Physicochemical stability of cloxacillin solutions in polypropylene syringes at 125 mg/mL in 0.9% sodium chloride and dextrose 5% in water

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***Objectives***

Stability study of cloxacillin solutions at 125 mg/mL diluted in 0.9% NaCl and in DSW, stored in polypropylene syringes, unprotected from light, at 20-25°C after a 48 hours storage.

Introduction

Cloxacillin is indicated in methicillin-sensitive *Staphylococcus aureus* infections. The usual curative dosage ranges from 8 to 12 g per day. To reduce the number of daily administrations and the water intake, continuous concentrated solutions in an electric syringe pump should be considered.

Stability of high concentrations in 0.9% NaCl or in DSW is unknown.

Materials and Method

**Chemical stability**

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

- Forced degradation

<table>
<thead>
<tr>
<th>Acidic</th>
<th>Alkaline</th>
<th>Oxydative</th>
<th>Heat</th>
<th>Photolytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCl 0.05 M 3h</td>
<td>NaOH 0.01 M 30s</td>
<td>H₂O₂ 3%</td>
<td>90°C 2h30</td>
<td>UV Light 254 nm 1h</td>
</tr>
</tbody>
</table>

- Linearity: standard curve with 5 points: 1.2-2.8 mg/mL
- Repeatability and intermediate precision evaluated: 3-point measurement (1.2, 2.0, 2.8 mg/mL)

**2.** pH measurements (Bioblock Scientific pH meter)

3 syringes for each condition (S1 – S2 – S3)

**3.** RP-HPLC with DAD detector at 250 nm

- Column: C18 LiChrospher® 12.5 cm, Ø = 4 mm, particle size = 5 µm at 40°C
- Mobile phase: 35% of phase A and 65% of methanol
- Phase A: 2 mL of triethylamine + 16.98 g of tetrabutyrammonium >> 1 liter of ultrapure water. pH adjustment to 6 with NaOH 1M.
- Flow rate: at 0.5 mL/min
- Injection volume: 5 µL

**Physical stability**

- Visual examination: change of colour, precipitation, gas formation
- Subvisual examination: turbidimetry by spectrophotometry at 350, 410 and 550 nm (Safas Monaco UV m²)

**Results**

**1.** Validation of the method: RP-HPLC method

- Linearity: R² > 0.996
- Repeatability: [0.33% - 1.81%], Intermediate precision: [1.25% - 1.95%]
- Retention time of cloxacillin: 4.54 min

**2.** Stability indicating capacity

**HPLC results:**

- 0.9% NaCl

Chromatograms of 125 mg/mL cloxacillin solutions in 0.9% NaCl after preparation (A) and after 48-hour storage (B) with degradation products.

- DSW

Chromatograms of 125 mg/mL cloxacillin solutions in DSW after preparation (A) and after 48-hour storage (B) with degradation products.

- Sub-visible aspect: of the absorbance values progressively with two wavelengths (410 and 550 nm) and each condition.
- Visual aspect: of the intensity of the yellow colour (for example with 0.9% NaCl)

After the study, a precipitate has been observed 5 days after the preparation.

Conclusion

Stability of cloxacillin solutions at 125 mg/mL in 0.9% NaCl and DSW in polypropylene syringes is limited to 24 hours at room temperature.