PREPARATION OF SAMARIUM-153-EDTMP: PREVIOUS RESULTS

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SUMMARY.

Samarium-153-ethylenediaminetetramethylene phosphonate (^{153}Sm-EDTMP) has been proposed to palliate pain resulting from bone cancer. This paper describes the preparation of ^{153}Sm chloride with 4 to 8 mCi/ml, the ability of ^{153}Sm to complex with EDTMP in liquid and frozen dried forms. The evaluation of radiolabelled EDTMP is made with paper chromatographic system.

INTRODUCTION

Recent advances in targeted radiotherapy offer a new approach for the management of metastatic bone pain. A great part of the malady and mortality associated with cancer can be attributed to skeletal metastases [1].

Interest in employing radiopharmaceuticals for diagnosis and cancer therapy has increased and significant advances have been possible by combined developments in the fields of new chelates and of availability of a wider range of beta emitting nuclides [2].

Many different specific tumor-seeking radiopharmaceuticals are being applied both for diagnostic scintigraphy and treatment, using multiple routes and mechanisms to targe radionuclide at tumors [3].

Samarium-153 has favourable characteristics for imaging of its biological biodistribution with a principal gamma emission energy 0.103 MeV (28%) and for therapeutical use with the mean beta emssion energy 0.227 MeV (100%). Samarium-153 has a half-life of 46.7 hrs [4].

Among ^{153}Sm chelates, EDTMP has shown promise for the treatment of bone cancer. When ^{153}Sm is chelated to EDTMP, it forms in vitro and in vivo stable complex and it concentrates in bone tumors due to high metabolic avidity for phosphorous [5]

Approximately half of the injected dose of ^{153}Sm-EDTMP in rats, rabbits and dogs localizes in the skeleton, while the remainder is rapidly excreted into the urine with minimal uptake in nonosseous tissues. The physical half-life of 153Sm-EDTMP is 1.8 days [6].

METHODS AND MATERIALS

PREPARATION OF ^{153}SAMARIUM CLORIDE

Two-four mg of natural samarium oxide (99.9% of rare earth content expressed as Sm_2O_3, BHD) is converted to samarium nitrate by dissolving it in about 40-80 ul of 1 N nitric acid.

The sample is put into a high-purity quartz irradiation vial and evaporated to dryness, leaving a thin film of samarium nitrate fixed to the botton of the quartz vial. The quartz vial is flame-sealed and encapsulated in an aluminum container for irradiation.

The irradiation of samples takes place in the research reactor (IEA-R_1/IPEN). The available thermal flux is approximately 1.0*10E13 n/cm^2*sec. A run time of 8 hrs is sufficient to produce the activity for our research.

After irradiation, the quartz vial is removed from its aluminium capsule. The sample is measured for ^{153}Sm activity, transferred to a glove-box, broken, dissolved by heating in 2.0 ml of 0.1 N hydrochloric acid, and transferred to a glass vial. The $^{153}SmCl_3$ was diluted to the appropriate volume with 0.1N hycrochloric acid to produce a stock solution (0.9 mg of Sm/ml) which was used for complex preparation.

PREPARATION OF ^{153}Sm-EDTMP

In basic medium, ^{153}Sm-EDTMP can be readily prepared with a complexing yield not less than 97.5%.

a. EDTMP in solution

The ^{153}Sm-EDTMP was set up by adding 1.0 ml of $^{153}SmCl_3$ (0,9 mg Sm) to 60 mg/1.5 ml EDTMP at pH 9 (molar ratio 1:23, Sm/EDTMP, w/w). The pH of reaction mixture was risen to 10-11 and placed in 60-70°C water bath for 30 min. After incubation the pH was adjusted to 7.5-8.

b. EDTMP in lyofilized form

A kit formulation consistes of 60 mg of lyophilized EDTMP titrated with base to pH=10.3. Addition of 1.7 ml of a 0.1N ^{153}Sm chloride solution (0.9 mg Sm) yields a solution with a pH of 7.5-8 (molar ratio 1:23,Sm/EDTMP,w/w).

QUALITY CONTROL OF ^{153}Sm-EDTMP

Chromatographic procedures: The radiochemical purity of ^{153}Sm-EDTMP was performed using Whatman 3MM paper strips (1.5 cm x 13.0 cm) as support and two mixture of solvents, pyridine:ethanol:water (1:2:4, v/v/v) and ammonia:ethanol:water (0.1:2:4, v/v/v) as developing systems. The chromatograms were developed for a distance of 11.0cm. With the chromatographic procedures using ammonia:ethanol:water and pyridine:ethanol:water, ^{153}Sm-EDTMP migrated in close proximity to the solvent front, whereas ^{153}SmCl3 remained at the origin.

A rapid evaluation of free ^{153}Sm and ^{153}Sm-EDTMP was developed using a miniaturized chromatographic system with whatman 3MM paper strips (1.0 cm x 7.0 cm) as support and ammonia:ethanol:water (0.1:2:4, v/v/v) as solvent. The chromatograms were developed for a distance of 5.5cm. All the strips, between the spot point and front solvent, were cut in 0.5 cm and each piece counted in a well-type scintillation counter (ANSR gamma counter ABBOT LAB) with a 50-150 keV.

For a rapid and easy estimate of the radiochemical purity of ^{153}Sm-EDTMP, after setting up the distribution of radioactivity on the miniaturized cromatograms, the strips were cut in two portions

(section 1 and section 2).

STABILITY STUDY OF ^{153}Sm-EDTMP

The stability of 153-Sm-EDTMP for both preparations was tested for 8 days using a miniaturized chromatographic system.

RESULTS AND CONCLUSIONS

In basic medium, the EDTMP solution and frozen dried forms are readily complexed to ^{153}Sm with yield not less than 97.5%. The complexing yields of both methods (n=6) evaluated by miniaturized chromatographic system were given in Table 1.

TABLE 1. % Complexing yields of ^{153}Sm-EDTMP.

(1^{rst} day) Labelling n=6	EDTMP in solution	EDTMP kit formulation
1	98.81	98.55
2	98.35	98.23
4	99.17	97.94
5	99.04	98.47
6	98.27	98.77

The Fig. 1 shows the chromatographic behaviour of ^{153}SmEDTMP compared with that of ^{153}Sm chloride using Whatman 3MM paper strips (15x130mm) as support and pyridine:ethanol:water (1:2:4, v/v/v) and ammonia:ethanol:water (0.1:2:4, v/v/v) as developing solvent.

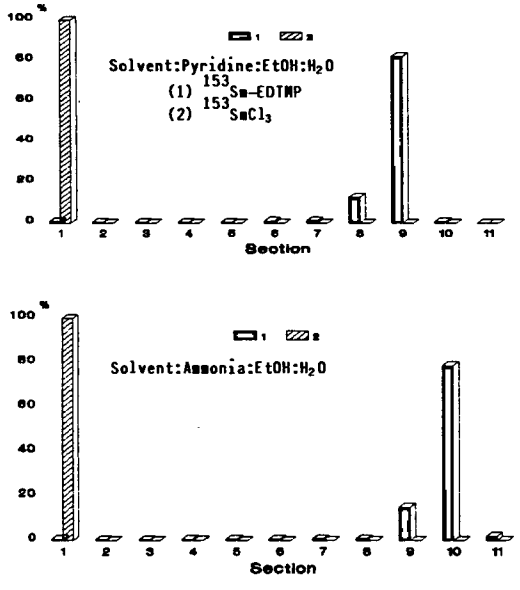

FIG 1 - Chromatographic behaviour of ^{153}Sm-EDTMP and $^{153}SmCl_3$ by using Whatmann 3M strips (15x130 mm) and ammonia:ethanol:water and pyridine:ethanol:H_2O as solvent.

The distribution of radioactivity using a miniaturized chromatographic system with Whatman 3MM paper strips (10 x 70 mm) as support and ammonia:ethanol:water (0.1:2:4, v/v/v) as solvent is given in Fig 2. In the same figure, a rapid evaluation of free ^{153}Sm and ^{153}Sm-EDTMP by cutting the cromatograms in two sections is shown.

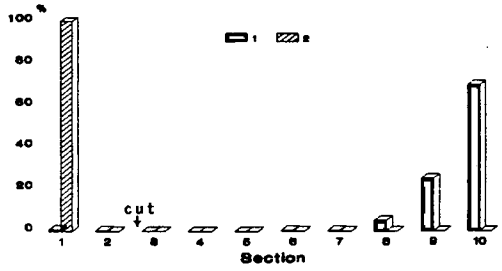

FIG 2 - Chromatographic behaviour of ^{153}Sm-EDTMP and $^{153}SmCl_3$ by using Whatmann 3M strips (10x700 mm) and ammonia:ethanol:water.

Samarium-153-EDTMP was shown to be stable for at least 8 days after labelling by using EDTMP in solution or after reconstitutuion of the kits directly with ^{153}Sm/HCl. Table 2 summarizes the stability of the final products.

TABLE 2. ^{153}Sm-EDTMP Stability Studies.

Day	EDTMP In solution (%)	EDTMP Kit formulation (%)
1	98.81	98.55
2	98.05	98.26
4	98.16	98.59
8	98.12	98.80

ACKNOWLEDGMENTS

We wish to thank M.Sc Felicitas M. Wirkner from IPEN/CNEN-SP for assistence in the graphical fitting and Dr. Mitiko Saiki from IPEN/CNEN-SP for Sm_2O_3 supply. This work was supported by Instituto de Pesquisas Energéticas e Nucleares/Comissão Nacional de Energia Nuclear-São Paulo (IPEN/CNEN-SP). The EDTMP was a gift from Monsanto do Brasil.

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