waters, USA), Waters automated gradient controller, Ultraviolet detector, Ray-test gamma detector, Autochro data module control autochro-WIN analysis program , 0.2 μm

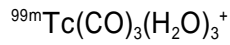
New Zealand White () 25 mg/kg () 6 mg/kg (Diacam, SIMENSE,

Germany) 140 keV 10% $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^-$ 37MBq (1mCi)/0.5ml 30

ICON (Simense, Germany)



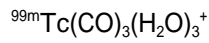
가



Alberto

98 %

가



2)



^{99m}Tc -tricarbonyl

Fig 1.

HPLC



^{99m}Tc -tricarbonyl

10.0, 3.8

37 KBq (μCi)/ml

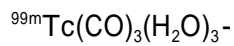
37 GBq (Ci)/ml

^{99m}Tc -tricarbonyl

^{99m}Tc -tricarbonyl

8

[Fig 1.]



^{99m}Tc

^{99m}Tc -tricarbonyl

Table

1, 2

DMSA, ECD, MAG₃, DISIDA, DTPA, MIBI

(>90%),

MDP, EDTMP, MIBG

L-alanine, L-tyrosine, glycine, triglycine, glycine

methyl ester, methionine, tryptopane, histidine

90%

glutathion 2

peak가

가

[Table 1]

[Table 2]

^{99m}Tc -tricarbonyl

New Zealand white

5, 180

Fig 2

5

^{99m}Tc -tricarbonyl

, 180

^{99m}Tc -tricarbonyl-ECD and -HMPAO

^{99m}Tc -tricarbonyl-DTPA

^{99m}Tc -DTPA

^{99m}Tc -tricarbonyl

^{99m}Tc -tricarbonyl-glycine

^{99m}Tc -tricarbonyl-triglycine

^{99m}Tc -tricarbonyl

^{99m}Tc -tricarbonyl

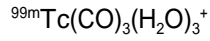
^{99m}Tc -tricarbonyl

[Fig 2.]

^{99m}Tc -tricarbonyl

^{99m}Tc -tricarbonyl

Alberto

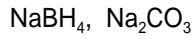


1). ()가

(low-spin d^6)

Alberto

^{99m}Tc -tricarbonyl



NaK tartrate

CO 가

가

CO 가

2).

NaK tartrate

가

, 가

CO 가

가

Alberto

,

가

^{99m}Tc -tricarbonyl

95%

98%

^{99m}Tc -tricarbonyl

^{99m}Tc -tricarbonyl

$\mu\text{Ci/ml}$

Ci/ml

Alberto

160 $\text{Ci}/\mu\text{M}$ of ^{99m}Tc -tricarbonyl-histidine

2). ^{99m}Tc -tricarbonyl

8

^{99m}Tc -

tricarbonyl

HPLC

$^{99m}\text{TcO}_4^-$, ^{99m}Tc -tricarbonyl

10, 3.8

^{99m}Tc -tricarbonyl

가 $^{99m}\text{TcO}_4^-$

가

^{99m}Tc -tricarbonyl

glycine

6.7

DISIDA

21.1

Alberto

^{99m}Tc -

tricarbonyl

가

, ^{99m}Tc -tricarbonyl

180

^{99m}Tc -tricarbonyl

DMSA, ECD, MAG_3 , DISIDA, DTPA, MIBI

(>90%)

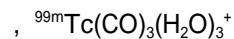
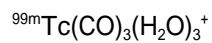
^{99m}Tc

^{99m}Tc -

tricarbonyl

^{99m}Tc -tricarbonyl-glycine

-triglycine



가

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Table 1. Labeling yield of ^{99m}Tc -tricarbonyl precursor with ^{99m}Tc labeling compound

compound	labelling yield ¹	retention time (min) ²
DMSA	> 98%	19.3
ECD	> 95%	20.6
HMPAO	> 90%	17.7
MAG ₃	> 90%	17.1
DISIDA	> 95%	21.1
DTPA	> 98%	13.2
MIBI	> 99%	20.3
MDP	No reaction	
EDTMP	No reaction	
MIBG	No reaction	

1: Reaction condition of $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$: CO flushing 30 min before reaction, then $^{99m}\text{TcO}_4^-$ in 3 ml saline react with CO gas bubbling at 75 °C for 30 min.

2: HPLC condition : Mobile phase - gradient system based on 0.05 M TEAP buffer and 100% MeOH

Column - μ Bondapak C-18 column (3.9 × 300 mm)

Flow rate - 1 ml/min

Table 2. Labeling yield of ^{99m}Tc -tricarbonyl precursor with amino acids

compound	labelling yield ¹	retention time (min) ²
L-alanine	> 98%	11.3
L-tyrosine	> 95%	16.9
glycine	> 95%	6.7
triglycine	> 95%	9.2
glycine methyl ester	> 99%	20.3
methionine	> 98%	15.3
5 methyl DL-tryptopane	> 98%	19.9
histidine	> 95%	17 22
glutathion	< 40%	13.0
	< 50%	18.0

1: Reaction condition of $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$: CO flushing 30 min before reaction, then $^{99m}\text{TcO}_4^-$ in 3 ml saline react with CO gas bubbling at 75 °C for 30 min.

2: HPLC condition : Mobile phase - gradient system based on 0.05 M TEAP buffer and 100% MeOH

Column - μ Bondapak C-18 column (3.9 × 300 mm)

Flow rate - 1 ml/min

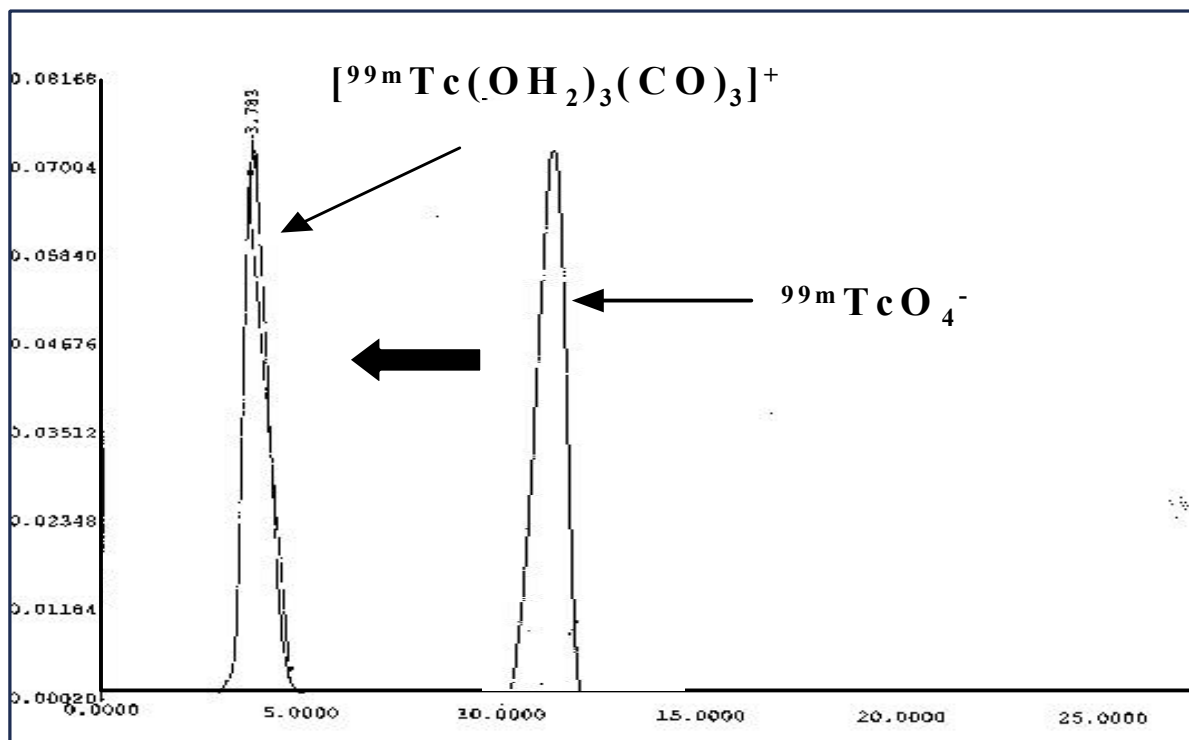


Fig 1. The chromatogram of free $^{99m}\text{TcO}_4^-$, ^{99m}Tc -tricarbonyl precursor
HPLC condition : Mobile phase - gradient system based on 0.05 M TEAP buffer
and
100% MeOH; Column - μ Bondapak C-18 column (3.9 \times 300 mm);
Flow rate - 1 ml/min

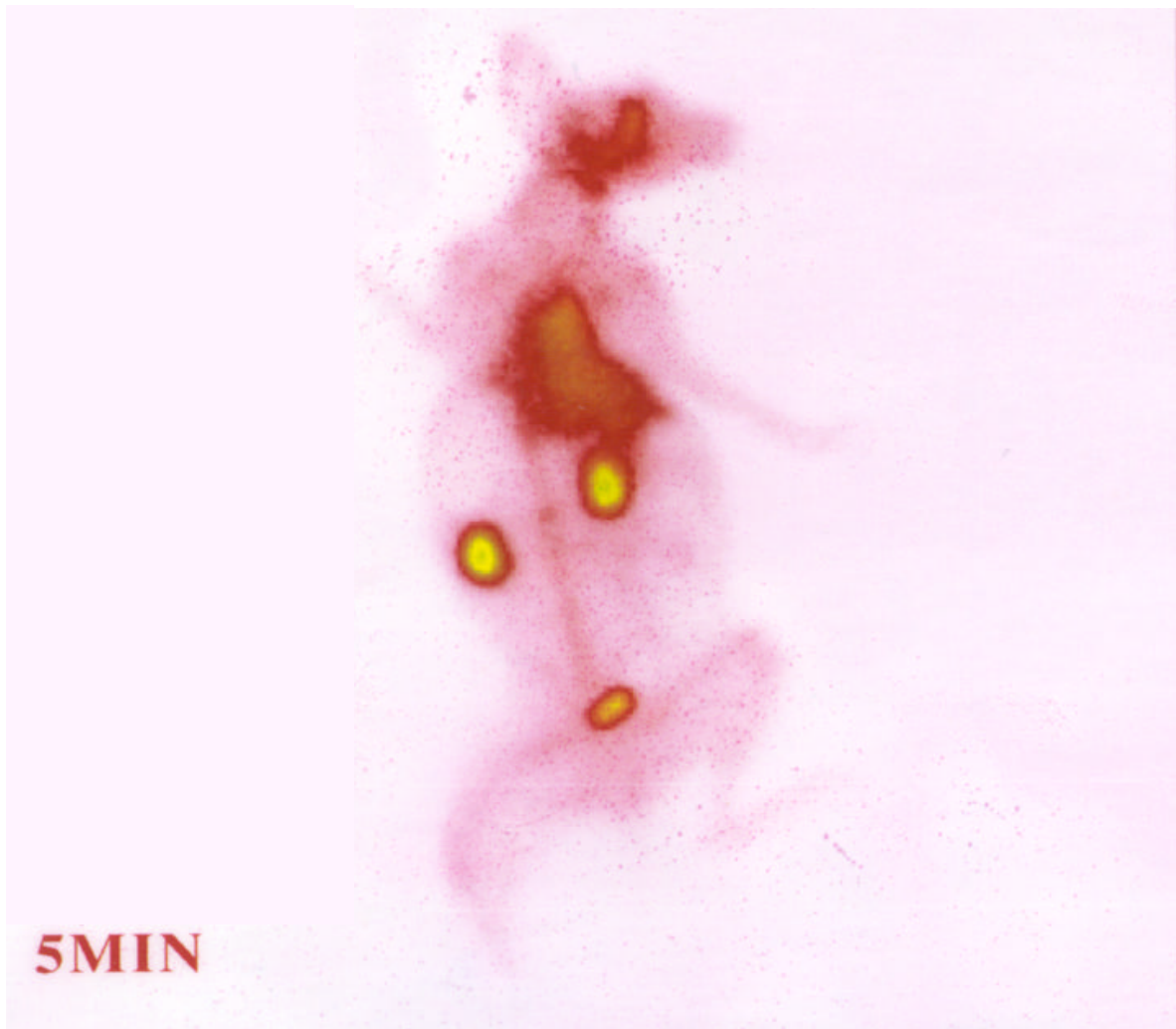


Fig 2. The image of rabbit administered ^{99m}Tc -tricarbonyl precursor at 5 min after injection