

Determination of Inorganic Anion Impurities in a Water-Insoluble Pharmaceutical by Ion Chromatography with Suppressed Conductivity Detection

Khalil Divan, Brian M. De Borba, and Jeff S. Rohrer, Dionex Corporation, Sunnyvale, CA USA

INTRODUCTION

The U.S. FDA is responsible for protecting consumers by ensuring that pharmaceuticals are safe by requiring manufacturers to verify drug substance and drug product identity, strength, quality, and purity characteristics. Inorganic impurities may be derived from the raw materials or reagents used during the manufacturing process of the pharmaceutical compound.¹ Although low concentrations of many inorganic impurities have few toxicological consequences, significant variation in the impurity levels from batch-to-batch can indicate that the manufacturing process of the drug product is not adequately controlled.^{2,3} Analysis of water-insoluble pharmaceuticals by ion chromatography (IC) can lead to precipitation of the drug in the IC system, potentially causing excess backpressure and column contamination. Here the authors provide a simple approach to determine anionic impurities in a proprietary water-insoluble pharmaceutical preparation using preconcentration/matrix elimination followed by separation using a hydroxide-selective IonPac[®] AS15 column with electrolytically generated potassium hydroxide eluent and suppressed conductivity detection.⁴

EXPERIMENTAL

A Dionex ICS-3000 Reagent-Free™ ion chromatography system with:

EluGen[®] EGC II KOH cartridge

IonPac AG15 (2 × 50 mm) and AS15 (2 × 250 mm)

ASRS[®] 300 (2 mm) suppressor operating at 60 mA in recycle mode

Chromeleon[®] Chromatography Data System was used for system control and data processing.

Standard Preparation

All calibration standards were prepared in deionized water from serial dilutions of their respective 1000 mg/L stock solutions. Calibration standards were prepared from the low µg/L to mg/L range to cover the expected concentration range in the sample.

Sample Preparation

To prepare a final sample concentration of 0.30 mg/mL (w/v), dissolve 30 ± 2 mg of the sample in 100 mL of ACS grade CH₃OH. Sonicate the solution for approximately 15 min to fully dissolve the solid material.

RESULTS AND DISCUSSION

The IonPac AS15 column is a high-capacity, hydroxide-selective, anion-exchange column specifically developed for the rapid and efficient separation of trace concentrations of inorganic anions and small organic acids in samples with a range of ionic strengths.

The use of electrolytically generated hydroxide eluent produces an exceptionally low background and baseline noise, which is one factor that enabled the quantification of 0.001% (w/w) or less of inorganic anion impurities in the pharmaceutical sample analyzed in this study.

Figure 1 shows the separation of common anions using the IonPac AS15 column after a 100 µL preconcentration and 1 mL matrix elimination with DI water.

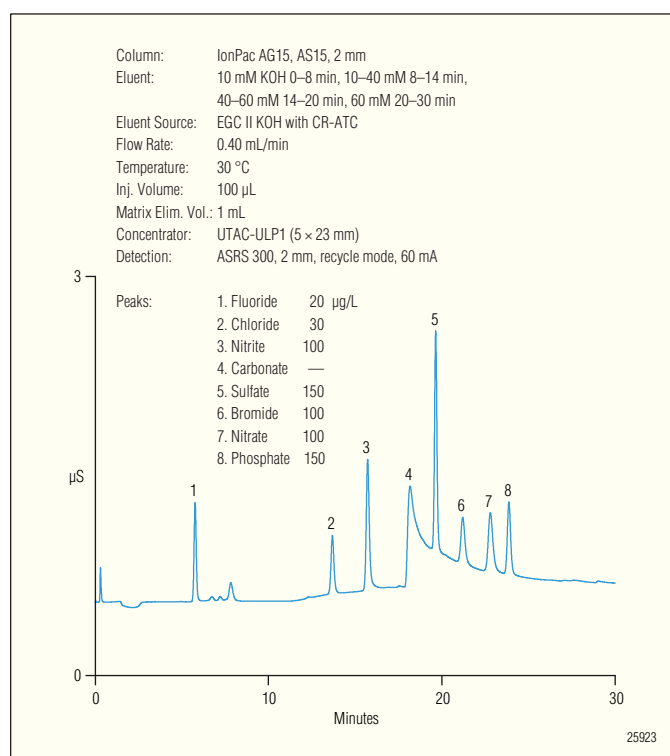


Figure 1. Separation of common inorganic anions using the IonPac AS15 column.

Figure 2 shows a representative blank of 100% CH₃OH. As shown below, trace concentrations of chloride, sulfate, and nitrate were detected in the blank.

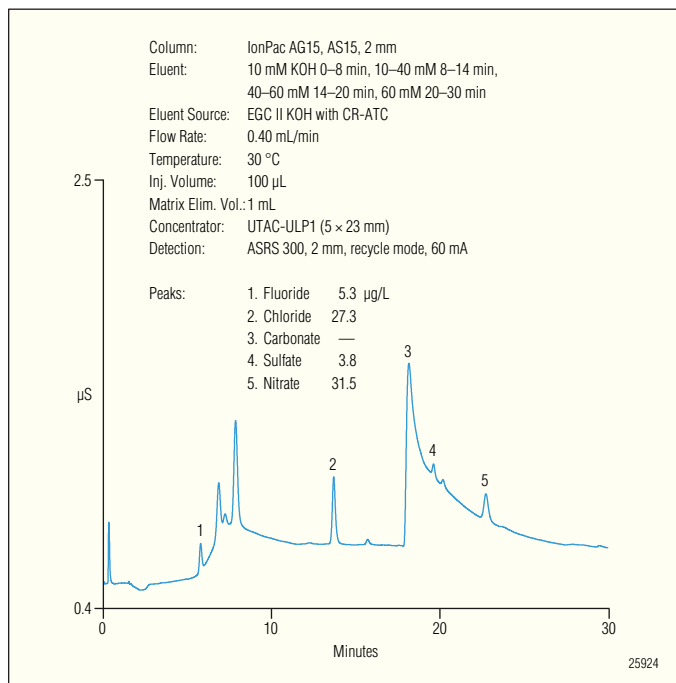


Figure 2. Target anions detected in a representative CH₃OH blank.

Sample Analysis

The method performance was evaluated by analyzing three different preparations of the pharmaceutical sample over three days.

Figure 3 shows the determination of trace anions in a 0.30 mg/mL proprietary pharmaceutical sample.

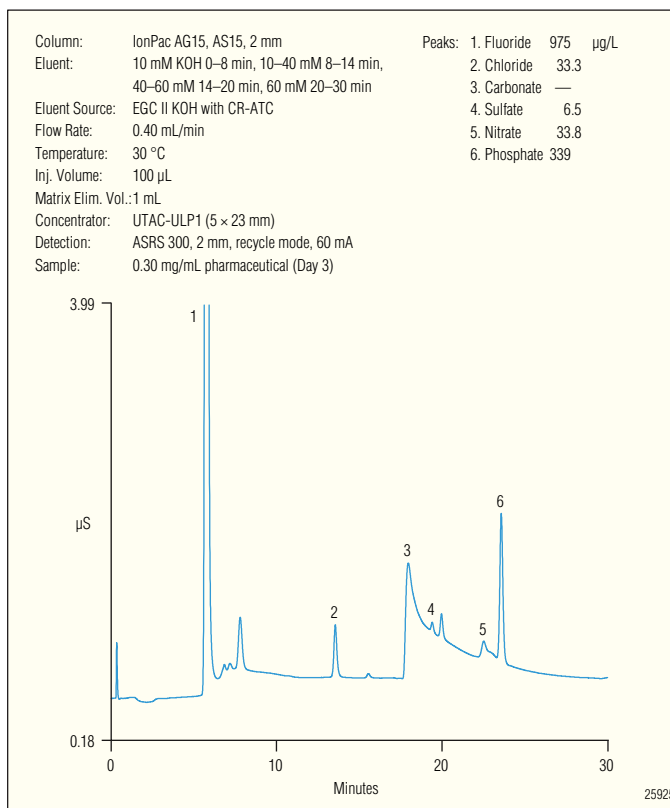


Figure 3. Determination of inorganic anion impurities in a proprietary water-insoluble pharmaceutical compound.

When the sample is corrected for the CH₃OH blank, the concentrations of chloride, sulfate, and nitrate were determined to be significantly less than the background concentrations. Therefore, the application primarily focused on the main anion constituents, fluoride and phosphate, in the pharmaceutical sample.

Table 2. Summary of Data Obtained for Target Anions in a Water-Insoluble Pharmaceutical Product					
Day	Analyte	Amount Found (µg/L)	% (w/w) in a 0.30 mg/mL Pharmaceutical	Retention Time RSD ^a	Peak Area RSD ^a
1	Fluoride	973.5	0.25	0.06	0.12
	Phosphate	328.9	0.08	0.02	1.1
2	Fluoride	953.9	0.24	0.12	1.3
	Phosphate	349.0	0.09	0.01	0.76
3	Fluoride	974.5	0.25	0.04	0.38
	Phosphate	339.0	0.09	0.01	0.40

^an = 6

2 Determination of Inorganic Anion Impurities in a Water-Insoluble Pharmaceutical by Ion Chromatography with Suppressed Conductivity Detection

A possible source of fluoride in the sample is from the use of calcium salts during the manufacturing process. In addition, phosphate is commonly used in buffer solutions during the preparation of the final product.

For a sample spiked with 948 µg/L fluoride and 302 µg/L phosphate, the calculated recoveries were 102.6% and 107.7%, respectively. This indicates the method performed well for the determination of the target anions in a proprietary pharmaceutical compound.

CONCLUSIONS

The method described here demonstrates a simpler approach to determination of trace anions in a water-insoluble pharmaceutical by avoiding potential complications of column contamination and excess column backpressure that can occur from analyzing these sample types.

The IonPac AS15 column provided efficient separation of common anions from low- to high-µg/L concentrations. In addition, the use of electrolytically generated hydroxide eluent eliminates the problems associated with manually prepared eluents and therefore further increases the ease-of-use and method automation.

This method demonstrated good linearity, sensitivity, precision, and accuracy for determining inorganic anion impurities in a water-insoluble pharmaceutical compound.

REFERENCES

1. Roy, J. Pharmaceutical Impurities – A Mini Review. *AAPS Pharm. Sci. Tech.* **2002**, 3(2), 1–8.
2. Hulse, W.L.; Grimsey, I.M.; De Matas, M. The Impact of Low-Level Inorganic Impurities on Key Physicochemical Properties of Paracetamol. *Int. J. Pharm.* **2008**, 349, 61–65.
3. Basak, A.K.; Raw, A.S.; Al Hakim, A.H.; Furness, S.; Samaan, N.I.; Gill, D.S.; Patel, H.B.; Powers, R.F.; Yu, L. Pharmaceutical Impurities: Regulatory Perspective for Abbreviated New Drug Applications. *Adv. Drug Deliv. Rev.* **2007**, 59, 64–72.
4. Dionex Corporation. *Determination of Inorganic Anion Impurities in a Water-Insoluble Pharmaceutical by Ion Chromatography with Suppressed Conductivity Detection*. Application Note 220, LPN 2180, March 2009, Sunnyvale, CA.

Reagent-Free is a trademark and ASRS, Chromeleon, 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./Canada (847) 295-7500

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 Sweden (46) 8 473 3380
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 2411-01 2/10
©2010 Dionex Corporation