

Now sold under the
Thermo Scientific brand



Determination of *N*-Methylpyrrolidine in Cefepime Using a Reagent-Free Ion Chromatography System

INTRODUCTION

Cephalosporins are currently the most prescribed class of antibiotics worldwide for the treatment of bacterial infections.¹ Their low toxicity and broad range antimicrobial activity against Gram-negative and Gram-positive bacteria have contributed to their widespread use.^{1,2} Third generation cephalosporins were developed with enhanced activity against Gram-negative bacilli, but are less active against Gram-positive bacilli. Therefore, further synthetic modifications were incorporated to achieve a more balanced antimicrobial spectrum, which resulted in fourth-generation cephalosporins.³ Cefepime (Figure 1A) is a semi-synthetic, fourth generation cephalosporin that is commonly prescribed for the treatment of pneumonia, febrile neutropenia, urinary tract infections, skin or soft-tissue infections, and abdominal infections.⁴

Cefepime is unstable and will degrade slowly even during storage at 4 °C. Degradation is more rapid at higher temperatures, with cefepime content decreasing by 10% at 37 °C in approximately 13 h.⁵ This can be problematic if cefepime is kept at room temperature or body temperature during infusion over extended periods of time. Degradation of cefepime includes cleavage of the R2 side chain and opening of the β-lactam ring to yield 2-[[[(2-amino-4-thiazolyl)((*Z*)-methoxyimino)acetyl]amino]acetoaldehyde and *N*-methylpyrrolidine (NMP, Figure 1B).⁵ The accumulation of alkaline degradation products increases the pH and therefore increases the rate of cefepime degradation. The degradation of cefepime is also associated with colorimetric changes from a colorless solution (no degradation) to a characteristic orange/brown appearance (complete degradation).⁶

The primary concerns with degradation are loss of potency and the potential toxicity of degradation products to patients. According to one study, an administration of 50 mg/kg NMP in monkeys for 28-30 consecutive days caused ataxia and esotropia (“cross-eyes”) during or shortly after treatment.⁷ Although this dose was approximately 25-fold higher than the maximum NMP likely to contaminate a daily 6 g dose of cefepime, and no significant effects were observed with lower doses, the potential for side effects is still of concern. Therefore, the determination of NMP in cefepime is critical to assess the purity of the pharmaceutical product due to the potential toxicity of NMP to patients.

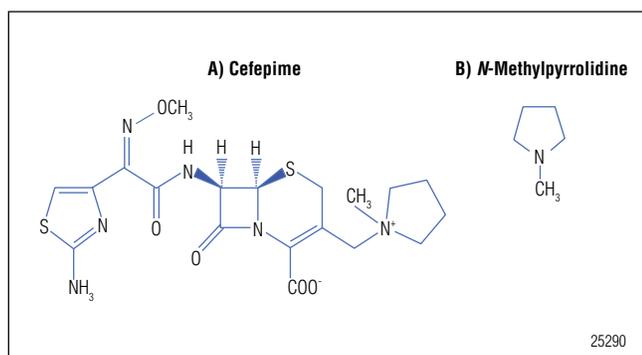


Figure 1. Chemical structures of A) cefepime and B) *N*-methylpyrrolidine.

The current U.S. Pharmacopeia (USP) compendial method for determining the limit of NMP in cefepime describes the use of cation-exchange chromatography with a 10 mM nitric acid/10% acetonitrile eluent followed by direct conductivity detection. This yields a typical background conductance of approximately 3500 μS .^{8,9} The significantly higher background conductance generated by direct conductivity detection (i.e., non-suppressed conductivity detection) relative to suppressed conductivity detection produces higher baseline noise and therefore higher detection limits. Larger injection volumes are required to achieve adequate sensitivity. However, non-suppressed conductivity detection requires low-capacity resins with dilute eluents to achieve a reasonably low background signal. The conflicting requirements of low column capacity and high injection volume make method optimization difficult. The dilute eluents result in long retention times and low sample throughput. A more detailed comparison between non-suppressed and suppressed conductivity detection can be found in Dionex Application Note 157.¹⁰

The current USP method has additional disadvantages. The USP methods for cefepime hydrochloride and cefepime for injection require nitric acid as a diluent (0.01 N and 0.05 N, respectively). These dilutions yield a sample pH ≤ 2 , even though cefepime is most stable at pH values between 4 and 6.⁵ Degradation of the sample during testing can lead to artificially high results. Other disadvantages include the 3–4 h time required per injection and a retention time difference of 10–15% between NMP in the test (sample) and standard solutions.^{11,12}

This application note describes a cation-exchange chromatography method that significantly reduces the time between injections relative to the current USP method (by approximately 3 h) due to the very low hydrophobic character of the IonPac[®] CS17 column, enabling a faster elution of strongly retained compounds (e.g., cefepime). The proposed method is also simplified by using an electrolytically generated methanesulfonic acid (MSA) eluent and requires only a deionized water source for operation. The method uses a Reagent-Free[™] ion chromatography system with the IonPac CS17 column and suppressed conductivity detection for the determination of NMP in cefepime

hydrochloride. The IonPac CS17 is a hydrophilic, moderate capacity (363 $\mu\text{eq}/\text{column}$, 2 x 250 mm), carboxylate-functionalized cation exchanger that was specifically developed for the separation of hydrophobic and polyvalent amines. This stationary phase can also successfully separate hydrophilic amines from common cations. The linearity, detection limits, precision, and recovery of NMP in cefepime hydrochloride are determined. The limit of quantitation for this method is approximately 0.001% NMP, well within the limit of 0.3% set in the USP method.⁸

EQUIPMENT

Dionex ICS-3000 Reagent-Free Ion Chromatography system with Eluent Generation (RFIC-EG[™] system) consisting of:

- SP Single Pump or DP Dual Pump module
- EG Eluent Generator module with EGC II MSA eluent generator cartridge (EluGen[®] II MSA; P/N 058902) and Continuously Regenerated Anion Trap Column (CR-CTC II; P/N 066262)
- DC Detector/Chromatography module (dual temperature zone configuration)
- AS Autosampler with sample tray temperature control
- Chromeleon[®] Chromatography Management Software
- 1.5 mL glass injection vials with caps and septa (Dionex P/N 058902)

REAGENTS AND STANDARDS

- Deionized water, Type 1 reagent grade, 18 M Ω -cm resistivity or higher
- Methanesulfonic acid, (Dionex, P/N 033478)
- DL-Arginine (Sigma-Aldrich; P/N A4881)
- N-Methylpyrrolidine (Sigma-Aldrich, P/N M79204)

SAMPLES

- Cefepime hydrochloride (USP, Catalog # 1097636), Lot G0D116 was used in this study.
- Cefepime Hydrochloride System Suitability RS (USP, Catalog # 1097647), Lot F0C095 was used in this study.

CONDITIONS

Column:	IonPac CS17 Analytical, 2 × 250 mm (P/N 060561) IonPac CG17 Guard, 2 × 50 mm (P/N 060563)
Eluent:	6 mM MSA from 0–7.5 min, step change to 85 mM at 7.5 min, 85 mM from 7.5–20 min, step change back to 6 mM at 20 min, 6 mM from 20–30 min ^a
Eluent Source:	EGC II MSA with CR-CTC II
Flow Rate: ^b	0.4 mL/min
Injection Volume:	5 µL (full loop)
Temperature:	40 °C (column compartment) (50 °C was used for the system suitability test) 30 °C (detector compartment)
Detection:	Suppressed conductivity, CSRS [®] 300 (2 mm), AutoSuppression [®] recycle mode, 100 mA
Background	
Conductance:	0.5–0.7 µS
Noise:	0.2–0.4 nS
System	
Backpressure:	~2300 psi

^aThe column was equilibrated an additional 5 min at 6 mM MSA prior to injection.

^bThe equivalent flow rate for this application using a 4 mm CS17 column would be 1.6 mL/min. At this flow rate, the maximum MSA concentration is 62.5 mM due to the suppressor current limitations. Therefore, we strongly recommend using a 2 mm column for this application, which requires relatively low flow rates. This enables the use of a higher MSA concentration to remove cefepime from the column, and reduces eluent consumption and waste production.

PREPARATION OF REAGENTS AND STANDARDS

Eluent Solution

Generate the MSA eluent online by pumping high quality deionized water (18 MΩ-cm resistivity or better) through the EGC II MSA cartridge. Chromeleon software will track the amount of MSA used and calculate the remaining lifetime.

Alternatively, prepare 100 mM MSA by carefully adding 9.61 g of concentrated MSA to a 1 L volumetric flask containing about 500 mL of deionized water. Bring to volume and mix thoroughly. Degas the eluents and store in plastic labware. Proportion this MSA solution with degassed deionized water to generate the appropriate eluent concentrations listed in the method conditions.

Standard Solutions

Accurately dispense and weigh 0.16 mL NMP (d = 0.819 g/mL at 25 °C) beneath a well ventilated fume hood in a 100 mL volumetric flask, bring to volume with deionized water, and mix to prepare a final NMP concentration of 1.31 mg/mL. Store the stock solution at 4 °C when not in use. Prepare working standards for generating the calibration curve with an appropriate dilution of the stock standard in deionized water. Store at 4 °C.

SAMPLE PREPARATION

Accurately weigh 100 mg of cefepime hydrochloride into a 20 mL scintillation vial, dissolve in 10 mL of deionized water, and mix. Prepare the simulated Cefepime for Injection solution by combining 100 mg of cefepime hydrochloride with 72.5 mg of arginine in a 20 mL scintillation vial. Dissolve in 10 mL of deionized water and mix. Prepare the cefepime system suitability sample by weighing 10 mg of the sample into a 1.5 mL glass AS vial. Dissolve the solution in 1 mL of deionized water and mix. Further dilute the sample to a final concentration of approximately 1.4 mg/mL prior to analysis. Note: These solutions should be analyzed within an hour if stored at 25 °C or within 10 h if stored between 4–6 °C. We strongly recommend that the AS sample tray temperature control be set to at least 6 °C for the duration of this method.

RESULTS AND DISCUSSION

Previous studies have demonstrated with mass spectrometry data that degradation of cefepime includes cleavage of NMP and opening of the cephem (β -lactam ring). Similar degradation pathways have been observed with other cefepime related compounds.⁷ An increase in the percentage of NMP in the drug would be indicative of a decrease in the potency of the active component. Therefore, it is critical to determine the amount of NMP in cefepime to assess the purity and stability under different storage conditions over time. The USP monograph specifies a limit of <0.3% NMP in cefepime hydrochloride and <1% in Cefepime for Injection.^{8,9} The latter is a dry mixture of cefepime hydrochloride and L-arginine. The L-arginine is added at an approximate concentration of 725 mg/g of cefepime to maintain the pH of the constituted solution between 4 and 6.⁴

In an acidic media, cefepime is positively charged and therefore is expected to be retained on a cation-exchange column. This can be problematic due to the large size of the molecule, which can produce a longer retention time, a broader peak shape, and therefore a lower sample throughput. The use of organic solvent, as described in the USP monograph, can decrease the retention time and improve the peak shape of cefepime by reducing the hydrophobic interaction with the stationary phase. However, cefepime is still reported to elute as a broad peak at approximately 55 min. In addition, the monograph recommends that the column be flushed with a column rinse solution, which is a more concentrated solution than the eluent, for 30 min at 1 mL/min after each injection of 10 mg/mL of cefepime hydrochloride. This significantly increases the time required for each sample injection and can cause a lack of retention time stability. There is significant opportunity to improve the current method.

Separation

The IonPac CS18 was initially investigated for the determination of NMP in cefepime, but preliminary experiments showed that the IonPac CS17 was superior for this application. Its low hydrophobic character produced a more efficient cefepime peak, shorter retention times, and higher sample throughput. The separation of NMP in cefepime hydrochloride was optimized on the CS17 by using an initial concentration of 6 mM MSA to elute NMP and then a step change to 85 mM at 7.5 min to remove the cefepime from the column. An increase in column temperature from 30 to 40 °C and flow rate from 0.25 to 0.40 mL/min improved sample throughput by

reducing the cefepime retention time from 20 to 12 min.

The IonPac CS17 provides several advantages over the cation-exchange column described in the current USP monograph by 1) allowing the use of a simple acidic eluent with no organic solvent, 2) reducing the cefepime retention time to 12 min relative to the 55 min described in the USP monograph, 3) increasing the sample throughput from approximately 3–4 h to 35 min, and 4) by not requiring a separate “column rinse solution” to remove cefepime from the column.

Figure 2 compares the separation of a 25 μ g/mL NMP standard to the cefepime hydrochloride solution prepared in deionized water, using the IonPac CS17 column with an electrolytically generated MSA eluent. The retention time of NMP was approximately 5.3 min in both the standard and sample solutions. An additional 5 min column equilibration was added before each analysis, resulting in a total analysis time of 35 min. It was also determined that common cations, which may appear in the blank or other sources, did not interfere with the determination of NMP.

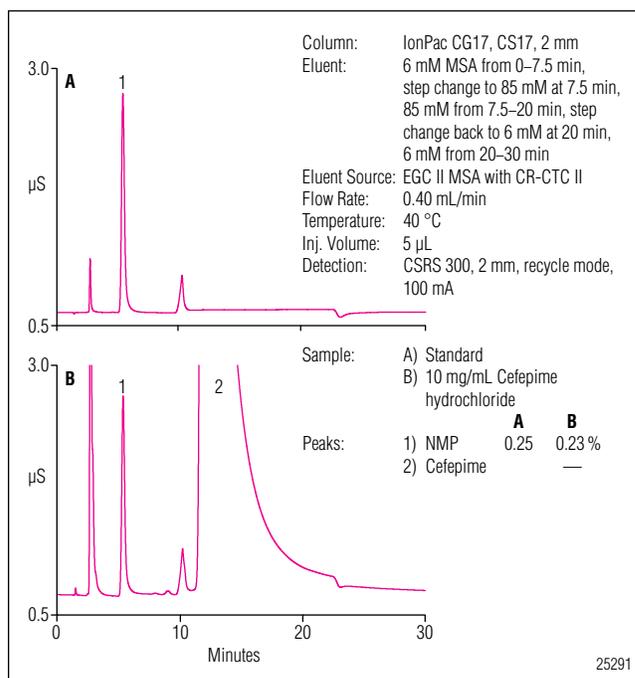


Figure 2. Comparison of the separation of NMP in A) a standard solution and B) cefepime hydrochloride.

Linearity, Limit of Quantitation, Limit of Detection

To determine the linearity of the method, calibration standards were injected in duplicate at eight concentration levels in the range of 0.45–200 µg/mL of NMP. A plot of peak area versus concentration produced a correlation coefficient (r^2) value of 0.9999 using a least squares regression fit. The USP compendial method for validation <1225> specifies a signal-to-noise (S/N) ratio of 10 for the determination of the limit of quantitation (LOQ).¹³ The baseline noise was determined by measuring the peak-to-peak noise in a representative one-minute segment of the baseline where no peaks elute. Typical baseline noise for this method using the CSRS 300 suppressor in the recycle mode is 0.2–0.4 nS/min. The LOQ for NMP was determined to be 0.10 µg/mL (S/N = 10), which represents 0.001% NMP in a 10 mg/mL cefepime hydrochloride solution. The limit of detection (LOD) for NMP was estimated to be 0.03 µg/mL (S/N = 3).

Accuracy and Precision

The performance of the method was evaluated with replicate injections of standard and sample solutions, and the recovery of known concentrations of NMP added to cefepime hydrochloride samples. The relative standard deviations (RSDs) of the retention times and measured peak areas were calculated from 10 replicate injections of standard solutions prepared at concentrations of 25 and 50 µg/mL NMP. The calculated peak area precisions for replicate injections of these NMP standards were 1.2% and 0.3%, respectively. The average NMP retention time was 5.3 min and the retention time precision was <0.1% for the standard solutions.

The method was used to assay three independently prepared sample solutions prepared at 10 mg/mL cefepime hydrochloride from a single USP lot over three consecutive days. The average NMP concentration detected in cefepime was $0.236 \pm 0.003\%$. This value meets the <0.3% NMP specification for cefepime hydrochloride according to the USP 31-NF 26 monograph. The intraday retention time and peak area precisions (i.e., a sequence of consecutive injections, $n = 10$) were $\leq 0.8\%$ and $\leq 1.3\%$, respectively. The between-day retention time and peak area precisions over three consecutive days (i.e., day-to-day, $n = 30$) were 0.5% and 1.5%, respectively. Table 1 summarizes the amount of NMP determined in the independently prepared cefepime sample solutions and the retention time and peak area precisions.

Table 1. Summary of NMP Determined in Independently Prepared Solutions of 10 mg/mL Cefepime Hydrochloride over Three Consecutive Days

Day	n	Average NMP (%)	Average Retention Time (min)	Retention Time RSD	Peak Area RSD
1	10	0.232	5.3	0.3	1.36
2	10	0.239	5.3	0.8	0.99
3	10	0.236	5.3	0.1	1.01

The accuracy of the method was evaluated by spiking three different concentrations of NMP in the sample and calculating the recoveries based on the difference in response between the unspiked and spiked sample. For the samples spiked with 0.26, 0.52, and 1.0% NMP, the average recoveries for triplicate injections were $102.0 \pm 3.2\%$, $100.6 \pm 0.8\%$, and $97.8 \pm 0.4\%$, respectively, suggesting that the method is accurate.

Cefepime for Injection contains a mixture of the hydrochloride salt and a sufficient amount of L-arginine to provide a reconstituted solution pH between 4 and 6. Arginine is reported to be strongly retained on the cation-exchange column described in the current USP method. The combination of arginine and cefepime, which is also strongly retained, can significantly increase the analysis time required for each sample as has been reported for the USP method.¹² Based on data from previous experiments, arginine is not expected to be problematic for this assay. In addition, the signal response from arginine after suppression should be significantly less than a direct conductivity system. This was confirmed by preparing a solution containing cefepime and arginine. Figure 3 shows an example chromatogram of 10 mg/mL cefepime containing approximately 7.25 mg/mL arginine. As shown, NMP was well-resolved from arginine and no significant difference in the amount of NMP, relative to previous sample preparations, was observed. However, the resolution between NMP and arginine can be improved further by reducing the starting MSA concentration from 6 to 5 mM. The retention time and peak area precisions for triplicate injections of the simulated Cefepime for Injection sample were 0.6% and 1.1%, respectively using the conditions described in Figure 3. (Note: arginine can not be quantified using this method.)

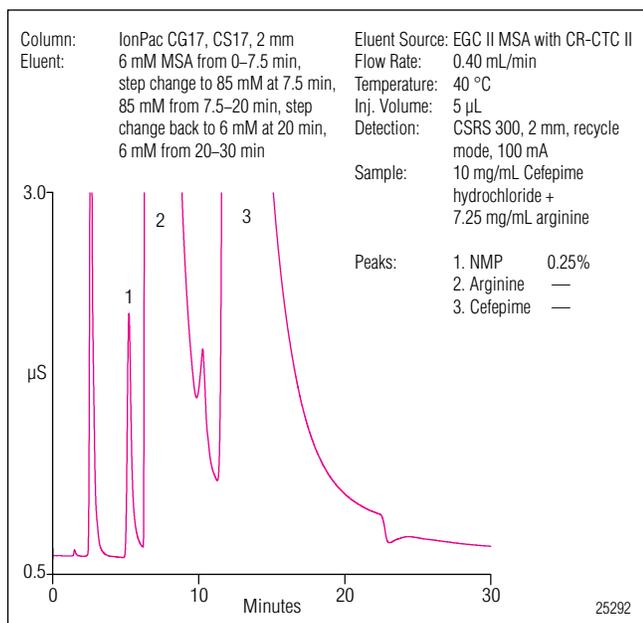


Figure 3. Determination of NMP in a simulated Cefepime for Injection sample.

The method described in this application note was also used to determine the concentration of NMP in the USP cefepime system suitability sample. This material consists of a mixture of 93.8% cefepime hydrochloride, 0.9% cefepime related compound A, and 1.4% cefepime related compound B. The USP requires the analysis of this sample to assess the resolution between cefepime and its related compounds, but does not require the determination of the limit of NMP. However, the analysis of the system suitability sample with the IonPac CS17 column further demonstrates a significant lack of influence of the active pharmaceutical ingredient (i.e., cefepime) on the determination of NMP relative to the current USP method. In addition, the presence of three high molecular weight compounds could have increased the complexity of the analysis due to their strong hydrophobic characteristics.

An initial analysis of this sample using the method conditions previously described produced low resolution between NMP and an unidentified peak, which is most likely derived from the cefepime related compounds, with $R_s = 0.82$. Therefore, further optimization was required to improve the resolution of NMP and remove cefepime and its related compounds from the column within a reasonable time. Reducing the initial MSA concentration from 6 to 2 mM provided an R_s value of 1.39, but increased the NMP retention time from 5.3 to ~12.5 min and total analysis time from 35 to 45 min. In addition, an increase in the column temperature from 40 to 50 °C

was determined to further improve the separation by decreasing the NMP retention time to 11.5 min, slightly decreasing the retention of cefepime, and improving the resolution between NMP and the unidentified peak with an R_s value of 1.67. The process of modifying the method conditions to produce an optimum separation for NMP in the USP cefepime system suitability sample was simplified by altering the electrolytically generated MSA eluent concentration using the Chromeleon workstation.

Figure 4 demonstrates the separation of NMP in the cefepime system suitability sample using the optimized conditions shown in the chromatogram. The modified method was used to assay three independently prepared dilutions of approximately 1.4 mg/mL each on three different days. The average NMP concentration in the cefepime system suitability sample was $0.80 \pm 0.02\%$. The detection of a significantly higher NMP concentration, relative to the USP cefepime hydrochloride sample, was expected due to the presence of other cephalosporins related to cefepime, which contain NMP as part of their chemical structure. The intraday retention time and peak area precisions from six replicate injections were $<0.1\%$ and $\leq 0.7\%$, respectively. The between-day retention time and peak area precisions for replicate injections over three different non-consecutive days ($n = 18$) were 0.3% and 2.7%, respectively. Table 2 summarizes the data for NMP in three independently prepared cefepime system suitability samples.

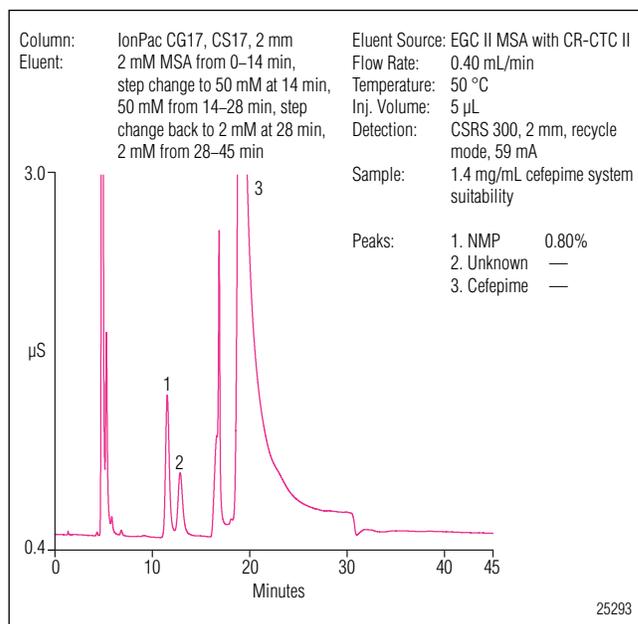


Figure 4. Determination of NMP in USP Cefepime Hydrochloride System Suitability RS sample.

Table 2. Summary of NMP Determined in Independently Prepared Solutions of 1.4 mg/mL Cefepime Suitability Sample over Three Days

Day	n	Average NMP (%)	Average Retention Time (min)	Retention Time RSD	Peak Area RSD
1	6	0.81	11.5	0.03	0.39
2	6	0.82	11.5	0.02	0.74
5	6	0.77	11.5	0.04	0.35

Sample Stability

An earlier study demonstrated that the percentage of cefepime remaining after 24 h was 90% when stored at 25 °C. This is currently the USP limit for some cefepime related compounds; however, neither the US nor the European Pharmacopoeia has set a limit of degradation of cefepime in solution.⁶ A decrease in the cefepime concentration should correspond to an increase in the NMP concentration. Previous research has shown that NMP in cefepime does increase if stored at 25 °C or at elevated temperatures (40 and 60 °C).^{11,12} In this study, we examined the stability of NMP in cefepime when stored at room temperature (25 °C), in a cooled AS sample tray (4 °C), and in the freezer (-17 °C) up to four consecutive days. Three independently prepared solutions containing 10 mg/mL cefepime hydrochloride each were subjected to the different temperature environments and analyzed in duplicate. Figure 5 shows the results from this study. As illustrated in this graph, the most significant increase in NMP was observed when the solution was stored at 25 °C. In approximately one hour, the NMP concentration increased from 0.23 to 0.27% and continued to increase to nearly 2% over the next three days. No further studies were attempted for NMP stored at this temperature due to the formation of a precipitate and a change in solution color, which is in agreement with previous observations.¹⁴ For cefepime stored at 4 °C, the NMP concentration did not significantly change within 6 h. However, within approximately 24 h the percent NMP increased from 0.22 to 0.29%. For cefepime stored at -17 °C, no significant increase in NMP concentration was observed after 96 h of storage.

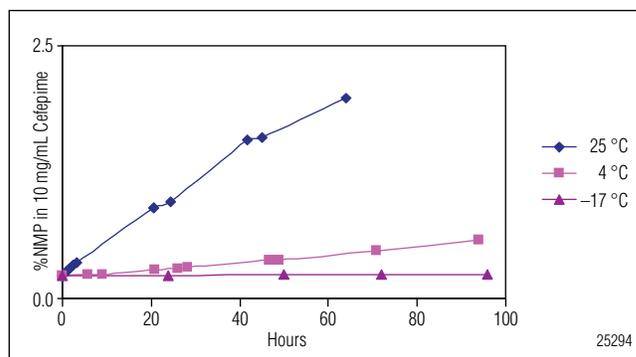


Figure 5. Stability of NMP in USP Cefepime Hydrochloride RS sample.

CONCLUSION

The IonPac CS17, a hydrophilic weak-acid cation-exchange column, combined with suppressed conductivity detection, was successfully used for the determination of NMP in cefepime hydrochloride, cefepime for injection, and cefepime system suitability samples. This method enabled the separation of NMP in less than 10 min. It also provided efficient removal of strongly retained compounds that allowed significantly lower analysis times and good retention time stability relative to the current method for the limit of NMP in cefepime hydrochloride described in USP monograph USP 31-NF 26. In addition, the described method used a simple electrolytically generated MSA eluent, without the organic solvent required for the method in the USP monograph. This also reduced the time required to optimize the separation of NMP from an unidentified peak in the system suitability sample, because the eluent concentration could be controlled simply by changing the current, instead of reformulating eluents. The exceptionally low baseline background and noise using suppressed conductivity detection enabled the quantification of 0.001% NMP in cefepime hydrochloride, which is significantly better than would be anticipated using a non-suppressed conductivity system.

REFERENCES

- 1) Sader, H.S.; Jones, R.N. Historical Overview of the Cephalosporin Spectrum: Four Generations of Structural Evolution. *Antimicrob. Newsl.* **1992**, *8*, 75-84.
- 2) Yahav, D.; Paul, M.; Fraser, A.; Sarid, N.; Leibovici, L. Efficacy and Safety of Cefepime: A Systematic Review and Meta-Analysis. *Lancet Infect. Dis.* **2007**, *7*, 338-348.
- 3) Sader, H.S.; Fritsche, T.R.; Jones, R.N. Potency and Spectrum Trends for Cefepime Tested Against 65746 Clinical Bacterial Isolates Collected in North American Medical Centers: Results from the SENTRY Antimicrobial Surveillance Program. *Diagn. Microbiol. Infect. Dis.* **2005**, *52*, 265-273.
- 4) U.S. Food and Drug Administration. Maxipime®: (Cefepime Hydrochloride) for Injection. NDA 50-679/S-021. http://www.fda.gov/medwatch/SAFETY/2003/03MAR_PI/Maxipime_PI.pdf (accessed November 14, 2007).
- 5) Sprauten, P.; Beringer, P.; Gill, M.; Louie, S.; Synold, T. Temperature Stability and Antibacterial Activity of Cefepime During Continuous Infusion Administration. *Presented at the Forty-Second Interscience Conference on Antimicrobial Agents and Chemotherapy*, San Diego, CA, September 27-30, 2002.
- 6) Sprauten, P.F.; Beringer, P.M.; Louie, S.G.; Synold, T.W.; Gill, M.A. Stability and Antibacterial Activity of Cefepime During Continuous Infusion. *Antimicrob. Agents Chemother.* **2003**, *47*, 1991-1994.
- 7) Baririan, N.; Chanteux, H.; Viaene, E.; Servais, H.; Tulkens, P.M. Stability and Compatibility Study of Cefepime in Comparison with Ceftazidime for Potential Administration by Continuous Infusion Under Conditions Pertinent to Ambulatory Treatment of Cystic Fibrosis Patients and to Administration in Intensive Care Units. *J. Antimicrob. Chemother.* **2003**, *51*, 651-658.
- 8) United States Pharmacopeia. The National Formulary. *Cefepime Hydrochloride*. USP 31, NF 26, **2008**, 1669.
- 9) United States Pharmacopeia. The National Formulary. *Cefepime for Injection*. USP 31, NF 26, **2008**, 1670.
- 10) Dionex Corporation. *Comparison of Suppressed to Nonsuppressed Conductivity Detection for the Determination of Common Inorganic Cations*. Application Note 157; LPN 1560. Sunnyvale, CA, 2004.
- 11) Chen, G.; Liu, G.; Qin, F.; Wang, Y. A Simple and Sensitive GC Method for the Determination of *N*-Methylpyrrolidine in Cefepime and its Preparation. *J. Pharmaceut. Biomed. Anal.* **2003**, *33*, 797-801.
- 12) Liu, H.; Sunderland, V.B. Determination of *N*-Methylpyrrolidine in Cefepime for Injection by Capillary Electrophoresis with Indirect UV Detection. *Chromatographia* **2004**, *59*, 653-657.
- 13) United States Pharmacopeia. The National Formulary. *General Chapter <1225>, Validation of Compendial Methods*. USP 27, NF 22, **2004**, 2622-2625.
- 14) Rabouan-Guyon, S.M.; Guet, A.F.; Courtois, P.Y.; Barthes, D.M.C. Stability Study of Cefepime in Different Infusion Solutions. *Int. J. Pharm.* **1997**, *154*, 185-190.

SUPPLIERS

Sigma-Aldrich Chemical Company, P.O. Box 14508, St. Louis, MO 63178, USA. Tel: 1-800-325-3010 www.sigma-sial.com.

U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852, USA. Tel: 1-800-227-8772 www.usp.org

Maxipime is a registered trademark of Bristol-Myers Squibb Co. Reagent-Free and RFIC are trademarks and AutoSuppression, Chromeleon, CSRS, EluGen, and IonPac are registered trademarks of Dionex Corporation.

Passion. Power. Productivity.



Dionex Corporation

1228 Titan Way
P.O. Box 3603
Sunnyvale, CA
94088-3603
(408) 737-0700

North America

U.S. (847) 295-7500
Canada (905) 844-9650

South America

Brazil (55) 11 3731 5140

Europe

Austria (43) 1 616 51 25 Benelux (31) 20 683 9768 (32) 3 353 4294
Denmark (45) 36 36 90 90 France (33) 1 39 30 01 10 Germany (49) 6126 991 0
Ireland (353) 1 644 0064 Italy (39) 02 51 62 1267 Switzerland (41) 62 205 9966
United Kingdom (44) 1276 691722

Asia Pacific

Australia (61) 2 9420 5233 China (852) 2428 3282 India (91) 22 2764 2735
Japan (81) 6 6885 1213 Korea (82) 2 2653 2580 Singapore (65) 6289 1190
Taiwan (886) 2 8751 6655

www.dionex.com

LPN 2005 PDF 09/16
©2016 Dionex Corporation