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Physico-Chemical Stability of Sodium Thiosulfate Infusion Solutions in Polyolefin Bags at Room Temperature over a Period of 24 Hours

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Abstract

Background: Many publications described sodium thiosulfate used to prevent the renal toxicity induced by cisplatin hyperthermic intraperitoneal chemotherapy. After around 60 or 90 minutes of hyperthermic chemotherapy, cisplatin was drained and then, sodium thiosulfate was infused by intravenous route. Sodium thiosulfate is used in two steps: a first step, at 9 g/m^2 in 250 mL of 0.9 % sodium chloride over 10 minutes followed by a second step, at 12 g/m^2 in 1000 mL of 0.9 % sodium chloride over 6 hours. The purpose of this work was to study the stability of sodium thiosulfate at 16 mg/mL in 0.9 % sodium chloride polyolefin bags 1000 mL and at 72 mg/mL in 0.9 % sodium chloride polyolefin bags 250 mL, at 25 °C, protected or unprotected from light.

Methods: Chemical stability was analysed by high performance liquid chromatography (HPLC) coupled to a photodiode array detector after preparation and after 6-hour or 24-hour storage. The method was validated according to the International Conference on Harmonisation (ICH). Physical stability was evaluated by visual and subvisual inspection (turbidimetry by UV spectrophotometry at 550 nm). Three bags for each condition were prepared. On each time of the analysis, three samples were prepared for each bag and analysed by HPLC. pH values were evaluated on each moment of the analysis.

Results: Sodium thiosulfate solutions diluted in 0.9 % sodium chloride at 16 and 72 mg/mL retained more than 95 % of the initial concentration during 24 hours. Concerning pH measurements, the maximum variation was 0.24 pH unit. No visual modification such as colour change, precipitation or gas formation was observed. The absorbance at 550 nm obtained for each sample was less than 0.010 AU.

Conclusions: Sodium thiosulfate solutions at 16 mg/mL in 1000 mL 0.9 % sodium chloride and at 72 mg/mL in 250 mL 0.9 % sodium chloride are stable physically and chemically over a period of 24 hours at 25 °C, with or without protection from light. This stability study allows the use of sodium thiosulfate in renal protection protocols during cisplatin hyperthermic intraperitoneal chemotherapy.

Keywords: stability drug, chemotherapy, nephroprotective, sodium thiosulfate

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Introduction

Sodium thiosulfate (Figure 1) is an inorganic compound used as an antidote to cyanide poisoning [1]. Bishop *et al.* described "the two chemical processes which significantly affect the stability of thiosulfate" [2]:

Oxidation decomposition: $S_2O_3^{2-} + 2O_2 + H_2O \rightarrow 2SO_4 + 2H^+$

Acid decomposition: $S_2O_3^{2-} + H^+ \rightarrow HSO_3^- + S$

Okabe *et al.* described another indication for sodium thiosulfate to prevent the incidence of chemotherapy-induced renal toxicity after an intraoperative intracavitary hyperthermic chemotherapy with

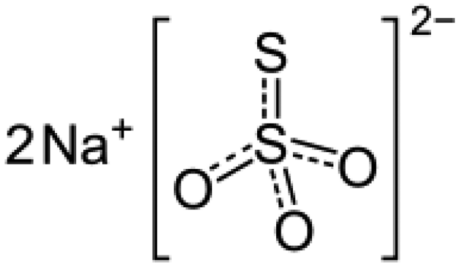

Figure 1: Chemical structure of sodium thiosulfate.

cisplatin [3]. This technique is used to treat malignant pleural mesothelioma. Sodium thiosulfate forms an inactive complex with cisplatin. Richards *et al.* described a detailed procedure where they used sodium thiosulfate: "after tumor resection, a 1-hour intracavitary lavage [...] with a solution of cisplatin in dialysate maintained at 42 °C. [...] Immediately after the lavage, intravenous sodium thiosulfate was administered for renal protection as a 4 g/m^2 bolus in 250 mL over 10 minutes followed by 12 g/m^2 over 6 hours." [4]. Teng *et al.* reported a case of a patient with pleural metastasis of ovarian carcinoma and treated with hyperthermic intrathoracic chemotherapy by cisplatin during 60 minutes. After this contact time, cisplatine was drained and ringer lactate was used to flush. They used the same protocol and posology as in a publication by Richards *et al.* [5]. Van Driel *et al.* recently added intravenous sodium thiosulfate in patients with newly diagnosed stage III epithelial ovarian, fallopian tube, or peritoneal cancer which are treated with cytoreductive surgery with cisplatine hyperthermic intraperitoneal chemotherapy (HIPEC). To prevent nephrotoxicity, sodium thiosulfate was administered at the start of perfusion as an intravenous bolus (9 g/m^2 in 200 mL), followed by a continuous infusion (12 g/m^2 in 1000 mL) over 6 hours. [6]. The use of thiosulfate allowed in a high dose of cisplatin administration (100 mg/m^2) with no renal failure reported. The addition of HIPEC to interval cytoreductive surgery in these patients resulted in longer recurrence-free survival and overall survival than surgery alone, and has become a new standard of treatment.

In the literature, the stability data available on sodium thiosulfate are limited [2, 7, 8]. The purpose of this work was to study the stability of sodium thiosulfate at 72 mg/mL in 250 mL of 0.9 % sodium chloride and at 16 mg/mL in 1000 mL of 0.9 % sodium chloride, at 25 °C, protected and unprotected from light after preparation of bags and after 6 hours and 24 hours. The low concentration corresponds to the infusion of 12 g/m^2/1000 ml for a patient with a Body Surface Area (BSA) of 1.33 m^2. The high concentration corresponds to the infusion of 9 g/m^2/250 mL for a patient with a BSA of 2 m^2 [6].

Materials and methods

Preparation of test solutions

All manipulations were performed inside a biological safety cabinet.

Stability study in polyolefin bags: Easyflex® 0.9 % sodium chloride 250 mL (MacoPharma, batch 17K24B, Easyflex®), 1000 mL (MacoPharma, batch 824016L13A, Easyflex®) and sodium thiosulfate 25 % (Natriumthiosulfat® 25 %, Solution for Infusion, Dr F. Köhler Chemie, batch 1,708,711–02/2019) were used.

The bags are overfilled compared to the theoretical volume of 250 mL and 1000 mL. In this stability study, the 0.9 % sodium chloride bags are filled to 263 mL and 1016 mL respectively. This overfilling was removed for this stability study.

For the preparation of the concentration at 72 mg/mL, 72 mL of 0.9 % sodium chloride was removed and 72 mL of sodium thiosulfate 25 % were injected in a 250 mL 0.9 % sodium chloride bags. For the preparation of the concentration at 16 mg/mL, 64 mL of 0.9 % sodium chloride was removed and 64 mL of sodium thiosulfate 25 % were injected in a 1000 mL 0.9 % sodium chloride bags. Three preparations were realised for each concentration and stored at 25 °C in a climatic chamber with light protection and in a room under fluorescent light.

Chemical stability of solutions

HPLC assay

Sodium thiosulfate concentrations were analysed by a stability-indicating reversed-phase high-performance liquid chromatography (RP-HPLC) assay with photodiode array detection. A liquid- chromatography validated method was used as described by Schulz L. *et al* [7]. The HPLC system consisted of an ELITE LaChrom VWR/Hitachi plus autosampler, a VWR photodiode array (PDA) detector L-2455 and a VWR L-2130 HPLC-pump. Data were acquired and integrated by using EZChrom Elite (VWR, Agilent). The column used was LiChrospher® 100 RP-8, LiChroCART® 125–4, particle size 5 µm, length 12.5 cm

(Analytical Chromatography, Merck) at 25 C°. The mobile phase consisted of 1.361 g/L potassium dihydrogen phosphate (KH_2PO_4; Merck; lot no. AMM044447): solution 1. Tetrabutylammonium hydrogen sulfate 1.698 g/L (Acros Organics; lot no. A0390610) was dissolved in a solution of methanol:solution1 (15:85) (Methanol; Carlo Erba-Dasit Group; lot no. AM0444477402). The pH was adjusted at 7.0 with sodium hydroxide 1N (Merck; lot no. B0764495526).

The flow rate was set at 1 mL/minute, with an injection volume of 10 µL. The detection wavelength was set at 210 nm. The temperature of the injector was set at 20 °C. Under these conditions, the retention time of sodium thiosulfate was around 4.5 minutes. The calibration curve was constructed from plots of peak area versus concentration. The linearity of the method was evaluated for five concentrations (140, 160, 180, 200, 220 µg/mL).

Ten millilitres of sodium thiosulfate 250 mg/mL were diluted in 1000 mL of 0.9 % sodium chloride. This solution was used to prepare standard curves by diluting with 0.9 % sodium chloride. The repeatability and intermediate precision were assessed at three concentrations 140 µg/mL, 180 µg/mL and 220 µg/mL, 80, 100 and 120 % of the targeted concentration of sodium thiosulfate. Repeatability and intermediate precision were expressed as relative standard deviation (RSD). For intermediate precision, three injections of the three different concentrations were assayed daily on three consecutive days. To demonstrate the specificity of the method, a solution for each excipient of sodium thiosulfate 25 % [1] (glycine, sodium hydroxide, sodium chloride, disodium phosphate dodecahydrate, edetate of sodium) was realised and analysed by HPLC.

The stability-indicating capability of the method was evaluated by analysing forced degraded sodium thiosulfate solutions.

Acidic degradation: a solution of 720 µg/mL sodium thiosulfate 1 mL was diluted with 1 mL HCl 0.5 M stored at 25 °C for 60 minutes, neutralised by 1 mL of NaOH 0.5 M and diluted with 1 mL of 0.9 % sodium chloride to obtain a theoretical concentration of 180 µg/mL.

Oxidative degradation: a solution of 720 µg/mL sodium thiosulfate 1 mL was diluted with 1 mL H_2O_2 0.3 % (Merck; lot no. K487438107B) stored at 25 °C, diluted with 2 mL of 0.9 % sodium chloride to obtain a theoretical concentration of 180 µg/mL.

UV degradation: a solution of 180 µg/mL sodium thiosulfate was exposed 20 minutes under a sun-like spectrum lamp at 254 nm (Vilbert Lourmat®).

Alkaline degradation: a solution of 720 µg/mL sodium thiosulfate 1 mL was diluted with 1 mL NaOH 0.1 M or 0.5 M or 1 M, stored at 25 °C for 60 minutes, neutralised by respectively 1 mL of HCl 0.1 M or HCl 0.5 M or HCl 1 M and diluted with 1 mL of 0.9 % sodium chloride to obtain a theoretical concentration of 180 µg/mL.

Heat degradation: a solution of 180 µg/mL sodium thiosulfate was exposed for 12 hours at 60 °C.

Sample dilution for analysis by RP-HPLC

At each time of the analysis, 15 mL were removed from each bag. The solutions were diluted before analysis with 0.9 % sodium chloride to obtain a concentration at 180 µg/mL for bags at 72 mg/mL and at 192 µg/mL for bags at 16 mg/mL. Samples were prepared in triplicate. After dilution, each sample was analysed by RP-HPLC. This process was repeated after a 6-hour and a 24-hour storage.

Total run time was set at 10 minutes.

Stability was defined as not less than 95 % of the initial sodium thiosulfate concentration [9].

pH measurement

The determination of the pH was performed using a Crison pH-meter pH25. Analysis was carried out directly after preparation and after 6 hours and 24 hours. pH measurements were considered to be acceptable if they did not vary by more than 1 pH unit from the initial measurement [10].

Physical stability of solutions

Physical stability was defined as the absence of particulate formation, haze, colour change, precipitation and gas evolution [11]. The samples were visually inspected against a white/black background with unaided eye at each analysis time. The subvisual aspect was assessed by using a Safas Monaco UV mc^2 spectrophotometer. The absorbance light was scanned at 550 nm [9]. The absorbance of more than 0.010 AU was considered as an evidence of turbidity, providing a quantitative determination of incompatibility. An absorbance reading less than 0.010 AU was considered to be a noise level [12].

Results

Reversed phase HPLC

The calibration curve was linear, the correlation coefficient was 0.99981. The equation of the calibration curve was y = 36,474.3644 x −188,492.067. The intra-day precision expressed as relative standard deviation (RSD) was between 0.08 % and 0.87 %. The intermediate precision expressed as relative standard deviation (RSD) was 0.40 % at 140 µg/mL, 0.56 % at 180 µg/mL and 0.82 % at 220 µg/mL. There is no interference observed on the chromatogram between sodium thiosulfate, excipients and degradation products.

Stability indicating capacity was proved by using various stressed conditions. A chromatogram without stressed degradation is presented in Figure 2. Chromatograms obtained after acidic, oxidative and UV light stressed conditions are presented in Figures 3, 4 and 5 respectively. After acidic, oxidative and UV light stressed conditions, 12 %, 11 % and 16 % of sodium thiosulfate were degraded respectively. The drug was subjected to alkaline and heat degradation, but no significant degradation of sodium thiosulfate was observed.

Chemical stability of solutions

HPLC assay

The mean percentage of the initial concentration for samples is represented in Table 1.

pH measurement

All samples had a pH in the range of 8.78 to 9.06 during the study. No significant modification of pH was observed during the whole stability study. The maximum variation obtained between the time of assay and time of preparation was 0.24 pH unit (Table 2).

Physical stability of solutions

Visual aspect

Visual examination of the samples under white light and against white/black showed no evidence of colour change, precipitation or gas development.

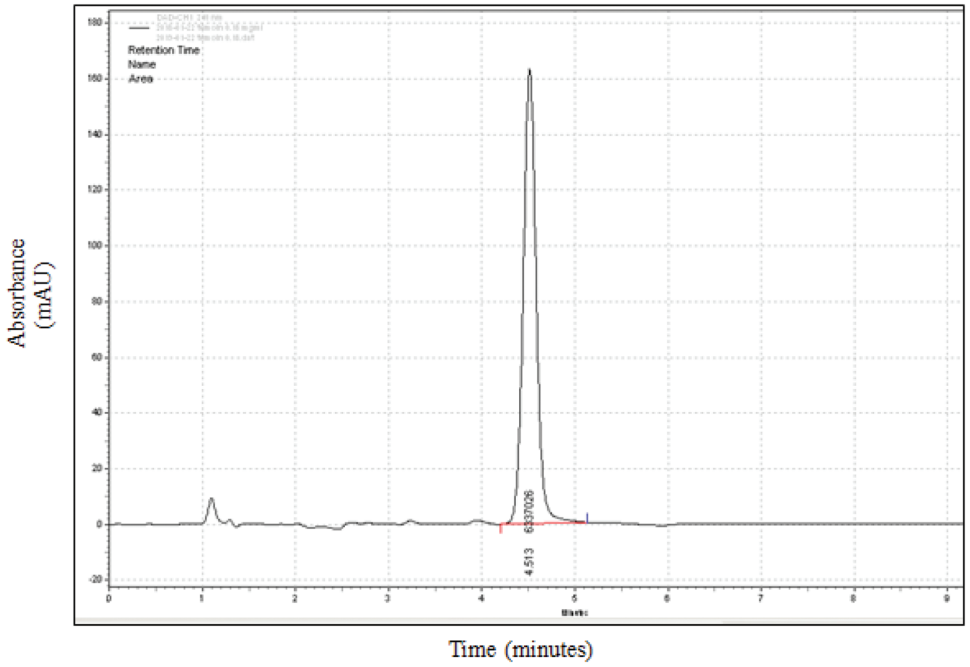

Figure 2: Chromatogram of sodium thiosulfate 180 µg/mL in 0.9 % sodium chloride without stressed conditions.

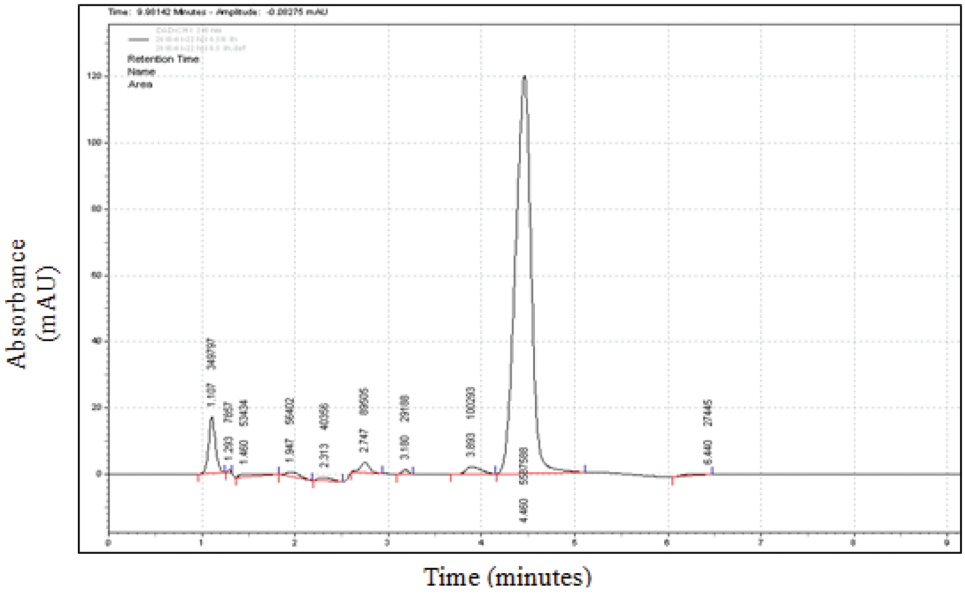

Figure 3: Chromatogram of sodium thiosulfate 180 µg/mL after acidic stressed conditions.

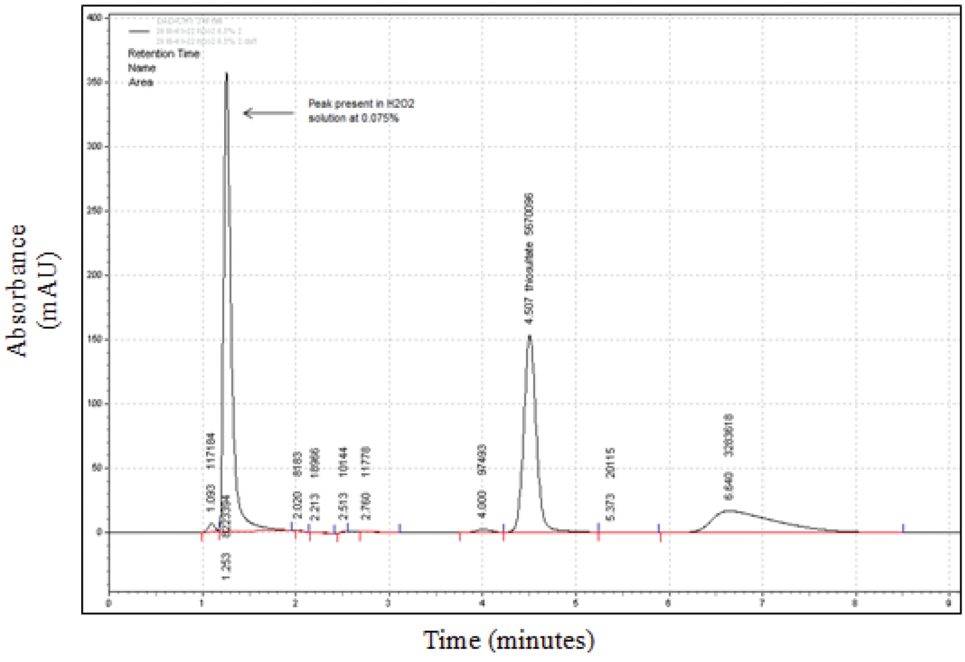

Figure 4: Chromatogram of sodium thiosulfate 180 µg/mL after oxidative stressed conditions.

Subvisual aspect

Concerning turbidity, no change was observed during all the stability study. The absorbance obtained for each sample on each time of analysis was less than 0.010 AU.

Discussion

Our results suggest that sodium thiosulfate infusion solutions (16 mg/mL and 72 mg/mL) diluted in 0.9 % sodium chloride are physico-chemically stable for 24 hours,

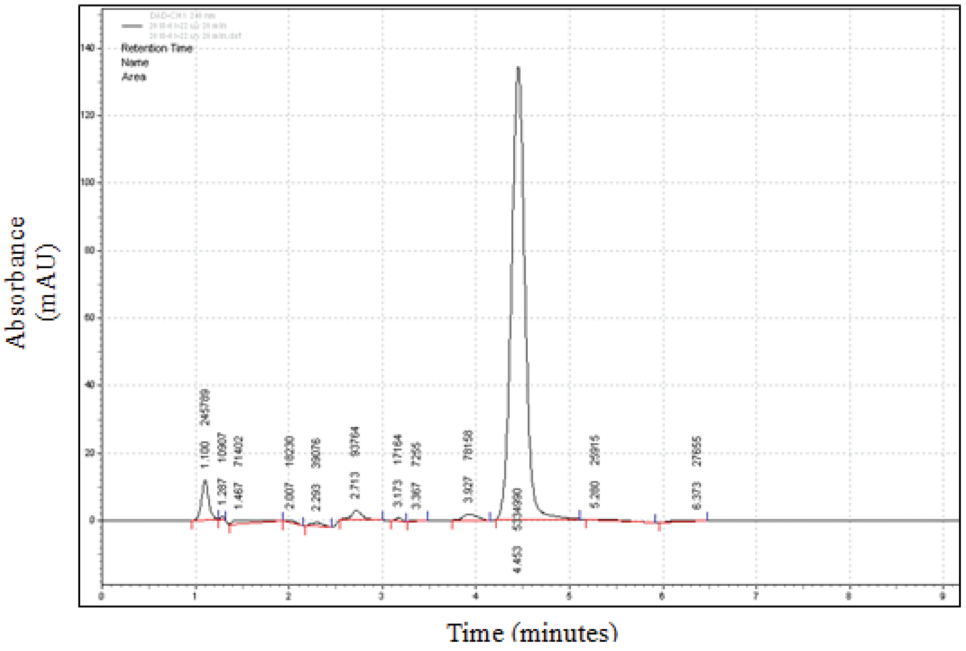

Figure 5: Chromatogram of sodium thiosulfate 180 µg/mL after UV light stressed conditions.

Table 1: Stability of sodium thiosulfate at 72 mg/mL and 16 mg/mL, at 25 °C, with and without light protection.

			Mean % of initial concentration ± SD*%		
		Bags	0 hour	6 hours	24 hours
Light 25 °C	72 mg/mL	1	100 ± 0.86 %	97.20 ± 1.05 %	97.25 ± 1.81 %
		2	100 ± 1.25 %	99.59 ± 0.78 %	97.18 ± 0.89 %
		3	100 ± 0.76 %	98.20 ± 0.16 %	97.46 ± 1.91 %
	16 mg/mL	1	100 ± 2.19 %	101.33 ± 1.44 %	101.61 ± 0.78 %
		2	100 ± 0.90 %	100.49 ± 1.56 %	102.65 ± 0.53 %
		3	100 ± 1.66 %	99.60 ± 1.69 %	102.59 ± 1.64 %
Protected from light 25 °C	72 mg/mL	1	100 ± 1.78 %	101.81 ± 1.27 %	100.94 ± 3.29 %
		2	100 ± 1.65 %	100.59 ± 0.59 %	99.29 ± 1.76 %
		3	100 ± 1.28 %	95.32 ± 1.48 %	98.41 ± 0.86 %
	16 mg/mL	1	100 ± 0.21 %	102.14 ± 0.37 %	100.31 ± 1.61 %
		2	100 ± 1.04 %	100.34 ± 1.21 %	97.74 ± 0.52 %
		3	100 ± 0.17 %	102.49 ± 0.34 %	101.01 ± 0.15 %

protected or not from light, at 25 °C. Solutions retained more than 95 % of initial concentration. In this stability study, the concentrations are close to 100 % of the initial concentration. These results are not in favour of an adsorption on the surface of the container or absorption.

Sodium thiosulfate was sensible to acidic and oxidative forced degradation, which is in accordance with the publication of Bishop et al [2].

Kilpatrick et al. quoted a publication written by Kolthoff et al. in 1921 were he studied the stability of sodium thiosulfate under various conditions [8]. He found "that sunlight hastened decomposition". In our study, we realised a forced degradation under a UV light at 254 nm. After 20 minutes, the sodium thiosulfate solution lost 16 % of the initial concentration. During our stability study, we did not observe a difference between results for solutions protected or not from white light. No degradation products were observed during the stability study. This discordance with the study of Kolthoff can be explained by the difference between the conditions:

Table 2: pH measurements of sodium thiosulfate at 72 mg/mL and 16 mg/mL, at 25 °C, with and without light protection.

		Bags	0 hour	6 hours	24 hours
Light 25 °C	72 mg/mL	1	8.82	8.96	8.98
		2	8.81	8.94	8.96
		3	8.79	8.94	8.93
	16 mg/mL	1	9.05	8.98	8.84
		2	9.05	8.97	8.83
		3	9.06	8.97	8.82
Protected from light 25 °C	72 mg/mL	1	8.92	8.93	8.81
		2	8.9	8.93	8.78
		3	8.89	8.91	8.8
	16 mg/mL	1	8.8	8.8	8.82
		2	8.8	8.81	8.83
		3	8.8	8.82	8.81

the solvent was water in Kolthoff's study, it was not an infusion bag but only a solution and solutions were exposed to the sunlight, it cannot be compared to the UV light used in our forced degradation.

These stability data are in accordance with data from Schulz *et al.* [7]. They determined a 48-hour stability for a mixture 1.8 mg/mL sodium thiosulfate and 0.18 mg/mL nitroprussite, at room temperature, protected from light.

Conclusion

Sodium thiosulfate solutions at 16 mg/mL in 1000 mL 0.9 % sodium chloride and at 72 mg/mL in 250 mL 0.9 % sodium chloride are stable physically and chemically over a period of 24 hours at 25 °C. The results are not in favour of an adsorption on the surface of the container or absorption.

This stability study allows the administration of sodium thiosulfate at concentrations used in renal protection protocols during cisplatin hyperthermic intraperitoneal chemotherapy.

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Conflict of interest statement: Authors state no conflict of interest. All authors have read the journal's Publication ethics and publication malpractice statement available at the journal's website and hereby confirm that they comply with all its parts applicable to the present scientific work.

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