Application Note AN-S-401

Nitrite in duloxetine hydrochloride API

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

Recently, the FDA released a guidance document for pharmaceutical manufacturers regarding the control of nitrosamine impurities in medications [1]. Nitrosamine presence in drugs can be risky for patients as these compounds are carcinogenic, even at trace levels. However, nitrosamine formation can be avoided by controlling and monitoring the nitrite concentration in pharmaceutical products and raw materials. Developing processes to reduce or eliminate nitrosamine formation requires sensitive analytical methods for the determination of nitrite in complex matrices.

Dimethylamine is used during the synthesis of many pharmaceuticals. Under acidic pH, dimethylamine reacts with nitrite to form nitrosamines [2]. Duloxetine hydrochloride is an active pharmaceutical ingredient (API) against depression and other nervous system diseases. This Application Note describes the analysis of nitrite in duloxetine hydrochloride with ion chromatography (IC) using a Metrosep A Supp 10 column with direct UV/VIS detection at 215 nm. The Metrohm intelligent Pre-Concentration Technique with Matrix Elimination (MiPCT-ME) is used for sample preparation.

SAMPLES AND STANDARDS

Duloxetine hydrochloride was received as a powder from a pharmaceutical company. Approximately 0.05 g of sample 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 (approx. 5 min) and filled up to the line with UPW. A 0.1 mL aliquot of 1.0 mol/L sodium hydroxide was added, and the contents were mixed. The prepared sample solution was filtered using a 0.2 µm syringe filter and then passed through an IC-Ag sample preparation cartridge to remove any chloride ions. With automated sample preparation (MiPCT-ME), 2 mL of the sample solution was preconcentrated and the matrix was eliminated using 3 mL UPW.

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

EXPERIMENTAL

The prepared sample solution was injected directly using MiPCT-ME (Figure 1) and analyzed using the method parameters given in Table 1.

Anionic components were isocratically separated on a Metrosep A Supp 10 - 250/4.0 column and the background was reduced to a minimum with sequential suppression. The UV/VIS detector signal at 215 nm was recorded. The total run time was 40 minutes. The method accuracy was confirmed by a study where samples were spiked with 4 µg/L NO_2^- 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 duloxetine hydrochloride API.

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 detection at 215 nm

RESULTS

Nitrite was quantified in duloxetine hydrochloride with a chromatographic separation method as described in USP <621> (Figure 2) [3].

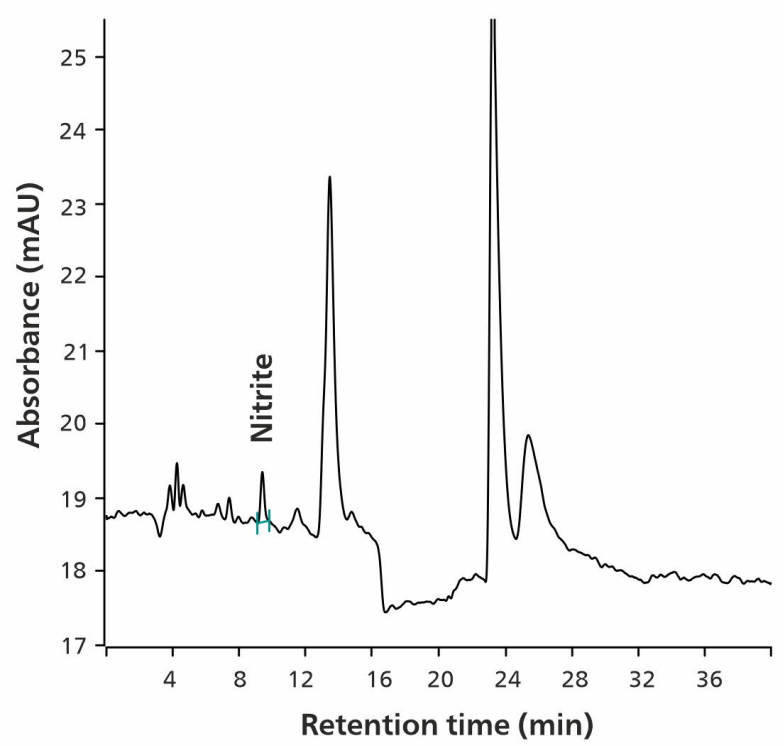

Figure 2. Chromatogram of 177 µg/kg nitrite in duloxetine hydrochloride.

Using the MiPCT-ME setup, the method was found to be highly sensitive, able to quantify trace levels of nitrite present in the sample matrix. The method accuracy, confirmed by the spiking study, achieved recovery values between 80 to 120 %.

CONCLUSION

The presented IC method with the Metrosep A Supp 10 column can be used to quantify trace levels of nitrite in duloxetine hydrochloride according to USP <621>. The high sensitivity was achieved by using preconcentration, and the interfering sample matrix was eliminated with an inline matrix elimination technique. This procedure is accurate and robust, and in contrast to manual preconcentration techniques, no additional work is needed for this automated inline process.

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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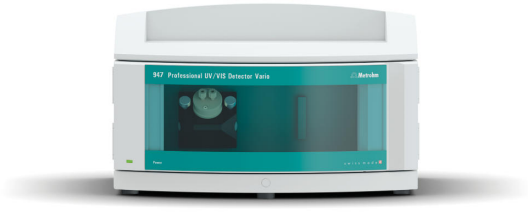
CONFIGURATION

940 Professional IC Vario ONE/SeS/PP

The 940 Professional IC Vario ONE/SeS/PP is the intelligent IC instrument with **sequential suppression** and a **peristaltic pump** for suppressor regeneration. The instrument can be used with any separation and detection methods.

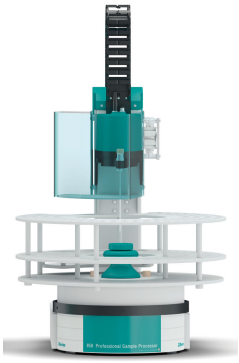
Typical areas of application:

- Anion or cation determinations with sequential suppression and conductivity detection
- Trace analysis for anions or cations
- Online monitoring for anions or cations



947 Professional UV/VIS Detector Vario SW

As an intelligent, single-wavelength detector, the 947 Professional UV/VIS Detector Vario SW permits a secure and reliable quantification of substances active in the ultraviolet or visible range. One wavelength can be selected.



858 Professional Sample Processor – Pump

The 858 Professional Sample Processor – Pump processes samples from 500 µL to 500 mL. The sample transfer takes place either with the installed bidirectional two-channel peristaltic pump or with an 800 Dosino.

Metrosep A Supp 10 - 250/4.0

The Metrosep A Supp 10 - 250/4.0 separation column is based on a high-capacity polystyrene-divinylbenzene copolymer with a particle size of only 4.6 µm. The longest column of the A Supp 10 product range offers the greatest selectivity and flexibility. Utilization of the MSM-HC is particularly recommended with longer chromatogram duration. Changes in temperature, flow and composition of the eluent also enable a wide variety of separations of anions on this separation column.

The Metrosep A Supp 10 - 250/4.0 has a very high capacity. It is suitable for samples with high ionic strength, for complex separation tasks and for analyzing samples in which great differences in concentration between the individual components are present.

Metrosep A PCC 2 HC/4.0

For anion preconcentration and matrix elimination. The enlargement of the packing bed increases the capacity of the two preconcentration columns completely made of PEEK. The high capacity is required primarily when matrix effects might cause an overloading of the preconcentration column or when samples with high ionic strength are to be analyzed.