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Evaluation of the ^{153}Sm-EDTMP radiochemical purity using three chromatographic methods

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^{153}Sm-EDTMP has been widely used to palliate pain resulting from metastatic bone cancer. Its radiochemical purity is normally determined by ion exchange, paper chromatography and thin layer chromatography. Paper chromatography showed to be a rapid and reliable method, when used for the complex obtained in high ligand concentrations. However, when the complex was prepared in low ligand concentrations, the results presented significant differences from those obtained by ion exchange and thin layer chromatography. This work presents a comparative study on ^{153}Sm-EDTMP radiochemical purity determinations, using these three methods to evaluate the complex obtained in high and low ligand concentrations.

Introduction

In 1984, ^{153}Sm-EDTMP was prepared, for the first time, by GOECKELER,[1] who indicated its usefulness to palliate pain resulting from metastatic bone cancer. Now, this complex is produced in several countries. The quality control methods to determine its radiochemical purity (complexing yield), are routine procedures as ion exchange chromatography (Sephadex C-25 cationic resin columns), thin layer chromatography (TLC-SG plates) and paper chromatography.[2]

The evaluation in a Sephadex C-25 column can be performed in 20–25 minutes, while the evaluations by TLC-SG and paper chromatography can last over 60 minutes or more. It depends on the solvent mixture and on the dimensions of the strip.

In 1994, GASIGLIA and OKADA[3] presented the solvent mixture ammonium hydroxide/ethanol/water (0.1:2:4 v/v/v) for paper chromatography. Using Whatman 3 MM paper in a miniaturized system (7×1 cm^2 strips), the chromatograms were developed in 20–25 minutes, for a distance of 5 cm. The $^{153}Sm^{3+}$ was precipitated as $^{153}Sm(OH)_3$ at the origin ($R_f = 0$) and the complex ran with the solvent to the solvent front ($R_f = 0.95$). ^{153}Sm-EDTMP, obtained in molar ratio: [ligand]/[Sm] = 23 and ligand concentration of 0.06–0.08M, was evaluated using this method and it showed radiochemical purity higher than 98%.

When the solvent mixture ammonium hydroxide/ethanol/water (0.1:2:4 v/v/v) was replaced by the solvent mixture ammonium hydroxide/ /methanol/water (0.2:2:4 v/v/v), the developing time was reduced to approximately 15 minutes. No alterations were observed in the R_f values of both $^{153}Sm^{3+}$ and ^{153}Sm-EDTMP and in the complexing yields results.[4]

In further and unpublished studies by the same group, when the complex was prepared in lower ligand concentration, significant differences were observed in the labeling yields determined by paper chromatography, compared to those determined in Sephadex C-25 columns.

The aim of this work was to compare the complexing yields of the ^{153}Sm-EDTMP prepared in molar ratio = 20 and in ligand concentrations of 0.1, 0.05, 0.025 and 0.01M, determined by three different methods: ion exchange chromatography (Sephadex C-25 column), thin layer chromatography (TLC-SG) and paper chromatography (Whatman 3 MM paper).

Experimental

Preparation of $^{153}SmCl_3$

Natural samarium oxide (Sigma) was converted into samarium nitrate by dissolution with 1N nitric acid. Samarium aliquots of 10 mg were placed into high purity quartz vials and evaporated to dryness. Each vial was flame-sealed, encapsulated into an aluminum can and irradiated under a thermal flux of 1.5–3.0 n·cm^{-2}·s^{-1}. After the irradiation, the quartz vial was removed from its aluminum can in a hot cell and cut at the top. The ^{153}Sm was recovered as $^{153}SmCl_3$ by adding 2×1 ml of saline solution, under heating (80–90 °C).

Preparation of the EDTMP solution

An 0.2M EDTMP solution was prepared by dissolving the solid acid (Monsanto) with concentrated sodium hydroxide solution, under cooling condition. The pH was then adjusted to 8.0 with sodium hydroxide solution.

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Preparation of ^{153}Sm-EDTMP

The complex was prepared by mixing the EDTMP and $^{153}SmCl_3$ solutions, at room temperature, and the pH was adjusted to 7.0–7.5. The mixture was incubated during 30 minutes. Radiochemical concentrations varied from 37 to 185 MBq/ml (1 to 5 mCi/ml).

Determination of the complex radiochemical purity

By ionic exchange in Sephadex C-25 columns: Aliquots of the complex (100–200 µl) were put on the top of the 1.2 cm diameter ×2 cm height Sephadex C-25 columns (approximately 0.33 g of dry resin). The complex was eluted with 40 ml of saline solution at 1.5–2.0 ml/min whereas the $^{153}Sm^{3+}$ and the $^{153}Sm(OH)_3$, eventually formed, were retained in the columns. The columns radioactivity were measured in a dose calibrator (Capintec CRC-120) before and after the elution and decay corrections were performed. The complexing yields (CY) were calculated using this formula: CY (%) = [1-(residual activity/initial activity)] ×100.

By thin layer chromatography (TLC-SG): TLC aluminum sheets silica gel 60 (Merck) were cut into 10× 1.5 cm^2 strips for these determinations. The solvent mixture ammonium hydroxide/methanol/water (1:2:4 v/v/v) was used to develop the chromatograms for 9 cm, in 75–85 minutes. The strips were cut into 1 cm pieces and the radioactivity of each piece was measured in the ANSR gamma-counter (Abbot Laboratories). For R_f determinations, the radioactivity was assumed to be concentrated at the center of each piece. Complexing yields were determined using this formula: CY (%) = [1-(activity at the origin/total activity)] ×100.

By paper chromatography (Whatman 3 MM paper): 7×1 cm^2 paper strips (miniaturized system) and the solvent mixture ammonium hydroxide/methanol/water (0.2:2:4 v/v/v) were used for these determinations. The chromatograms were developed for 5 cm in approximately 15 minutes. The strips were cut into 0.5 cm pieces. The radioactivity measurements of each piece and R_f determinations were performed like in the TLC-SG method. For an easy and rapid determination of the complexing yields, after setting up the radioactive distribution, the strips were cut in two portions at 1 cm from the origin. The yields were calculated by the same formula used in TLC-SG determinations.

For each ligand concentration, five experiments were performed and all chromatographic determinations were performed in triplicate.

Results and discussion

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

Figure 1 shows a typical ^{153}Sm-EDTMP elution curve, obtained in Sephadex C-25 and valid for all ligand concentrations (LC). Figure 2 presents the chromatographic behavior of $^{153}SmCl_3$ (R_f = 0) and ^{153}Sm-EDTMP (R_f = 0.8–0.9) determined by TLC-SG. Figure 3 presents the chromatographic behavior of $^{153}SmCl_3$ (R_f = 0) and ^{153}Sm-EDTMP (R_f = 0.95 in LC = 0.1 and 0.05M and R_f = 0.85 in LC = 0.025 and 0.01M) determined by paper chromatography.

Complexing yields

The ^{153}Sm-EDTMP complexing yields, determined by the three methods, for all ligand concentrations, are shown in Table 1. In LC = 0.1M, the average yields determined by the three methods have practically the same value: 99.67±0.09% (Sephadex), 99.53±0.24% (TLC-SG) and 99.21±0.24% (paper). In LC = 0.05M the average yield determined by paper (98.75±0.45%) was slightly lower than those obtained in Sephadex (99.73± 0.04%) and TLC-SG (99.72±0.08%). In LC = 0.025M, the average yield determined by paper (96.80±0.89%) was approximately 3% lower than the average yields obtained in Sephadex (99.76±0.07%) and TLC-SG (99.43±0.26%). In LC = 0.01M, the average yield determined by paper (89.27±1.54%) was about 10% lower than those obtained in Sephadex (99.72±0.06%) and TLC-SG (98.75±0.74%).

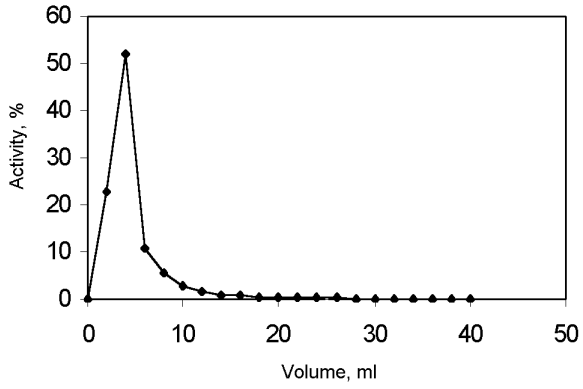

Fig. 1. ^{153}Sm-EDTMP elution curve in Sephadex C-25 resin

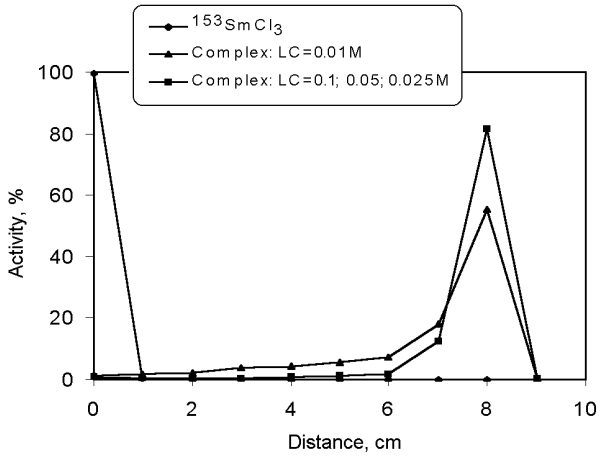

Fig. 2. Chromatographic behavior of $^{153}SmCl_3$ and ^{153}Sm-EDTMP determined by TLC-SG

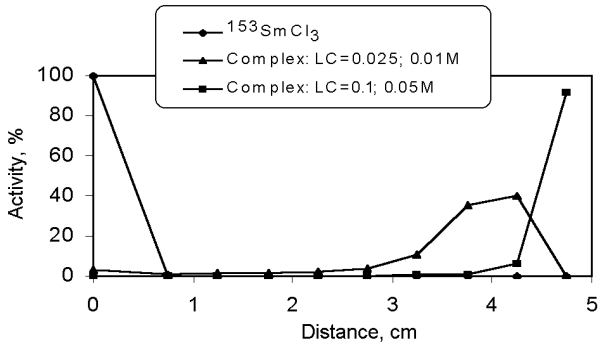

Fig. 3. Chromatographic behavior of $^{153}SmCl_3$ and ^{153}Sm-EDTMP determined by paper chromatography

Table 1. Complexing yields (in %) of ^{153}Sm-EDTMP obtained in molar ratio = 20

Ligand concentration, M	Experiment No.	Yield Sephadex	TLC-SG	Paper
0.1	1	99.71	99.32	99.34
	2	99.52	99.72	99.49
	3	99.70	99.49	99.28
	4	99.65	99.30	98.92
	5	99.76	99.84	99.00
	$\bar{x}$	99.67	99.53	99.21
	sd	0.09	0.24	0.24
0.05	1	99.74	99.76	98.82
	2	99.68	99.59	98.87
	3	99.78	99.80	99.39
	4	99.72	99.76	98.36
	5	99.73	99.68	98.29
	$\bar{x}$	99.73	99.72	98.75
	sd	0.04	0.08	0.45
0.025	1	99.64	99.17	96.81
	2	99.76	99.14	97.94
	3	99.83	99.51	97.15
	4	99.78	99.61	96.59
	5	99.80	99.73	95.50
	$\bar{x}$	99.76	99.43	96.80
	sd	0.07	0.26	0.89
0.01	1	99.79	99.39	90.74
	2	99.77	99.19	87.95
	3	99.66	99.25	87.34
	4	99.65	97.76	90.53
	5	99.75	98.16	89.80
	$\bar{x}$	99.72	98.75	89.27
	sd	0.06	0.74	1.54

These observed differences in ^{153}Sm-EDTMP complexing yields also appear to be related to the chromatogram shapes. While in Fig. 1, the elution curve is representative for all ligand concentrations, the chromatograms showed in Figs 2 and 3 were affected by ligand concentration. In Fig. 2 (TLC-SG) the chromatogram representative for ligand concentrations of 0.1, 0.05, and 0.025M showed low complex dispersion. In LC = 0.01M, it was observed a higher complex dispersion, but the chromatogram shape was kept close to that representative for the higher ligand concentrations. In Fig. 3 (paper chromatography) the

chromatogram shape changed sensibly when ligand concentration was reduced from 0.1–0.05M to 0.025–0.01M. In these lower ligand concentrations it was observed an effective complex dispersion along the chromatographic strips.

Conclusions

The results showed that the evaluations in Sephadex C-25 columns and TCL-SG presented the same results in ligand concentrations from 0.1 to 0.025M. Only in LC = 0.01M, the average yield determined by TLC-SG was slightly lower than that obtained in Sephadex. Evaluation by paper chromatography, while it is an easy and rapid method, can produce erroneous results depending on the ligand concentration. In this specific case (molar ratio = 20), paper chromatography is to be used only in ligand concentrations higher than 0.05M.

When evaluated by paper chromatography, the complex prepared in low ligand concentrations, is probably decomposed by the alkaline mixture, giving an additional $^{153}Sm(OH)_3$ precipitation and a false yield. In TCL-SG determinations, when the solvent mixture is prepared with ammonium hydroxide in higher proportion, this phenomena, however, appears to occur only in ligand concentration of 0.01M.

These results indicate the Sephadex C-25 columns as the more appropriate method to evaluate the chemical purity of the ^{153}Sm-EDTMP complex prepared in low ligand concentrations.

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