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# Evaluation of the stability of aciclovir in elastomeric infusion devices used for outpatient parenteral antimicrobial therapy

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## ABSTRACT

**Objectives** To investigate the stability of aciclovir solutions in elastomeric devices used for outpatient parenteral antimicrobial therapy (OPAT).

**Methods** Triplicates of two elastomeric devices, Accufuser and Easypump II, were filled with a solution of 200 mg, 2400 mg, and 4500 mg aciclovir in 240 mL 0.9% w/v saline. Devices were stored at room temperature for 14 days, followed by 24 hours storage at 32°C. Assessment using a stability indicating assay, pH and subvisible particle analysis was undertaken at 11 time points throughout the study.

**Results** Aciclovir solution at 200 mg and 2400 mg in 240 mL was stable for 14 days at room temperature (<20°C) and 24 hours of 32°C 'in-use' temperature exposure, remaining above the 95% limit for NHS stability protocols. The high dose 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. The precipitate was confirmed as aciclovir and precipitation was not a sign of chemical degradation.

**Conclusions** Aciclovir concentrations above 2400 mg/240 mL are liable to precipitation and cannot be recommended for OPAT services because of heightened risks of nephrotoxicity. Aciclovir solution can be given as a continuous 24-hour infusion for OPAT services at a concentration range of 200–2400 mg in 240 mL in Accufuser and Easypump II elastomeric devices following 14 days storage at room temperature, protected from light.

## INTRODUCTION

Aciclovir is an antiviral drug introduced in 1982 as a topical agent and later in 1983 for intravenous (IV) treatment of herpes virus infections.<sup>1</sup> It can be used to treat infections caused by herpes simplex virus (HSV), varicella-zoster virus and Epstein-Barr virus.<sup>2,3</sup> Structurally, it is a guanine nucleoside analogue and therefore serves as a false substrate in the synthesis of viral DNA, effectively blocking the synthesis of viral DNA and the proliferation of the virus.<sup>4</sup>

Aciclovir is available in various dosage forms including topical preparation, oral formulations and IV solution or powder for injection. Oral aciclovir has a limited use and efficacy due to poor bioavailability.<sup>5</sup> Currently, IV aciclovir remains the gold standard for the treatment of HSV encephalitis,

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There are limited data on aciclovir stability in the outpatient parenteral antimicrobial therapy (OPAT) setting. Despite this, continuous infusion of IV aciclovir is currently being used in OPAT.

## WHAT THIS STUDY ADDS

⇒ Aciclovir solution at 200 mg and 2400 mg in 240 mL was stable for 14 days at room temperature (<20°C) and 24 hours of 32°C 'in-use' temperature exposure.  
⇒ High concentration of aciclovir (4500 mg/240 mL) massively precipitates when exposed to OPAT 'in-use' temperature of 32°C.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In the concentration range of 200 mg/240 mL to 2400 mg/240 mL, aciclovir solution in saline is stable, allowing the use of continuous aciclovir infusion in OPAT services.  
⇒ Precipitation of aciclovir at the highest concentration tested (4500 mg/240 mL) at 32°C would preclude its use in any clinical setting.

where treatment duration is at least 2 weeks,<sup>6</sup> and for congenital HSV infections in neonates.<sup>7</sup>

Outpatient parenteral antimicrobial therapy (OPAT) programmes are designed to support early hospital discharge for patients requiring parenteral therapy, which extends beyond the patient's need to otherwise remain in hospital. As such, OPAT has been used to effectively complete IV aciclovir therapy in clinically improving patients with HSV encephalitis.<sup>8,9</sup> However, there are limited data on aciclovir stability in the OPAT setting. Despite this, continuous infusion of IV aciclovir is currently being used in OPAT.<sup>8</sup>

Data from non-OPAT condition stability studies suggest aciclovir is stable without any significant loss of potency when reconstituted in 5% dextrose or 0.9% sodium chloride solution at a concentration of 5 mg/mL at 5°C and 25°C for up to 37 days.<sup>10</sup> However, an icy white precipitation of aciclovir was observed at 5°C which re-dissolved when the temperature was brought to 25°C. A later study<sup>11</sup> tested aciclovir stability at low (1 mg/mL), intermediate (7 mg/mL) and high (10 mg/mL) concentrations using 5% dextrose or 0.9% sodium



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chloride at 4°C and 23°C. No precipitate was noted for the low concentration when stored at 4°C; however, at the intermediate and higher concentrations tested, precipitation was noted and as previously reported. Similarly, in another study aciclovir 5 mg/mL solution in 0.9% sodium chloride did not precipitate when stored at 4°C with stability demonstrated for at least 21 days of refrigeration.<sup>12</sup> A recent study with similar conditions reported an extended fridge stability at 5 mg/mL concentrations of >63 days.<sup>13</sup>

Continuous infusions of antimicrobial agents, traditionally given in multiple daily doses, are convenient for OPAT services and patients where appropriate stability allows. Elastomeric devices delivering a continuous infusion of antimicrobials are often pre-filled, stored in a fridge for up to 14 days for convenience, then attached to the patient for 24-hour infusion. Previous studies have shown that the temperature of the antimicrobial solution in OPAT infusion pumps exceeds the usual ambient room temperature of 25°C. Generally, 32°C is considered the maximum in-use temperature reached in most parts of the world although, in some hot climate zones, this may reach up to 34°C.<sup>14</sup> Unfortunately, no stability data exist for aciclovir at these in-use temperature conditions and including the range of doses of clinical interest, as required by the UK National Health Service (NHS) protocol for the assessment of the stability of small molecules, the Yellow Cover Document (YCD).<sup>15</sup>

The lack of regulatory-compliant stability data has limited the usage of aciclovir in OPAT despite the high clinical interest. The aim of this study was to investigate the suitability of continuous infusion of aciclovir in the OPAT setting by evaluating its stability in two elastomeric infusion devices. Stability was assessed in line with the requirements of the UK NHS YCD, with the exception of the room temperature storage condition which was not compliant with the requirement of  $25 \pm 2^\circ\text{C}$ .

## MATERIALS AND METHODS

### Materials

Acetonitrile HPLC Lichrosolv (Merck, Darmstadt, Germany) was HPLC grade. Disodium hydrogen phosphate was AR grade from Merck (Darmstadt, Germany). Aciclovir for calibrators and quality control samples (QCs) was DBL aciclovir IV infusion (Batch: H161213AA, Hospira Australia, Mulgrave, Australia), the same batch used to generate the test samples. Guanine (used for degradation identification) was sourced from Sigma-Aldrich (St Louis, USA). Water used was Milli-Q. Two infusion devices, Easypump II LT 270–27-S (lot no 19E29GE221; B Braun Ltd, Sheffield, UK) and Accufuser VAWC0100L (lot no 1BBC170; Vygon UK Ltd, Swindon, UK) were used. Normal saline (0.9% w/v NaCl) was obtained from Baxter Healthcare Pty Ltd, New South Wales, Australia.

### Assay method

Calibrators were prepared by dilution of the aciclovir pharmaceutical product with water to concentrations of 0.4, 0.6, 0.7, 0.8, 0.9 and 1 mg/mL. QCs were prepared by dilution of the aciclovir pharmaceutical product with water to concentrations of 0.833, 10 and 18.75 mg/mL. Calibrators were stored in separate aliquots at  $-80^\circ\text{C}$  until required.

The chromatography was adapted from the stability-indicating method of Malabagal *et al*,<sup>16</sup> using an Acquity UPLC BEH C18 (1.8  $\mu\text{m}$ ) 2.1  $\times$  30 mm analytical column (Waters, Milford, USA) as the stationary phase. The mobile phase was 97% 25 mM phosphate buffer at pH 3.0 with 3% acetonitrile delivered isocratically at 0.4 mL/min with a 3 min run time. Aciclovir and

guanine were detected at wavelengths of 252 nm and 247 nm, respectively.

Calibrators, QCs and test samples were thawed at room temperature then vortex mixed. Calibrators and low concentration (0.833 mg/mL) QCs and samples were centrifuged and then directly injected. Samples and QCs at the intermediate and high concentrations were centrifuged and then diluted with a dilution factor of 12.5 (50  $\mu\text{L}$  of sample combined with 575  $\mu\text{L}$  water) and 22.5 (40  $\mu\text{L}$  of sample combined with 860  $\mu\text{L}$  water), respectively, prior to injection.

### Assay performance

Calibrators from 0.4 to 1 mg/mL ( $n=7$  levels) were used to create the calibration curve, covering a range of 48–125% of the nominal test concentration. Linearity of the method was established from three separate calibration lines: slopes were 4434, 4504 and 4468; intercepts were  $-95178$  to  $-4504$  and  $-90900$ ; correlation coefficients ( $r^2$ ) were 0.99992, 0.99881 and 0.99934, with all calibrators being within 0.3%, 1.6% and 1.3% of nominal, respectively.

Precision (%RSD) of the assay, demonstrated by replicate analysis ( $n=9$ ) of QCs, was 1.2% at 0.833 mg/mL and 1.2% at 18.75 mg/mL. Accuracy (% bias) from the same QCs was  $-0.2\%$  (0.833 mg/mL) and  $-1.1\%$  (18.75 mg/mL).

With regard to specificity, aciclovir gave a peak at retention time 1.33 min. Guanine eluted with baseline separation prior to aciclovir at 0.47 min. Huidobro *et al*<sup>17</sup> reported that impurities were all more strongly retained than aciclovir, so a secondary chromatographic method that included a gradient of acetonitrile from 3% to 20% was used to search for the impurities during validation, but none were found. The mean peak purity index for chromatograms of the samples was 1.000.

### Preparation of aciclovir-filled infuser devices

The required volume of aciclovir solution for IV infusion was transferred into a sterile measuring cylinder in a Class II biosafety cabinet and subsequently diluted to volume with normal saline to make a centralised stock solution at the desired concentration. Three concentrations of aciclovir were tested. These concentrations were selected to cover the clinical range of doses (concentrations) corresponding to low dose (200 mg/240 mL = 0.833 mg/mL), intermediate dose (2400 mg/240 mL = 10 mg/mL) and high dose (4500 mg/240 mL = 18.75 mg/mL) when the devices are filled to the volume of 240 mL. The nominal reservoir fill volume of 240 mL was transferred from the central stock solution to each device using a 60 mL syringe; devices were prepared in triplicate at each concentration. Flow restrictors and in-line filters were removed from all devices to enable sampling and the outlet line was clamped.

Aciclovir-filled devices were stored at room temperature (reported as  $<20^\circ\text{C}$ ). Each device was wrapped with aluminium foil to completely cover its surfaces and prevent exposure to light during storage and sampling. Following the 14 days of room temperature storage, the devices were stored within an incubator at the maximum expected in-use temperature of  $32^\circ\text{C}$  for 24 hours. Duplicate samples were collected from each individual device for the two device types that were tested at three concentrations in triplicate devices at 11 different time points which included 0, 12, 24, 48, 96, 168, 240 and 336 hours at room temperature and 344, 348 and 360 hours at  $32^\circ\text{C}$  in-use temperature (running phase). A total of 396 samples were collected and an aliquot of 0.5 mL of each sample was immediately stored in a  $-80^\circ\text{C}$  freezer for concentration measurement.

Samples were collected from each device for visual analysis of colour, clarity and any precipitation at similar time points of sampling for concentration measurement. The pH of these samples was measured using an Orion double junction semi-micro pH electrode with Eutech pH700 pH metre (Eutech Instruments, Singapore). The study was run in two batches: low and high dose initially, followed by the intermediate dose. Sub-visible particles assessment was performed using Zetasizer Nano series (Malvern Instruments, Worcestershire, UK) in the initial phase of the study. In the second phase, sub-visible particle counts were performed at 0 hours (just after reconstitution) and at 24 hours, 168 hours, 336 hours and 360 hours using a Beckman Coulter HIAC 9703+ Series precision liquid particle sampler. The HIAC analysis of each sample was performed in triplicate for each of the three replicate devices at each time point.

### Forced degradation

Forced degradation of aciclovir was investigated under the following conditions: (1) water, kept at room temperature (RT); (2) water, kept in the oven (initially 60°C but changed to 38°C after 20 hours); (3) 0.1 M HCl, kept at RT; (4) 1 M HCl, kept at RT; (5) 0.1 M NaOH, kept at RT; (6) 1 M NaOH, kept at RT; (7) 3% H<sub>2</sub>O<sub>2</sub>, kept at RT; (8) 0.1 M HCl, kept in the oven (initially 60°C but changed to 38°C after 20 hours); (9) 1 M HCl, kept in the oven (initially 60°C but changed to 38°C after 20 hours); (10) 0.1 M NaOH, kept in the oven (initially 60°C but changed to 38°C after 20 hours); and (11) 1 M NaOH, kept in the oven (initially 60°C but changed to 38°C after 20 hours)

## RESULTS

### Colour, clarity and precipitation

The room temperature on sampling days was determined to be 19.0±0.5°C. During 14 days of room temperature storage, aciclovir solution in both the Easypump II LT 270–27-S and Accufuser VAWC0100L elastomeric infusion pumps was clear and colourless with no visible precipitation in samples collected or within the body of the infusers. However, from day 7 onwards, small crystals were noted at the tip of the sampling tube for the intermediate and high concentration while the body of the infuser was clear. During the subsequent exposure to in-use temperature of 32°C, at the low concentration (200 mg/240 mL) and intermediate concentration (2400 mg/240 mL) the solution

remained clear, colourless and no visible precipitation was noted. However, a massive white precipitation was noted for the high concentration (4500 mg/240 mL). A sample of the recovered precipitant paste (0.11 g) was dissolved in 3 mL of 0.1 M NaOH. Injection of the solution revealed a massive (off-scale) aciclovir peak. For comparison, a solution of guanine in 0.1 M NaOH was injected producing a peak at its expected earlier retention time. This confirmed the precipitate to be aciclovir.

### Sub-visible liquid particles

All samples scanned for sub-visible liquid particle analysis were within the USP <788> sub-visible particle testing requirements.<sup>18</sup> However, no samples of the high concentration at in-use temperature were scanned for sub-visible particle analysis due to the significant visible precipitation.

### pH Changes

Changes in the pH of the aciclovir solution from baseline in the two elastomeric devices are summarised in tables 1 and 2. Overall, the pH gradually decreased during storage at room temperature and substantially during exposure to in-use temperature of 32°C. The highest reduction was observed at the low concentration, which was the most diluted in terms of NaOH content (each vial of aciclovir IV infusion formulation contained 92.9 mg NaOH in 20 mL).

### Aciclovir concentration

Figures 1 and 2 show the percentage of aciclovir remaining within the infusers during room temperature storage and exposure to 32°C, respectively. The mean (SD) percentage of aciclovir remaining at each time point for the Accufuser and Easypump devices is shown in tables 3 and 4, respectively. Aciclovir solution demonstrated high stability at room temperature with >98% remaining unchanged for 14 days. At 32°C aciclovir remained stable at the low (200 mg/240 mL) and intermediate (2400 mg/240 mL) dose with >95% active pharmaceutical ingredient remaining after 24 hours. However, at the high dose (4500 mg/240 mL) there was a rapid decline in aciclovir concentration with ≥20% loss within 4 hours of exposure to 32°C. This decline in concentration parallels the massive white precipitation observed during this temperature.

Following forced degradation, only strong acidic conditions (1M HCl) stored at 60°C for 24 hours resulted in conversion

**Table 1** Observed change in pH of aciclovir solution in the Accufuser VAWC0100L elastomeric infusion device during storage at room temperature and subsequent exposure to in-use temperature of 32°C

Temperature condition	Time (hours)	Observed mean±SD pH and change in mean pH from baseline by concentration					
		Low concentration		Intermediate concentration		High concentration	
		Observed pH	Δ pH	Observed pH	Δ pH	Observed pH	Δ pH
Room temperature (<20°C)	0	10.24±0.01	0.00	11.20±0.00	0.00	11.25±0.01	0.00
	12	10.30±0.01	0.05	11.16±0.04	-0.04	11.25±0.01	0.00
	24	10.27±0.03	0.03	11.08±0.01	-0.12	11.27±0.01	0.01
	48	10.17±0.03	-0.07	11.06±0.00	-0.14	11.22±0.02	-0.03
	96	10.02±0.06	-0.23	10.93±0.02	-0.27	11.25±0.05	-0.01
	120	9.85±0.07	-0.39	10.95±0.03	-0.25	11.15±0.04	-0.11
	168	9.67±0.09	-0.57	10.70±0.04	-0.50	11.04±0.08	-0.21
	240	9.47±0.11	-0.77	10.58±0.03	-0.62	10.94±0.11	-0.31
In-use temperature (32°C)	344	7.43±0.24	-2.81	10.45±0.04	-0.75	10.44±0.05	-0.82
	348	6.91±0.02	-3.33	10.45±0.04	-0.75	10.28±0.09	-0.98
	360	6.86±0.04	-3.38	10.37±0.03	-0.83	10.06±0.21	-1.20

**Table 2** Observed change in pH of aciclovir solution in the Easypump II LT 270–27-S elastomeric infusion device during storage at room temperature and subsequent exposure to in-use temperature of 32°C

Temperature condition	Time (hours)	Observed mean±SD pH and change in mean pH from baseline by concentration					
		Low concentration		Intermediate concentration		High concentration	
		Observed pH	Δ pH	Observed pH	Δ pH	Observed pH	Δ pH
Room temperature (<20°C)	0	10.11±0.01	0.00	11.03±0.00	0.00	11.13±0.01	0.00
	12	10.23±0.04	0.12	11.07±0.01	0.04	11.26±0.02	0.13
	24	10.22±0.02	0.11	11.05±0.01	0.02	11.27±0.01	0.14
	48	10.08±0.04	-0.03	11.04±0.01	0.01	11.22±0.01	0.09
	96	9.88±0.02	-0.23	10.92±0.04	-0.11	11.22±0.01	0.09
	120	9.71±0.02	-0.40	10.96±0.00	-0.07	11.06±0.02	-0.07
	168	9.50±0.04	-0.61	10.75±0.04	-0.28	10.92±0.02	-0.22
	240	9.26±0.06	-0.85	10.61±0.04	-0.42	10.82±0.02	-0.32
In-use temperature (32°C)	336	9.00±0.04	-1.11	10.53±0.06	-0.50	10.74±0.01	-0.39
	344	7.28±0.4	-2.83	10.56±0.05	-0.47	10.35±0.02	-0.78
	348	6.82±0.02	-3.29	10.53±0.06	-0.50	10.18±0.04	-0.95
	360	6.85±0.05	-3.26	10.45±0.05	-0.58	9.82±0.08	-1.31

of aciclovir to guanine. Aciclovir under all other conditions was stable ( $\geq 95\%$  remaining) for at least 24 hours.

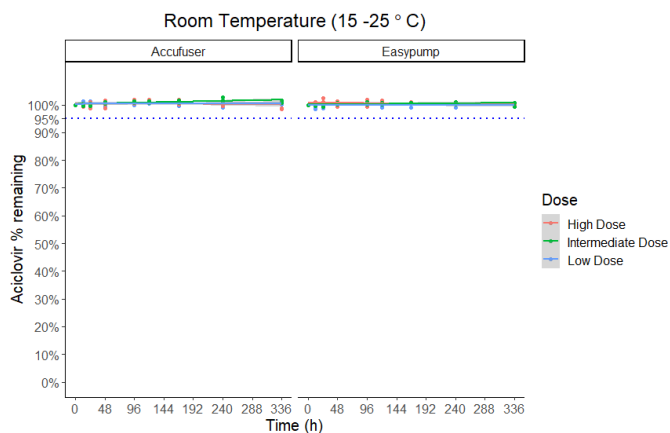
## DISCUSSION

Treatment courses with IV aciclovir for severe HSV infection can be prolonged, even when the patient is clinically improved, due to lack of suitable oral treatment options. Typical dosing of IV aciclovir with infusions 8-hourly will usually preclude its use in an OPAT setting. Once-daily continuous infusion would be desirable and could allow OPAT use if aciclovir stability was maintained over the 24-hour infusion. In this study, for the first time, the stability of aciclovir in two elastomeric infusion pumps was tested during 14 days of room temperature storage followed by 24 hours exposure to in-use temperature of 32°C at a low, intermediate and high concentration in accordance with most of the UK NHS YCD requirements. Storage at room temperature was interpreted in line with the European Pharmacopoeia rather than the UK NHS stability testing protocol, which specifies room temperature as  $25 \pm 2^\circ\text{C}$ . As such, our data are not fully compliant with the UK NHS stability protocol. However, our results importantly show that the suitability of aciclovir delivered via OPAT as a continuous infusion is dependent on the

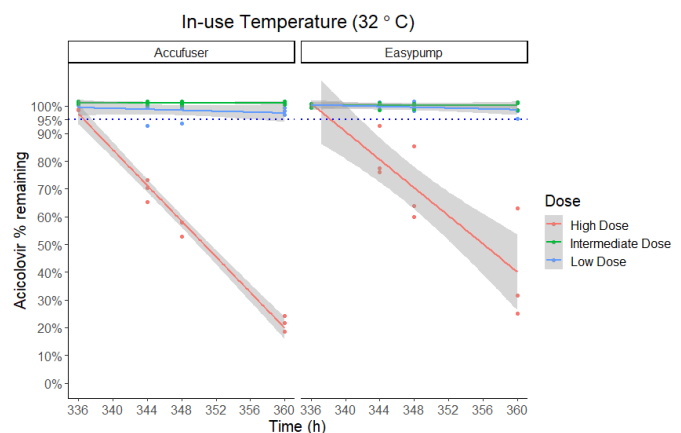
concentration. For 14 days storage at room temperature aciclovir remained stable in solution (figure 1) with no sign of precipitation within the body of the infusers at any of the concentrations tested. At the in-use temperature of 32°C, the low and intermediate doses retained stability above the 95% cut-off, but there was significant precipitation and consequent loss of stability in the high-dose devices. Due to the lack of degradation of any of the concentrations of aciclovir stored at room temperature, we were unable to calculate a degradation rate which could have been applied to a storage period at 25°C. The mid-range concentration (2400 mg/240 mL) showed no degradation in the 24 hours at 32°C while the low concentration results indicated a low level of degradation (2%) at this temperature for 24 hours.

Translating this into clinical practice, continuous IV infusion of aciclovir in the OPAT setting is possible at the usual dose used for HSV encephalitis of 30 mg/kg/24 hours. The concentration range we tested would allow for dosing at a weight range of between 6.7 kg and 80 kg, so incorporating a proportion of the paediatric population as well as adult patients.

Significant precipitation (rather than degradation) of aciclovir (figure 2) was observed and confirmed by HPLC analysis during



**Figure 1** Percentage of aciclovir remaining during room temperature (15–25°C) storage for 14 days (336 hours) by device and dose (low dose=200 mg/240 mL; intermediate dose=2400 mg/240 mL; high dose=4500 mg/240 mL). The grey band shows 95% CI.



**Figure 2** Percentage of aciclovir remaining during exposure to in-use temperature of 32°C following 14 days (336 hours) storage at room temperature by device and dose (low dose=200 mg/240 mL; intermediate dose=2400 mg/240 mL; high dose=4500 mg/240 mL). The grey band shows 95% CI.

**Table 3** Percentage of aciclovir remaining in the Accufuser VAWC0100L elastomeric infusion device during storage at room temperature and subsequent exposure to in-use temperature of 32°C

Temperature condition	Time (hours)	Mean and SD of percent remaining by initial concentration					
		200 mg/240 mL		2400 mg/240 mL		4500 mg/240 mL	
		Mean	SD	Mean	SD	Mean	SD
Room temperature (<20°C)	0	100.00	0.00	100.00	0.00	100.00	0.00
	12	100.25	0.86	100.10	0.49	100.03	0.51
	24	99.92	1.32	100.05	0.32	100.31	1.28
	48	100.44	0.93	100.77	0.33	100.20	1.50
	96	100.55	0.72	101.01	0.31	101.04	0.75
	120	101.09	0.66	100.97	0.40	101.16	0.54
	168	100.60	0.90	101.29	0.51	100.78	1.02
	240	99.92	0.90	101.87	0.87	100.59	0.84
	336	100.49	0.71	101.17	0.42	99.31	1.37
In-use temperature (32°C)	344	97.48	4.19	101.07	0.60	69.62	4.07
	348	97.57	3.46	100.96	0.62	56.17	2.96
	360	98.11	1.31	101.01	0.58	21.46	2.92

in-use temperature at very high dosing concentrations (equivalent to 45 mg/kg/24 hours for a 100 kg non-obese adult). Such doses are not commonplace in clinical practice but were included in this study in case of emergent evidence for efficacy in severe infection in the future. The observation of precipitation at high concentration is in agreement with others.<sup>11</sup> Precipitation of aciclovir is not an in vitro problem only; it can occur in vivo in renal tubules if the maximum solubility of free aciclovir (2500 mg/L at 37°C in water) is exceeded. In one case report, a cloudy white precipitate of needle-shaped crystals was observed at the base of the urinary catheter of a patient following IV aciclovir administration.<sup>19</sup> IV infusion of a high concentration may risk acute kidney injury due to tubular damage and, as such, adequate hydration is an essential co-therapy.<sup>20 21</sup> Indeed, the most common mechanism of aciclovir-induced acute kidney injury is due to crystal obstruction.<sup>22</sup>

Any off-label use of higher concentrations (dose) of aciclovir in the OPAT setting requires a careful safety consideration. Although the slow continuous infusion in OPAT is advantageous in minimising the risk of precipitation when compared with the traditional 1–2 hours of infusion for inpatient intermittent treatment with aciclovir, maintaining and monitoring a

fluid balance in outpatient settings may not be practical. Thus, hydration advice and education should be an important part of the OPAT assessment for clinically improving patients to be discharged on aciclovir. Similarly, monitoring of renal function should be undertaken in the OPAT setting as is advised in the inpatient setting in accordance with the product data sheet for IV aciclovir.<sup>23</sup>

The pH of the aciclovir solution in the devices was high due to the composition of the clinical formulation used for reconstitution. Each vial of the IV solution for injection contained 92.9 mg NaOH in 20 mL designed to keep the pH at approximately 11 for sustained stability of the solution during storage. Further reconstitution with saline in the devices did not lower the pH much for the intermediate and high concentrations (tables 1 and 2). The relatively lower pH observed at the low concentration (although >9) is most likely related to the low concentration of NaOH when the clinical formulation was diluted to the low aciclovir concentration. Overall, given the high pH of the aciclovir saline solution, infusion via a peripherally inserted central catheter (PICC) line may be necessary to ensure better haemodilution to avoid local irritancy with peripheral infusion. PICC lines are usually recommended at the extremes of pH (<5 or >9) to minimise irritation.<sup>24</sup>

**Table 4** Percentage of aciclovir remaining in the Easypump II LT 270–27-5 elastomeric infusion device during storage at room temperature and subsequent exposure to in-use temperature of 32°C

Temperature condition	Time (hours)	Mean and SD of percent remaining by initial concentration					
		200 mg/240 mL		2400 mg/240 mL		4500 mg/240 mL	
		Mean	SD	Mean	SD	Mean	SD
Room temperature (<20°C)	0	100.00	0.00	100.00	0.00	100.00	0.00
	12	99.49	1.23	99.77	0.11	100.38	0.61
	24	99.73	1.03	99.67	0.29	101.54	0.75
	48	100.13	0.36	100.35	0.31	100.55	1.02
	96	100.03	0.65	100.46	0.35	100.18	1.46
	120	99.89	1.02	100.56	0.34	100.94	0.65
	168	100.01	0.99	100.66	0.18	100.74	0.32
	240	99.71	0.61	100.66	0.46	100.51	0.31
	336	99.80	0.66	100.27	0.75	100.13	0.52
In-use temperature (32°C)	344	100.11	1.26	100.16	1.37	82.12	9.31
	348	99.88	1.70	99.99	1.14	69.75	13.80
	360	98.18	2.79	100.26	1.63	39.86	20.30

Given the limitation of our study in storing the filled devices at room temperature, we would advise that clinicians wishing to use aciclovir in elastomeric devices in clinical practice should store these at a temperature below 20°C prior to use. Bearing in mind the good chemical stability shown by the drug, individual units may consider appropriate extrapolation of aciclovir stability to NHS YCD room temperature storage (up to 25°C) while assuring that the aciclovir concentration will remain above the 95% limit.

## CONCLUSIONS

At the low concentration of 200 mg/240 mL and intermediate concentration of 2400 mg/240 mL (and other concentrations within that range) aciclovir saline solution is 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. The data from this study provide critical support for increased use of aciclovir in OPAT in line with the wide clinical interest, particularly in the paediatric patient population. However, precipitation of aciclovir at the highest concentration tested (4500 mg/240 mL) at 32°C would preclude this high dose in any clinical setting.

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**Correction notice** The licence for this paper has been changed to Open Access since it was first published.

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