Preparation and bio-distribution of bone tumor therapeutic radiopharmaceutical ^{153}Sm-TTHMP

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Abstract TTHMP (triethylenetetraaminehexamethylenephosphonic acid) was labeled with ^{153}Sm. The labeling condition, stability, mole ratio of ^{153}Sm to TTHMP, rabbit bone imaging and bio-distribution of ^{153}Sm-TTHMP in mice were investigated. The results showed that weak basic media and high concentration ligands were favorable to form ^{153}Sm-TTHMP; labeling compounds were stable at pH 7 in 7 days. The results also indicated that the chemical mole ratio of ^{153}Sm-TTHMP is $n(^{153}\mathrm{Sm}) : n(\mathrm{TTHMP}) = 1 : 1$ and skeleton uptake of ^{153}Sm-TTHMP is high((13.96±3.51)%/g at 1h post injection and (13.54±2.98)%/g at 48h post injection), while the non-target tissue uptake is relatively low, so ^{153}Sm-TTHMP is a promising bone tumor therapeutic agent.

Keywords Bone tumor, Therapeutic radiopharmaceuticals, ^{153}Sm-TTHMP, Bio-distribution

CLC numbers R979, R817, O628

1 Introduction

^{153}Sm-EDTMP (ethylene diamine tetramethylene phosphonate) has been developed to palliate extreme skeletal pain caused by disseminated bony metastases for many years.[1-3] Researches showed that the excessive ligand was necessary in the preparation of ^{153}Sm-EDTMP to prevent its dissociation that caused higher liver uptakes.[4,5] But the research by Luo Shunzhong also indicated that the excessive ligand decreased the absorption of ^{153}Sm-EDTMP on hydroxyapatite that is the main components of skeleton.[6] It is well known that stability is a very important factor in designing new pharmaceuticals. Since base on TTHMP (triethylene tetraamine hexamethylene phosphonate) can provides four of N and twelve of O as donor atoms when it coordinates with $^{153}Sm^{3+}$, the compound ^{153}Sm-TTHMP will be more stable than ^{153}Sm-EDTMP. In this paper, we describe how TTHMP is synthesized and labeled with ^{153}Sm to evaluate the possibility as a bone tumor pharmaceutical.

2 Experimental

2.1 Materials

TTHMP was synthesized in our laboratory and IR, NMR and elemental analyses were carried out for the identification.

Samarium chloride solution (containing 370 MBq ^{153}Sm/mL) was prepared by irradiating natural samarium oxide in the research reactor of our Institute and dissolving the irradiated target (3 GBq/g Sm_2O_3) with diluted hydrogen chloride.

The other chemical agents, all were of analytic purity, were purchased commercially and not purified for use.

2.2 Preparation of ^{153}Sm-HHTMP

$^{153}SmCl_3$ was added to a vial containing TTHMP, and then the pH of solution was adjusted to a certain value. After sealing, the vial was placed for reaction about 30 min at room temperature. The purity of ^{153}Sm-TTHMP complex was measured using radio-paper chromatographic method with pyridine: ethanol:

Supported by CAEP Foundation (20020537)

Received date: 2002-06-20

water (1:2:4 *V*/*V*) as developing agent. The R_f values of free $^{153}Sm^{3+}$ and ^{153}Sm-TTHMP were 0 and 0.7, respectively.

2.3 Stability of ^{153}Sm-TTHMP

The pH value of ^{153}Sm-TTHMP solution obtained under optimum conditions was changed to 7.0 and then the purity of ^{153}Sm-TTHMP complex was analyzed at different time intervals.

2.4 Rabbit imaging

About 74MBq of ^{153}Sm-TTHMP in ~0.5mL was injected through the ear vein of a New Zealand rabbit, and the rabbit was imaged by a SPECT instrument, provided by Elscint Israel, at 24 h post-injection.

2.5 Bio-distribution

Bio-distribution study was performed in Kunming mice weighing (18±2) g. 18.5 kBq of ^{153}Sm-TTHMP in ~0.1mL was injected through tail vein and the mice were sacrificed at specific time intervals by cervical dislocation. The tissues and organs were excised, weighed and counted over a NaI(Tl) scintillation detector with flat geometry. For skeletal uptake studies, femur bone was chosen. The distribution of activity in different organs was calculated as percent injected dose/g.

3 Results and discussion

3.1 Influence of pH on ^{153}Sm-TTHMP formation

The stability of ^{153}Sm-complexes is affected by the hydrolysis of Sm^{3+} and the higher pH values of solution exasperate the hydrolysis. Fig.1 showed the dependence of pH on labeling yield of ^{153}Sm-TTHMP.

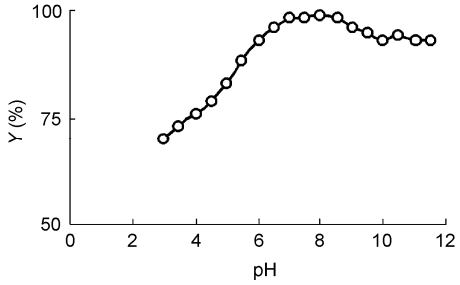

Fig.1 Effect of pH on yield with about 0.5 mg of TTHMP added.

The labeling yield increased from 70% to 98.6% when the pH was changed from 3.0 to 7.5, but the yield decreased lightly when the pH was changed from 8.5 to 11.5. So the optimum pH is 7.0 to 8.5. Though increasing ligand can widen the pH range in which satisfied labeling yield can be gotten, it is not advantageous to promote ligand concentration because of the competitive adsorption of ligand on bone.

3.2 Influence of ligand on ^{153}Sm-TTHMP formation

The influence of ligand on the labeling efficiency of ^{153}Sm-TTHMP was given in Fig. 2, from which we can find that the labeling efficiency increased with amount of TTHMP when TTHMP was less than 0.5 mg, and the labeling efficiency reached 97% when ligand was 0.5 mg.

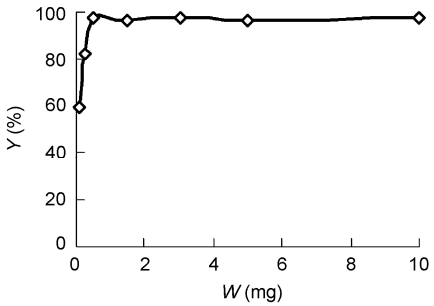

Fig.2 Effect of ligand on yield for the pH = 7.5 solution.

Based on Fig. 1 and Fig. 2, we can conclude that the most favorable pH values for forming ^{153}Sm-TTHMP are 7.0-8.5 when ligand is more than 0.5 mg.

3.3 The mole ratio of ^{153}Sm to TTHMP in ^{153}Sm-TTHMP

The mole ratio of ^{153}Sm to TTHMP in ^{153}Sm-TTHMP was studied by equal mole serial method. To a vial containing 12 mg of Sm, in the form of Sm^{3+}, 18.5 kBq of $^{153}SmCl_3$ and some TTHMP were added, and then the pH of solution was adjusted to 8.0. The solution was placed at room temperature about 30 min and then the labeling yield of ^{153}Sm-TTHMP was determined by radiopaper chromatography. The results shown in Fig.3 indicated that the labeling yield increased quickly with *n*, mole ratio of TTHMP to Sm in vial, when *n* was less than 1, and

the labeling yield was almost constant when *n* was more than 1, which implied that the mole ratio of ^{153}Sm to TTHMP in ^{153}Sm-TTHMP was 1:1.

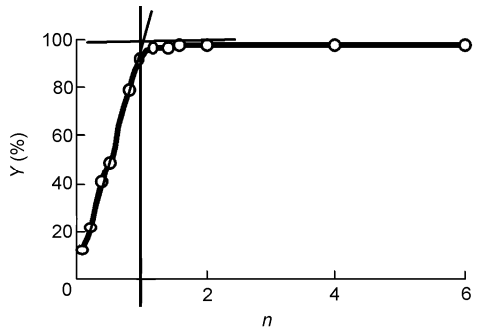

Fig.3 Mole ratio of ^{153}Sm to TTHMP in ^{153}Sm-TTHMP.

3.4 Stability of ^{153}Sm-TTHMP in vivo

Fig.4 showed ^{153}Sm-TTHMP was very stable and the radiochemical purity of ^{153}Sm-TTHMP was more than 96% in 8 d.

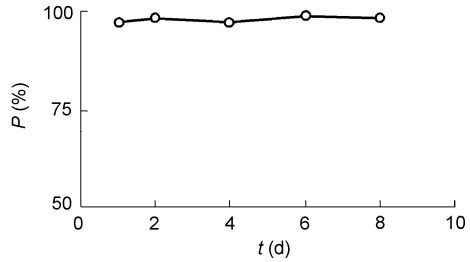

Fig.4 Stability of ^{153}Sm-TTHMP.

3.5 ^{153}Sm-TTHMP imaging in rabbit

For comparison, ^{153}Sm-EDTMP was prepared according to literature.[1] About 74MBq of ^{153}Sm-TTHMP and ^{153}Sm-EDTMP were injected into two rabbits, respectively. The two rabbits were imaged at 24 h after injection, and Fig.5 and Fig.6 were gotten. Fig.5 indicated that ^{153}Sm-TTHMP was mainly adsorbed by skeleton of rabbit, and skeleton in Fig.5 was as clear as that in Fig.6.

3.6 Bio-distribution of ^{153}Sm-TTHMP in mice

Bio-distributions of ^{153}Sm-TTHMP and ^{153}Sm-EDTMP were compared in Table 1 and Table 2. The skeleton uptake of ^{153}Sm-TTHMP got the highest value at 1 h post injection and maintained relatively high value at 48 h. The compound was mainly excreted by kidney and the uptake of other organs or tissues were relatively low, and the retentates in all soft tissues were very low at 3 h post-injection. In conclusion, ^{153}Sm-TTHMP, displaying excellent bio- distribution, was an attractive reagent to develop bone tumor therapeutics.

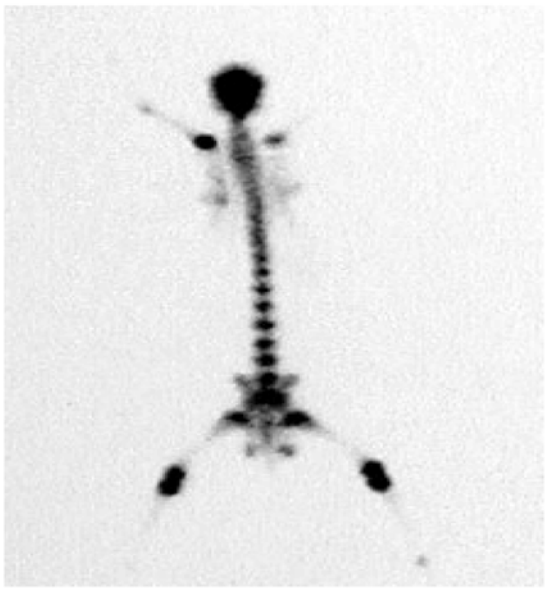

Fig.5 Rabbit skeleton imaging at 24 h after injection of ^{153}Sm-TTHMP.

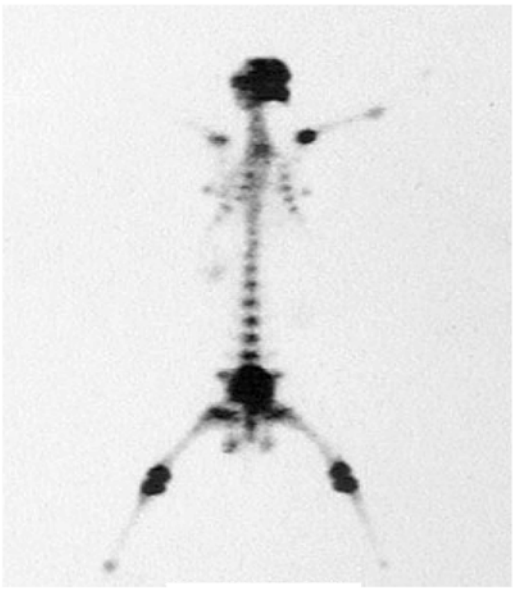

Fig.6 Rabbit skeleton imaging at 24 h after injection of ^{153}Sm-EDTMP.

Table 1 Bio-distribution of ^{153}Sm-TTHMP in mice (n = 5)

Tissues	Bio-distributions at different time (%ID /g tissue)					
	0.5 h	1 h	3 h	6 h	24 h	48 h
Blood	2.35±0.05	0.21±0.01	0.01±0.00	0.01±0.00	0.002±0.00	0.0018±0.00
Heart	0.13±0.02	0.06±0.04	0.02±0.01	0.02±0.01	0.03±0.00	0.03±0.01
Liver	0.42±0.21	0.11±0.01	0.17±0.05	0.19±0.02	0.23±0.06	0.22±0.03
Spleen	0.51±0.01	0.033±0.01	0.04±0.020	0.05±0.01	0.04±0.00	0.03±0.00
Kidney	2.13±0.04	1.03±0.24	0.60±0.07	0.51±0.20	0.53±0.11	0.47±0.03
Muscle	0.72±0.06	0.02±0.00	0.02±0.00	0.04±0.02	0.01±0.00	0.02±0.00
Bone	16.70±2.36	25.31±4.52	24.08±3.69	23.31±2.98	24.95±2.77	25.22±4.65

Table 2 Bio-distribution of ^{153}Sm-EDTMP in mice (n = 5)

Tissues	Bio-distributions at different time (%ID /g tissue)					
	0.5 h	1 h	3 h	6 h	24 h	48 h
Blood	0.16±0.01	0..05±0.01	0.01±0.00	0.01±0.00	0.002±0.00	0.002±0.00
Heart	0.17±0.06	0.07±0.00	0.06±0.01	0.04±0.01	0.04±0.00	0.02±0.01
Liver	0.26±0.02	0.22±0.01	0.17±0.02	0.19±0.03	0.27±0.06	0.22±0.02
Spleen	0.19±0.04	0.20±0.02	0.13±0.01	0.08±0.01	0.05±0.00	0.08±0.00
Kidney	2.04±0.25	1.85±0.15	0.86±0.05	0.65±0.03	0.43±0.11	0.52±0.03
Muscle	0.33±0.04	0.13±0.06	0.05±0.02	0.03±0.01	0.01±0.00	0.03±0.01
Bone	18.60±2.22	23.37±3.45	24.12±3.87	25.23±4.56	23.05±4.02	24.56±3.78

References

1 Luo S Z, Pu M F, Qiao J *et al*. Nucl Sci Tech, 1995, **16**(3): 146-149

2 Serafini A N. Q J Nucl Med, 2001, **45**(1): 91-99

3 Berna L, Martin F, Cunill C *et al*. Rev Esp Med Nucl, 2001, **20**(2): 130-131

4 Volkert W A, Deutsch E A. Advances in metals in medicine[M]. Abrams M J Eds, JAI Press, 1993, 115-149

5 Volkert W A, Hoffman T J. Chem Rev, 1999, **99**: 2269-2292

6 Luo S Z, Qiao J, Pu M F *et al*. Nucl Tech (in Chinese), 1996, **19**: 236-240