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Introduction

Etoposide : Manufacturer's stability data

- C = 0.2 mg/mL -> 96 hours
 - C = 0.4 mg/mL -> 48 hours
- } **C > 0.4 mg/mL = risk of precipitation**

... and patients with fluid restrictions ? ➔ Etoposide phosphate (Etopophos®) → no limit concentration

Etopophos®: frequent stockouts, financial aspect:
Etoposide 200 mg/mL ≈ 4 € - Etopophos® 100 mg ≈ 30 €

Objectives

① Physicochemical stability study of etoposide

- C = 0.38 ; 0.74 ; 1.26 ; 1.75mg/mL
- Containers : polyolefin bags (Easyflex®, MacoPharma)
- Solvent = 0.9% sodium chloride (NaCl 0.9%) ; 5% glucose (G5%)
- Storage = 25°C not protected from light ; 2-8 °C protected from light
- Analysis = on days 0, 9, 16, 21, 28 and 61

② Impact of the mechanical action of an infusion volumetric pump and use of an administration set including an 0.2 µm in-line micro-filter.

D61

Materials and Method

Chemical stability

① Validation of the analytical method as recommended by ICH Q2(R1)

Method : HPLC-DAD detector at 285 nm

- C18 LiChrospher® 12.5 cm , particle size=5µm
- Mobile phase: gradient :
S1: formic acid: triethylamine: ultrapure water (1:1:998)
S2: : formic acid: triethylamine: acetonitrile (1:1:998)
- Flow rate: 1 mL/min
- Injection volume: 50 µL
- Forced degradation: HCl 0.5M (15 min) ; NaOH 0,01M (5 min); H₂O₂ 3% ; UV (15 min, 30 min, 1h, 12h under a lamp at 254 nm) ; heat (15 min, 30 min, 1h, 2h at 60°C)

② pH measurement

Physical stability

Visual examination : change of colour, precipitation, gas formation

Subvisual examination : turbidimetry by spectrophotometry at 550 nm

➔

 2 bags for each condition (B1 – B2)

Action of an infusion volumetric pump

- One bag for each condition
 - Each solvent : NaCl 0.9% or G5%
 - Each temperature : 25°C or 2-8°C
 - C : 0.38, 0.74, 1.26 and 1.75 mg/mL
- } Visual examination
HPLC analysis

Use of an administration set including an 0.2 µm in-line micro-filter

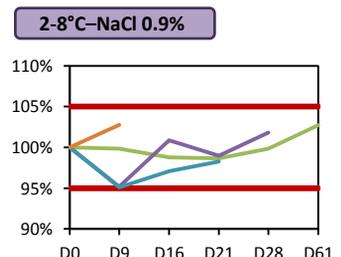
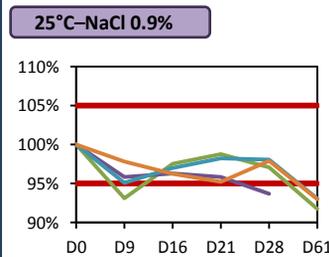
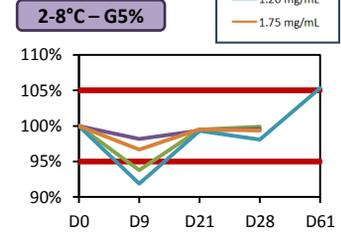
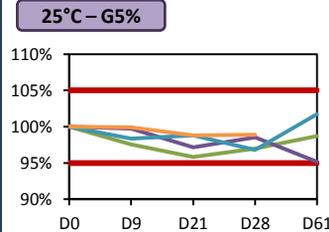


Results

① Validation : HPLC method

- Linearity : r²>0.999 (Standard curve 5 points : 10-90 µg/mL)
- Repeatability and intermediate precision : CV<2.25 %
- Stability indicating capacity : degradation products observed

② Chemical stability –HPLC



pH measurement : no modification

③ Physical stability

- : precipitation
- : no visual modification



		25°C					2-8°C				
		D9	D16	D21	D28	D61	D9	D16	D21	D28	D61
NaCl 0.9%	0.38 mg/mL										
	0.74 mg/mL										
	1.26 mg/mL										
	1.75 mg/mL										
G5%	0.38 mg/mL										
	0.74 mg/mL										
	1.26 mg/mL										
	1.75 mg/mL										

Subvisual aspect : no modification

Conclusion



Etoposide solution diluted in G5% up to a concentration at 1.75 mg/mL : stable for 28 days at 25°C !



Higher risk of precipitation in these conditions :

- ① Alternative to Etopophos®
- ② Preparation in advance
- ③ Use an administration set with an in-line micro-filter
- ① storage at 2-8°C
- ② NaCl 0.9% and a high concentration