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Tin Quantification in Lyophilized Reagents by Dithiol Spectrophotometric Method

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1. Introduction

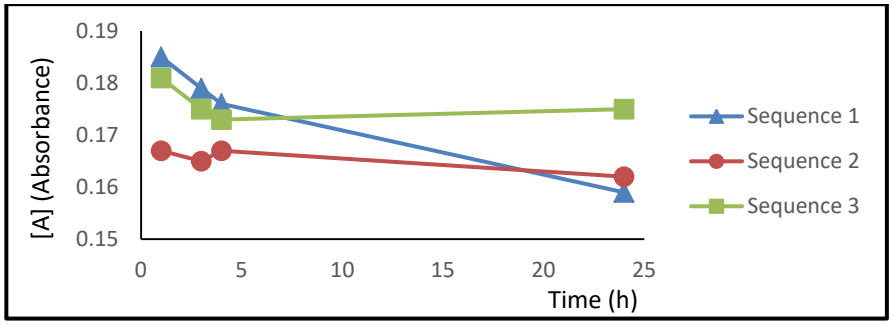
In Brazil, National Sanitary Surveillance Agency (ANVISA) regulates the commercial production of radiopharmaceuticals through RDC 658/2022 [1] and 128/2022 [2]. Radiopharmaceuticals must be analyzed according to the tests and must meet the specifications described in monographs, i.e. radiochemical purity, radionuclidic purity, chemical purity, bacterial endotoxins, sterility test and other tests from general chapter applicable to the product [3]. The radiochemical purity of ^{99m}Tc-radiopharmaceutical labeling is strongly dependent of the presence of the reducing agent in the proper chemical form at the time of addition of $Na^{99m}TcO_4$. Stannous ion, Sn(II), is used as a reducing agent in the range of approximately 30–1500 μg in lyophilized reagent (LR) preparation. There are many methods for tin quantification, as ICP (inductively coupled plasma) analysis, redox titration, and polarographic methods, but a specific requirement for tin in LR, based in the reaction with 4-methyl-1,2-dimercaptobenzene (dithiol) is described in European Pharmacopoeia (EP) [4]. Clark was one of the first to study the use of dithiol as reagent for spot test and colorimetric determination of tin and observed that a pink color developed within seconds if stannous ion is present; with stannic ion the color took longer to develop and the test was less sensitive [5]. A trace of thioglycolic acid was added, the whole tin was rapidly reduced and the sensitivity of the test became independent of the initial state of oxidation of tin [6]. The objective of this work was to quantify the tin content in lyophilized reagents (DEX-500-TEC, ECD-TEC and TIN-TEC) using dithiol spectrophotometric method described in European Pharmacopoeia.

2. Methodology

Dithiol, thioglycolic acid and sodium lauryl sulfate (SDS) (Sigma-Aldrich) solutions were prepared according to LR monograph and procedure described in the European Pharmacopoeia [4]. 1900i Shimadzu UV-VIS spectrophotometer was used, and the absorbance measurements were carried out at wavelength of 532 nm. A 5 ppm tin standard solution was prepared, and the sequence of addition of the reagents and the stability of the complex tin-dithiol in the cuvette was evaluated measuring the absorbance up to 24 hours (n=1 for each sequence). Calibration curves of Sn in 0.50-10.0 ppm (μg/mL) concentration range was obtained to quantify tin in DEX-500-TEC, ECD-TEC and TIN-TEC.

3. Results and Discussion

European Pharmacopeia [4] describes in the monographies of lyophilized reagents a procedure for tin quantification based in the reaction of tin and dithiol adding the solutions in the cuvette, in the sequence: standard solution, thioglycolic acid, dithiol and SDS. In a previous work, we observed that the method was not selective to Sn(II) but is applicable to tin total quantification and also that the appearance of color and turbidity were dependent of the sequence of addition of these reagents. Since Williams and Whitehead introduced surfactant as dispersing agent to improve the stability of tin-dithiol color complex [7], we tested the addition of SDS prior dithiol or standard solution in the reaction medium. In this work, we evaluated the influence of the sequence of the addition of the reagents and the results of the stability of the color of the complex tin-dithiol up to 24 hours are described in Fig. 1.



Sequence	Reagents
1	Standard solution > thioglycolic acid> dithiol > SDS
2	Standard solution > SDS > thioglycolic acid> dithiol
3	SDS > thioglycolic acid> dithiol > Standard solution

Figure 1: Influence of sequence of addition of the reagents to the stability of tin-dithiol complex color

Fig. 1 shows that the Sequence 3, i.e., SDS, thioglycolic acid, dithiol and sample produced a more stable complex. In the sequence established in European Pharmacopeia the color fades indicating that the complex tin-dithiol degraded.

Fig. 2 presents the calibration curve of tin in 0.50-10.0 ppm range by using Sequence 3 for addition of the reagents of dithiol method.

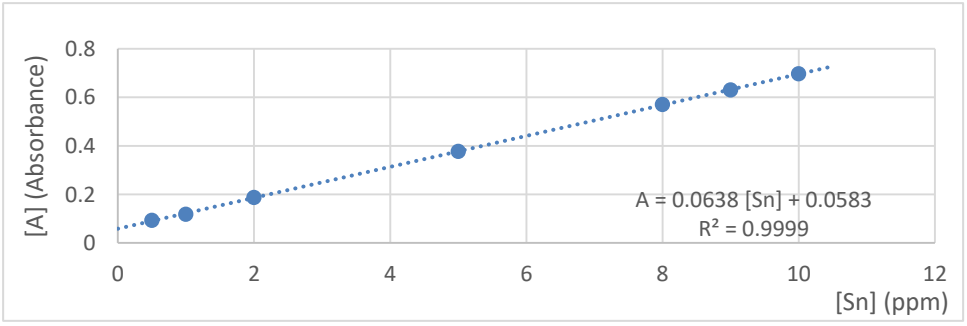


Figure 2: Calibration curve of tin by using Sequence 3 of dithiol method.

The equation of the analytical curve was A = 0.0638 [Sn] + 0.0583 and r > 0.99, indicating good correlation in the range. The linearity of the curve was up to 20 ppm; between 20 and 60 ppm there is not a linear increase in the absorbance with the tin concentration.

Tin concentration in DEX-500-TEC, ECD-TEC and TIN-TEC LR were determined. Each LR has distinct mass of stannous chloride dihydrate and the percentages of recovery calculated by ratio of the mass of tin from dithiol method related to mass of tin from formulation of LR are represented in Table I.

Table I: Recovery (%) of tin in LR with dithiol method

Product	% Tin recovery in LR
DEX-500-TEC	100.1%
ECD-TEC	47.5%
TIN-TEC	39.6%

Tin quantification in the DEX-500-TEC showed satisfactory result (100%) with no interference in the recovery percentage. On the other hand, low recovery of tin in ECD-TEC (47.5%) may be caused by EDTA complexing agent present in the formulation. TIN-TEC developed a different color (yellowish) and consequent low tin recovery (39.6%), probably due the fluoride ion, or another excipient, interfering in the development of the complex tin-dithiol. The interference of each raw material on the method needs to be evaluated.

4. Conclusions

Dithiol spectrophotometric method described in European Pharmacopoeia is useful for total tin determination but it is necessary to evaluate the interference of each component of LR formulation. The presence of complexants stronger than dithiol can suppress or change the formation of tin-dithiol complex, interfering in the color development and in the analytical signal. Therefore, the European pharmacopoeia method for determining tin with dithiol cannot be applied to samples with matrices containing complexing agents without study of the interference.

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