Application Note AN-S-401

酸度洛西汀API中的硝酸

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].

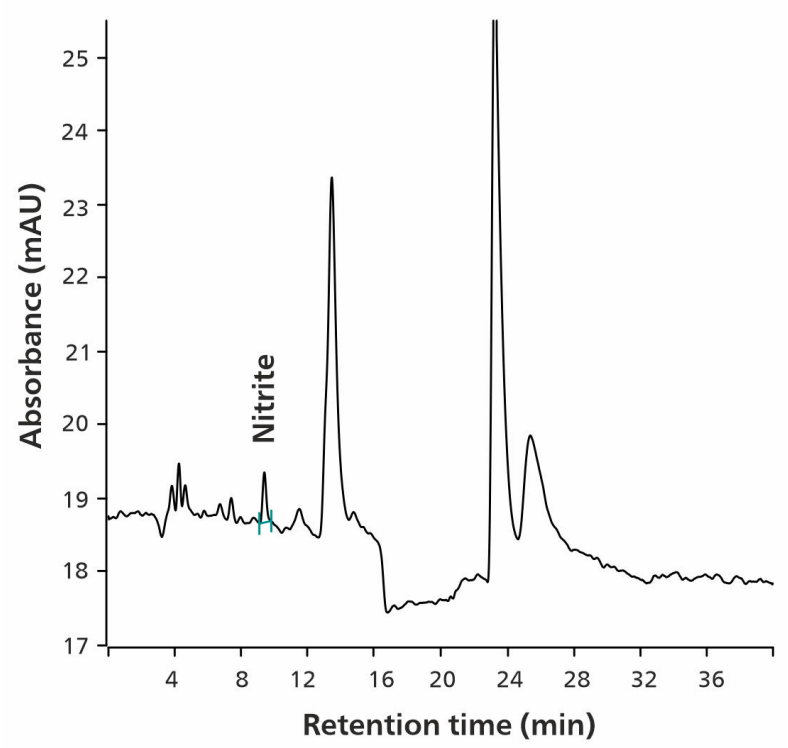

Figure 2. Chromatogram of 177 µg/kg nitrite in duloxetine hydrochloride.

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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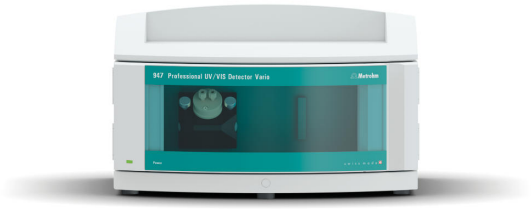
CONFIGURATION

940 Professional IC Vario ONE/SeS/PP

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。

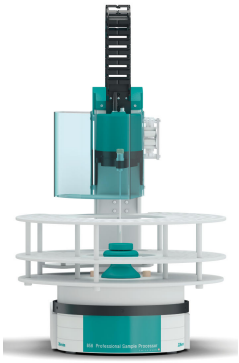
典型的用范:

- 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 品系列中最的柱可提供最大的性和活性。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(完全由 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。