Stability of daptomycin reconstituted vials and infusion solutions

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ABSTRACT

Objectives Daptomycin is a cyclic lipopeptide with selective action against drug-resistant Gram-positive bacteria. The stability of daptomycin solutions in different containers while stored at different temperatures was assessed.

Methods Daptomycin vials were reconstituted with NaCl (50 mg/mL). Daptomycin infusion solutions (5.6 and 14.0 mg/mL) were prepared in polypropylene infusion bags. All test solutions were stored either under refrigeration or at room temperature over 7 days. Samples were withdrawn on days 0, 2, 4 and 7 and assayed in triplicate using a stability-indicating high-performance liquid chromatography (HPLC) method.

Results The HPLC analysis revealed no significant loss in daptomycin concentration in vials or bags when stored at 2–8°C. All samples remained clear and colourless and there were no significant changes in pH throughout the study period.

Conclusions Reconstituted daptomycin vials (50 mg/mL) and infusion bags (5.6 and 14 mg/mL) were found to be physicochemically stable over a period of 1 week when stored at 2–8°C.

INTRODUCTION

Daptomycin is a cyclic lipopeptide antibiotic with selective action against drug-resistant Gram-positive bacteria, which has received approval from the US Food and Drug Administration[1] based on a pivotal randomised trial versus standard therapy for bacteraemia and endocarditis caused by *Staphylococcus aureus*.[2] It is a concentration-dependent rapid bactericidal antibiotic that acts by binding to and inserting into the bacterial cytoplasmic membrane, resulting in rapid depolarisation and deregulation of several cell functions such as DNA, RNA and protein synthesis. This antimicrobial is selectively active against aerobic, anaerobic and facultative Gram-positive bacteria including β-haemolytic streptococci, methicillin-resistant *S. aureus*, vancomycin-resistant enterococci and vancomycin-resistant *S. aureus*.[3]

This activity profile makes daptomycin a particularly valuable treatment option for serious infections such as complicated skin, soft tissue or bloodstream infections and right-sided infective endocarditis caused by *S. aureus*[4] including those in immunocompromised patients.[5]

Daptomycin should be administered intravenously once a day. Dosage regimens remain a matter of discussion, but increasing the initial approved dose from 4 to 10 mg/kg per day for severe infections seems effective.[6]

According to product information, 50 mg/mL reconstituted vials and diluted solutions are stable up to 48 h if stored at 2–8°C. Extending the stability period based on physicochemical stability data could improve vial optimisation, minimise drug wastage, and improve logistic issues by allowing preparation in advance or outpatient parenteral antibiotic therapy.

In the present study, the physicochemical stability of daptomycin in reconstituted vials (50 mg/mL) and polypropylene (PP) normal saline infusion bags (5.6 and 14 mg/mL) while stored at different temperatures (25°C and 5±3°C) was assessed.

METHODS

Stability studies were performed with the commercially available product. Daptomycin 350 mg glass vials (Cubicin; Novartis Europharm, Horsham, West Sussex, UK; lot PB002D and PB001A) were reconstituted to 50 mg/mL according to package instructions by adding 7.0 mL 0.9% NaCl infusion solution. Daptomycin infusion solutions containing 5.6 and 14.0 mg/mL were prepared in prefilled normal saline PP infusion bags (Sodium Chloride 0.9% Fleboflex; Grifols, Barcelona, Spain; batch J-0248) by injecting 5.6 and 14 mL from a reconstituted vial into infusion bags with 44.4 and 36 mL normal saline, respectively. All test solutions were stored protected from light either under refrigeration (5±3°C) or at room temperature (25°C) over a period of 7 days. For each concentration and storage condition, two test solutions were prepared from different batch vials.

Samples were withdrawn immediately after preparation of the test solutions (day 0) and after 2, 4 and 7 days of storage and assayed in triplicate.

Daptomycin concentration was analysed using stability-indicating reversed-phase high-performance liquid chromatography (HPLC). The HPLC method of Tobin *et al*[7] for daptomycin in serum was adapted. The HPLC system consisted of an Agilent 1200 system comprising a quaternary pump, an autosampler, a thermostatically controlled column compartment, and a diode array UV–vis detector. The analytical column was a Zorbax eclipse XDB-C18 (150 mm×4.6 mm; 5 µm particle size).

The mobile phase consisted of 70% phosphate buffer solution (pH 5.5) and 30% acetonitrile (supergradient grade) (Applichem Panreac; Panreac Química, Barcelona, Spain). The flow rate was set at 1.2 mL/min with an injection volume of 50 µL. Results were analysed at a detection wavelength of 223 nm. Column temperature was maintained at 30°C.

The method was validated following the ICH Q 2 (R1) guidelines for stability studies.[8] Suitability of

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the HPLC method was proven by analysing forced degraded samples (HCl, NaOH, H_2O_2, heat).

Linearity of the method was evaluated at five different concentrations of daptomycin (62.5, 125, 250, 500 and 1000 µg/mL). The calibration curve was constructed by analysing plots of peak area versus daptomycin concentrations.

Repeatability was assessed using two different solutions (250 and 350 µg/mL) with sixfold injection. Intermediate precision was validated by analysing two control solutions (280 and 500 µg/mL) by two different operators.

Robustness of the assay was proven using different percentages of components of the mobile phase (30:70, 29:71, 31:69) and different temperatures (28°, 30° and 32°C).

Limit of detection (LOD) and quantification limit (LOQ) were calculated based on the SD of the response (σ) and the slope (S) of the calibration curve (LOD=3.3×σ/S; LOQ=10×σ/S).

The pH values of the test solutions were measured on day 0, 2, 4 and 7 of storage (Basic 20 Ph-Meter; Crison Instruments, Barcelona, Spain).

Test solutions were visually checked for changes in colour and precipitates whenever samples were withdrawn for quantitative analysis. Test solutions without changes or precipitates were defined as physically stable.

For solutions stored in plastic bags, weight was recorded at all sampling times to determine possible water loss due to diffusion of water vapour.

Chemical stability was defined as retention of at least 95% of the initial concentration.

RESULTS

The HPLC method developed was found to be suitable for the stability studies of daptomycin. The method was robust. Forced degradation assays revealed peaks corresponding to the intact daptomycin and additional peaks of unknown degradation products (figure 1). These were clearly separated from the daptomycin peak.

The correlation coefficient of the calibration curve was 0.9997 and proved linearity. Repeatability, calculated as the coefficient of variation, was 0.34% for 250 µg/mL and 4.6% for 350 µg/mL solutions. Intermediate precision (coefficient of variation) was 2.64% for 280 µg/mL and 1.62% for 500 µg/mL solutions. LOD was 13.32 µg/mL and LOQ was 40.36 µg/mL.

The daptomycin concentrations of the reconstituted vial and infusion solutions remained unchanged over the entire study period of 7 days when stored at 5±3°C (real temperature of storage: minimum=4°C; maximum=7.6°C). Stability was affected by neither the container material (glass vial, PP bag) nor the concentration (50, 5.6 and 14 mg/mL). Regarding storage temperature, stability during the study period was demonstrated only for refrigerated samples. Samples stored at room temperature (range 20.6–24.1°C) were found to be stable for only 2 days for all conditions (figure 2).

The mean percentage of the initial concentration remaining was >95% for all samples at 5±3°C over all the study days (table 1). None of the chromatographic peaks observed in samples subjected to forced degradation were detected in any sample during the study.

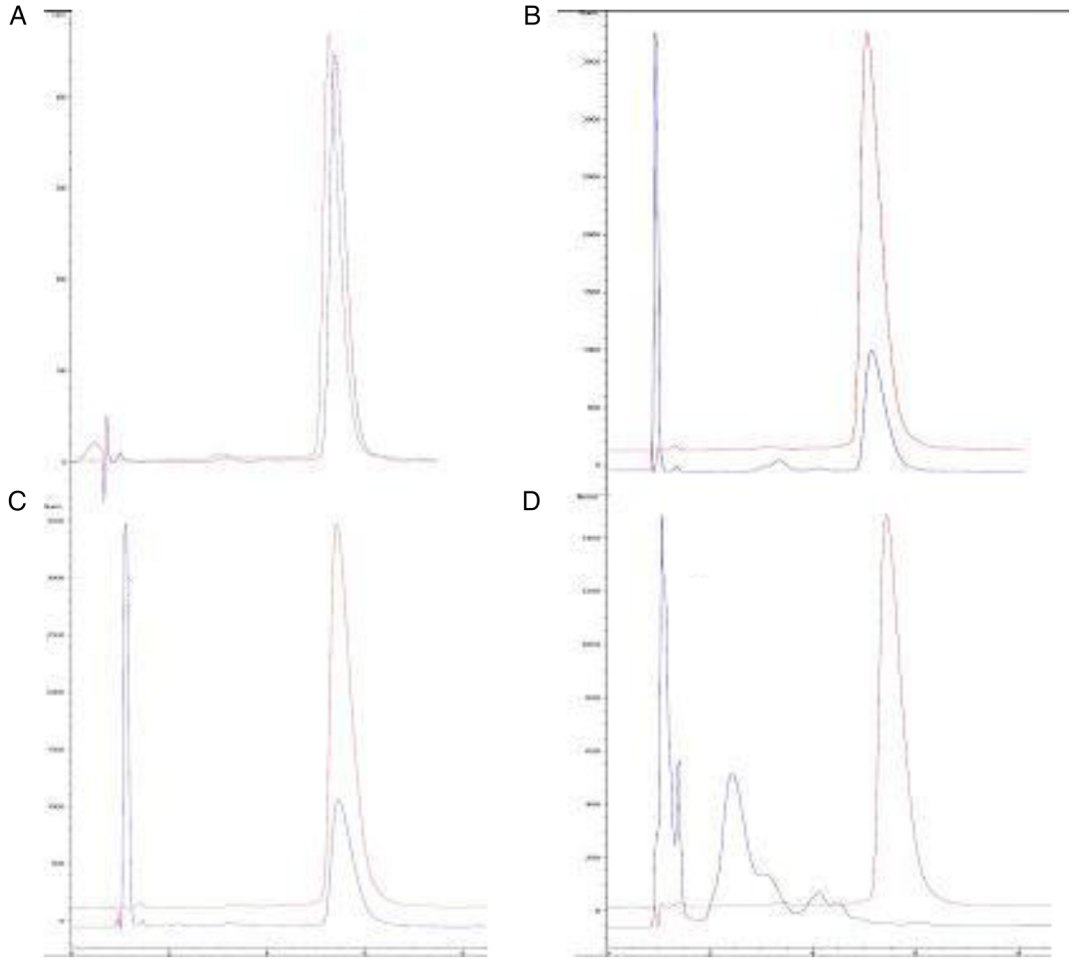

Figure 1 Forced degradation chromatograms for temperature (A), acid (B), oxidative (C) and basic (D) conditions.

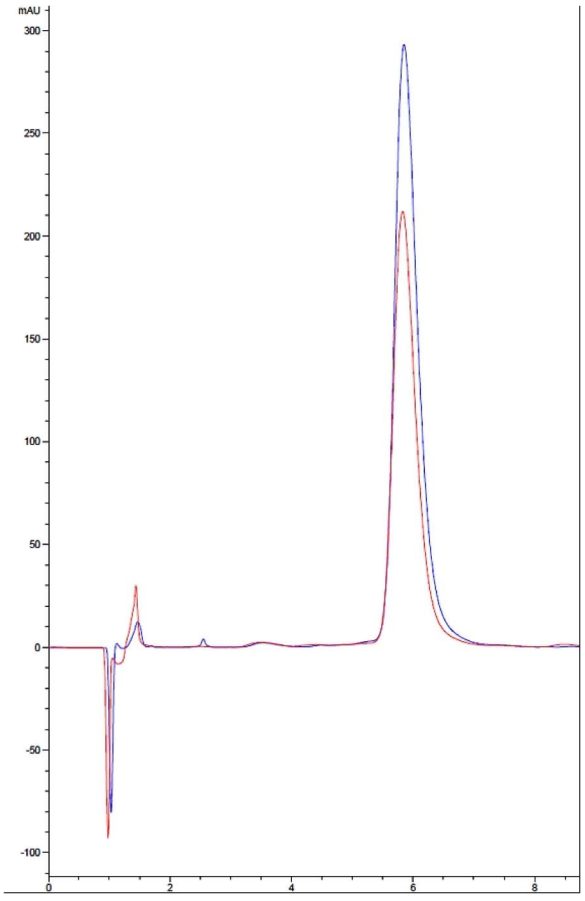

Figure 2 Overlaid chromatograms of the solution stored at room temperature at day 0 (blue) and 4 (red) for the vials at 50 mg/mL.

All solutions were also found to be physically stable for at least 1 week. Neither change in colour nor precipitation was detected by visual inspection during the study period. pH measurements remained stable over the study period (maximum change 0.08) (table 1). No significant water loss was detected (<0.5%) for the plastic bags.

DISCUSSION

Our results suggest that daptomycin reconstituted vials (50 mg/mL in normal saline) and infusion solutions (5.6 and 14 mg/mL in normal saline) are physicochemically stable over a period of at least 1 week at 2–8°C.

These results are consistent with the study of Ortega *et al*,[9] which showed that an admixture of daptomycin 5 mg/mL and heparin sodium 100 USP units/mL was stable when stored in PP syringes for up to 14 days at 4°C and −20°C.

Our data could improve logistic issues by allowing drug preparation in advance and minimising drug wastage.

Stability was not probed for all samples stored at room temperature for more than 2 days, although 14 mg/mL bags remained stable for 4 days. Lai and Brodeur[10] evaluated the stability of nine daptomycin admixtures at room temperature. All samples were compatible and remained stable, but this study was only performed over 120 min, which probably explains the lack of concentration loss. Another two studies have been performed to evaluate daptomycin stability in peritoneal solutions. In addition to the relationship between glucose concentration and daptomycin degradation, a clear relationship between temperature and antibiotic degradation was found.[11 12]

Stability of the antimicrobial agent is a major consideration when considering outpatient parenteral antimicrobial therapy.[13] Stability period extension may permit implementation of this mode of therapy with daptomycin.

A limitation of our study was that no subvisual evaluation was performed. Regarding the number of samples, current guidelines recommend that a stability study should be performed in three different batches in the final containers for each condition.[14] However, our study included only two samples for each condition.

Our data should allow us to extend reported daptomycin solution stability periods in real practice. To our knowledge, this is the first study to try to extend approved daptomycin solution stability. However, owing to the risk of microbiological contamination, handling using a strict aseptic technique is also critical to ensure stability.

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Table 1 Stability of daptomycin solutions under different conditions

		Value at 5±3°C for		Value at room temperature for	
Sample type	Days of storage	Concentration*	pH	Concentration	pH
Vial 50 mg/mL	0†	100±0.9	4.55	100±0.55	4.56
	2	102.5±4.9	4.58	96.3±3.8	4.59
	4	104.5±2.8	4.60	86.7±4.1	4.58
	7	100.6±1.2	4.63	–‡	–
Bag 5.6 mg/mL	0†	100±0.3	4.52	100±0.4	4.57
	2	105.8±9.0	4.57	96.9±5.9	4.57
	4	98.7±1.2	4.57	91.7±5.2	4.57
	7	98.5±2.3	4.55	–‡	–
Bag 14 mg/mL	0†	100±0.8	4.61	100±0.1	4.55
	2	100.6±1.1	4.60	101.6±4.9	4.60
	4	102.4±1.3	4.60	98.0±2.1	4.58
	7	103.4±4.8	4.59	92.7±5.9	4.62

n=6 for all results.
*Mean %±SD of initial concentration remaining.
†Initial concentration: 49.2±3.5 mg/mL, 5.2±0.3 mg/mL and 13.7±0.6 mg/mL for vials and bags, respectively.
‡Study was not continued for samples below the stability limit (95%).

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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