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PREPARATION OF SAMARIUM-153-EDTMP AND DETERMINATION OF ITS RADIOCHEMICAL PURITY USING PAPER CHROMATOGRAPHY

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Samarium-153-ethylenediaminetetramethylene-phosphonate (^{153}Sm-EDTMP) has been used to palliate pain resulting from bone cancer. This paper describes the preparation of $^{153}SmCl_3$ from irradiated natural samarium and the ability of ^{153}Sm to complex with EDTMP in liquid and in freeze-dried forms. The evaluation of radiolabeled EDTMP was done by paper chromatography. A rapid evaluation of free $^{153}SmCl_3$ and ^{153}Sm-EDTMP was developed using a miniaturized chromatographic system.

INTRODUCTION

Recent advances in targeted radiotherapy offer a new approach for management of metastatic bone pain. Interest in employing radiopharmaceuticals for diagnosis and therapy has increased and significant advances have been pos-

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sible by combined developments in the fields of new chelates and availability of a wider range β-emitting nuclides[1].

Samarium-153 has excellent physical properties as radiotherapeutic agent. It is a β-emitter ($E_{\beta max}$ = 0.8 meV) with 46.8 h half-life. The average β-particle energy is approximately one-third of its maximum energy. Samarium-153 also emits a 103-keV γ-ray suitable for imaging with conventional γ-cameras[2,3]. This radioisotope is produced by neutron activation of ^{152}Sm. When ^{152}Sm (99% enriched ^{152}Sm) is irradiated in high thermal fluxes the ^{153}Sm yields are in the order of curies. The radioactive impurities (^{154}Eu, ^{155}Eu) appear in trace amounts[2].

Samarium-152 thermal cross-section is 220 barns, but it also has an epithermal resonance integral cross-section of 3,168 barns that will increase the production in reactors with high epithermal fluxes[3].

Reactors with thermal fluxes of about $1x10^{13}$ $n.cm^{-2}.sec^{-1}$ can produce ^{153}Sm from natural samarium (26.7% ^{152}Sm) in the order of millicuries. These yields are suitable for in vitro studies and for distribution studies in mice. Radioactive impurities like ^{152}Eu, ^{154}Eu and ^{155}Eu obtained when natural samarium is irradiated do not affect these studies.

Samarium forms complexes with several phosphonic acids[2,4]. Among ^{153}Sm chelates, ^{153}Sm-EDTMP has shown to be a promising agent for the treatment of bone cancer.

When ^{153}Sm is chelated to EDTMP, it forms stable complexes in vitro and in vivo, which will localize in bone with a high specificity[2]. The structure of ethylenediaminetetramethylenephosphonic acid (EDTMP) is depicted in Figure 1.

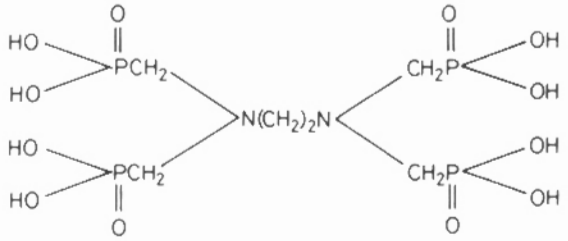

Fig. 1. Structure of EDTMP

Samarium-153-EDTMP complex can be prepared from EDTMP in solution under heating[2,4,5] or from kit formulation, at room temperature[6,7].

This work describes the ^{153}Sm-EDTMP labeling, the yields obtained in both methods and the stability of ^{153}Sm-EDTMP using paper chromatography.

EXPERIMENTAL

Reagents: Natural samarium oxide, BDH, analytical grade. EDTMP, Monsanto Chemical Corporation. Other reagents: Merck, analytical grade. pH strips: Merck Neutralit.

Equipments: ^{153}Sm activities: Radioisotope Calibrator Capintec model CRC 120. Chromatogram strips countings: ANSR Gamma Counter, Abbot Laboratories. EDTMP titrations: pH-meter Metrohm Herisau Model E-520.

Preparation of $^{153}SmCl_3$

Natural samarium oxide was converted into samarium nitrate by dissolution with 1N nitric acid. Samarium

amounts of 2 to 4.1 mg were put into a high purity quartz vial and evaporated to dryness, leaving a thin film of samarium nitrate on the botton of the vial. It was flame-sealed and encapsulated into an aluminium container.

The samples were irradiated in the research reactor IEAR-1. Its maximum available thermal flux is 1.5×10^{13} $n.cm^{-2}.sec^{-1}$

After irradiation, the quartz vial was removed from its aluminium container in a hot cell. The sample was measured for ^{153}Sm activity and transferred to a glove box. The quartz vial was broken at the top and 2x1 ml of 0.1N hydrochloric acid were introduced. The vial was heated (80-90 ^{o}C) and the ^{153}Sm solution was transferred to a glass vial. $^{153}SmCl_3$ solutions were diluted with 0.1N hydrochloric acid to produce a stock solution (0.9 mg Sm ml^{-1}) used for complex preparations.

Preparation of ^{153}Sm-EDTMP

The ^{153}Sm-EDTMP complex was prepared as follows:

a) EDTMP in solution: The ^{153}Sm-EDTMP was prepared by adding 1.0 ml of $^{153}SmCl_3$ solution (0.9 mg Sm) to 60 mg/1.5 ml EDTMP at pH 9 (molar ratio 1:23, Sm/EDTMP). The pH of reaction mixture was raised to 10-11 with sodium hydroxide solution. The mixture was placed into a 60-70 ^{o}C water bath for 30 min. After heating the pH was adjusted to 7.5-8 with hydrochloric acid.

b) EDTMP in lyophilized form: A kit formulation consists of 60 mg EDTMP titrated with sodium hydroxide to pH 10.3 and further lyophilized. Addition of 1.7 ml of a $^{153}SmCl_3$ solution in 0.1N hydrochloric acid (0.9 mg Sm) to the kit yields a solution with pH of 7.5-8 (molar ratio 1:23, Sm/EDTMP).

Radiochemical purity of ^{153}Sm-EDTMP

Three chromatography systems were tested for ^{153}Sm-EDTMP radiochemical purity determination.

System 1: Support: Whatman 3MM paper strips 1.5x13.0 cm.
Solvent: pyridine, ethanol, water 1:2:4 v/v/v.
System 2: Support: Whatman 3MM paper strips 1.5x13.0 cm.
Solvent: ammonium hydroxide, ethanol, water 0.1:2:4 v/v/v.
System 3: Support: Whatman 3MM paper strips 1.0x7.0 cm (miniaturized).
Solvent: ammonium hydroxyde, ethanol, water 0.1:2:4 v/v/v.

The chromatograms were developed for a distance of 11.0 cm in approximately 75-85 min (systems 1 and 2) and for a distance of 5.0 cm in 20-25 min (system 3).

For R_f determinations the strips were cut in 1 cm (system 1 and 2) and 0.5 cm (system 3) pieces and the activity of each piece was measured. The radioactivity was assumed to be concentrated at the center of each piece.

Studies of ^{153}Sm-EDTMP stability

The stability of ^{153}Sm-EDTMP obtained in both preparations was investigated for 8 d.

RESULTS AND DISCUSSION

Yields of ^{153}Sm

A run of 7 to 8 h produced the ^{153}*Sm yields listed in* Table 1. The quartz vials measured after ^{153}Sm transference to the glass vials showed negligible residual activities.

TABLE 1

^{153}Sm yields obtained at a thermal flux of 1.5×10^{13} n.cm^{-2}.sec^{-1} at the end of irradiation

Sample No.	Samarium mass, mg	Irradiation time, h	Activity, mCi Theoretical	Obtained
1	2.5	7.56	25.4	19.9
2	3.1	8.00	33.1	24.6
3	4.1	7.55	43.7	33.6
4	2.0	7.45	20.0	18.6
5	3.1	7.00	29.1	24.3
6	2.0	7.70	20.6	19.1
7	4.1	8.20	44.7	33.7
8	3.0	8.13	32.5	25.7

Chromatographic behavior of $^{153}SmCl_3$ and ^{153}Sm-EDTMP

Figure 2 shows the chromatographic behavior of ^{153}Sm-EDTMP compared with that of $^{153}SmCl_3$ using systems 1 and 2. Figure 3 shows the chromatographic behavior using system 3.

The ranges of R_f values found for $^{153}SmCl_3$ and ^{153}Sm-EDTMP are presented in Table 2.

For a rapid and easy estimate of the radiochemical purity of ^{153}Sm-EDTMP, after setting up the radioactive distribution (system 3), the strips were cut in two portions. Then the activity of each portion was determined. In Figure 3 the position for strips cutting is indicated. This procedure was used for all complexing yield determinations.

Complexing yields

In basic medium ^{153}Sm-EDTMP can be readily prepared with complexing yields higher than 97.5%.

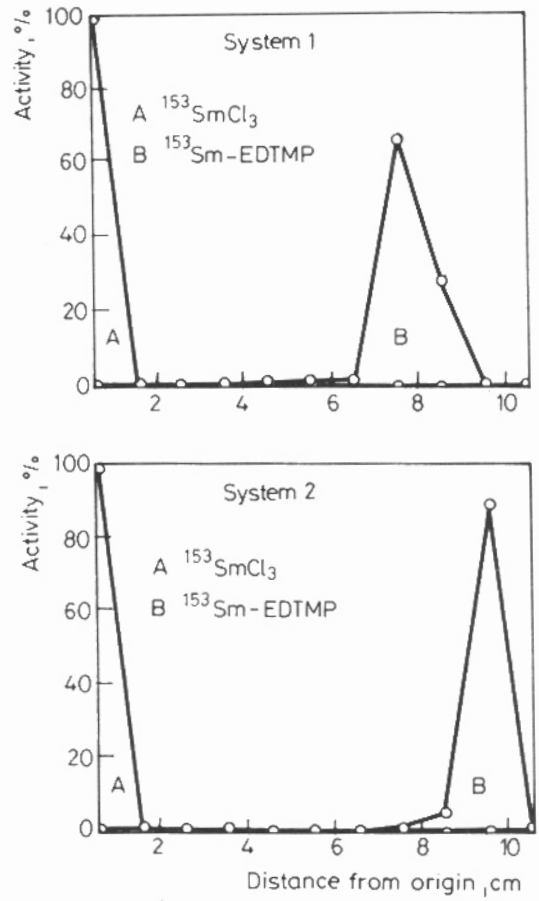

Fig. 2. Chromatographic behavior of ^{153}Sm-EDTMP and $^{153}SmCl_3$ using systems 1 and 2

The complexing yields in both methods (n=6) are given in Table 3.

^{153}Sm-EDTMP stability

The complex remained stable for at least 8 d after labeling using EDTMP in solution and after reconstitution of the kits with ^{153}Sm/HCl. Table 4 summarizes the complex stability over time.

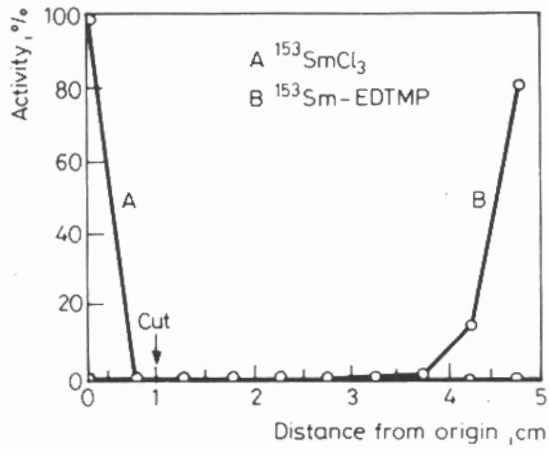

Fig. 3. Chromatographic behavior of ^{153}Sm-EDTMP and $^{153}SmCl_3$ using system 3

TABLE 2

Range of R_f values for $^{153}SmCl_3$ and ^{153}Sm-EDTMP

System	$^{153}SmCl_3$	^{153}Sm-EDTMP
1	0	0.70-0.75
2	0	0.85-0.90
3	0	0.88-0.94

ADDENDUM

Further studies showed that the developing time in the miniaturized chromatographic system can be reduced to approximately 15 min. This is possible when the solvent mixture ammonium hydroxide, ethanol, water 0.1:2:4, v/v/v is replaced by a solvent mixture ammonium hydroxide, methanol, water 0.2:2:4 v/v/v. No significant alterations

TABLE 3

%Complex yields of ^{153}Sm-EDTMP (1st day)

Labeling No.	EDTMP In solution	EDTMP In kit formulation
1	98.8	98.6
2	98.4	98.2
3	99.1	99.2
4	99.2	97.9
5	99.0	98.5
6	98.3	98.8
Mean labeling	98.8±0.4	98.5±0.5

TABLE 4

^{153}Sm-EDTMP stability (%complexing yield)

Day	Labeling EDTMP in solution			Number EDTMP in kit formulation		
	1	3	6	1	3	6
1	98.8	99.1	98.3	98.6	99.2	98.8
2	98.1	98.4	99.0	98.3	99.7	98.2
4	98.2	98.5	98.7	98.6	99.5	98.5
8	98.1	99.0	98.2	98.7	99.1	98.4

were observed for R_f values of either $^{153}SmCl_3$ and ^{153}Sm-EDTMP or for EDTMP complexing yields.

*

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