Nitrite in hydroxypropyl methylcellulose

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).

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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

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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%.
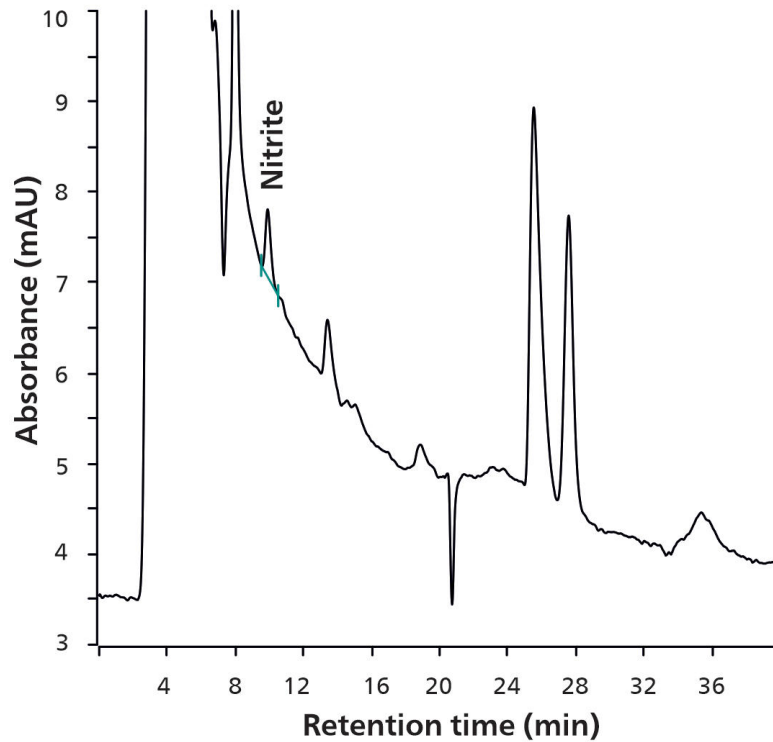

Figure 2. Chromatogram for 288 µg/kg nitrite in a hydroxypropyl methylcellulose sample.

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.

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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

Il 940 Professional IC Vario ONE/SeS/PP è l'intelligente strumento IC con **soppressione sequenziale** e **pompa peristaltica** per la rigenerazione del soppressore. Lo strumento può essere impiegato con qualsiasi metodo di separazione e di rilevamento. Campi d'impiego tipici:

- Determinazione di anioni o cationi con soppressione sequenziale e rilevamento della conduttività
- Analisi delle tracce per anioni o cationi
- Monitoraggio in linea per anioni o cationi

947 Professional UV/VIS Detector Vario SW

Il rilevatore intelligente di lunghezza d'onda singola 947 Professional UV/VIS Detector Vario SW consente di quantificare in modo sicuro e affidabile le sostanze attive nel campo ultravioletto o visibile. È possibile selezionare una lunghezza d'onda.

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858 Professional Sample Processor – Pump

L'858 Professional Sample Processor – Pump per il trattamento di campioni con volumi compresi tra 500 µL e 500 mL. Il trasferimento del campione avviene o attraverso la pompa peristaltica bidirezionale a doppio canale integrata o tramite un 800 Dosino.

Metrosep A Supp 10 - 250/4,0

La colonna di separazione Metrosep A Supp 10 - 250/4,0 è basata su un copolimero di polistirene/divinilbenzene ad alta capacità con una grandezza delle particelle di soli 4,6 µm. La più lunga colonna della famiglia A-Supp-10 offre la massima selettività e flessibilità. Soprattutto nei casi di maggiore durata del cromatogramma è consigliabile l'impiego dell'MSM-HC. Anche in questa colonna di separazione, le modifiche di temperatura, portata e composizione dell'eluente consentono le più svariate separazioni di anioni.

La Metrosep A Supp 10 - 250/4,0 ha una capacità estremamente elevata. È ideale per campioni con elevata forza ionica, per separazioni complesse e per analisi di campioni i cui componenti sono presenti a concentrazioni molto diverse tra loro.

Metrosep A PCC 2 HC/4.0

Per l'arricchimento anionico e l'eliminazione della matrice. L'ampliamento del letto denso aumenta la capacità delle due colonne di arricchimento, interamente realizzate in PEEK. L'elevata capacità viene richiesta soprattutto quando gli effetti matrice possono causare un sovraccarico della colonna di arricchimento oppure quando devono essere analizzati campioni con elevata forza ionica.

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