Application Note AN-S-402

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Ion chromatography method with automated sample preconcentration, matrix elimination, and UV/VIS detection

The FDA has recently issued some guidance for managing nitrosamine impurities in pharmaceutical products [1]. Even in trace quantities, the presence of carcinogenic nitrosamine in medications risks patients' safety. Controlling the nitrite concentration in pharmaceutical products and processes can help to prevent nitrosamine formation. For this reason, the determination of nitrite in pharmaceutical products and their raw materials with sensitive analytical methods is essential.

Often, dimethylamine is used to synthesize different medications. Under acidic conditions, it reacts with nitrite, forming nitrosamines [2]. This is also the case for the production of hydroxypropyl methylcellulose (Hypromellose), a common excipient. This Application Note covers the determination of nitrite in hydroxypropyl methylcellulose with ion chromatography (IC) using a Metrosep A Supp 10 column and direct UV/VIS detection at 215 nm. Sample preparation is performed with the Metrohm intelligent Pre-Concentration Technique with Matrix Elimination (MiPCT-ME).

SAMPLES AND STANDARDS

Hydroxypropyl methylcellulose (Hypromellose) was received as a powder from a pharmaceutical company. A 0.1 g sample portion was accurately weighed and transferred into a clean 10 mL volumetric flask containing 5.0 mL of ultrapure water (UPW). The content was dissolved using a vortex mixer for approximately 20 minutes and the flask was filled up to the mark with UPW.

The prepared sample solution was filtered through a 0.2 µm syringe filter and kept in a sample processor under closed conditions prior to analysis.

A single-point calibration was used with 4 µg/L NO_2^- prepared from a 1000 mg/L NIST certified standard (Sigma TraceCERT No. 67276).

EXPERIMENTAL

The sample was analyzed with a chromatographic separation technique as described in USP <621> [3] (**Figure 1**). A MiPCT-ME setup was used in conjunction with the method parameters in **Table 1**. A 2 mL sample was preconcentrated on a Metrosep A PCC 2 HC/4.0, and the matrix was eliminated with 3 mL of ultrapure water.

After injection, the anionic components were isocratically separated within 45 minutes on a Metrosep A Supp 10 - 250/4.0 column. The UV/VIS detector signal was recorded at 215 nm. Confirmation of the method accuracy was done with a spiking study. The sample was spiked with a nitrite standard at two concentration levels (1.0 µg/L and 4 µg/L), and the recovery values were evaluated.

Figure 1. Instrumental setup including a 940 Professional IC Vario (center), 947 Professional UV/VIS Detector Vario SW (top center), 858 Professional Sample Processor (right), and MiPCT-ME, performed with the Metrosep A PCC 2 HC/4.0 and a Dosino (left).

Table 1. IC method parameters for the determination of nitrite impurities in hydroxypropyl methylcellulose (Hypromellose).

Column	Metrosep A Supp 10 - 250/4.0
Eluent	5.0 mmol/L sodium carbonate 5.0 mmol/L sodium hydroxide
Flow rate	1.0 mL/min
Column temp.	45 ° C
Injection volume	2 mL (preconcentration volume)
Detection	UV/VIS detection at 215 nm

RESULTS

Nitrite was quantified in hydroxypropyl methylcellulose (**Figure 2**). The method was sensitive enough to quantify trace levels of nitrite present in the sample matrix. A two-level spiking study confirmed the method accuracy, achieving recoveries between 80 and 120%.

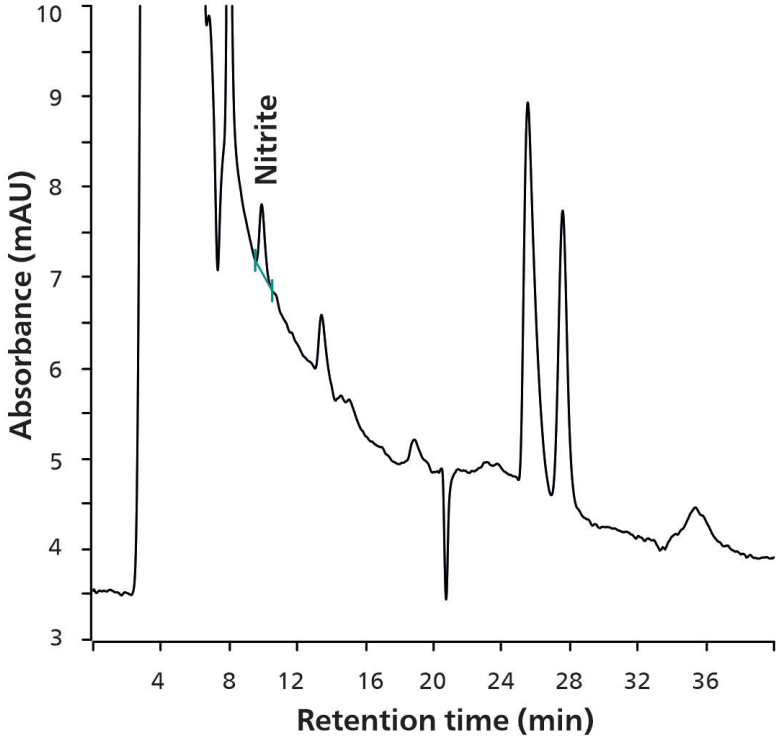

Figure 2. Chromatogram for 288 µg/kg nitrite in a hydroxypropyl methylcellulose sample.

CONCLUSION

Quantification of nitrite in hydroxypropyl methylcellulose according to USP <621> is possible with the presented IC method. Preconcentration of the sample offers higher sensitivity for the accurate determination of trace quantities of nitrite. Inline matrix elimination removes the interfering sample matrix before injection, further improving results. Separation of nitrite from other matrix components was achieved on the Metrosep A Supp 10 column. Method accuracy was confirmed by spiking studies.

This IC method is suitable for quality control of the impurity nitrite in pharmaceutical manufacturing processes involving the excipient hydroxypropyl methylcellulose.

REFERENCES

1. U.S. Department of Health and Human Services Food and Drug Administration; Center for Drug Evaluation and Research (CDER). Control of Nitrosamine Impurities in Human Drugs - Guidance for Industry. *Pharmaceutical Quality/Manufacturing Standards/ Current Good Manufacturing Practice (CGMP)* 2021.
2. U.S. Pharmacopeia. USP-NF Nitrosamine Impurities. *General chapter.* https://doi.org/10.31003/USPNF_M15715_02_01.
3. 〈621〉 *Chromatography.* https://doi.org/10.31003/USPNF_M99380_01_01.

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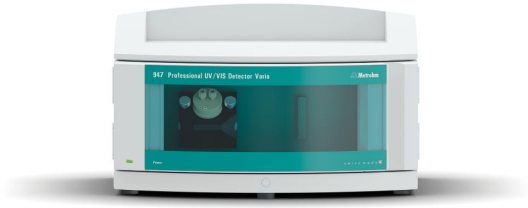
CONFIGURATION

940 Professional IC Vario ONE/SeS/PP

940 Professional IC Vario ONE/SeS/PP 是智能型子色器,有**序列抑制**和**蠕**用于抑制器再生。器可使用各分和方法。

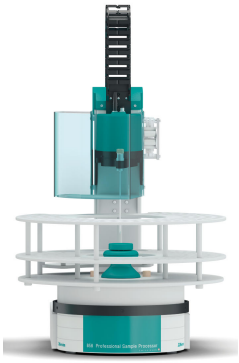
典型的用范:

- 子或子定,序列抑制法及
- 子或子的痕量分析
- 子或子的在控



947 Professional UV/VIS Detector Vario SW

智能波 器,947 Professional UV/VIS Detector Vario SW,可紫外光或可光区域内的活性物行安全可靠的定量操作。可一波。



858 Professional Sample Processor – Pump

858 Professional Sample Processor – Pump 可理体在 500 µL 至 500 mL 之的品。行品移,既可以使用内置的双向双通道蠕、也可通 800 Dosino 来行。

Metrosep A Supp 10 - 250/4.0

Metrosep A Supp 10 - 250/4.0 分柱基于高容量聚乙/二乙共聚物,其粒大小 4.6 µm。A-Supp-10 品系列中越 越的柱可提供越 越大的性和活性。特是在色分析的情况下,推荐使用 MSM-HC。在此分柱上也可修改各不同子分的温度、流速和淋洗液成分。

Metrosep A Supp 10 - 250/4.0 具有很高的容量。用于子度高的品、的分任以及用于分析各成分之度差很大的品。

Metrosep A PCC 2 HC/4.0

用于子富集和基消除。 加大型填充床可提高根富集柱(由 PEEK 制成)的容量。 其高容量主要用于基体效会致富集柱或需要高子度的品行分析的情况。