Application Note AN-C-194

IC Assays for Calcium and Magnesium according to USP

Two method validations according to U.S. Pharmacopoeia

Calcium carbonate has a wide applicability in the pharmaceutical industry as an excipient and also as an active ingredient, and in the food industry as a major dietary supplement.

The U.S. Pharmacopoeia (USP) monographs for calcium and magnesium carbonates tablets as well as calcium carbonate and magnesia chewable tablets currently describe manual titration as the assay procedure for calcium and magnesium. The USP has embarked on a global initiative to modernize many of the existing monographs across all compendia. In response to this initiative, two alternative analytical methods were developed to determine the analytes calcium and magnesium. This Application Note presents ion chromatography (IC) procedures using conductivity detection that provide better accuracy and specificity and are suitable for the intended purpose.

These validated IC methods offer a significant improvement to the existing assays because they can simultaneously determine both analytes calcium and magnesium, saving both time and effort.

BACKGROUND

Calcium is the most abundant mineral in the body. 99% of the body's calcium supply is stored in the bones and teeth, where it supports their structure and function. It is also necessary for blood clotting, nerve conduction, and muscle contraction. It is best to try to meet bodily calcium requirements with foods. For those who find it difficult to achieve, calcium supplements are helpful, sold independently as well as together with magnesium products.

The current USP monographs for calcium and magnesium suggest manual titration. The assays have a history of poor precision and accuracy. If one component has a much higher concentration than the other, correct quantification can be difficult. In addition, the sample matrix could affect the endpoint determination.

EXPERIMENTAL

For the sample stock solution, weigh and finely powder no less than 10 tablets. Transfer an accurately weighed portion of the powder (equivalent to about 6 mg of calcium) to a 100 mL volumetric flask and add 4 mL of 2 mol/L nitric acid solution. Dilute to volume with ultrapure water, mix well, and sonicate for 20 minutes at 50 °C until the solution is completely homogenized.

For the sample solution, transfer an appropriate volume of sample stock solution to a 50 mL volumetric flask and dilute it with ultrapure water to volume. The sample solution should contain nominally 15 µg/mL of calcium from the tablet. This sample solution is directly injected into the IC with an injection volume of 20 µL.

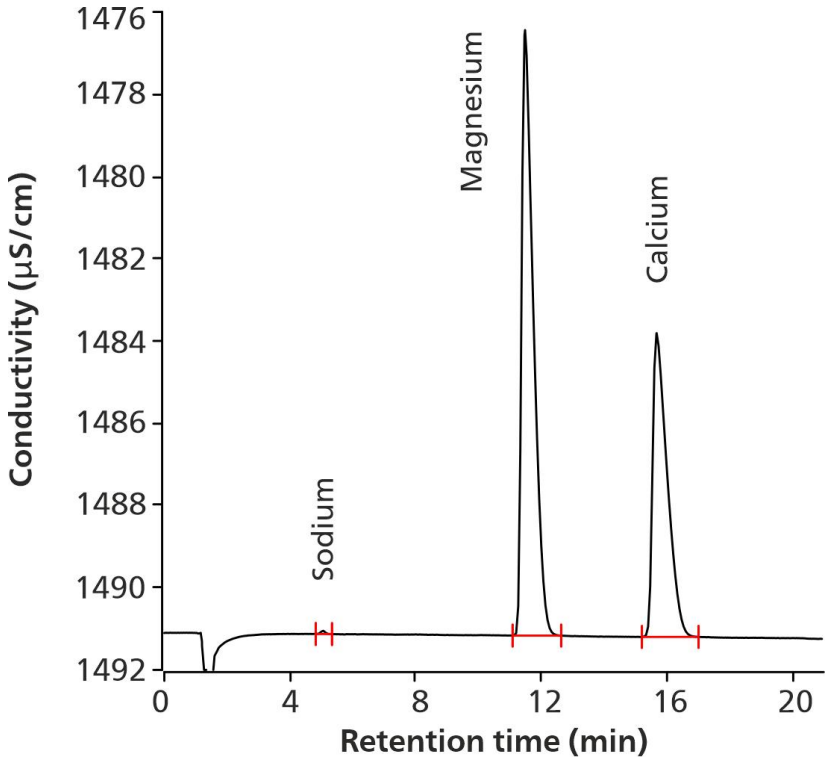

Figure 1. Conductivity signal of sodium, magnesium, and calcium in dietary supplement phosphate binder tablets (16.0 mg/L magnesium, 15.0 mg/L calcium, sodium not quantified) according to monograph "Calcium and Magnesium Carbonates Tablets" [1].

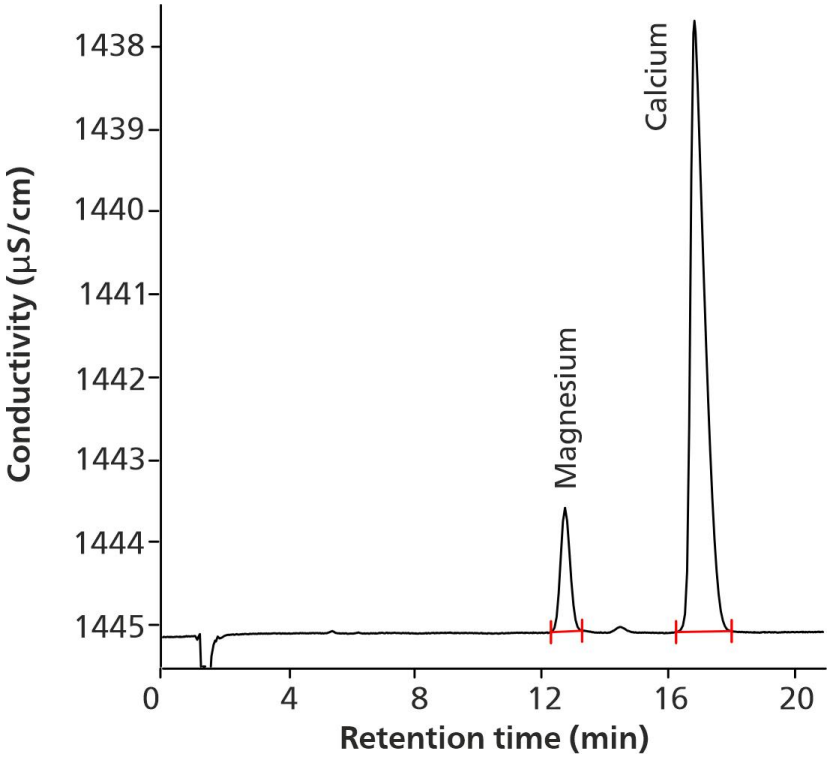

Figure 2. Conductivity signal of magnesium and calcium in Calcium 600 + D3 Plus Minerals chewable tablets (1.4 mg/L magnesium, 15.0 mg/L calcium) according to monograph "Calcium Carbonate and Magnesia Chewable Tablets" [2].

Calcium, magnesium, as well as other cationic components are readily separated on the column Metrosep C 6 - 150/4.0 (eluent: 4 mmol/L nitric acid, flow rate 0.9 mL/min, column temperature 30 °C) and detected with non-suppressed conductivity. Dietary supplement phosphate binder tablets (brand: MAGNEBIND® 300) were analyzed according to monograph "Calcium and Magnesium Carbonates Tablets" [1] (Figure 1). The Calcium 600 + D3 Plus Minerals chewable tablets (brand: Good Neighbor Pharmacy) were analyzed according to monograph "Calcium Carbonate and Magnesia Chewable Tablets" [2] (Figure 2). IC method parameters and sample preparation were the same for both monographs.

RESULTS

Two types of tablets were validated according to USP General Chapter <1225>, Validation of Compendial Procedures [3] to modernize the corresponding monographs from the USP. Calcium and magnesium were determined within a concentration range of 3.0–22.5 mg/L and of 0.5–20 mg/L, respectively, which is in the linear range of the conductivity detector and well above the limit of quantification.

Results for both developed IC methods fulfilled all USP acceptance criteria, as representatively shown in Table 1 for the calcium assay of the monograph calcium carbonate and magnesia chewable tablets. The IC method is appropriate to analyze multiple cations in one run, thus not only calcium and magnesium but also lithium, sodium, ammonium, and potassium can be quantified (if present).

Table 1. Selected performance characteristics for calcium.

Performance characteristics	Acceptance criteria	Results
System stability	RSD of 5 replicate injection areas should be NMT 0.5%	<0.3%
Solution stability	Change in peak area should be NMT 1% within 24 hours	<0.3%
Linearity of calibration	Correlation coefficient (R) NLT 0.999 Y-intercept bias: ± 2.0% of 100% linearity level response	>0.9999 0.3%
Repeatability of assay	Assay result with 90–110% RSD (relative standard deviation) (n = 6) is NMT 2%	99–102% <0.4%
Accuracy	Average % recovery should be 100 ± 2.0% of the manufacturer's CoA value	100–101%
Intermediate precision	Average results by a different analyst on a different day and using a different batch of column is NMT 3%	<1.5%

CONCLUSION

These validated methods describe an IC-based assay for simultaneous determination of calcium and magnesium in calcium and magnesium carbonates tablets as well as calcium carbonate and magnesia chewable tablets. These assays were validated according to the analytical performance characteristics outlined in USP General Chapter <1225> [3] and met corresponding limits.

The two analytes were easily separated on a cation-exchange Metrosep C 6 column and detected by non-suppressed conductivity within 20 minutes. As a multicomponent method, the concentrations of both analytes were determined in a single run compared to the two more time-consuming titration assays in the current monographs. Both assays using non-suppressed conductivity offer an easy, accurate, and robust measurement of the two analytes combined with a high sensitivity to replace the existing titration assays in the USP monographs.

REFERENCES

1. Calcium and Magnesium Carbonates Tablets, Monographs, U.S. Pharmacopeia/National Formulary: Rockville, MD.
2. Calcium Carbonate and Magnesia Chewable Tablets, Monographs, U.S. Pharmacopeia/National Formulary: Rockville, MD.
3. Validation of Compendial Procedures, General Chapters <1225> U.S. Pharmacopeia/National Formulary: Rockville, MD.

Internal references: AW IC CH6-1413-022020; AW IC CH6-1414-022020

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