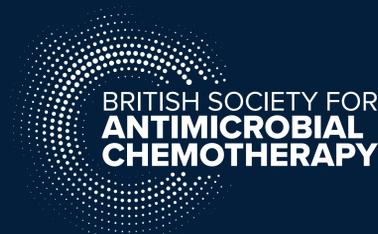


Evaluation of the stability of aciclovir in elastomeric infusion devices used for outpatient parenteral antimicrobial therapy (OPAT) services in accordance with the requirements of the UK NHS Yellow Cover Document



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P1460

INTRODUCTION

Treatment of herpes simplex encephalitis requires a prolonged course of an intravenous antiviral, such as aciclovir. With poor oral bioavailability and plasma levels, oral aciclovir is not a reliable treatment option for an intravenous to oral switch, necessitating an inpatient stay for patients who might otherwise be well enough for discharge. Three times daily administration of intravenous aciclovir is inconvenient for OPAT services, so a continuous infusion delivered by elastomeric device would be attractive. We aimed to investigate the stability of aciclovir solutions in elastomeric devices in accordance with the requirements of the UK National Health Service (NHS) Pharmaceutical Quality Assurance Committee Yellow Cover Document¹ (YCD) standards for the assessment of the stability of small molecules.

METHODS

Triplicate elastomeric devices, from B. Braun Medical Ltd. Easypump[®]II (Sheffield, UK) and Vygon Ltd. Accufuser[®] (Wiltshire, UK), were filled with 0.9%w/v saline, at 200 mg in 240 mL (low dose) and 4500 mg in 240 mL (high dose). Devices were stored at room temperature for 14 days, followed by 24 hours storage at 32°C. Stability assessment using a stability indicating method, pH and subvisible particle analysis was undertaken at 12 time points throughout the study.

CONCLUSIONS

While stable at room temperature for 14 days, it is likely that the changes in pH at 32°C affected the solubility of aciclovir and resulted in its precipitation. Further work is required to determine the maximum concentration of aciclovir that can provide adequate stability at clinically relevant concentrations for continuous infusion for OPAT services to meet YCD¹ or international requirements.

ACKNOWLEDGEMENTS

The authors would like to thank B. Braun Medical Ltd. and Vygon Ltd. for funding and in-kind provision of elastomeric devices.

ENQUIRIES

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REFERENCE

1. NHS Pharmaceutical Quality Assurance Committee. A standard protocol for deriving and assessment of stability: part 1 - aseptic preparations (small molecules). Edition 5, 2019.

RESULTS

Aciclovir solution at 200mg in 240 mL was stable in Accufuser[®] and Easypump[®]II elastomeric infusion pumps for 14 days at room temperature and 24 hours of 32°C 'in-use' temperature exposure, remaining above the 95% YCD limit (Figures 1 and 2). High dose aciclovir was also stable for 14 days at room temperature, but when stored at 32°C there was precipitation of aciclovir within 4 hours in both devices (Figure 3). There was very large pH change at the low concentration of aciclovir both at room temperature and 32°C, at high concentration there was a change of up to 1.3 units by the end of the in-use storage period. The precipitate was confirmed as aciclovir and precipitation was not a sign of chemical degradation.

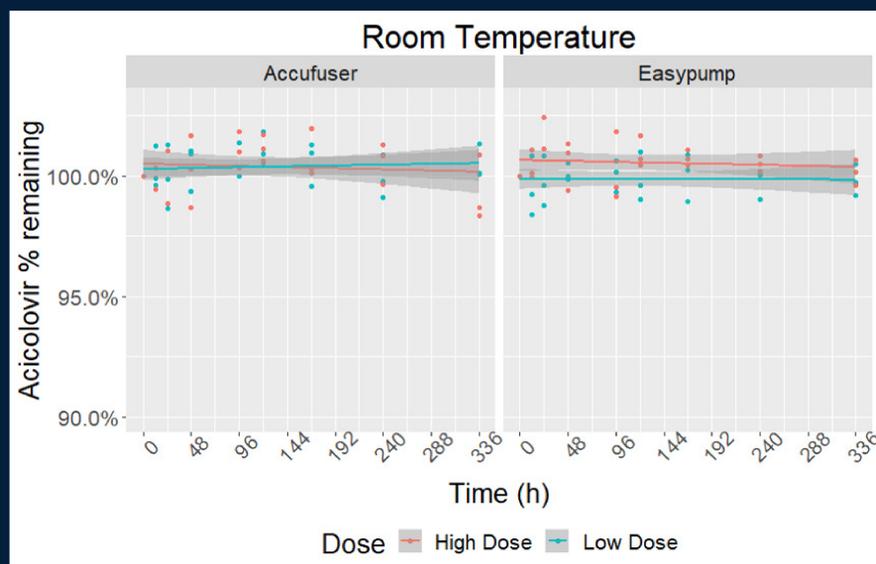


FIGURE 1. Percentage of aciclovir remaining in Easypump[®] II LT 270-27- S elastomeric infusion device during storage at room temperature for 14 days (336 hours) followed by 24 hour in-use temperature exposure at 32°C. Low dose (200 mg in 240 mL; high dose (4500 mg in 240 mL)

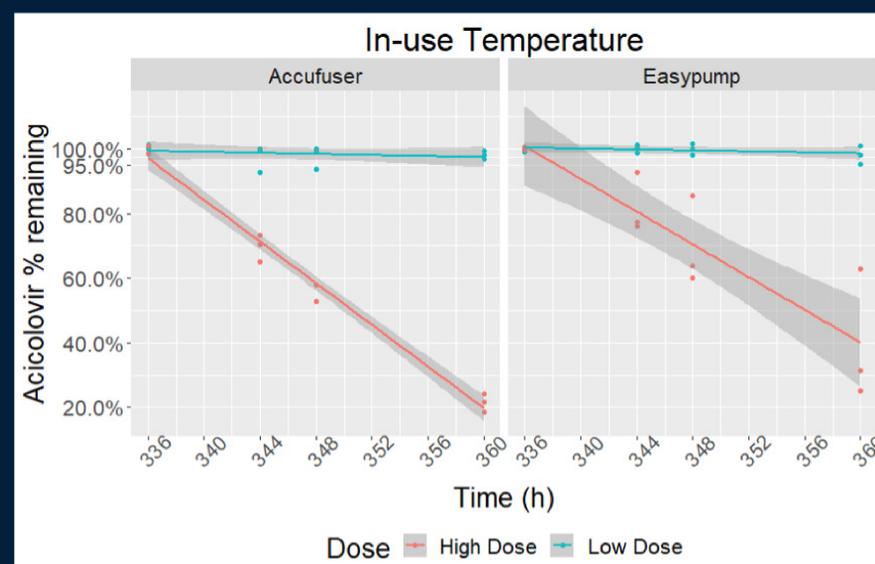


FIGURE 2. Percentage of aciclovir remaining during exposure to in-use temperature of 32°C following 14 days (336 h) room temperature storage, by device and dose (low dose: 200 mg in 240 mL; high dose: 4500 mg in 240 mL).

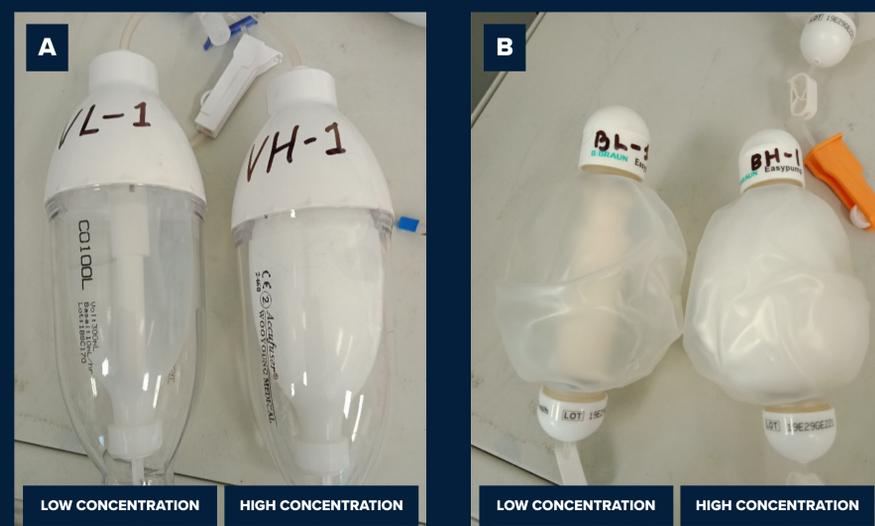


FIGURE 3. Visible precipitation of white substance noted at 4 hours of storage at 32°C, for the high concentration of aciclovir in Accufuser[®] (A) and Easypump[®] (B) infusion devices.