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].

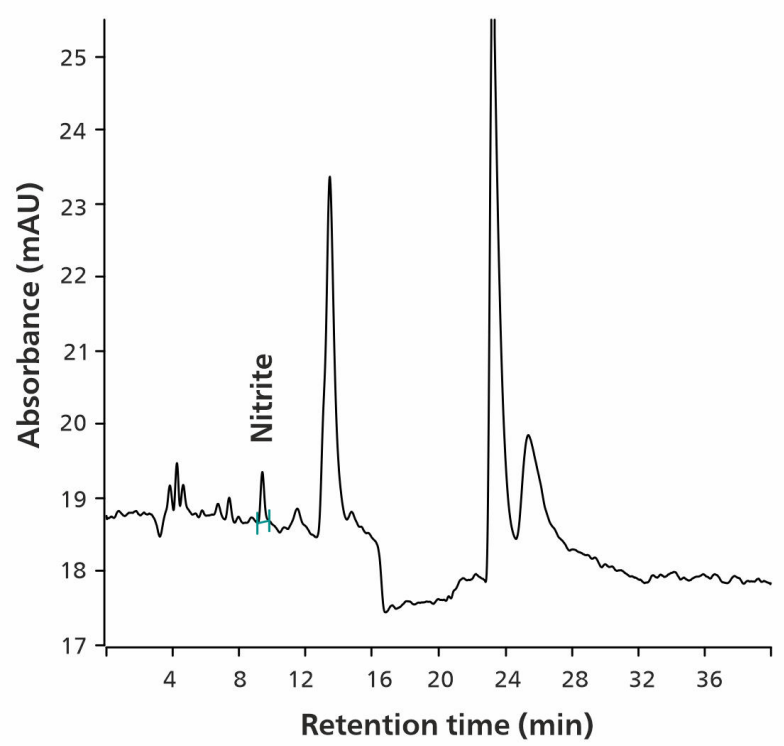


Figure 2. Chromatogram of 177 µg/kg nitrite in duloxetine hydrochloride.

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.

CONTACT

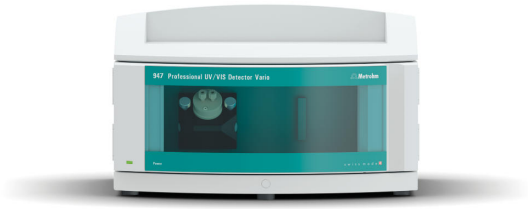
Metrohm Italiana Srl
Via G. Di Vittorio, 5
21040 Origgio (VA)
info@metrohm.it

CONFIGURATION

940 Professional IC Vario ONE/SeS/PP

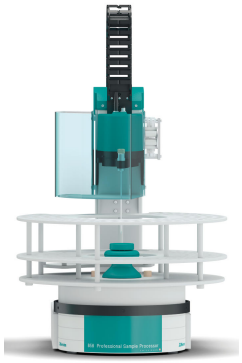
Il 940 Professional IC Vario ONE/SeS/PP è l'intelligente strumento IC con **soppressione sequenziale** e **pompa peristaltica** per la rigenerazione del soppressore. Lo strumento può essere impiegato con qualsiasi metodo di separazione e di rilevamento. Campi d'impiego tipici:

- 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.



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.