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Maria Apparecida T. Marcilio de ALMEIDA and Constância Pagano Gonçalves da SILVA

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DEPARTAMENTO DE PROCESSAMENTO

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DETERMINAÇÃO DO ION ESTANOSO EM CONJUNTOS DE REATIVOS LIOFILIZADOS PARA MARCAÇÃO COM ^{99m}Tc.

Maria Apparecida T. Marcilio de ALMEIDA
Constância Pagano Gonçalves da SILVA

COMISSÃO NACIONAL DE ENERGIA NUCLEAR
INSTITUTO DE PESQUISAS ENERGÉTICAS E NUCLEARES
Caixa Postal 11049 - Pinheiros
05499 - São Paulo - Brasil

RESUMO

Propomos a utilização de dois métodos simples para a determinação de Estanho (Sn^{+2}) em conjuntos de reativos liofilizados para marcação com ^{99m}Tc. Um dos métodos permite a quantificação do íon estanoso procedendo-se a uma titulação potenciométrica de Sn^{+2} em meio clorídrico e atmosfera de nitrogênio, com solução padronizada de KIO_3. Outro método empregado consiste na titulação potenciométrica de estanho (Sn^{+2} e Sn^{+4}) com solução padronizada de EDTA em pH 5,5 não havendo necessidade do emprego de nitrogênio durante a titulação. Ambos os métodos indicaram-nos que são adequados para utilização em determinações quantitativas rotineiras de conjuntos de reativos liofilizados contendo Sn^{+2} como redutor para marcação com ^{99m}Tc.

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ABSTRACT

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 redox platinum electrode. The second method consist of a complexiметric tiration of tin (Sn^{+2} and Sn^{+4}) using EDTA standart solution at pH 5.5-5.6 without use of nitrogen gas. The employed procedures indicates that both the 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}, and the content of stannous ion in kits is usually in the range of micrograms. The efficiency of labeling and stability of the kits depend upon the reducing agent concentration. Quantitative determination of tin (Sn^{+2}) content during the manufacture and storage of the kits preparations assures the control of Sn^{+2} in the radiopharmaceuticals.

The methods for the determination of Sn^{+2} in radiopharmaceuticals are cumbersome (2) (4) (9) or expensives (3) (5). Among all the methods reported for this purpose no one provides satisfactory accuracy when ascorbic acid is present or in albumin aggregates.

The methods proposed are: A) Potentiometric determination of Sn^{+2} with KIO_3 solution (1) (6); B) Complexometric determination of Sn^{+2} and 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 glycerol that keeps Sn^{+4} in solution (7) (8). The potentiometric titration with KIO_3 permits only determination of Sn^{+2} but it is interesting in kits that present anions (citrate, fluoride) which form suficiently strong complexes with tin (7).

MATERIAL AND METHODS

Tin (Sn^{+2}) standard solution prepared by $SnCl_2.2H_2O$ in 10% HCl to give a stock solution of 1mg Sn^{+2} /ml. The stannous determination was carried out with Cerium sulphate standard solution (4).

KIO_3 stock solution 0.01N: was prepared by dissolving 0.0891g KIO_3 in 250 ml nitrogen treated distilled eater.

The standard solutions prepared from the stock solution were adjusted from 10^{-3} N to 10^{-5} N (1) prior to analyses in agreement to the stannous content of the kits.

EDTA stock solution 0.01M (8).

The standard solutions prepared from the stock solution were adjusted from 5 x 10^{-3}M to 10^{-3} M (8) prior to analyses in agreement to the stannous content of the kits.

$Pb(NO_3)_2$ stock solution 0.01M (8).

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

Xylenol Orange as indicator: 0.1% aqueous solution.

Glycerol 50% v/v aqueous solution.
Acetic acid/Acetate buffer pH 5.5.
Redox platinum electrode attached to pH Meter E-520 Methrohm Herisau Potentiometer.
Radiopharmaceutical Kits analysed:

A. Potentiometric method: Diethyl triamino pentacetic acid (DTPA);
Methylen diphosphonate (MDP);
Stannous Citrate;
Iminodiacetic diisopropyl derivative (DISIDA);
Iminodiacetic n-butyl derivative (Butyl-IDA);
Sodium phytate;
Stannous fluoride;
Sodium pyrophosphate (PYR);

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

Procedure A - Potentiometric:

A redox platinum electrode and a teflon coated bar for magnetic stirrer are placed into a titration flask under a stream of nitrogen gas; 10 ml 1N HCl are placed into the flask with the lyophilized content of the kit. The solution is immediately titrated with the standard KIO_3 solution in 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 300mV at the end of the titration.

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

An excess of EDTA standard solution in the required concentration is added to 10ml acetic acid/acetate buffer pH 5.5 and 10ml 50% glycerol solution in a titration flask. The lyophilized kits are reconstituted with 2ml 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 colour changes to pink. The stannous (Sn^{+2}) content in the aliquot was calculed using the relationship: each ml of 0.01M EDTA standard solution is equivalent to 1.1869mg Sn^{+2}.

TABLE 1

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

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

TABLE 2

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

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

Note: *Kit content diluted (2μg/aliquot) prior the complexometric titration.

TABLE 3

Potentiometric and complexometric analysis of Sn^{+2} in radiopharmaceutical kits after expiration date, relatively 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

DISCUSSION AND RESULTS

The potentiometric method studied by several authors was adapted here for the analysis of kits without ascorbic acid in the formulation. The complexometric method was adapted in analysis of kits where the presence of ascorbic acid or proteins makes impossible the procedure with KIO_3 solution.

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

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

The two methods for Sn^{+2} determination in the radiopharmaceutical kits, prepared in our Institut require no elaborated equipment or especial reagents to carry out the procedures. The methods are very simple and adaptable to the analysis of Sn^{+2} content in most of radiopharmaceutical kits for labeling with ^{99m}Tc.

REFERENCES

1. CHERVU, L.; VALLABHAJOSYULA, B.; MANI, J.; CHUN, S.; BLAUFOX, M. Stannous Ion Quantitation in ^{99m}Tc Radiopharmaceutical Kits. Eur.J.Nucl.Med. 7: 291-293, 1982.

2. HAMBRIGHT, P.; ADABI, A. REID, J; MAITLAND, D.; PRESS, H. Jr.; CHERRY, M. Rapid spot test for stannous tin levels in ^{99m}Tc Kits. J.Nucl.Med.Technol. 5: 88-89, 1977.

3. KATO-AZUMA, A. & HAZUE, M. A new method for stannous Tin level determination in Ki' reagent for ^{99m}Tc radiopharmaceutical using Sn-Re redox coupling. In: KFA JULICH GmbH, Radio-pharmaceutical chemistry: proceedings of the 4th international simposium on Radiopharmaceutical Chemistry held in Julich, 23-27 August, 1982. Julich, Alemanha, p. 270, 1982.

4. KOLTHOFF, I.; ELVING, P.; SANDELL, B. Treatise on Analytical Chemistry, N.Y., Interscience, 1961.

5. McBRIDE, M.; GEORGE, R.; KESSLER, W.; SHAW, M. Stannous ion quantitation in pyrophosphate and polyphosphate radio - pharmaceutical kits using differential pulse polarography. J.Pharm.Sci. 66: 870-871, 1977.

6. MEINKEN, G.; SRIVASTA, S.; RICHARDS, R. Determination of micrograms of stannous tin in technetium labeling kits. J.Nucl. Med. 21: p.78, 1980.

7. PRIBIL, R. Applied Complexometric, Oxford, Pergamon Press, p.139-143, 1982.

8. RAOOT, K.; RAOOT, Sarala Selective Complexometric Determination of tin with mercaptans as releasing agents. Talanta 31 (6): 469-471, 1984.

9. SANDELL, E. B. Colorimetric Determination of traces of Metals 3 ed. New York, N.Y., Willey Interscience, p. 852, 1959.