PP-028

ARE COMMERCIALLY MULTI-DOSE FORMULATIONS THE BEST SOLUTION? A SPECTROSCOPICAL QUALITY STUDY OF CYCLOPHOSPHAMIDE

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Background

In the hospital setting, commercially available multi-dose formulations in solution are more practical, but also more expensive, in comparison to on site reconstituted products.

In Italy, Cyclophosphamide (CP) is sold by Baxter as a galenic solution with approximately 30 days stability at 2-8 °C, using safe compounding practices. Reconstitution of lyophilized Endoxan® (also sold by Baxter) in saline solution is less practical, but lower in cost. Its use is recommended within 2-3 hours from preparation.

The CP galenic solutions need release time after production and logistic cold chain distribution.

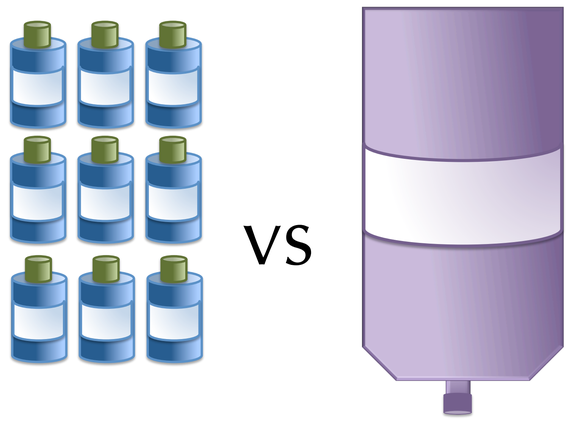
The institutional collaboration between the hospital pharmacy of Pisa University and NMR600 laboratory of Chemistry and Industrial Chemistry Department of Pisa University allows us to study stability and compatibility of drugs, and compounding therapies by NMR techniques.

Nuclear Magnetic Resonance (NMR) spectroscopy allows, unlike many other instrumental techniques in common use, the non-invasive analysis of the compounds and the absence of pre-treatments and manipulations on the samples.

Purpose

Identification of degradation products of CP and evaluation of its degradation profile.

Evaluate the stability of Baxter solution formulations of cyclophosphamide at delivery time and at the end of stability period and compare with stability profile of reconstituted saline solutions of solid CP (Endoxan®), guaranteeing the same storage temperature (2-8 °C).



Method

Analyses were performed directly on saline formulations stored at room temperature and 4 °C, without any kind of pre-treatment by using a high-resolution NMR spectrometer (600 MHz).

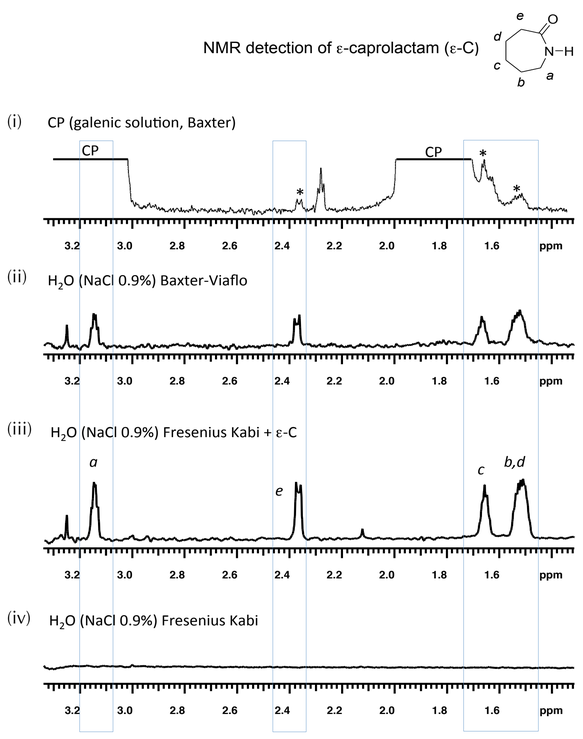
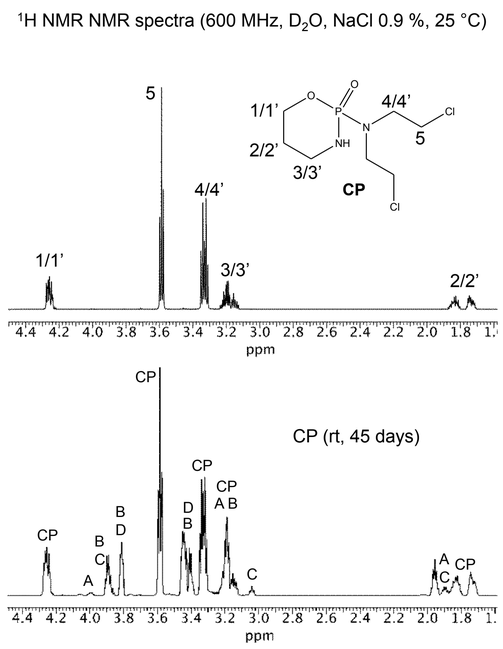


Figure 2 (i-iv)



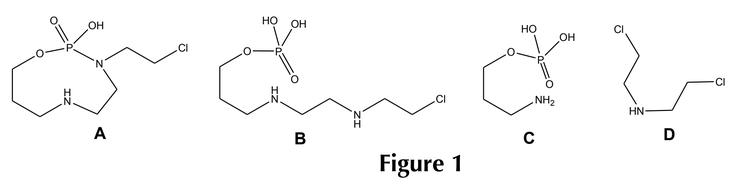


Figure 1

Table 1	Lyophilized Endoxan (4 °C)		Galenic CP solution (4 °C)		
%	12 days	40 days	Delivery time	End of stability period	End of stability period after simulation of use (90 min at rt for three times)
CP	99.5	98.3	97.5	94.6	95.8
A	0.5	1.1	1.4	2.0	1.6
B	n.d.	0.4	0.7	2.0	1.5
C*	n.d.	0.2	0.4	1.4	1.1

*CP degradation pathway to C and D produces the same amounts of C and D

Quantitative NMR analysis (600 MHz, D_2O NaCl 0.9 %, 25 °C, 18 mg/ml) of Baxter multi-dose formulation and reconstituted saline solution of Endoxan ®

Results

Degradation products of CP (A,B,C,D) were identified by 2D NMR spectroscopy. Their formation is favoured in a CP sample stored at room temperature for 45 days (Figure 1).

In the Baxter multi-dose formulations, more than 2% of degradation products are already present at delivery day. At the end of the stability period (approximately 30 days after), 5-6% of degradation products are detected.

In order to simulate the effect of temperature on multi-dose formulations in laboratory management, we studied degradation during the stability period (about 30 days), with 3 times exposition to room temperature of one and half hour each. In this condition, degradation products increase from 2% to 4.2%.

The reconstituted saline solution of solid CP were kept 12 days at 4 °C after preparation, to simulate a validation process. At 12 days 0.5% of degradation products is present. After 20 and 30 days, degradation products increase to about 1% and 2%, respectively.

The relative percentages of degradation products are shown in the Table 1.

NMR study highlighted the presence of traces of ε-caprolactam in multi-dose Baxter formulations. Traces of ε-caprolactam are already present in the saline solution (Baxter Viaflo®) as shown in Figure 2(i, ii). Its presence was confirmed by comparison with a standard of ε-caprolactam in different saline solutions (BBraun, Fresenius Kabi, Galenica Senense) Figure 2(iii, iv).

The presence of traces of ε-caprolactam does not seem to interfere with degradation pathways.

Conclusion

Stability of CP is highly dependent on storage conditions: the cold chain from factory to hospital and laboratory management.

Best temperature control can be achieved for in laboratory-reconstituted lyophilized Endoxan, rather than for multi-dose formulations.

The results encourage the reconstitution procedure thanks to a very good chemical stability at refrigerated conditions. Strict aseptic procedures are necessary, as with multi-dose formulations, to ensure the best therapy quality. Solid CP (Endoxan®) is ε-caprolactam free.

At last relevant economic advantages may be achieved.

The strong potential of Nuclear Magnetic Resonance is demonstrated as quantitative and non-invasive technique for detecting degradation products and eventual trace products. The technique could assist profitably the common pharmacy hospital practice also in terms of safety.

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