

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

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## BACKGROUND

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.

## METHOD

### > Sample reconstitution and storage:

- Reconstitution with water at 4°C or 25°C (25mg/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- 100 µl withdrawn under stirring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.*



\*ARGEMI Area and SAUBIN J. Study of the degradation of Azacytidine on a model of unstable drug using a stopped-flow method and further HPLC analysis with multivariate curve resolution. *ScienceDirect*, 115-116

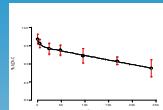
### > Physical stability study

- 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

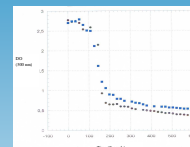
- Degradation follows a biphasic kinetic with rapid initial phase strongly dependent on temperature



- 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 periode 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%).

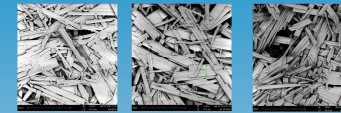
- The physical characteristics of suspension were not modified as regards sedimentation rate after storage at -22°C versus 4°C

+ 4°C: 144 s  
-20°C: 152 s



— AZC frozen in -22°C and defrosted at room temperature  
— Extemporaneously AZC reconstituted

- Any modification was observed as regards size and shape of crystals.



A B C

Aspects of the crystals of AZC kept in various temperatures

A: Suspension just after reconstitution  
B: Suspension stored in 4°C for 24 hours  
C: Suspension frozen in -22°C for 48 hours, then defrosted at room temperature

## 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.