Physicochemical stability of 25 mg/mL pemetrexed diarginine in partially-used vials and 3 and 12 mg/mL diluted in dextrose 5% in polyolefin bag.

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Introduction

Pemetrexed diarginine (PDA):
- New pemetrexed salt recently marketed by Mylan company
- Commercial form : ready-to-dilute 25 mg/ml solution

Available stability data:
- No stability data for partially used vial
- 24-hour stability after dilution at 3 and 12 mg/mL in dextrose 5% (D5W)
- pH between 8.3 and 9.0 (solution at 25 mg/mL)
- Colourless to slightly brown-yellow

Purpose

To study the stability of PDA solutions :

Concentration	3 and 12 mg/mL			25 mg/mL		
Solvent	D5W			None		
Container	100 mL polyolefin bag			Vial perforated with a spike		
Temperature	2-8°C	25°C	20-25°C	2-8°C	25°C	20-25°C
Light protection ?	Yes	Yes	No	Yes	Yes	No
Analysis time	D0, D7, D14, D28		D0, D4, D7	D0, D7, D14, D28		D0, D4, D7

Materials and methods

Chemical stability

The method was validated according to the International Conference on Harmonisation Q2(R1).

Method: RP-HPLC with DAD detector at 285 nm
- C18 LiChrospher® 20 cm , particle size= 5 µm
- Mobile phase: 145 mL acetonitrile + 1.7 mL glacial acetic acid + 1000 mL ultrapure water, pH 5.3
- Flow rate: 1 mL/min
- Injection volume: 20 µL
- Forced degradation: HCl 1 M (3 h); NaOH 1 M (2 h); H_2O_2 30 %; UV (40 h at 254 nm); heat (16 h at 80 °C)

Physical stability

Visual inspection: colour, precipitation and gaz formation

Subvisual inspection: turbidimetry with a spectrophotometer (350 nm, 410 nm and 550 nm)

pH measurement

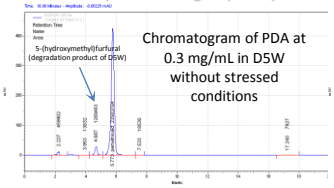
→ Two batch used

→ Two sample for each condition and each batch

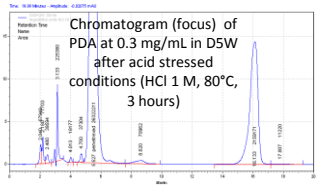
→ Stability = conservation of more than 95 % of the initial concentration and no significative subvisual and pH variation

Results

Validation: RP-HPLC method
- Linearity: $r^2 > 0,999$ (5-point standard curve: 50-150 µg/mL)
- Repeatability and intermediate precision: CV < 2 %
- Retention time: 5.6 min
- Stability indicating capacity:

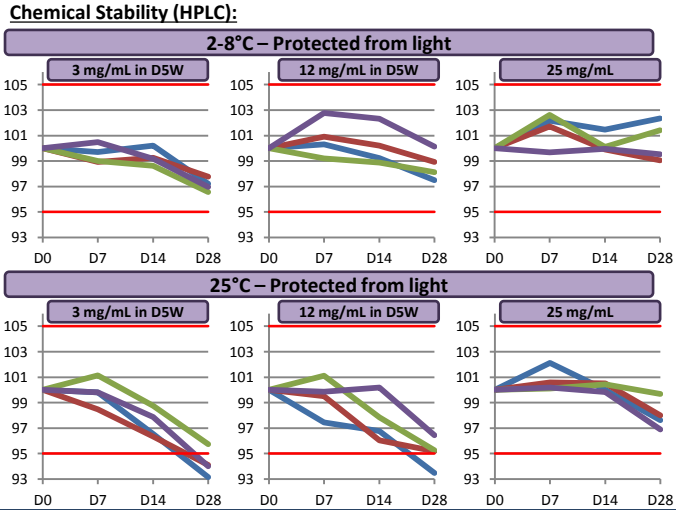


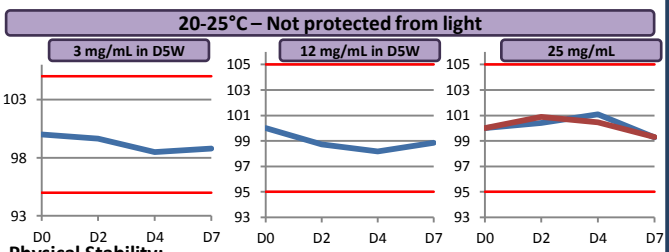
Chromatogram of PDA at 0.3 mg/mL in D5W without stressed conditions



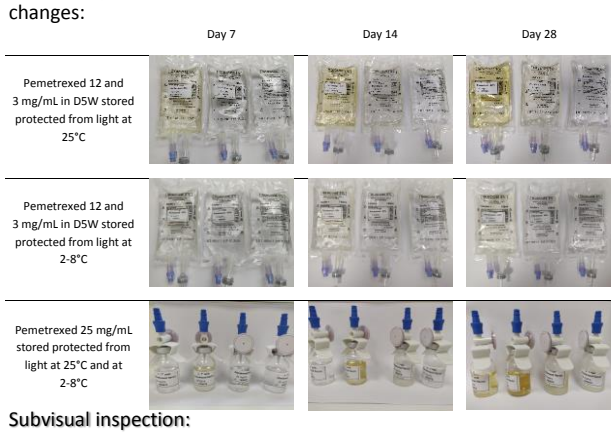
Chromatogram (focus) of PDA at 0.3 mg/mL in D5W after acid stressed conditions (HCl 1 M, 80°C, 3 hours)

Chemical Stability (HPLC):





Physical Stability:
- Visual inspection: no precipitate, no gaz formation, but colour changes:



- Subvisual inspection:
  - No significant change was observed at 550 nm
  - Absorbance at 350 nm and 410 nm has significantly increased because of colour change
- pH measurement: no significant modification (8.05 to 8.77)

Discussion - Conclusion

According to the manufacturer's specifications (colourless to slightly brown-yellow, pH 8.3-9.0) and to the chemical stability defined as more than 95% of the initial concentration:

PDA solutions in D5W at 3 and 12 mg/mL and PDA ready-to-dilute 25 mg/mL solutions protected from light were stable for 28 days at 2-8°C.

PDA solutions in D5W at 3 and 12 mg/mL and PDA ready-to-dilute 25 mg/mL solutions protected from light were stable for 7 days at 25°C.
PDA solutions in D5W at 3 and 12 mg/mL and PDA ready-to-dilute 25 mg/mL solutions not protected from light were stable for 7 days at 20-25°C.

For a preparation in advance with an optimal stability : the absence of colour change as an acceptance criterion leads to a 4-day stability at room temperature and a 7-day stability at 2-8°C to allow the use of the vial partially used perforated with a vented spike.

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