

Introduction

Myeloablative conditioning of the FORUM protocol in pediatrics =

Etoposide (VP16) at 60mg/kg + Total body irradiation

Literature data: stable 28d at room temperature and <1.75mg/mL



large volume incompatible with the administration of high doses in paediatrics

Objectif :

To determine the physico-chemical stability of VP16 injection solutions at 10mg/mL in bags of 0.9% NaCl and 5% Glucose (G5%).

Materials & Methods

- ❑ Etoposide 20mg/mL MYLAN
- ❑ NaCl 0.9% or G5% Freeflex® polyolefin bags (Fresenius Kabi)
- ❑ Bags produced in triplicate
- ❑ Chromatographic analysis: HPLC-DAD (Vanquish Thermo)
 - RP C18 column (250 mm x 4.6 mm; 5 µm) (Waters Symmetry Shield)
 - Mobile phase H₂O / Acetonitrile (70/30) at 1 mL/min
 - VP16 detection at λ = 285 nm
- ❑ pH measurement (EDGE pH meter, HANNA)
- ❑ Osmolarity measurement (OSMO1 osmometer, Radiometer)
- ❑ Monitoring of bag visual appearance (color, precipitates)

Results

1) The assay method is stability-indicating and complies with GERPAC recommendations

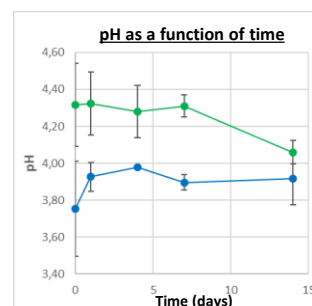
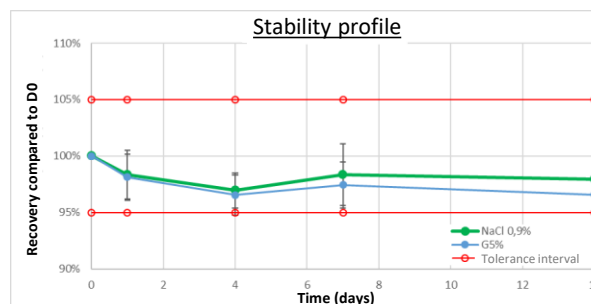
⇒ VP16-specific, linear, faithful and accurate from 50 to 150 µg/mL

2) Detection of degradation products after forced degradation

3) Stability of VP16 as a function of time

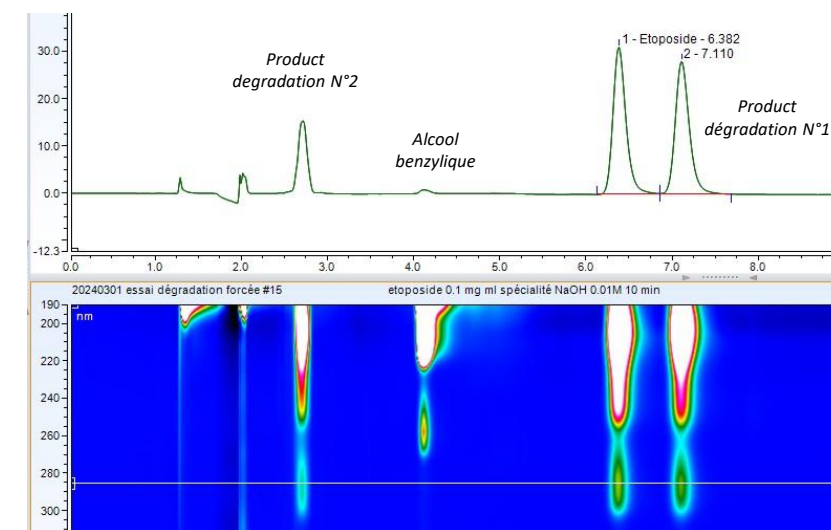
-> No change in macroscopic appearance was observed over the study period.

-> Formation of a precipitate in less than 24h during storage at 5 ± 3°C.



Solvent	Osmolarity (mOsm/L)	
	J0	J7
NaCl 0.9%	442 ± 11	444 ± 8
G5%	455 ± 21	461 ± 13

1/10 dilution for osmolarity measurement



Example: degradation with 0.01M NaOH for 10 min

Conclusion :

1) A concentrated solution of VP16 for injection at 10 mg/mL in NaCl 0.9% or G5% polyolefin bags is :

⇒ hyperosmolar

⇒ Stable



7 days at room temperature



<24h in refrigerator (precipitation)

2) Conclusive results for a clinical application in pediatrics: fluid intake divided by 5

Perspective :

Presence of several co-solvents (benzyl alcohol, polysorbate 80, macrogol 300 and ethanol): extractives study to be carried out.