

# Assay for Citrate and Phosphate in Pharmaceutical Formulations Using Ion Chromatography

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## Key Words

IonPac AS11, Adenine, Anticoagulant, Bicarbonate, Dextrose, Drug product, Electrolytes, Irrigation Solution, Rehydration, USP

## Introduction

Citric acid is a common ingredient found in many pharmaceutical formulations. The most common use of citric acid in pharmaceuticals is the effervescent effect it produces when combined with carbonates or bicarbonates in antacids and dentifrices. Citrate is also widely used as a flavoring and stabilizing agent in pharmaceutical preparations to mask the taste of medicinal flavors. Citric acid can act as a buffering agent and assist in the dispersion of suspensions to help maintain stability of the active ingredients<sup>1</sup> and improve the effectiveness of antioxidants.<sup>2</sup> It may also be used as an anticoagulant to preserve blood for transfusion and as an ingredient of rectal enemas.<sup>2</sup>

The United States Pharmacopeia (USP) has adopted several different assays for citrate in various pharmaceutical dosage forms. These analytical techniques include calorimetry, gravimetry, ion-exclusion chromatography, and reversed-phase liquid chromatography.<sup>3</sup> Method variation is usually required for many of these techniques to assay a specific dosage form. This method variation results in the use of different color-forming reagents, mobile phases, columns, and detectors. For instance, a dosage form containing citrate and phosphate requires the use of pyridine and acetic anhydride for the determination of citrate, and ammonium molybdate, hydroquinone, and sodium sulfite for a separate determination of phosphate. The prescribed assays are time consuming, labor intensive, require extensive analyst training, and may yield significant measurement errors.

Citrate has been successfully separated by ion-exchange,<sup>4,5</sup> ion-exclusion,<sup>6,7</sup> and reversed-phase<sup>8</sup> liquid chromatography in a wide range of sample matrices, including those of pharmaceutical and biological origin. The most commonly reported detection of these separations is indirect UV absorbance; however, conductivity and refractive index detection have also been used. Separation of citric acid by



reversed-phase liquid chromatography requires a low mobile phase pH to inhibit the ionization of citric acid.<sup>8</sup> Furthermore, ion-exclusion separations generally have long retention times for citric acid unless an organic modifier is used.<sup>7</sup> Because citrate is a very poor absorbing analyte, a mobile phase with a strong UV-absorbing chromophore is required for indirect UV detection.<sup>9</sup> Chalgari and Tan described a citrate assay for some pharmaceutical dosage forms with USP monographs that uses ion chromatography (IC) with indirect photometric detection.<sup>10</sup> This method used trimesic acid, a UV-absorbing eluent, as the mobile phase to detect citrate as a negative peak at a wavelength of 280 nm. However, the method required proper pH adjustment of the mobile phase with NaOH to produce consistent retention times. The retention time of citric acid decreases as its ionization decreases at low pH values (pH 3.2–4.5) and increases at higher pH values (pH 4.5–6.0) as ionization increases.<sup>11</sup>

IC with suppressed conductivity detection is the chromatographic technique of choice for citrate determinations.<sup>12</sup> In addition, IC can simultaneously determine phosphate and other anions that are present in some pharmaceutical formulations and uses eluents that do not require expensive reagents or pH adjustments. Aliphatic carboxylic acids, such as citric acid, generally exhibit high affinities for anion-exchange stationary phases. Thus, low-ionic-strength carbonate/bicarbonate buffer solutions are typically not suitable as eluents. However, when hydroxide eluents are used, citric acid can be easily eluted from the column.<sup>13</sup>

In this application note, we report on the validation of an IC method for the determination of phosphate and total citric acid in pharmaceutical formulations with a hydroxide-selective, anion-exchange column and suppressed conductivity detection. The method incorporates an electrolytic eluent generator to automatically produce a simple isocratic potassium hydroxide eluent, allowing the separation of phosphate and citrate on a Thermo Scientific™ Dionex™ IonPac™ AS11 column in less than 10 min. The results indicate that this method can replace 18 USP monographs for the assay of citric acid or phosphate in *USP 27-NF 22*. The method was evaluated in terms of linearity, precision, accuracy, ruggedness, and limit of quantitation for phosphate and citrate.

## Equipment

- A Thermo Scientific™ Dionex™ ICS-2000 Reagent-Free™ Ion Chromatography (RFIC™) System was used in this work. The Dionex ICS-2000 RFIC system is an integrated ion chromatograph and consists of the following:
  - Eluent generator
  - Column heater
  - Pump with degas
  - Thermo Scientific™ Dionex™ EluGen™ EGC II KOH Cartridge (P/N 058900)
  - Thermo Scientific™ Dionex™ CR-ATC CR-ATC (P/N 060477)
- Thermo Scientific™ Dionex™ AS50 Autosampler
- Thermo Scientific™ Dionex™ Chromeleon™ 6.5 Chromatography Workstation

This application note is also applicable to other RFIC systems.

## Reagents and Standards

- Deionized water (DI), Type I reagent-grade, 18 M $\Omega$ -cm resistivity or better
- Citric acid (USP, Catalog #1134368)
- Sodium dihydrogen phosphate monohydrate, NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O (EMD Millipore®)
- Calcium chloride dihydrate, CaCl<sub>2</sub>·2H<sub>2</sub>O (Fisher Scientific™)
- Sodium acetate anhydrous (Fluka®)
- Sodium chloride (J. T. Baker®)
- Magnesium chloride hexahydrate, MgCl<sub>2</sub>·6H<sub>2</sub>O (Sigma-Aldrich®)
- Sodium citrate dihydrate (Sigma-Aldrich)
- Potassium chloride (Sigma-Aldrich)
- Sodium hydroxide, 50% (J. T. Baker)

## Conditions

Columns:	Dionex IonPac AS11 Analytical, 4 × 250 mm (P/N 044076) Dionex IonPac AG11 Guard, 4 × 50 mm (P/N 044078)
Eluent:	20 mM potassium hydroxide
Eluent Source:	Dionex ICS-2000 EG with CR-ATC
Flow Rate:	2.0 mL/min
Temperature:	30 °C
Injection:	10 $\mu$ L
Detection:	Suppressed conductivity, Thermo Scientific™ Dionex™ ASRS™ ULTRA II Suppressor, 4 mm (P/N 061561) Thermo Scientific™ Dionex™ AutoSuppression™ recycle mode 100 mA current
System Backpressure:	~2300 psi
Run Time:	10 min

## Preparation of Solutions and Standards

### Eluent Solution

Generate 20 mM KOH eluent online by pumping deionized (DI) water through the Dionex ICS-2000 EG device. Set the eluent concentration using Chromeleon Chromatography Management Software software or from the front LCD panel of the Dionex ICS-2000 system. Chromeleon software tracks the amount of KOH used and calculates the remaining lifetime of the Dionex EGC II KOH cartridge.

Alternatively, prepare 20 mM NaOH by pipetting 1.05 mL of 50% (w/w) aqueous NaOH from the reagent bottle into a 1.00 L volumetric flask containing about 500 mL of degassed DI water. Bring to volume with degassed DI water, mix, and degas by sparging with helium or sonicating under vacuum for 10 min. Atmospheric carbon dioxide readily dissolves in dilute basic solutions, forming carbonate. Carbonate contamination of eluents can affect analyte retention times, resulting in performance that is not equivalent to electrolytically producing the hydroxide eluent online using an eluent generator. Store the eluent in plastic labware. Maintain an inert helium atmosphere of 3–5 psi in the eluent reservoir to minimize carbonate contamination.

### Stock Standard Solutions

An official USP citric acid reference standard was dried in an oven at 105 °C for 2 h immediately before use. To prepare a 500 mg/L citric acid stock standard, weigh exactly 250 mg of the dried citric acid, add to a 500 mL volumetric flask, and dilute to volume with DI water. To prepare a mixed citrate/phosphate stock standard with 300 mg/L phosphate (as NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O), weigh 150 mg NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O, add to a 500mL volumetric flask containing 250 mg citric acid, and dilute to the mark with DI water. Store in polypropylene bottles at 4 °C.

## Working Standard Solutions

Prepare working standard solutions at lower concentrations by adding an appropriate amount from the stock standard solutions and 5 mL of 20 mM NaOH to a 100 mL volumetric flask. Dilute to the mark with DI water. The 20 mM NaOH solution used for standard and sample preparation should be prepared fresh daily.

## Sample Preparation

All liquid samples should be appropriately diluted with DI water so that the concentration of citrate and phosphate fit within the calibration range. For solid citrate samples, such as potassium citrate extended release tablets that contain insoluble components, a portion equivalent to approximately 100 mg citric acid (powdered form) was added to 300 mL of hot DI water (~80 °C) and magnetically stirred for approximately 30 min while maintaining the temperature between 70 and 80 °C. The solution was allowed to cool and then transferred to a 500 mL volumetric flask and diluted to volume with DI water to prepare the sample stock solution. For completely soluble solid samples containing citrate (e.g., effervescent tablets), a finely ground portion equivalent to approximately 100 mg citric acid should be added to 300 mL of DI water in a 500 mL volumetric flask and diluted to the mark to prepare the sample stock solution. In this study, most samples were diluted 1000-fold for citrate determinations and approximately 200-fold for phosphate determinations.

## System Preparation and Setup

Prepare the Dionex ASRS ULTRA II suppressor for use by hydrating it. Use a disposable plastic syringe and push approximately 3 mL of degassed DI water through the “Eluent Out” port and 5 mL of degassed DI water through the “Regen In” port. Allow the suppressor to sit for approximately 20 min to fully hydrate the suppressor screens and membranes. Install the Dionex ASRS ULTRA II suppressor for use in the recycle mode according to the *Installation and Troubleshooting Instructions for the ASRS ULTRA II* (Document No. 031956).

Install the Dionex EGC II KOH cartridge in the Dionex ICS-2000 system and configure it with Chromeleon chromatography software. Condition the cartridge as directed by the Dionex EGC II Quickstart Guide (Document No. 031909) for 30 min with 50 mM KOH at 1 mL/min. Install a 4 × 50 mm Dionex IonPac AG11 guard column and 4 × 250 mm Dionex IonPac AS11 analytical column. Make sure that the system pressure displayed by the pump is at an optimal pressure of approximately 2300 psi when 20 mM KOH is delivered

at 2.0 mL/min so the degas assembly can effectively remove hydrolysis gas from the eluent. If necessary, install additional backpressure tubing supplied with the Dionex ICS-2000 system shipping kit to adjust the pressure to 2300 ± 200 psi. Because the system pressure can rise over time, trim the backpressure coil as necessary to maintain a system pressure between 2100 and 2500 psi.

## Results and Discussion

In general, highly charged analytes, such as citrate, are difficult to elute from most anion-exchange columns without using a concentrated eluent. To reduce the elution time, the eluent anion should have a high selectivity for the resin. Therefore, an anion-exchange column with a high selectivity toward hydroxide eluent, in combination with a low anion-exchange capacity of 45 µeq/column, was chosen to assay for citric acid. This column allows the separation of a wide range of inorganic and organic anions, including polyvalent ions, such as citrate, using a low to moderate eluent concentration. In addition, a hydroxide eluent has the following advantages: (1) it is readily available, (2) it can be electrolytically generated at an appropriate concentration, and (3) it is suppressed to water to yield an exceptionally low background conductance and lower noise, therefore improving the limits of detection and quantitation. An electrolytically generated potassium hydroxide eluent was used for the separation of phosphate and citrate in different pharmaceutical formulations to increase method automation and allow easy method transfer between laboratories. The assay was evaluated in terms of linearity, limit of quantitation, specificity, precision, accuracy, and ruggedness.

All calibration standards used in this assay were prepared in 1 mM NaOH. A total of 12 calibration data sets were acquired using either combined citric acid and phosphate standards or standards containing only citric acid. A calibration curve was generated with citrate in the range of 2–100 mg/L using seven concentration levels for the combined standard to assay formulations containing citrate and phosphate, and in the range of 5–70 mg/L using five concentration levels for assay of dosage forms containing only citrate. A calibration curve was generated with phosphate in the range of 1.2–60 mg/L. Each calibration was linear over the specified range using a least-squares regression curve with correlation coefficient ( $r^2$ ) of 0.9990 or better. Figure 1A shows a chromatogram of a combined phosphate and citrate standard separated on a Dionex IonPac AS11 and Figure 1B shows the same analytes analyzed in an anticoagulant citrate, phosphate, dextrose, and adenine dosage form.

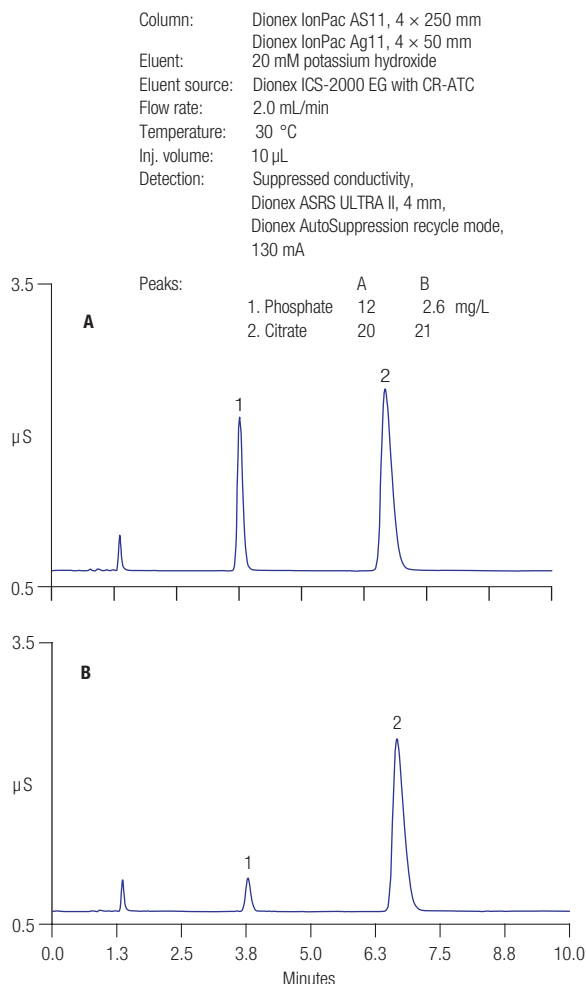


Figure 1. Separation of phosphate and citrate on the Dionex IonPac AS11 column with (A) standard and (B) assay for citrate in an anticoagulant citrate, phosphate, dextrose, and adenine dosage form.

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).<sup>14</sup> The baseline noise was determined by measuring the peak-to-peak noise in a representative 1 min segment of the baseline where no peaks elute. Typical baseline noise for this method using the Dionex ASRS ULTRA II suppressor in the recycle mode is approximately 2 nS/min. The determined LOQ for phosphate and citric acid over three consecutive days was approximately 0.2 mg/L (S/N = 10). The method validation did not require a determination of the detection limit. Table 1 summarizes the calibration and LOQ data.

Table 1. Summary of calibration and limit of quantitation data for citrate and phosphate.

Analyte	Concentration Range (mg/L)	Coefficient of Determination Range <sup>a</sup> (r <sup>2</sup> )	LOQ <sup>a</sup> (mg/L)
Citrate	2–100	0.9993–0.9994	0.20
Citrate	5–70	0.9990–0.9998	0.20
Phosphate	1.2–60	0.9999	0.20

<sup>a</sup>For three independent calibrations (3 days).

Method performance was measured in terms of the precision of replicate sample injections and recovery of spiked samples. The relative standard deviations (RSDs) of the measured peak areas were calculated for the target analytes prepared at a concentration of approximately 20 mg/L citrate and 12 mg/L phosphate. The intraday precision (i.e., a sequence of consecutive injections) for citrate and phosphate from independently prepared solutions analyzed on three separate days was <1% for citrate and <0.5% for phosphate on each day. The interday (i.e., day-to-day) precision for a three-day period (i.e., three independent sample preparations) for citrate was <2% and for phosphate <1%. Recoveries were determined by adding known amounts of analyte to the sample solutions. The calculated recoveries were within 95% to 105% for all samples. Table 2 summarizes the precision and recovery data for citrate and phosphate.

Table 2. Accuracy and precision for citrate and phosphate in pharmaceutical formulations.

Analyte	Intraday Precision Range (% RSD)	Interday Precision Range (% RSD)	Range of Recoveries (%)
Citrate	0.16–0.91 <sup>a</sup>	0.49–1.94 <sup>a</sup>	93.5–105.1 <sup>c</sup>
Phosphate	0.19–0.49 <sup>b</sup>	0.41–0.51 <sup>b</sup>	94.8–104.8 <sup>d</sup>

<sup>a</sup>Precision range for eight samples analyzed on three separate days from independently prepared solutions containing citric acid

<sup>b</sup>Precision range for two samples analyzed on three separate days from independently prepared solutions containing phosphate

<sup>c</sup>Added 1–2.5 mg/L citric acid to nine samples prepared at 100% of the target concentration

<sup>d</sup>Added 0.6–1.5 mg/L phosphate to two samples prepared at 100% of the target concentration

The USP defines ruggedness as a measure of the reproducibility of the method obtained by the analysis of the same samples under a variety of conditions. Ruggedness is typically expressed as the lack of influence on the assay results under different conditions that would normally be expected from laboratory to laboratory and from analyst to analyst when operating under the specified method parameters. We evaluated ruggedness of the method by using analysts, instruments, batch lots of the same column, and eluent preparation procedures as variables. The precision was determined by using the average measured concentrations (based on duplicate injections) and calculating the RSDs for the separate assays. Table 3 shows the precisions for each variable tested for both an individual analyst and for both analysts. For analyst A, the RSDs ranged from 0.17% to 2.00% compared to 0.31% to 2.60% for analyst B. The greatest total RSD for both analysts was approximately 2.40%. Based on these data, the method was found to be rugged in terms of the variables investigated.

Sample	Analyte	Analyst A (% RSD)	Analyst B (% RSD)	Total (% RSD)
Anticoagulant citrate phosphate dextrose adenine solution for citrate assay	Citrate	0.17	0.31	1.51
Anticoagulant citrate phosphate dextrose adenine solution for phosphate assay	Phosphate	2.00	2.60	2.17
Citric acid, magnesium oxide, sodium carbonate irrigation solution	Citrate	0.93	1.60	2.39
Potassium citrate extended-release tablets	Citrate	1.65	0.64	1.72

Table 4. Comparison of the citrate and phosphate concentrations obtained by IC with suppressed conductivity detection to the label amounts.

Sample	Analyte	Label Amount (mg/mL) <sup>a</sup>	Experimental Average <sup>c</sup> ±SD (mg/mL) <sup>a</sup>
Anticoagulant citrate phosphate dextrose adenine solution for citrate assay	Citrate	20.17	21.18 ± 0.10
Anticoagulant citrate phosphate dextrose adenine solution for phosphate assay	Phosphate	2.22	2.81 ± 0.010
Citric acid, magnesium oxide, sodium carbonate irrigation solution	Citrate	29.6	29.9 ± 0.4
Potassium citrate extended-release tablets	Citrate	10 meq	10.3 ± 0.2 meq
Anticoagulant citrate phosphate dextrose solution for citrate assay	Citrate	20.17	20.79 ± 0.23
Anticoagulant citrate phosphate dextrose adenine solution for phosphate assay	Phosphate	2.22	2.20 ± 0.02
Magnesium citrate oral solution	Citrate	NLT <sup>b</sup> 75.9	86.9 ± 1.8
Sodium citrate and citric acid oral solution	Citrate	126.4	128.3 ± 1.6
Sodium bicarbonate and citric acid effervescent tablets	Citrate	1000 mg/tab	1044.7 ± 21.5 mg/tab
Multiple electrolytes injection type 2	Citrate	0.513	0.517 ± 0.003
Oral rehydration solution	Citrate	1.92	2.55 ± 0.05

<sup>a</sup>Amounts expressed as mg/mL citric acid or NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O unless otherwise noted

<sup>b</sup>NLT = Not less than

<sup>c</sup>Average and standard deviation of three independent determinations, two injections per day

Table 4 summarizes the results from the assay of nine different pharmaceutical formulations for citric acid and phosphate (if present). The same samples were analyzed on three consecutive days using independently prepared standards and diluted dosage solutions. The calculated concentrations of these samples measured on separate days was consistent with a maximum difference of approximately 2% from day to day. In most cases, the measured values were very close to the label amounts and within the specifications according to their respective *USP 27-NF 22* monographs. However, the assay for phosphate in the anticoagulant solution and the assay for citrate in the oral rehydration solution were outside the specifications established by the USP. The amounts stated on the labels are based on the average from 20 to 25 sample containers. In this applications note, the values are based on the assay of one or two bottles. Also, the methods used to determine the label values are based on current USP procedures that are significantly different than the method presented in this application note. Therefore, the difference in the formulation label values and the experimental

values may be due to method variation, variation in the precision of the current USP methods, and the differences in sample size used to establish the label and experimental values.

### Conclusion

An IC method using a low-capacity, hydroxide-selective, anion-exchange column with suppressed conductivity detection provides an efficient and rapid separation of phosphate and citrate in different pharmaceutical formulations. This method meets USP performance requirements in terms of specificity, linearity, precision, and recovery of samples spiked with phosphate and citrate. There are currently nine different USP assays for 18 pharmaceutical formulations for citrate or citrate/phosphate in USP monographs. Laboratories that currently support multiple USP citrate assays for different pharmaceutical formulations may be able to standardize on this single IC assay. This assay can incorporate electrolytic generation of the potassium hydroxide eluent to enhance the consistency of the results between analysts and laboratories.



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## Suppliers

- U.S. Pharmacopeia, 3601 Twinbrook Parkway, Rockville, MD 20852 USA, Tel.: 800-227-8772, [www.usp.org](http://www.usp.org).
- VWR Scientific Products, 1310 Goshen Parkway, West Chester, PA 19380 USA, Tel: 800-932-5000, [www.vwr.com](http://www.vwr.com).
- Sigma-Aldrich Chemical Co., P.O. Box 14508, St. Louis, MO 63178 USA, Tel: 800-325-3010, [www.sigma-aldrich.com](http://www.sigma-aldrich.com).
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