Physicochemical stability study of Cabazitaxel Zentiva® in vials after “opening” and in diluted solutions in infusion bags of 3 types.

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Materials and methods

Chemical stability

1. Method : RP-HPLC with DAD detector at 232 nm1
   - C18 LiChrospher® 12.5 cm, particle size= 3.5 µm
   - Mobile phase : isocratic mode : 42% of water for chromatography, 32% of methanol and 26% of acetonitrile
   - Flow rate : 1.2 mL/min Injection volume: 25 µL

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

- Forced degradation to evaluate stability indicating capability

<table>
<thead>
<tr>
<th>ACIDIC DEGRADATION</th>
<th>ALKALINE DEGRADATION</th>
<th>PHOTOLYTIC DEGRADATION</th>
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<tbody>
<tr>
<td>HCl - 1.69 M 10 min</td>
<td>NaOH - 0.05 M 1 min</td>
<td>24 h</td>
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- Linearity : standard curve with points : 50 – 400 µg/mL
- Repeatability and intermediate precision : 3-point measurement (100, 200 and 300 µg/mL)
- Specificity

2. pH measurements (Cisron pH25 pHmeter) : for each infusion bags

Acceptance criteria ± 10% of initial concentration and no visual or significative pH value modification

Study design

NaCl 0.9% - D5W
0.1 and 0.26 mg/mL
3 x Freeflex® 2-8°C
3 x Viaflo® and 3 x Easyflex® at 25°C

Two different batches at 25°C

Physical examination : change of colour, precipitation, gas formation

Physical stability

Results

1. Validation of the method
   - Linearity : R² > 0.9957
   - Repeatability : [0.43-1.15%]
   - Intermediate precision : [0.82-1.65%]
   - Retention time : 9.5 min
   - Stability indicating capability :

2. A. Chemical stability - HPLC analysis
   - Infusion bags : average of the 3 bags per condition

- Chromatogram of cabazitaxel solution at 200 µg/µL, after alkaline degradation (NaOH 0.05 M 1 min)

2. B. Chemical stability in infusion bags pH values
   - No modification : maximum variation at D14 : 0.39 pH unit and 0.24 at D28

3. Physical stability
   - No visual modification

Conclusion

Cabazitaxel Zentiva® 20 mg/mL vials with a SPIKE were physically and chemically stable for 28 days at 25°C, allowing the remainder of the vial to be used over several days.

Cabazitaxel Zentiva® solutions diluted at 0.1 and 0.26 mg/mL in NaCl 0.9% or in D5W were physically and chemically stable for 28 days at 2-8°C in Freeflex® infusion bags or 25°C in Viaflo® and Easyflex® infusion bags, allowing preparations in advance.