Stability of sodium thiosulfate, used as a nephroprotective drug in hyperthermic intraperitoneral chemotherapy by cisplatin.

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Introduction

Sodium thiosulfate can be used to **prevent nephrotoxicity** induced by cisplatin hyperthermic intraperitoneal chemotherapy (HIPC). (Van Driel *et al.)*

Protocol for sodium thiosulfate administration in this indication:

① After 60-90 min of HIPC : cisplatin was drained
② Sodium thiosulfate was infused in two steps :
1. at 9 g/m² in 250 mL of 0.9% sodium chloride (NaCl 0.9%) over 10 minutes
2. Followed by 12 g/m² in 1000 mL of NaCl 0.9% over 6 hours.

→ **no stability data in the litterature**

Objectives

Physicochemical stability study of sodium thiosulfate

- Containers : polyolefin bags (Easyflex®, MacoPharma)
- Solvent : NaCl 0.9%
- Storage : 25°C, protected and unprotected from light
- Analysis : after preparation, after 6 hours and 24 hours.

① Concentration (C) = 72 mg/mL in 250 mL NaCl 0.9%
→ **1st step of protocol with BSA = 2 m²**
② C= 16 mg/mL in 1000 mL NaCl 0.9%
→ **2nd step of protocol with BSA = 1.33 m²**

BSA : Body Surface Area (m²)

Materials and Method

Chemical stability

① Method : RP-HPLC with DAD detector at 210 nm

- Column: C8 LiChrospher® 12.5 cm, particle size=5 µm at 25°C
- Mobile phase:
  a. Solution 1 : KH_2PO_4 1.361 g/L
  b. Tetrabutylammonium hydrogen sulfate 1.698 g/L dissolved in methanol:solution 1 (15:85, v:v %)
  c. pH ajusted at 7.0 with NaOH 1N
- Flow rate : 1 mL/min
- Injection volume: 10 µl
- Forced degradation: HCl 0.5M (60 min); H_2O_2 0.3%; UV (20 min under a lamp at 254 nm)

→ **validation of the analytical method as recommended by ICH Q2 (R1)**

② pH measurement

→ **3 bags for each condition (B1 – B2 – B3)**

Physical stability

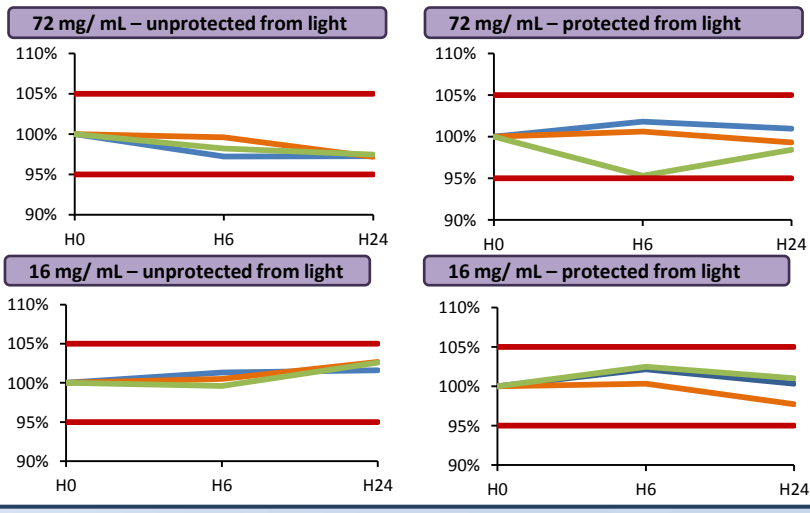
→ **Visual examination** : change of colour, precipitation, gas formation → **Subvisual examination** : turbidimetry by spectrophotometry at 550 nm

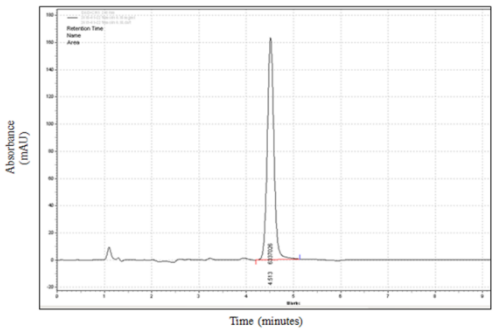
Results

① Validation : HPLC method

- Linearity : R^2>0.999 (Standard curve 5 points : 140-220 µg/mL)
- Repeatability and intermediate precision : CV<1 %
- Stability indicating capacity : degradation products observed

② Chemical stability –HPLC





Chromatogram of sodium thiosulfate 180 µg/mL in NaCl 0.9% without stressed conditions,

pH measurement : no modification [8.78-9.06]

③ Physical stability

- Visual aspect : no modification
- Subvisual aspect : no modification

Conclusion

Sodium thiosulfate at 16 mg/mL in 1000 mL NaCl 0.9% and at 72 mg/mL in 250 mL NaCl 0.9% → Stable for **24 hours at 25°C** Protected or not from light → Use in renal protection protocols during cisplatine HIPC