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STANNOUS ION DETERMINATION IN ^{99m}Tc RADIOPHARMACEUTICAL KITS

Maria Apparecida T. Marcilio de Almeida,
Constância Pagano Gonçalves da Silva

Comissão Nacional de Energia Nuclear - SP,
Instituto de Pesquisas Energéticas e Nucleares,
Caixa Postal 11049-Pinheiros,
05508-900-São Paulo, Brasil

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Two simple and selective methods for determination of stannous ion in radiopharmaceutical kits are proposed. One of this permits the estimation of stannic ion. The first method used is a potentiometric titration of Sn^{2+} in HCl medium, using KIO_3 solution under nitrogen gas and a platinum redox electrode. The second method consists of a complexometric titration of tin (Sn^{2+} and Sn^{4+}) using an EDTA standard solution at pH 5.5-5.6 without the use of nitrogen gas. The procedures employed indicate that both methods can be used for routine quantitative determination of tin in most labeled radiopharmaceuticals.

INTRODUCTION

The radiopharmaceutical kits preparation for ^{99m}Tc complexation involves the reducing agent Sn^{2+}. The content of stannous ion in kits is usually in the range of micrograms. The efficiency of labeling and

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stability of the kits depend upon the reducing agent concentration. Quantitative determination of tin (Sn^{2+}) content during manufacture and storage of the kits preparation assures the control of Sn^{2+} in the radiopharmaceuticals.

The methods for the determination of Sn^{2+} in radiopharmaceuticals are cumbersome[1-3] or expensive[4,5]. Among all the methods reported for this purpose no one provides satisfactory accuracy when ascorbic acid or albumin aggregates are present.

The methods proposed are: A) Potentiometric determination of Sn^{2+} with KIO_3 solution[6,7]. B) Complexometric determination of Sn^{4+} with EDTA solutions. This last method is based on the ability of EDTA to form complexes with Sn^{2+} and Sn^{4+}. Furthermore, the determinations are free from problems of tin oxidation during the process. The determination of Sn^{2+} separately from Sn^{4+} is only possible with the help of selective masking agents such as glycerol that keeps Sn^{4+} in solution[8,9]. The potentiometric titration with KIO_3 permits only the determination of Sn^{2+} but it is interesting in kits that present anions (citrate, fluoride) which form sufficiently strong complexes with tin[8].

MATERIAL AND METHODS

Tin(Sn^{2+}) standard solution prepared from $SnCl_2.2H_2O$ in 10% HCl to give a stock solution of 1 mg Sn^{2+} ml^{-1}. The stannous determination was carried out with cerium sulfate standard solution[2].

KIO_3 stock solution 0.01M: it was prepared by dissolving 0.0891 g KIO_3 in 250 ml nitrogen-treated distilled water.

The standard solutions prepared from this stock solution were adjusted to $10^{-3}M$ - $10^{-5}M$[6] prior to analyses in agreement with the stannous content of the kits.

EDTA stock solution 0.01M[9].

The standard solutions prepared from the stock solution were adjusted from $5x10^{-3}M$ to $10^{-3}M$[9] prior to analyses in agreement with the stannous content of the kits.

$Pb(NO_3)_2$ stock solution 0.01M[9].

The standard solutions prepared from the stock solution were adjusted from $5 \times 10^{-3}M$ in agreement with the standard EDTA solution used in titrations.

Xylenol orange as indicator: 0.1% aqueous solution.

Glycerol 50% v/v aqueous solution.

Acetic acid/acetate buffer 0.2M pH 5.5.

Redox platinum electrode attached to a pH Meter E-520 Methrohm Herisau Potentiometer.

Radiopharmaceutical kits analyzed:

A. Potentiometric method: Diethylene triamine pentaacetic acid (DTPA);
Methylene diphosponate (MDP);
Stannous citrate;
Iminodiacetic acid diisopropyl ester (DISIDA);
Iminodiacetic acid n-butyl ester (Butyl-IDA);
Sodium phytate;
Stannous fluoride;
Sodium pyrophosphate (PYR);

B. Complexometric method: Sodium pyrophosphate (PYR);
Calcium gluceptate;
Stannous ascorbate;
Sodium phytate;
Human Albumin Macroaggregated (MAA).

Procedure A: Potentiometric

A platinum redox electrode and a teflon coated bar for magnetic stirrer are placed into a titration flask under a stream of nitrogen gas; 10 ml of 1M HCl is placed into the flask with the lyophilized content of the kit. The solution is immediately titrated with the standard KIO_3 solution of the required concentration. The standard titration curve is characteristic for the potentiometric Sn^{2+} titration with KIO_3 standard solution and presents a potentiometric response of about 300 mV at the end of the titration.

The stannous (Sn^{2+}) content in the aliquot was calculated using the relationship: each ml of 0.01M KIO_3 stock solution is equivalent to 0.594 mg Sn^{2+}.

Procedure B: Complexometric

An excess of EDTA standard solution in the required concentration is added to 10 ml acetic acid/acetate buffer pH 5.5 and 10 ml 50% glycerol solution in a titration flask. The lyophilized kits are reconstituted with 2 ml of water and the solution placed into the titration flask. The excess of EDTA is titrated with $Pb(NO_3)_2$ standard solution and xylenol orange as indicator: at the end point the yellow sharp color changes to pink. The stannous (Sn^{2+}) content in the aliquot was calculated using the relationship: each ml of 0.01M EDTA standard solution is equivalente to 1.1869 mg Sn^{2+}.

RESULTS AND DISCUSSION

The potentiometric method studied by several authors was adapted here for the analysis of kits without ascorbic acid in the formulation. The complexometric method

TABLE 1

Potentiometric analysis of Sn^{2+} in various radiopharmaceutical kits (minimum 6 titrations)

Type of kit	KIO_3 standard solution, M	Sn^{2+} stated, mg	Sn^{2+} found, mg
MDP	$5x10^{-4}$	0.394	0.392 ± 0.02
DTPA	$2x10^{-4}$	0.131	0.123 ± 0.015
PYR	10^{-3}	1.052	1.049 ± 0.046
Sn citrate	10^{-3}	1.052	1.060 ± 0.014
DISIDA	$5x10^{-4}$	0.263	0.289 ± 0.022
Butyl-IDA	$5x10^{-4}$	0.263	0.253 ± 0.007
Na phytate	$5x10^{-4}$	0.526	0.485 ± 0.020
SnF_2	$2x10^{-4}$	0.094	0.087 ± 0.007

was adapted in analysis of kits where the presence of ascorbic acid or proteins makes the procedure with KIO_3 solution impossible.

The evaluation data of kits are presented in Tables 1 and 2. The products were analyzed prior to their expiration date and the results are in agreement with respect to the radiochemical purity of higher than 95% in all kits analyzed.

Table 3 shows the deterioration of Sn^{2+} which occurs several months after the expiration date. These results are in agreement with the radiochemical analysis and in some kits the Sn^{4+} analyses confirm oxidation of the kit content.

The two methods for Sn^{2+} determination in the radiopharmaceutical kits prepared in our Institute require no elaborated equipment or special reagents to carry

TABLE 2

Complexometric analysis of Sn^{2+} in various radiopharmaceutical kits (minimum 6 titrations)

Type of kit	EDTA standard solution, M	Sn^{2+} stated, mg	Sn^{2+} found, mg
PYR	$5x10^{-3}$	1.052	1.045 ± 0.014
Ca gluceptate (with ascorbic acid)	$2x10^{-3}$	0.135	0.141 ± 0.019
Na phytate	$2x10^{-3}$	0.530	0.525 ± 0.043
MAA	10^{-3}	0.053	0.059 ± 0.003
*Stannous ascorbate	10^{-2}	32.8	29.20 ± 2.96

*Kits content diluted (2 μg/aliquot) prior to the complexometric titration.

TABLE 3

Potentiometric and complexometric analysis of Sn^{2+} in radiopharmaceutical kits after the expiration date, relative to the fresh lyophilized product

Type of the kit	Month after expiration date	Sn^{2+} found, %
MDP	4	84.84
	7	52.50
	12	52.50
	16	53.00
PYR	7	51.92
	21	52.55
DISIDA	8	41.23
DTPA	5	82.72

out the procedures. The methods are very simple and adaptable to the analysis of Sn^{2+} content in most radiopharmaceutical kits for labeling with ^{99m}Tc.

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