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# Compatibility and stability of daptomycin lock solutions in combination with gentamicin, azithromycin, heparin and trisodium citrate

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**Abstract**

**Background:**

Antibiotic lock therapy is an interventional modality used for treatment and prevention of central-line associated bloodstream infections. Stability and compatibility data for combinations are lacking, limiting clinical use.

**Objective:**

Compatibility and stability of daptomycin lock solutions in combination with azithromycin, gentamicin, and heparin or sodium citrate were evaluated up to 96 hours.

**Methods:**

Eight candidate lock solutions were prepared for compatibility and stability testing. All solutions were prepared in glass vials, and included daptomycin 1mg/mL in varying combinations with heparin 100 – 1,000 units/mL, trisodium citrate, azithromycin and/or gentamicin. Lactated Ringer's solution was added as a diluent in a sufficient quantity to bring the total volume up to 5mL. Drug stability in the admixture was determined by the degradation of the components. The quantification of drugs was performed using Waters Alliance HPLC using Phenomenex Luna C8 (2), 150*2.6mm, 5µ column. A gradient run was executed for 20 minutes with 0.45% ammonium dihydrogen phosphate, pH 3.25 as eluent A and acetonitrile as eluent B at a flow rate of 1.0mL/min. Each solution was visually inspected for particulates and color change. Lock solutions were tested in triplicate.

**Results:**

Daptomycin degradation was <10% for all solutions at 48 hours, and for 7 of the 8 solutions at 72 hours. Gentamicin degradation was <5% for solutions in combination with daptomycin and trisodium citrate. No physical incompatibilities were detected.

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**Conclusion:**

Study data support the stability and compatibility of daptomycin with additives in solution, allowing for fewer exchanges and longer dwell times for a lock solution. The addition of azithromycin or gentamicin may offer synergy and/or extended spectrum of activity. Daptomycin bioactivity with trisodium citrate needs confirmation**.**

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## Introduction

Central-line associated bloodstream infections (CLABSI) remain a significant problem in patients with indwelling central venous catheters (CVC).[1] Bacterial biofilm formation, which may begin as early as 24 hours after CVC insertion, enhances the pathogenicity and virulence of many bacterial species, including Staphylococcal species.[2] Although definitive treatment of CLABSI involves systemic antibiotics and CVC removal, salvage of the catheter may be attempted. The Infectious Diseases Society of America guidelines support the instillation of a highly concentrated antibiotic solution in the infected catheter lumen, commonly referred to as antimicrobial lock therapy (ALT), in conjunction with systemic antibiotics in cases of catheter salvage.[3] Prophylactic ALT is also recommended in high-risk patients with recurrent CLABSI.[4,5] Lock therapy often includes an antibiotic, concentrated 100-1,000 times the MIC of planktonic bacteria, plus an anticoagulant in solution.[6,7]

Vancomycin remains the most commonly studied antibiotic in lock solutions; however, there are concerns of inability to adequately treat and eradicate biofilm-embedded organisms.[8-10] Daptomycin, a lipoglycopeptide antibiotic, possesses potent activity against slime-producing *Staphylococcus epidermidis* and methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MRSA), validated in several *in vitro* catheter infection models.[11-15] Calcium supplementation, often in the form of Lactated Ringers (LR) solution, is required for activity.[12] Although limited, some clinical data report the success with daptomycin lock therapy when combined with heparin in solution against CLABSI.[10,16,17] The use of a macrolide in combination with daptomycin in a lock solution demonstrated effectiveness against biofilm producing organisms.[18]

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To date, physical stability and chemical compatibility data of daptomycin with antibiotics and anticoagulants in lock solution are limited and exclude lock solutions that may be used in clinical practice.[19] We sought to investigate the 96-hour compatibility and stability of daptomycin 1mg/mL, reconstituted with LR solution, in combination with gentamicin, azithromycin, and heparin or citrate. We also report a brief review of the available compatibility and stability data of daptomycin in lock solutions.

**Methods**

Preparation of solutions:

Eight candidate solutions were identified for compatibility and stability testing. The stock solutions were prepared as follows. Daptomycin (Lot No. CDC156, Cubist) 500mg vial was reconstituted with 10mL of 0.9% sodium chloride solution (Lot No. C863498, Baxter) to get 50mg/mL of daptomycin. Five mL of the stock solution was further diluted with 45mL of Lactated Ringers Solution (C861054, Baxter) to get a final concentration of 5mg/mL of daptomycin. A 500mg vial of azithromycin (Lot No. 6102707, APP Pharmaceuticals) was reconstituted with 5mL of 0.9% sodium chloride solution to get a concentration of 100mg/mL of azithromycin. Five mL of the azithromycin stock solution was further diluted to 10mL with 5mL of 0.9% sodium chloride solution to a concentration of azithromycin 50mg/mL. One mL of 80mg/mL solution of gentamicin (Lot No. 05270, Hospira Inc.) was diluted with 5.33mL of 0.9% sodium chloride solution to get a final concentration of 15mg/mL. Anticoagulant additives of heparin at concentrations of 100 and 1,000 units/mL and trisodium citrate 24mg/mL (2.4%) were evaluated. Formulas were developed and verified to provide lock solutions that were prepared using commercially available products in an institutional pharmacy, including heparin

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(500units/mL and 1,000units/mL) and trisodium citrate 4% (40mg/mL). All solutions were prepared with LR solution to provide adequate calcium supplementation (50mcg/mL) required for daptomycin lock activity. The details of each candidate solution are given in Table 1.

Physical compatibility:

All the samples prepared were examined at room temperature on the table top. The change in color, precipitation, and formation of turbidity of each of the solution was monitored visually for 0hrs, 24hrs, 48hrs, 72hrs, and 96hrs.

Chemical stability:

Chemical stability was assessed by a determination of degradation/loss of potency of the components of the admixture. The quantification of the drugs (except heparin) was examined using Waters Alliance HPLC equipped with a quaternary pump, vacuum degasser, thermostat-controlled column compartment, thermostat-controlled autosampler, and diode-array detector 2996, all controlled by Empower Chromatography Manager.[20] The analysis was carried out in Phenomenex Luna C8(2), 150*2.6mm, 5µ column using eluent A consisting of 0.45% Ammonium dihydrogen phosphate, pH 3.25 and Acetonitrile as eluent B at a flow rate of 1.0mL/min. The initial gradient was started with 100% eluent A for 4 minutes, during 5 minutes to 10 minutes the ratio of eluent A/eluent B was changed from 100:0 to 50:50 which was kept constant until 12 minutes followed by eluent A 100% from 13 minutes to 20 minutes. The retention time for daptomycin, gentamicin, and heparin were 12.2, 10.1, and 10.2 minutes respectively[21]. Before the actual analysis, mini validation was carried out to establish the specificity, linearity, accuracy, and repeatability of the method. The method was found to be specific with no interference of blank peaks or the impurities with the main drugs. Linearity was

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established for concentrations ranging from 5ug/mL to 6ug/mL. The accuracy and repeatability were carried out for 3 and 6 samples with %RSD of 0.64 and 0.91 respectively. All samples were tested in triplicate, and the analysis was carried out at 0hrs, 24hrs, 48hrs 72hrs, and 96hrs. The stability was determined by the percent decrease in drug concentration in each sample.

**Results**

Daptomycin in combination with heparin at 1,000 units/mL and 100 units/mL in solution (Solutions 1 and 2) was found to have less than 2% degradation at 72 hours. At 96 hours, daptomycin concentrations were approximately 82-84% of baseline. In combination with trisodium citrate 2.4%, daptomycin concentrations were approximately 93% of baseline at 96 hours. When daptomycin was combined with azithromycin 5mg/mL in 3 candidate solutions (Solutions 4, 5 and 6), concentrations were >90% at 96 hours for all candidate solutions. Daptomycin appeared to degrade more rapidly when combined with gentamicin 3mg/mL in solution (Solutions 7 and 8). When combined with gentamicin alone, daptomycin concentrations were sustained above 90% for 72 hours. The addition of trisodium citrate, along with gentamicin and daptomycin, resulted in approximately 10% degradation of daptomycin at 48 hours. Gentamicin concentrations were also evaluated for solutions 7 and 8 and were maintained above 95% for the entire 96-hour study period. No visual changes were noted during the 96-hour period for any of the candidate solutions. Complete results for daptomycin and gentamicin concentrations for all 8 candidate solutions are available, where applicable, in Table 1. Concentrations of heparin, trisodium citrate, and azithromycin were not evaluated. Bioactivity of the antimicrobials or anticoagulants were not determined.

**Discussion**

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Daptomycin possesses significant biofilm activity against common skin commensals, including *S. epidermidis* and *S. aureus*, which are responsible for the majority of CLABSI.[9,13,14,22] Daptomycin penetration into a *S. epidermidis* biofilm is rapid, within minutes, and diffusion is 28% of that in pure water.[23] Disruption of Staphylococcal biofilms from plastic bases has been demonstrated on both pre-formed and mature biofilms.[24] A high rate of clinical success with daptomycin (1mg/mL to 5mg/mL) lock therapy has been shown in a case report, case series, and retrospective study. Heparin at variable concentrations (100 units/mL to 5,000 units/mL) has been used as the anticoagulant in solution.[10,16,17]

Daptomycin lock solutions at varying concentrations (0.5 to 5mg/mL) have demonstrated success against slime producing Staphylococcal species through *in vitro* models.[11-14,22] The addition of ethanol to daptomycin lock solutions has enhanced activity.[11,12,] Previous studies have demonstrated only the physical compatibility up to 48 hours for daptomycin 5mg/mL and sodium citrate 4% in solution.[25] The present study confirmed physical compatibility with sodium citrate 2.4% and established chemical stability extended through 96 hours. This concentration of trisodium citrate examined in our study is achievable using the commercially available 4% product. The use of citrate in a lock solution offers an alternative anticoagulant to heparin and may possess antibiofilm and synergistic activity with antibacterial therapy. However, because of the calcium chelating properties of citrate, use with daptomycin in a lock solution should be confirmed in an in vitro model of infection. Simulated Y-site compatibility study of daptomycin 19.6mg/mL and heparin 98units/mL demonstrated physical and chemical stability for up to 120 minutes at room temperature.[26] In this same study, daptomycin 19.2mg/mL and gentamicin 1.5mg/mL were shown to be physically compatible and chemically stable at 2 hours.[26] In the present study, we investigated up to 96-hour stability and

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compatibility, confirming 48-hour daptomycin stability at room temperature for all candidate solutions, including heparin concentrations at 1,000 and 100 units/mL. Five of the 8 candidate solutions maintained >90% daptomycin concentrations, which may allow for extended dwell times as a lock therapy, such as between hemodialysis sessions. Gentamicin stability at 3mg/mL was confirmed with and without citrate in the solution for 96 hours. Use of daptomycin and gentamicin in a lock solution together may allow for possible synergy against Staphylococcal species and extended spectrum of therapy for polymicrobial infections.

Macrolide antibiotics have demonstrated anti-biofilm activity against a number of bacterial organisms. Use of azithromycin has reduced the growth of Pseudomonal biofilms *in vitro* and impacted *Pseudomonas* infections despite no inherent antibacterial activity.[27,28] Additionally, another member of the macrolide class, clarithromycin, has previously demonstrated disruption of *S. epidermidis* biofilms.[29] Azithromycin in combination with ceftriaxone at a dose of 512mg/L resulted in bactericidal activity against slime-producing Staphylococcal species.[21] In this same investigation, the combination of azithromycin at concentrations up to 1,024mg/L did not result in enhanced anti-biofilm activity of daptomycin at 2mg/L and 5mg/L.[21] Conversely, clarithromycin, in combination of daptomycin, was able to completely prevent the regrowth of two biofilm-producing Staphylococcal strains in a catheter model with a MIC over 128mg/L.[18] However, we investigated azithromycin concentrations 5 times higher in combination with daptomycin, which may provide additional dose-dependent biofilm activity. Given the stability of daptomycin at 96 hours of >90% in these candidate solutions, these data support further study of bioactivity of the azithromycin and daptomycin in combination in a lock solution.

There are several limitations to the present study. Lock solutions were only observed for

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up to 96 hours. Although the observation time was limited, degradation was limited over the study period for most combinations. It is custom to exchange lock solutions frequently with the CVC is in use (eg before hemodialysis session), thus this time period is clinically relevant. Regulations from USP 800 will also dictate expiration of lock solutions.[30] Additionally, samples were only studied at one temperature and it is unknown if refrigeration impacts stability and compatibility. Higher temperatures that mimic the intra-lumen and hub of a CVC are infrequently studied. Lastly, glass vials were used which may not translate specifically to drug degradation in a CVC.

**Conclusion**

Daptomycin possesses potent anti-biofilm activity and has limited, but proven clinical success as a lock solution. These study data support the extended stability and compatibility of daptomycin for 48-96 hours with heparin in solution, allowing for prolonged dwell times and fewer lock solution exchanges. Although the addition of citrate to daptomycin resulted in prolonged stability and compatibility, it is unknown if this will adversely impact daptomycin activity. The addition of gentamicin and/or azithromycin to daptomycin in a lock solution may provide synergy and/or extended spectrum of activity and warrants further investigation at these concentrations.

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**Table 1. Daptomycin and gentamicin concentrations of candidate lock solutions**

| Solutions | 0hrs | 24hrs | 48hrs | 72hrs | 96hrs |
|---|---|---|---|---|---|
| | Percentage of Daptomycin | | | | |
| Solution 1: Daptomycin 1mg/mL + Heparin 1,000 units/mL (TAV: 5 mL) | 99.86 | 99.93 | 101.18 | 98.33 | 83.99 |
| Solution 2: Daptomycin 1mg/mL + Heparin 100 units/mL (TAV: 5 mL) | 101.09 | 101.34 | 101.16 | 99.42 | 82.12 |
| Solution 3: Daptomycin 1mg/mL + Trisodium citrate 24mg/mL (2.4%) (TAV: 5 mL) | 102.45 | 101.71 | 102.41 | 101.94 | 93.26 |
| Solution 4: Daptomycin 1mg/mL + Azithromycin 5mg/mL + Heparin 1,000 units/mL (TAV: 5 mL) | 100.81 | 102.16 | 101.79 | 101.84 | 91.45 |
| Solution 5: Daptomycin 1mg/mL + Azithromycin 5mg/mL + Heparin 100 units/mL (TAV: 5 mL) | 103.25 | 102.70 | 101.54 | 100.33 | 101.36 |
| Solution 6: Daptomycin 1mg/mL + Azithromycin 5mg/mL + Trisodium citrate 24mg/mL (2.4%) (TAV: 5 mL) | 102.90 | 103.96 | 101.37 | 101.27 | 103.31 |

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|---|---|---|---|---|---|
| Solution 7: Daptomycin 1mg/mL + Gentamicin 3mg/mL (TAV: 5 mL) | 100.51 | 99.80 | 97.18 | 91.56 | 78.99 |
| Solution 8: Daptomycin 1mg/mL + Gentamicin 3mg/mL + Trisodium citrate 24mg/mL (2.4%) (TAV: 5 mL) | 98.98 | 94.13 | 90.66 | 86.69 | 81.55 |
| | **Percentage of Gentamicin** | | | | |
| Solution 7: Daptomycin 1mg/mL + Gentamicin 3mg/mL (TAV: 5 mL) | 99.31 | 98.69 | 97.36 | 96.75 | 96.98 |
| Solution 8: Daptomycin 1mg/mL + Gentamicin 3mg/mL + Trisodium citrate 24mg/mL (2.4%) (TAV: 5 mL) | 97.17 | 97.00 | 95.20 | 95.48 | 95.24 |

TAV=total actual volume

All daptomycin solutions were reconstituted and supplemented with Lactated Ringer's solution containing 50mcg/mL of calcium. (Heparin 1000- Lot No. WG114N, Sagent, Heparin 500- Lot No. 6003055, APP Pharmaceuticals, sodium citrate (Lot No. c856641, Baxter).