The stability of cyclophosphamide (CPA) and mesna mixture is shortened by cyclophosphamide instability causing quick pH decrease in solution

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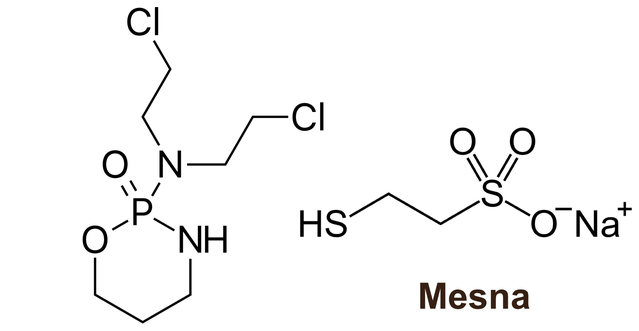
Background and Importance

- Cyclophosphamide (CPA) and mesna are commonly co-administered in oncological therapies to prevent bladder toxicity caused by metabolization of CPA.
- Mesna can be administered at a dose equivalent to the total dose of CPA divided into 3 administrations, with the first mixed within the same infusion bag as CPA to facilitate the work of nurses.
- Stability studies could allow the anticipated preparation of the mixture in centralized unit in hospital pharmacy.



Cyclophosphamide **Mesna**

Objectives and aim

Evaluate the **stability of CPA/mesna mixture** in polyolefin bags at 5°C and 25°C with a stability indicating method

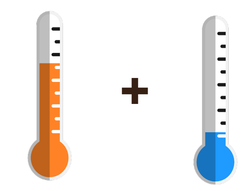
Investigate on causes of instability of the mixture

Materials and Methods

0.9% NaCl
Polyolefin bags

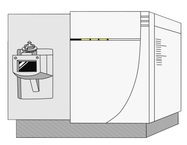
CPA/mesna 1/0.33 mg.mL^{-1}

CPA/mesna 10/3.3 mg.mL^{-1}



25°C + **5°C**

Stability study:



HPLC-UV quantification

pH

Osmolality

Visible and subvisible particles

30 days of conservation

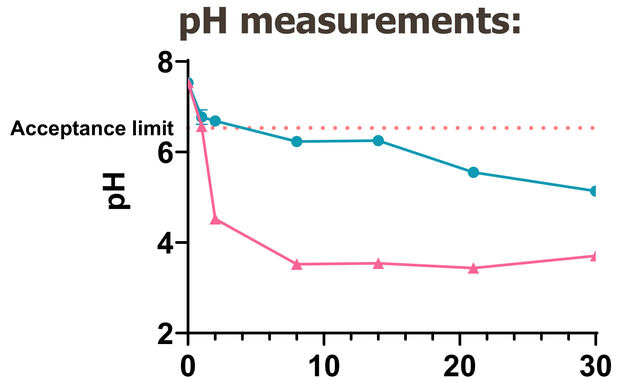
Results

Over the 30 days period:

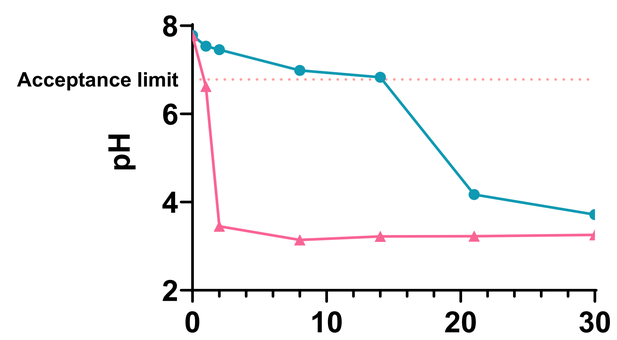
- Osmolality
- Visual examination
- Visible/subvisible particles
- HPLC quantification : 8 days at 25°C
  14 days at 5°C

⚠ pH : decrease > 1 unit (acceptance limit)
within the first day at 25°C
Slowed with 5°C conservation

pH measurements:



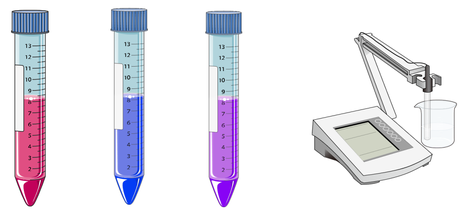
CPA/Mesna 1/0.33 mg.mL^{-1}



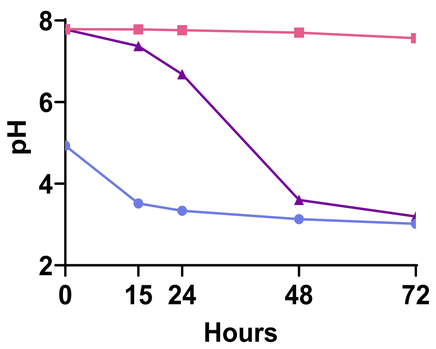
CPA/Mesna 10/3.3 mg.mL^{-1}

5°C conservation
25°C conservation

Subsequent investigations:



Mesna 3.3 mg.mL^{-1}, CPA 10 mg.mL^{-1} and CPA/mesna 10/3.3 mg.mL^{-1}
pH measurement during 72h at 25°C



Mesna 3.3 mg.mL^{-1}
CPA 10 mg.mL^{-1}
CPA/mesna 10/3.3 mg.mL^{-1}

The degradation of CPA dictates the pH of the mixture

Conclusion and Relevance

- **Shelf life of 48 hours at 5°C** for mixture of CPA/mesna from 1/0.33 mg.mL^{-1} to 10/3.3 mg.mL^{-1}
- Shelf life is **limited by pH decrease**
- No CPA degradation product detected with UV detection. A complementary study using HPLC-CAD (Charged Aerosol Detector) was able to detect a degradation product at 24 hours under 25°C conservation.
- Previous CPA stability studies (1) concluded 7 days of shelf life at 5°C **without pH measurement**.
- Our results indicate CPA in solution induces a fast pH drop even at 5°C
- New studies focused on CPA shelf life should be carried out.

Share our results !

3PC-035

References
(1) Beijnen et al., « Chemical stability of two sterile, parenteral formulations of cyclophosphamide (Endoxan) after reconstitution and dilution in commonly used infusion fluids. » J Parenter Sci Technol. 1992;46(4):111-6

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