

# Determination of Morpholine in Linezolid by Ion Chromatography

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## Key Words

Antibiotics, Dionex IonPac TCC-ULP1 Column,  
Dionex IonPac CS19 Column, Suppressed Conductivity

## Introduction

Morpholine is a six-membered heterocyclic compound that features amine and ether functionalities, making it a commonly used compound in organic synthesis.<sup>1,2</sup> Substituted morpholine derivatives are the core of various natural products and biologically active compounds. Thus, morpholine has been used in the production of many types of therapeutic agents such as antibacterials,<sup>3,4</sup> antimicrobials,<sup>5</sup> anticancers,<sup>6</sup> antitussives,<sup>7</sup> antimalarials,<sup>8</sup> anticonvulsants,<sup>9</sup> and analgesics.<sup>10</sup>

Morpholine is used as a building block in a multistep synthesis to produce linezolid (Figure 1), which is a synthetic antibiotic of the oxazolidinone class.<sup>11-13</sup> As a member of this drug class, linezolid is effective against most Gram-positive bacteria, such as those causing infections of the skin, pneumonia, and infections caused by *Enterococcus faecium*, a resistant bacterium. Because morpholine is used in the preparation of linezolid, it can remain as an impurity in the final product. The level of impurities in a drug substance or product must be carefully controlled and monitored because impurities can diminish the pharmacological efficacy of the active pharmaceutical ingredient (API) or cause unwanted side effects. Therefore, a sensitive method is needed to determine morpholine in synthetic drugs such as linezolid.

Although linezolid and its degradation products are usually assayed by high-performance liquid chromatography (HPLC) with UV detection,<sup>14</sup> morpholine lacks a suitable chromophore for detection. Therefore, cation-exchange ion chromatography (IC) with suppressed conductivity detection is considered the best alternative to selectively determine morpholine in linezolid.

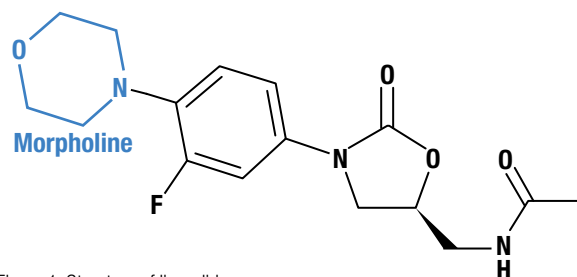


Figure 1. Structure of linezolid.

## Goal

To develop an IC method for the determination of low  $\mu\text{g/L}$  concentrations of morpholine in linezolid using a Reagent-Free™ IC (RFIC™) system with suppressed conductivity detection

## Equipment

- Thermo Scientific™ Dionex™ ICS-5000+ system,\* including:
  - SP Single Pump
  - EG Eluent Generator module
  - DC Detector/Chromatography compartment
  - Dionex AS-AP Autosampler with Sample Syringe, 5.0 mL syringe (P/N 074308) and 8500  $\mu\text{L}$  buffer line (P/N 075520)
- Thermo Scientific Dionex EGC 500 MSA Eluent Generator Cartridge (P/N 075779)
- Thermo Scientific Dionex CR-CTC 500 Continuously Regenerated Cation Trap Column (P/N 075551)
- Thermo Scientific™ Dionex™ IonPac™ TCC-ULP1 Ultralow Pressure Trace Cation Concentrator Column (P/N 063783)
- Vial Kit, Polystyrene with Caps and Blue Septa, 10 mL (P/N 074228)
- Thermo Scientific™ Dionex™ Chromeleon™ Chromatography Data System (CDS) software, version 7.1

\*This application can also be performed on any Dionex ICS system.

## Reagents and Standards

- Deionized (DI) water, Type I reagent grade, 18 M -cm resistance or better
- Morpholine, Certified ACS, ≥99% (Fisher Scientific P/N M263-1)
- Linezolid, 25 mg (Fisher Scientific P/N NC0418023)
- Methanol, CH<sub>3</sub>OH, Certified ACS, ≥99.8% (Fisher Scientific P/N A412)

### Conditions

Columns:	Dionex IonPac CG19 Guard, 2 × 50 mm (P/N 076029) Dionex IonPac CS19 Analytical, 2 × 250 mm (P/N 076028)
Eluent:	7.5 mM Methanesulfonic Acid (MSA)
Eluent Source:	Dionex EGC 500 MSA Cartridge with Dionex CR-CTC 500 Continuously Regenerated Cation Trap Column
Flow Rate:	0.25 mL/min
Inj. Volume:	100 µL
Matrix Elim. Volume:	1 mL DI water
Concentrator Column:	Dionex IonPac TCC-ULP1 Ultralow Pressure Trace Cation Concentrator, 5 × 23 mm
Detection:	Suppressed conductivity, Thermo Scientific™ Dionex™ CSRS™ 300 Cation Self-Regenerating Suppressor, 2 mm, recycle mode, 7 mA current*
System Backpressure:	~2400 psi
Background Conductance:	~0.3 µS
Noise:	~0.4 nS/min peak-to-peak
Run Time:	15 min

\* Equivalent or improved results may be achieved with the Thermo Scientific™ Dionex™ ERS™ 500 Electrolytically Regenerated Suppressor.

## Preparation of Solutions and Reagents

### CH<sub>3</sub>OH Diluent, 10%

Mix 100 mL of ACS-grade CH<sub>3</sub>OH with 900 mL DI water, filter through a 0.2 µm nylon filter unit, and degas for 10 min.

### Standard Solutions

#### Morpholine stock solution, 1000 mg/L

Transfer 0.1 mL of morpholine into a 100 mL volumetric flask and dilute to volume with DI water.

#### Morpholine secondary stock solution, 1 mg/L

Transfer 0.1 mL of 1000 mg/L morpholine stock solution to a 100 mL volumetric flask and dilute to volume with DI water.

### Working standard solutions

Prepare working standard solutions by diluting the 1 mg/L secondary stock solution as required with DI water. Prepare the working standard solutions on the day of analysis.

## Sample Preparation

Weigh approximately 5 ± 0.2 mg of linezolid on an analytical balance and dissolve the solid in 50 mL of 10% CH<sub>3</sub>OH in a 50 mL volumetric flask.

## System Preparation and Configuration

Install and configure the Dionex AS-AP Autosampler in Push Concentrate Mode. Follow the instructions in the Dionex AS-AP Autosampler Operator's Manual (Document No. 065361) to calibrate the sample transfer line to ensure accurate and precise sample injections. Adjustments must be made to the injection conditions because carryover of morpholine between injections was observed during this study when using the default setting under Sampler in the Instrument Method of Chromeleon CDS software version 7.1. Therefore, set the Wash Volume to 5 mL on the second sampler options page (titled General Settings) in the Instrument Method Wizard. Install a 5 mL sample syringe and an 8500 µL buffer line assembly.

To perform the matrix elimination, use the following procedure:

- In the Instrument Method Wizard, on the first sampler options page, select the PushConcentrate injection mode.
- Select the Reagent Flush check box and specify the Source Vial (the vial from which to aspirate the reagent) and Source Volume (the volume in µL) of reagent to be flushed through the concentrator column. To use a vial as the source of the matrix elimination solution, choose the appropriate vial number from the dropdown menu next to Source Vial. A position relative to the current vial (containing the sample) can also be chosen (e.g., use CurrentVial + 1 to designate the vial next to the current vial as the source of the matrix elimination solution). Enter 1000 µL in the box for Source Volume.

Prepare the Dionex CSRS 300 Cation Self-Regenerating Suppressor for use by hydrating the internal membrane. Push 3 mL of DI water through the Eluent Out port and 5 mL of DI water through the Regen In port. Allow the suppressor to sit for 20 min to ensure complete hydration before installing it in the system. For more information on installation and operation of the Dionex CSRS 300 Cation Self-Regenerating Suppressor, consult the product manual (Document No. 031956).

Condition the Dionex EGC 500 MSA cartridge before first use by running 50 mM MSA at 1 mL/min for 30 min. For more information on installation and operation of this cartridge, consult the product manual (Document No. 065018-04).

Install a Dionex IonPac TCC-ULP1 concentrator (5 × 23 mm) in place of the sample loop using 0.005 in. i.d. PEEK tubing with the direction of sample loading opposite the direction of analytical flow. For more information on installation and operation of this concentrator, consult the product manual (Document No. 034973-06).

Install the Dionex IonPac CG19 Guard (2 × 50 mm) and CS19 Analytical (2 × 250 mm) columns in the lower compartment of the DC. After connecting to the inlet of the column, pump 7.5 mM MSA at 0.25 mL/min through the column with the outlet directed to waste for at least 30 min before connecting the column outlet to the suppressor using 0.005 in. i.d. PEEK tubing. Keep the lengths of the connecting tubing to a minimum.

## Results and Discussion

### Sample Preparation

The solubility of the API in water or other aqueous solutions is a primary consideration in the development of a suitable IC method for pharmaceuticals. The limited solubility of drugs and intermediates in aqueous solutions poses a potential challenge because this can lead to precipitation of the API in the chromatography system, causing excessive backpressure and column contamination. Linezolid is marginally soluble in water with a solubility of approximately 3 mg/mL,<sup>15</sup> but its solubility increases at pH values below 3 and at higher temperatures.<sup>16</sup>

Because this method provides sufficient sensitivity for morpholine, linezolid was prepared with a final concentration of 0.1 mg/mL (w/v). Therefore, no organic solvent was needed to achieve a complete dissolution at room temperature. In this method, however, a 10% CH<sub>3</sub>OH solution was used to prepare the sample solution to expedite linezolid dissolution.

### Matrix Elimination

Another consideration in the development of an IC method for pharmaceuticals is the interaction between the API and the ion-exchange column. Some APIs are charged with certain degrees of hydrophobicity and can be strongly retained on the ion-exchange column.

In the early stages of this study, samples were directly injected after dissolution of linezolid without further pretreatment. However, a decrease in column capacity was observed over time. To investigate whether linezolid was retained on the column, a Thermo Scientific Dionex ICS-Series Variable Wavelength Detector was used to monitor the effluent from the conductivity detector at 254 nm. This experiment demonstrated that linezolid was not eluted from the column within 30 min using the method conditions developed for morpholine. When the MSA concentration was increased to 60 mM, a very broad peak was eluted after 60 min. This peak was believed to be linezolid. These results suggest that linezolid was strongly retained on the separation column.

Although linezolid is not ionized in aqueous media above pH 4 (pKa = 1.7),<sup>17</sup> in the acidic eluent (pH ~2), linezolid is positively charged and retained on the cation-exchange column. In addition to the electrostatic interaction, the retention likely includes some hydrophobic interaction with the column. Therefore, matrix elimination is necessary for this analysis to increase the lifetime of the separation column.

In this work, a Dionex IonPac TCC-ULP1 concentrator column was used to trap morpholine from the sample, while the uncharged linezolid was removed by matrix elimination using 1 mL of DI water. This configuration enables the determination of trace concentrations of morpholine in linezolid without extensive and laborious sample pretreatment.

The effect of matrix elimination was demonstrated by comparison of the retention time of morpholine with and without matrix elimination. Seventy injections of 0.1 mg/mL linezolid resulted in retention time losses for morpholine of 0.61% with matrix elimination and 2.14% without matrix elimination.

## Separation

The Dionex IonPac CS19 column set separated morpholine and other common cations within 15 min using 7.5 mM MSA. Use of the concentrator column caused a small fluctuation in backpressure during the switching of the injection valve and led to a slight disturbance in the baseline. The concentrator also caused an approximate 15% increase in retention times of the cations when compared to a direct 100  $\mu$ L injection. A chromatogram of 10% CH<sub>3</sub>OH matrix blank obtained using the matrix elimination condition is shown in Figure 2. The Dionex IonPac CS19 column set offers unique selectivity for small polar amines; therefore, morpholine was separated from other common cations with excellent peak shape using simple isocratic MSA elution with no need to add organic solvent to the eluent. Figure 3 shows the elution of morpholine at approximately 9.0 min with no interference.

## Calibration, Limit of Detection, and Limit of Quantitation

In this study, calibration curves with six concentration levels ranging from 5 to 200  $\mu$ g/L were constructed using morpholine secondary stock solution. The results yielded a linear relationship of peak area to concentration for morpholine with a coefficient of determination ( $r^2$ ) >0.999. To determine the limit of detection (LOD) and limit of quantification (LOQ), the baseline noise was first determined by measuring the peak-to-peak noise in a representative 1 min segment of the baseline where no peaks elute. The LOD and LOQ were then calculated from a 5  $\mu$ g/L morpholine standard. The results of the calibration, LOD, and LOQ are summarized in Table 1.

Table 1. Results of calibration, LOD, and LOQ on morpholine.

Analyte	Range ( $\mu$ g/L)	Coefficient of Determination ( $r^2$ ) <sup>a</sup>	LOD <sup>b</sup> ( $\mu$ g/L)	LOQ <sup>c</sup> ( $\mu$ g/L)
Morpholine	5–200	0.9995	0.86	2.9

<sup>a</sup> Linear fit

<sup>b</sup> LOD = 3  $\times$  signal-to-noise ratio (S/N)

<sup>c</sup> LOQ = 10  $\times$  S/N

Columns: Dionex IonPac CG19 Guard, 2  $\times$  50 mm  
Dionex IonPac CS19 Analytical, 2  $\times$  250 mm  
Eluent Source: Dionex EGC 500 MSA with Dionex CR-CTC 500  
Eluent: 7.5 mM MSA  
Flow Rate: 0.25 mL/min  
Inj. Volume: 100  $\mu$ L  
Conc Column: Dionex IonPac TCC-ULP1  
Detection: Suppressed conductivity, Dionex CSRS 300, 2 mm, 7 mA, recycle mode

Peaks: 1. Sodium 4. Magnesium  
2. Ammonium 5. Calcium  
3. Potassium

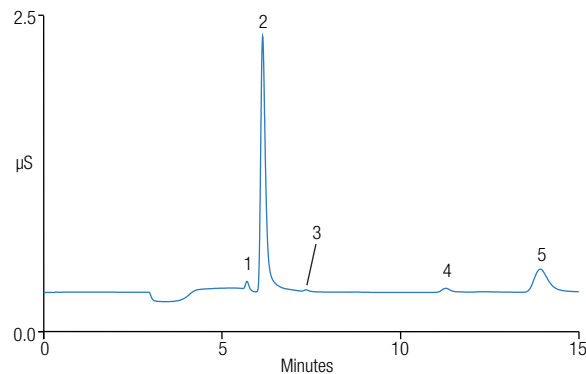


Figure 2. 10% CH<sub>3</sub>OH matrix blank.

Columns: Dionex IonPac CG19 Guard, 2  $\times$  50 mm  
Dionex IonPac CS19 Analytical, 2  $\times$  250 mm  
Eluent Source: Dionex EGC 500 MSA with Dionex CR-CTC 500  
Eluent: 7.5 mM MSA  
Flow Rate: 0.25 mL/min  
Inj. Volume: 100  $\mu$ L  
Conc Column: Dionex IonPac TCC-ULP1  
Detection: Suppressed conductivity, Dionex CSRS 300, 2 mm, 7 mA, recycle mode

Peaks: 1. Ammonium —  $\mu$ g/L 4. Magnesium —  
2. Potassium — 5. Calcium —  
3. Morpholine 20

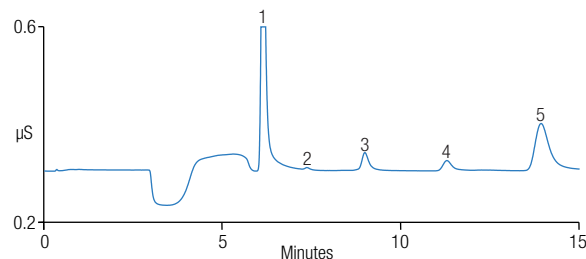


Figure 3. 20  $\mu$ g/L morpholine in 10% CH<sub>3</sub>OH.

### Sample Analysis

The U.S. Pharmacopeia monograph for linezolid requires that the total impurities and any individual unspecified impurity be <0.5% and <0.08%, respectively.<sup>18</sup> In this study, the detection limit of morpholine in 0.1 mg/mL linezolid was 0.7 µg/L (0.0007% of linezolid), which easily meets these requirements. Figure 4, Chromatogram A shows 0.1 mg/mL linezolid with no morpholine detected.

### Sample Accuracy and Precision

To validate the determination of morpholine in linezolid, the method accuracy was evaluated by spiking 10, 20, and 30 µg/L of morpholine into the sample solution. The intraday recoveries of 10–30 µg/L spiked morpholine and between-day recoveries of 10 µg/L spiked morpholine were in the range of 98.8–101% and 99.9–103%, respectively, as shown in Tables 2 and 3. Figure 4, Chromatogram B shows 0.1 mg/mL linezolid in 10% CH<sub>3</sub>OH spiked with 30 µg/L morpholine.

Columns: Dionex IonPac CG19 Guard, 2 × 50 mm  
 Dionex IonPac CS19 Analytical, 2 × 250 mm  
 Eluent Source: Dionex EGC 500 MSA with Dionex CR-CTC 500  
 Eluent: 7.5 mM MSA  
 Flow Rate: 0.25 mL/min  
 Inj. Volume: 100 µL  
 Conc Column: Dionex IonPac TCC-UPL1  
 Detection: Suppressed conductivity, Dionex CSRS 300, 2 mm, 7 mA, recycle mode

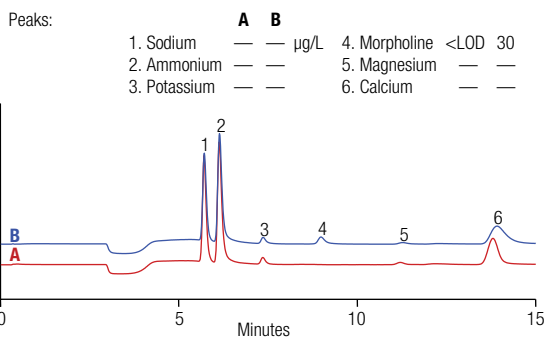


Figure 4. A) 0.1 mg/mL linezolid in 10% CH<sub>3</sub>OH and B) 0.1 mg/mL linezolid in 10% CH<sub>3</sub>OH spiked with 30 µg/L morpholine. A 10% signal offset has been applied.

Table 2. Recoveries of morpholine in linezolid.

Amount Found (ppb)	Amount Spiked (ppb)	Total Found (ppb)	Peak Area RSD (n = 3)	Recovery (%)
<LOD	10	9.99	2.38	99.9
<LOD	20	19.8	0.85	98.8
<LOD	30	30.3	0.64	101

Table 3. Between-day recoveries of morpholine in linezolid.

	Amount Found (ppb)	Amount Spiked (ppb)	Total Found (ppb)	Peak Area RSD (n = 3)	Recovery (%)
Day 1	<LOD	10	9.99	2.38	99.9
Day 2	<LOD	10	10.3	2.70	103
Day 3	<LOD	10	10.1	0.78	101

Method precision was evaluated with seven injections of standard and sample solutions. The retention time and peak area RSDs for seven consecutive injections of 10 µg/L morpholine were 0.07% and 1.30%, respectively. The retention time and peak area RSDs for seven consecutive injections of 0.1 mg/mL linezolid spiked with 10 µg/L morpholine were 0.09% and 1.56%, respectively. Figure 5 shows an overlay of seven chromatograms of 0.1 mg/mL linezolid spiked with 10 µg/L morpholine in DI water.

### Conclusion

This study demonstrates an IC method for determining low concentrations of morpholine in linezolid. Sample solutions of 0.1 mg/mL linezolid were constituted in 10% CH<sub>3</sub>OH to speed the dissolution of linezolid. To prevent column contamination by linezolid, in-line matrix elimination was performed to concentrate trace morpholine on a Dionex IonPac TCC-ULP1 concentrator column, followed by removal of the uncharged linezolid with DI water using the Dionex AS-AP Autosampler. An RFIC system achieved efficient separation using the Dionex IonPac CS19 column set with electrolytically generated high-purity MSA eluent, and trace morpholine was detected using suppressed conductivity. The RFIC system enhanced the level of automation and ease of use. The method was validated with intraday and between-day recovery studies on spiked linezolid samples. In addition to the trace analysis of morpholine, this IC method also allows simultaneous determination of sodium, ammonium, potassium, and other cations present in the sample.

Columns: Dionex IonPac CG19 Guard, 2 × 50 mm  
 Dionex IonPac CS19 Analytical, 2 × 250 mm  
 Eluent Source: Dionex EGC 500 MSA with Dionex CR-CTC 500  
 Eluent: 7.5 mM MSA  
 Flow Rate: 0.25 mL/min  
 Inj. Volume: 100 µL  
 Conc Column: Dionex IonPac TCC-ULP1  
 Detection: Suppressed conductivity, Dionex CSRS 300,  
 2 mm, 7 mA, recycle mode

Peaks: 1. Sodium — µg/L 4. Morpholine 10  
 2. Ammonium — 5. Magnesium —  
 3. Potassium — 6. Calcium —

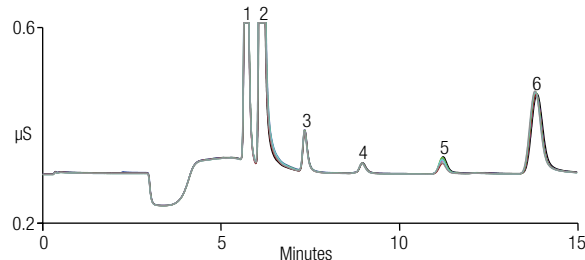


Figure 5. Overlay of seven chromatograms of 0.1 mg/mL linezolid spiked with 10 µg/L morpholine.

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