Physicochemical stability of fortified ceftazidime eye drops at 20 mg/mL stored at -20°C

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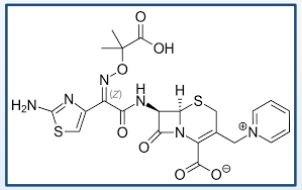


INTRODUCTION

- The treatment of infectious keratitis is one of the ophthalmic emergencies.
- It requires the use of fortified antibiotic eye drops.
- **Ceftazidime** is combined with gentamicin and vancomycin.
- **Ceftazidime** is only stable for a few days at a temperature of 4-8°C.
- Geographical distance poses a problem for the supply of a hospital preparation with a limited shelf life.
- Freezing the 20 mg/mL preparation at -20°C is possible but requires reliable stability data.

OBJECTIVE

- Evaluate the physicochemical stability of **ceftazidime** diluted with 0.9% NaCl to a concentration of 20 mg/mL, stored for 32 days at -20°C, then assess stability after thawing (4-8°C) for a period of 10 days in an opaque polyethylene dropper bottle.

CONCLUSION

Opaque polyethylene dropper bottle	NaCl 0,9% C° 20mg/mL	Storage : -20°C Stable for 32 days	Then stable for 10 days after thawing Storage at +4°C

MATERIALS AND METHODS

STUDY DESIGN

3 batches

1.Freezing at -20°C
Analyses on days 0, 14, 21 and 32
n = 3 per analysis

2.Thawing TD0 = D32 (storage at 4°C)
Analyses TD0, TD3,TD5, TD7 and TD10 (=D42)

At each analysis time:
Assessment of **chemical stability**, hplc (maximum variation: +/- 10% of initial c°)
Measurement: ph, osmolarity
Physical stability visual and subvisual analysis

CHEMICAL STABILITY

- Reverse phase **HPLC**, with a DAD detector at 260 nm; column: C18 Acclaim® 25 cm, diameter: 4.6 mm, particle size = 5 µm.
- Mobile phase: isocratic 0.1M ammonium acetate/acetonitrile (90/10), adjusted to pH 7.5.
- Flow rate: 1.0 mL/min Injection volume: 10 µL
- Forced degradation: 0.01M NaOH (5 min) 1M HCl (5 min) Temperature 75 °C 30 min

Analytical method validation in accordance with ICHQ2 (R1)

→ **Linearity, repeatability, and intermediate accuracy**

- **pH measurement**: Accumet AB135 (maximum variation of one pH unit)
- **Osmolarity measurement**: Osmomat 3000 (maximum variation of 2%)

PHYSICAL STABILITY

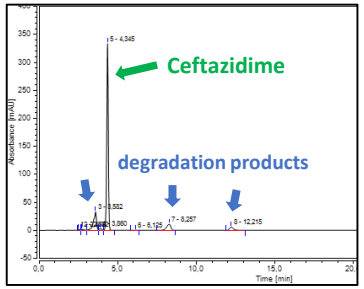
- **Visual inspection:** check for color change, precipitation, or gas formation.
- **Subvisual inspection:** particle count (size 10 and 25 µm)

Particle counter: Beckman Coulter

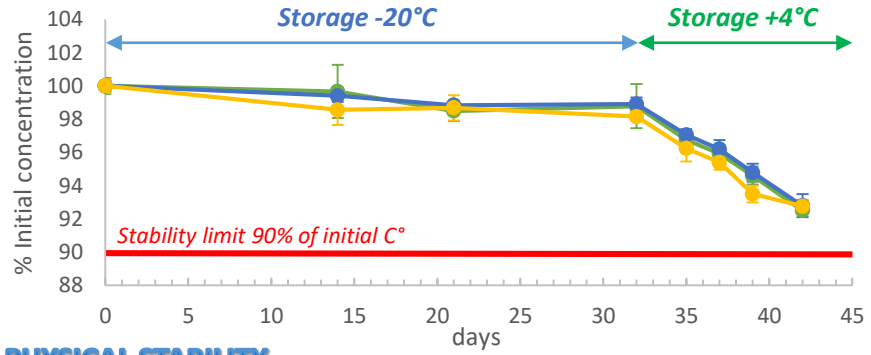
RESULTS

METHOD VALIDATION

- **Linearity** : $R^2 > 0.9999$
- **Repeatability and intermediate precision**: CV < 2%
- **Ceftazidime retention time:** 4.35 min
- Six degradation products observed



CHEMICAL STABILITY



- **pH**: maximum variation: 0.22 units (frome 7.17 to 6.95)
- **Osmolarity:** maximum variation of 1.3% during the study

PHYSICAL STABILITY

- **Subvisual inspection**: Complies with the European Pharmacopoeia particle count test (size 10 and 25 µm)
- **Visual inspection:** No gas formation, precipitate, or color change