Preparation and characteristics of ^{117m}Sn–HEDTMP

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Abstract Tin-117m($t_{1/2}$ 14d; γ 159 keV, 86%) is an ideal tracer for studying biological behavior of tin compounds as well as for developing clinically-useful radiopharmaceuticals. It had been reported that Sn-117m[4+] DTPA has unexpectedly high bone uptake and bone-to-blood ratio, and is potentially useful as an agent for skeletal scintigraphy and radiotherapy of bone tumors. In this work, HEDTMP [N-(2-hydroxyethyl) ethlenediamine-1,1,2-tri (methylene phosphonic acid)] was synthesized. Let it form complex with ^{117m}Sn. The formation conditions, stability and distribution coefficient between oil and water of the complex were investigated.

Keywords ^{117m}Sn, HEDTMP, Bone tumor

CLC numbers O621.3+5, R817.5 A

1 INTRODUCTION

Majority of patients (>70%) are sure to endure continuous bone pain when osseous metastases take place during the deterioration of malignant tumor.[1] People are given enlightenment of organic phosphorus compound which has been widely used to treat osseous loose in clinical. People began to take them to bone cancer and osseous metastases cancer. At present, HEDP MDP have been widely applied. But long-term use of HEDP will hamper the mineraliztion of normal bone. What's more, it may lead kidney competence to come down when it's injected rapidly through vein.[2] Therefore, other similar compounds for example EDTMP, DTPMP, HEDTMP *et al.* were put into research subsequently.

The therapeutical effective nuclides for pain palliation of bone tumor are ^{89}Sr, ^{153}Sm, ^{32}P etc. But myelosuppression about $^{89}SrCl_2$ and ^{153}Sm-EDTMP and the effect causing a fall in platelets have been reported. Marrow depression has been noted with ^{32}P and ^{186}Re.

A number of compounds containing ^{117m}Sn were studied, especially ^{117m}Sn-DTPA.[3,4] ^{117m}Sn has certain physical characteristics (half-life of 13.6 d, low-energy-conversion electrons, gamma photon of 158.6 keV) that suggest that it may be a favorable agent for

Manuscript received date: 2001-10-30

single photon emission compute tomography and radionuclide therapy.

Sn has two oxidation states:+2, +4. For stannic chalets, higher bone uptake, faster blood clearance and reduced soft-tissue concentration were observed. Therefore we choose stannic to do detailed studies, our conc.HCl-H_2O_2 method is handy and reliable.

2 MATERIALS

^{117m}Sn was provided in our institute. HEDTMP was synthesized in our laboratory and the structure was confirmed by IR, m.p. and elemental analysis. Other chemicals used were of reagent grade.

3 METHODS

3.1 The preparation of stannic

After irradiation, the tin was dissolved in a minimal volume of conc.HCl, where a 10-fold molar excess of 30% hydrogen peroxide was added. The sample was then heated for five minutes in a bath of boiling water to remove away hydrogen peroxide.

3.2 The preparation of HEDTMP

HEDTMP was prepared according to Marich reaction principle, using N-(2-Hydroxy ethyl) ethylenediamine, formaldehyde solution, phosphorous acid, hydrochloric acid in boiling water bath. After reaction of 5 hours, the mixture was cooled and then crystallized using alcohol (95%). The crystallized product was confirmed by IR , melting point , element analysis.

3.3 The preparation of ^{117m}Sn-HEDTMP

$^{117m}SnCl_4$ was dripped in the aqueous solution of HEDTMP. The complexing yield was determined by paper chromatography.

4 RESULTS AND DISCUSSION

Radiochemical purity of the oxidation state of tin (^{117m}Sn(IV)) was assessed by paper chromatography. Paper chromatography was carried out using acetone, tetraone, normal saline (or saline containing 0.1% ligand), ammonia solution as developing solvents. Acetone's speed was the fastest. It took twenty minutes to develop 15 cm. The Rf value of ^{117}Sn(IV) was 0.28–0.61; tetraone was faster, the Rf value was 0.24–0.65. Ammonia solution was the slowest, it took eighty minutes to develop 15 cm, the Rf value was 0–0.33. ^{117m}Sn(IV)'s separate effect was not very good in normal saline. The Rf value of

chelated tin was 0 in acetone. So we choose acetone as developing solvent.

4.1 IR of HEDTMP

Fig.1 shows HEDTMP's characteristical absorb peak. 3017 v, 2634 v (PO-H), 1642 v (P-OH), 1188 v (C-N), 1051 v (P=O), 948 v (C-P-O), where v is unit wavenumber.

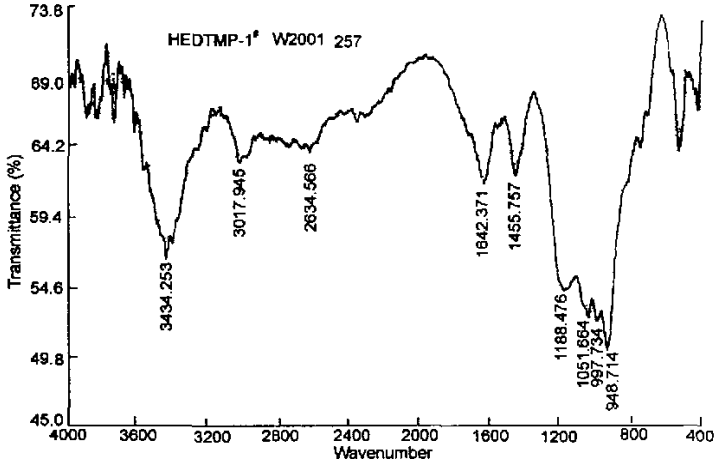

Fig.1 IR of HEDTMP

4.2 m.p.

Melting point of HEDTMP was 165.8–166.2°C.

4.3 Elemental analysis

Table 1 Elemental analysis of HEDTMP (%)

Molecule	N	C	H	P
Theoretical	7.25	21.76	5.44	24.09
Experimental	7.38	23.75	6.41	22.73

Above-mentioned analyses show that the structure of the synthesized HEDTMP is close to the expected one theoretically.

4.4 The effect of ligand dosage on labeling

From the following experiments we could conclude the effect of ligand dosage on labeling under different pH values.

0.1 mL 5×10^{-2}mol/L ligand+0.4 mg ^{117m}Sn(IV) $\longrightarrow$ muddy $\xrightarrow{pH=14-10}$ clear $\xrightarrow{pH=9-7}$ muddy

0.2 mL 5×10^{-2}mol/L ligand+0.4 mg ^{117m}Sn(IV) $\longrightarrow$ muddy $\xrightarrow{pH=14-9}$ clear $\xrightarrow{pH=7}$ muddy

0.3 mL 5×10^{-2}mol/L ligand+0.4 mg ^{117m}Sn(IV)$\longrightarrow$muddy$\overset{pH=7}{\longrightarrow}$clear,
the labeling efficiency was 98.5% after five minutes.

0.8 mL 5×10^{-2}mol/L ligand+0.4 mg ^{117m}Sn(IV)$\longrightarrow$a bit muddy $\overset{pH=7}{\longrightarrow}$clear,
the labeling efficiency was 98% after five minutes.

Excessive ^{117m}Sn(IV) may lead the solution muddy. Because ^{117m}Sn(IV) is easy to hydrolysis, the colloid formed. At this time, we dropped ligand to solution, solution was still muddy. The phenomenon showed once ^{117m}Sn(IV) formed colloid, it couldn't been fighted out even if existing excessive ligand. Heating had not effect. The solution was filtered through a sterile 0.2 μm filer, filtered liquid was spotted on chromatographic paper strip and was developed with acetone, the labeling efficiency was still high.

4.5 The effect of pH value on labeling efficiency

The reaction solution containing HEDTMP and ^{117m}Sn(IV) was adjusted pH value to 3, 5, 7, 9.5, 12 using 0.1 mol/L NaOH, or conc.HCl. Lay up five minutes, then the labeling efficiency was sacertained.

Table 2 The effect of pH value on labeling efficiency

pH Value	3	5	7	9.5	12
Labeling efficiency (%)	96.4	95	97.8	96.9	97.8

Table 2 shows that pH value had little influence on labeling efficiency. But after 24 hours, solutions of pH=9.5 and pH=12 became muddy, so we choosed range (pH=3–7) to do next experiment, because it was feasible to go on further distribution experiment in animals.

4.6 The effect of reaction time on yield

Ligand's dosage 0.8 mL, pH=7.5, clear reaction liquid was laid up separately 3min, 5min, 10min, 20min, observed the varying of labeling efficiency with time.

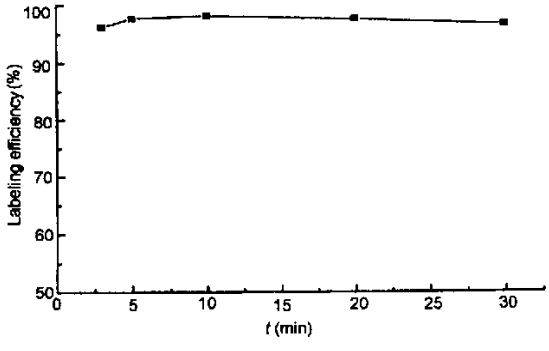

Fig.2 The effect of reaction time on labeling efficiency

From Fig.2, reaction time had unrelated to the labeling efficiency, the labeling efficiency was $\geq$95% in a few minutes.

4.7 The effect of temperature on yield

The reaction solution's pH was adjusted to 7.5, reacted five minutes at room temperature (about 25°C), the labeling efficiency was $\geq$95%.

4.8 Stability and lipophilicity of ^{117m}Sn(IV)-HEDTMP

The labeling efficiency was still $\geq$95% by the time of 120 h at room temperature, the labeling efficiency was $\geq$95% by the time of 8 h at 37°C. It provided factor for further experiments. From Ref.[5], N-octanol-Water partition coefficient $K_{ow} = (C_o)/(C_w) = (N_o)/(N_w)$. C_o: of ^{117m}Sn(IV)–HEDTMP in N-octanol. C_w: concentration of ^{117m}Sn(IV)–HEDTMP in water. N_o: radioactivity count in N-octanol. N_w: radioactivity count in water.

K_{ow} ^{117m}Sn(IV) $= 3.72 \times 10^{-2}$ K_{ow} ^{117m}Sn(IV) -HEDTMP$=8.13\times10^{-4}$

Rusults showed that they were hydrophilic. This accorded with our original study intentions and supplied data for further in-vivo behavior study.

5 CONCLUSION

Synthesized HEDTMP was contented with the expected structure. It was very easy to prepare ^{117m}Sn(IV) labeled HEDTMP. The labeling efficiency was $\geq$95% after several minutes at room temperature, but acidity and ligand dosage exerted a great influence on the exterior of reaction solution. Labeling efficiency was still high after filtration using a 0.2 μm filter. The complex was very stable at room temperature and 37°C. Determination of K_{ow} showed it was hydrophilic.

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