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

C.Polo[1], E. D'Huart[1,2], J. Vigneron[1,2] , A. Charmillon[3], B. Demoré[1,2,4]
1 : Pharmacy – University Hospital of Nancy, France
2 : Infostab, non profit association, Heillecourt, France
3 : Infectious and Tropical Diseases Unit, University Hospital of Nancy, France
4 : Lorraine University, APEMAC, Nancy, France

Virtual Congress
March 2021
N° 3PC-061
ATC code : J01

0.9% NaCl : 0.9% sodium chloride
D5W : Dextrose 5% in water

Introduction

Cloxacilline 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 D5W is **unknow**.

Objectives

Stability study of cloxacillin solutions at **125 mg/mL** diluted in **0.9% NaCl** and in **D5W**, stored in **polypropylene syringes**, **unprotected** from light, at **20-25°C** after a **48-hour storage**.

Materials and Method

Chemical stability

① 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 tetrabutylammonium >> 1 liter of ultrapure water. pH adjustment to 6 with NaOH 1M.

- **Flow rate** at 0.5 mL/min
- **Injection volume**: 5 µL

② Validation of the method as recommended by ICH Q2(R1)

- **Forced degradation**

Acidic	Alkaline	Oxydative	Heat	Photolytic
HCl 0.05 M 3h	NaOH 0.01 M 30s	H_2O_2 3 %	90°C 2h30	UV Light 254 nm 1h

- **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)

③ pH measurements (Bioblock Scientific pH meter)

Physical stability

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

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

Analysis times : 0, 6, 24 and 48 hours

Results

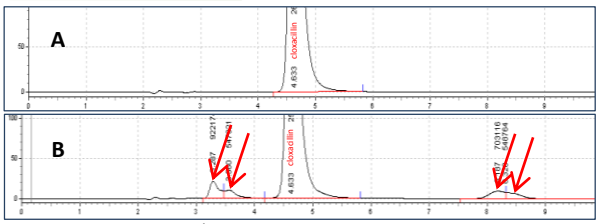
Chemical stability

① Validation of the method : RP-HPLC method

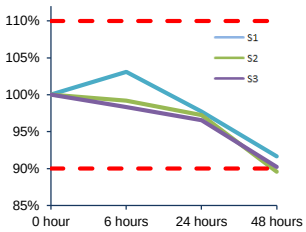
- **Linearity** : $R^2 > 0.996$
- **Repeatability** : [0.33 % - 1.81 %], **Intermediate precision** : [1.25 % - 1.95 %]
- **Retention time of cloxacillin** : 4.54 min

③ HPLC results :

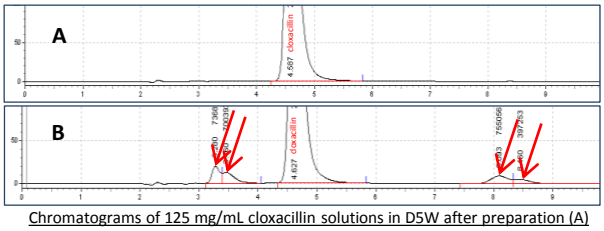
0.9% NaCl



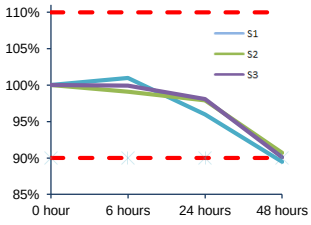
Chromatograms of 125 mg/mL cloxacillin solutions in 0.9% NaCl after preparation (A) and after 48-hour storage (B) with degradation products.



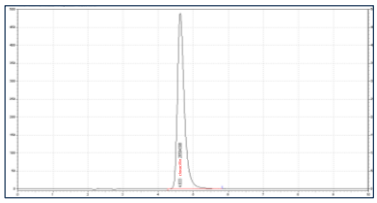
D5W



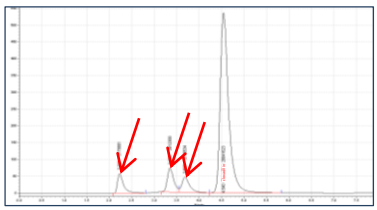
Chromatograms of 125 mg/mL cloxacillin solutions in D5W after preparation (A) and after 48-hour storage (B) with degradation products.



② Stability indicating capacity



Chromatogram of 125 mg/mL cloxacillin solutions without stressed conditions

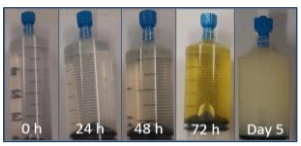


Chromatogram of 125 mg/mL cloxacillin solutions after oxydative stressed conditions (H_2O_2 3%) with degradation products.

④ pH measurement : ↘
for both solvents.
T0 → T24H : < 1 pH unit
T0 → T48H : > 1 pH unit

Physical stability

- **Sub-visual 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 D5W in polypropylene syringes is **limited to 24 hours** at room temperature.