

Stability testing of ceftazidime solutions for injection in elastomeric devices at 12 mg/mL and 25 mg/mL in 0.9% w/v saline for safe use in Outpatient Parenteral Antimicrobial Therapy (OPAT).



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INTRODUCTION

Ceftazidime (CAZ) is a third-generation beta-lactam cephalosporin used to treat Gram-negative bacterial infections, including *Pseudomonas aeruginosa*.

CAZ demonstrates temperature sensitive degradation. CAZ is unstable in aqueous solution leading to the formation of pyridine, a toxic degradation product. Safe use of CAZ in an outpatient parenteral antimicrobial therapy (OPAT) setting as an extended infusion relies on the control of temperature and drug concentration. Delivery of CAZ in elastomeric devices would be a convenient option for OPAT services.

Initial work demonstrated that CAZ stability was not improved by use of 0.3% w/v citrate buffer (data not shown), as previously demonstrated with a flucloxacillin study¹, so the study was performed using 0.9% w/v saline. At the same time levels of pyridine were analysed to ascertain if safe levels could be achieved for outpatient therapy.

METHODS

CAZ was reconstituted and diluted in 0.9% w/v saline in 240 mL containing 3 g (12 mg/mL) and 6 g (25 mg/mL) of drug, compounded into two different elastomeric devices (FOLFusor, Baxter and Easypump[®]II, B.Braun) and refrigerated (2-8°C) for 48 hours. Devices were then subjected to a 3-hour warm-up period, followed by 12 hours at 32°C (simulating surface skin temperature). All tests were carried out in triplicate in both devices and testing was carried out according to the latest NHS yellow cover document (YCD)² and British Pharmacopoeia (BP) requirements³. Concentrations of CAZ and pyridine were assayed concurrently and at least five time points using a stability indicating HPLC method, adapted by BSTL from literature⁴.

RESULTS

The BP limit for loss of CAZ in solutions for injection, from initial concentration remaining, is 90-110%; while pyridine levels are limited to not more than (NMT) 0.5% (w/w)³. These levels of pyridine are often reached before significant loss of CAZ. In this study the limits for pyridine were calculated based on a solution volume of 240 mL in both devices tested. At these concentrations the pyridine limit was 15 mg and 30 mg respectively. Levels of pyridine were kept within the limits of NMT 0.5% (w/w) by delivering 120 mL of the total 240 mL volume in simulated administration from both devices.

All data is compliant with the NHS YCD guidance for stability testing of small molecules² and the latest BP requirements for CAZ solutions for injection³, supporting storing CAZ solutions for 48 hours at 2-8°C, followed by a 3-hour warm up period at room temperature and a 12-hour administration period at 32°C.

Recorded losses of CAZ were all within the YCD limits of 90-110% and BP limits (Figure 1). Pyridine levels were NMT 0.5% w/w (Figures 2 and 3).

CONCLUSIONS

CAZ can be formulated and stored for 48 hours followed by a 12-hour infusion period at 32°C while maintaining between 90%-100% for the active ingredient; at the same time pyridine levels do not exceed BP limits when used as above.

Our data show that there is a role for CAZ infusion over 12 hours for OPAT services which have the capacity to prepare devices and use them within 48 hours. The data also shows that a 24-hour infusion is not possible for ceftazidime in elastomeric devices.

This model will not suit all OPAT services but provides a useful treatment option for services which can deliver it and can help to reduce the reliance on broad spectrum agents such as piperacillin/tazobactam and meropenem.

REFERENCES

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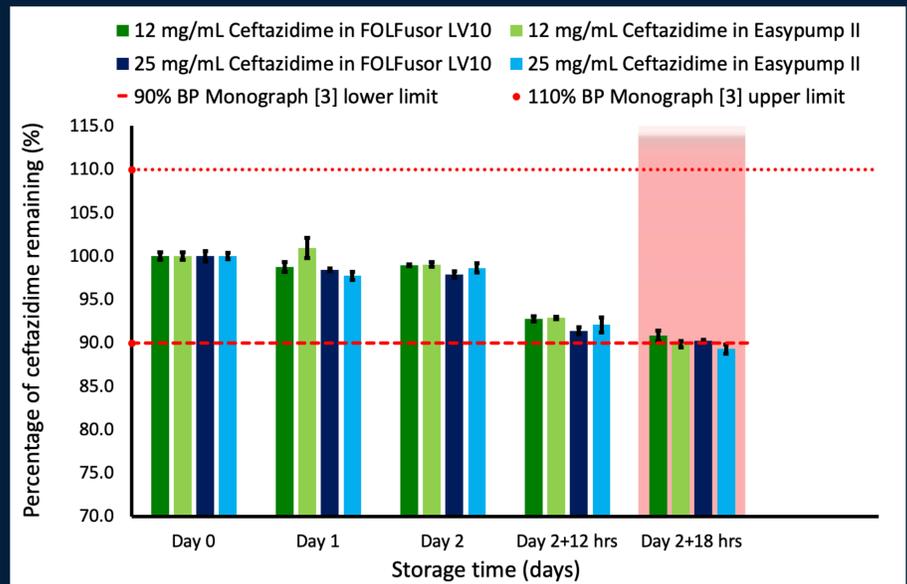


FIGURE 1. Recorded amounts of CAZ (%) remaining versus time (days)

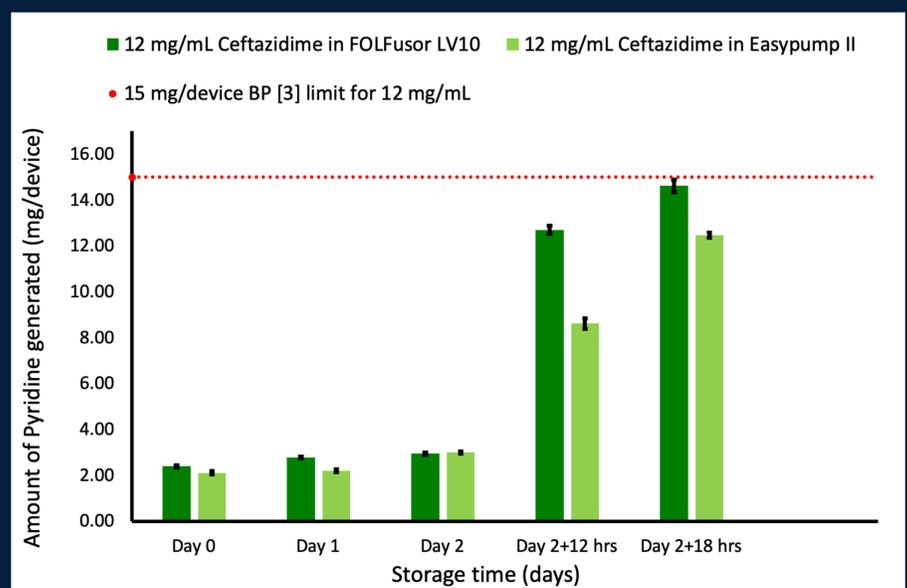


FIGURE 2. Recorded amount (15mg) of pyridine assayed per device

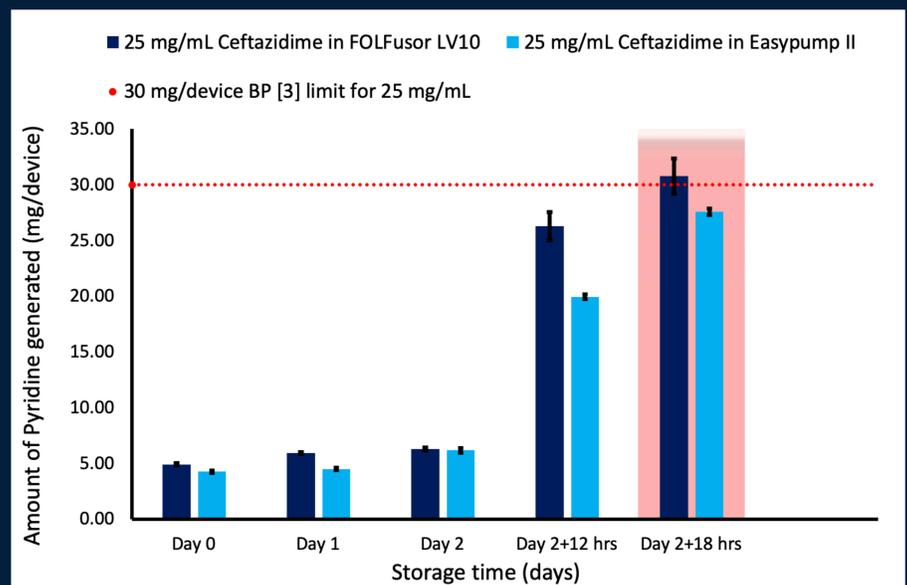


FIGURE 3. Recorded amount (30mg) of pyridine assayed per device

ACKNOWLEDGEMENTS

This study was supported by a donation from Baxter Healthcare Ltd. and consumables provided in-kind from Baxter Healthcare Ltd. and B. Braun Medical Ltd.

¹Members of the BSAC Working Group for Drug Stability Testing: Conor Jamieson (Chair), Mark Gilchrist, Tim Hills, Mark Santillo and Andrew Seaton.

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