PHYSICAL STABILITY OF DILUTED AZACYTIDINE SUSPENSIONS
STORED AT 4°C AND -20°C: PRELIMINARY RESULTS

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Azacytidine (AZC) is a nucleotide analogue used for the treatment of several hematological diseases. The manufacturer indicates a 8 hours stability at 4°C and a recommended regimen of 7 consecutive days. Thus, AZC syringes cannot be prepared in advance by hospital pharmacies. As no published data is available on the stability of AZC in suspension, we study the physicochemical stability of 25 mg/ml AZC suspensions under refrigeration and freezing.

BACKGROUND

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METHOD

Sample reconstitution and storage:
- Reconstitution with water at 4°C or 25°C (25 mg/ml)
- Storage 4°C or -20°C
- Time of analysis: up to 7 and 11 days for 25°C water and cold water respectively and 48 hours at -20°C
- Thawing at room temperature

Chemical stability
- 100 µl withdrawn under stirring
- Immediate dilution by iced water (0.5 mg/ml) and injection for analysis HPLC according Argemi et al.

Physical stability study
- Filtration on a 0.22 µm filter
- Analysis of sizes and shapes by scanning electron microscopy
- Sedimentation kinetics by following the decrease in absorbance at 500 nm

RESULTS

Degradation follows a biphasic kinetic with rapid initial phase strongly dependent on temperature

- The temperature of water for reconstitution influences the remaining % of AZC just after reconstitution:
  - 95.85% with ice water and 93.17% with water at 25°C
- The temperature of water does not influence the remaining % of AZC after a long period of time (several days): 91% at 7 days
- The % of degradation is very important during the first 24 hours but stays low after 24 hours of storage
- The rate of the initial degradation is higher when water at 25°C is used: (0.336% vs 0.162%).

CONCLUSION

If syringes are stored at 4°C immediately after reconstitution, the use of iced water permits only to slow the initial degradation step but is not essential since the total degradation remains inferior to 5% after 7 days with regard to initial concentration for both reconstitution temperatures. Therefore, the in-use stability period of AZC suspension is higher than recommended by the manufacturer. If required, freezing should also permit more long term storage of the suspension without any physical and chemical alterations.