EXTENDED CHEMICAL-PHYSICAL STABILITY OF 25MG/ML AZACITIDINE SUSPENSION

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Objectives

Azacitidine is used for hematologic pathologies. The summary of product characteristics (Vidaza®) indicates a 45 minutes at room stability and 22 hours using refrigerated (2°-8°C) water for injections (WFI) at reconstitution.

The purpose of the study was to assess the chemical-physical stability of azacitidine suspension 25mg/ml in the prescribed dilution conditions, simulating the hospital handling.

Materials and Study Design

Analytical activities were performed according to an approved protocol.
The validity of the reference material (azacitidine-Sigma Aldrich-batch-SLBD1299V) has been assessed before starting the analysis.
100mg of drug were reconstituted with 4ml of refrigerated (2°-8°C) WFI. The sample and standard suspension were stored at 5°C in a temperature controlled refrigerator.
Azacitidine concentrations were determined by a stability-indicating HPLC method at these following conditions:

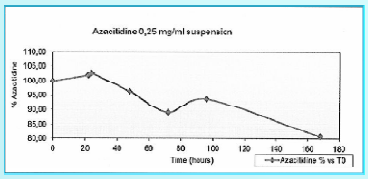
Parameter	Settings		
Column	X-Terra RP18, 150 x 4.6mm; 5µm		
Column temperature	25°C		
Autosampler temperature	4°C		
Mobile phase	A) Dissolve 2.85 g of Na2HPO4 and 2.72 g of KH2PO4 in 1000 ml of water; adjust pH=6.5 with H3PO4 85%. B) Acetonitrile: Water=40:60 (%v/v).		
	Time (min)	% A	% B
	0.0	100	0
	20.0	75	25
	21.0	100	0
	27.0	100	0
Flow rate	0.8 ml/min		
Detection	UV 230nm, Bw 4; Ref. 360nm, Bw 100		
Injection volume	20 µl		

At these conditions sample and standard suspension were analyzed at check points:

Check points							
Time (hour)	T_0	22	24	48	72	96	168
Temperature (°C)	r.t.	5°C					

Results

The azacitidine assay (%) determined by HPLC is reported in the table below.
Average values obtained by triplicate injections at each check point are reported.

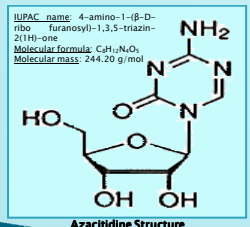


TIME (hour)	% Azacitidine Assay	% Azacitidine Assay vs t initial value
0h	110.73	102.62
22h	109.97	101.92
24h	107.90	100.00
48h	103.87	96.27
72h	96.01	88.98
96h	101.04	93.64
168h	87.18	80.80

Discussion

The % assay of azacitidine was calculated at each check point and the results were compared with the assessed values 100% for assay at t_0

For International Conference Harmonization guideline the solution can be considered stable if the % assay of azacitidine respect to the initial value is reduced less than 5%.



Azacitidine Structure

Calculation and expresion of results:

Concentration in the Standard solution (mg/ml)	$C_{std} = \frac{W_{std} \times P_{std}}{100 \times 100}$	W_{std}= weight of azacitidine reference standard (mg) P_{std}= purity declared of referenc standard (%) 100= volume of diluition of the reference standard (ml) 100= factor
Response factor (mg/ml)	$F_{std} = \frac{C_{std}}{A_{std}}$	A_{std}= peak area of azacitidine in standard solution
Concentration of Azacitidine (mg/ml) in the sample solution	$T(mg/ml) = As \times f_{std}$	As= peak area of azacitidine in sample solution
Concentration of the Azacitidine (%) in the sample solution	$T(\%) = \frac{T_{(mg/ml)}}{0.25} \times 100$	0.25= theoretical concentration (mg/ml) of azacitidine in the sample solution

Conclusions

The variation of the % assay of azacitidine respect to the initial value is less than 5% for at least 48hours.

There's an ongoing microbiological study on azacitidine suspension at our hospital. Positive results will allow us to use azacitidine suspension unused within 48hours of reconstitution with important cost saving.

References
•ICH Guideline:Stability testing of new drug sustances and products Q1A (R2)
•Note for guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99)

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