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Application Note

Use of a Proprietary Polar Column Chemistry for the Separation of Nitrosamines in Sartan and Ranitidine Drug Substances

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This is an Application Brief and does not contain a detailed Experimental section.

Abstract

This study demonstrates the unique advantages of the Waters XSelect HSS T3 Column Chemistry to separate and identify nitrosamine impurities found in Angiotensin II Receptor Blocker (ARB) and ranitidine drug substances.

Benefits

The XSelect HSS T3 Column enables reliable separation of nitrosamine impurities in valsartan, losartan, ibersartan, and ranitidine drug substances.

Introduction

N-nitroso compounds are considered to have extremely high carcinogenic potency. Several medications have been subject to recalls due to the presence of these impurities.[1,2] To ensure the safety of pharmaceutical products, steps must be taken to understand the source of these impurities and to ensure their removal from the final drug substance. Information on how to assess and control these carcinogenic impurities can be found in the ICH M7(R1) guideline.[3]

Here, we present a single method using a proprietary column technology and UHPLC with dual detection (photodiode array and ACQUITY QDa). This method simultaneously separates six nitrosamines specified by the FDA[1] including NDMA, NDEA, NEIPA, NDIPA, NDBA, and NMBA in valsartan, losartan, and ibersartan ARB drug substances. This method is also suitable for testing NDMA impurity in ranitidine drug substance.

Experimental

Parameter	Description
LC system	ACQUITY Arc with 2998 PDA and ACQUITY QDa detectors, passive pre-heater, and flow path 1
Column	XSelect HSS T3 3.5 µm, 4.6 x 100 mm
Column temp.	40 °C
Flow rate	1.1 mL/min
Injection volume	25.0 µL
Mobile phase	A: 0.1% Formic acid in water B: 0.1% Formic acid in methanol
Gradient	see gradient table below
Wash solvents	Purge: 70:30 water/methanol Sample wash: 70:30 water/methanol Seal wash: 90:10 water/acetonitrile
PDA detection	λ range: 210 – 400 nm, derived at 245 nm Sampling rate: 20 pts/sec
Mass detection	ACQUITY QDa detector Ionization mode: ESI+ Acquisition range: 50 – 500 m/z

Gradient:

Step	Time (min.)	%A	%B
1	Initial	95.0	5.0
2	0.50	95.0	5.0
3	14.00	5.0	95.0
4	15.00	5.0	95.0
5	15.10	95.0	5.0
6	19.00	95.0	5.0

Figure 1. Instrument conditions for the separation of nitrosamine impurities, sartan, and ranitidine drug substances.

Results and Discussion

A list of nitrosamine impurities and drug substances analyzed by the method is shown in Table 1. Separate stock solutions were prepared in methanol at 5.0 mg/mL. Stock solutions containing drug substance (DS) were mixed into one vial and diluted with 80:20 water:methanol to make a mixture at 0.1 mg/mL. The mixture was spiked with impurities at 1.0% and run on the ACQUITY Arc UHPLC System using the XSelect HSS T3 Column (Figure 2). The XSelect HSS T3 Column, due its unique polar chemistry, provided excellent retentivity for the nitrosamines and reliable separation for all analytes.

Common name	Compound	Monoisotopic mass (Da)
N-nitrosodimethylamine	NDMA	74.05
N-nitrosodiethylamine	NDEA	102.08
N-nitrosoethyl isopropylamine	NEIPA	116.09
N-nitrosodiisopropylamine	NDIPA	130.11
N-nitrosodibutylamine	NDBA	158.14
N-nitroso-N-methyl-4-aminobutyric acid	NMBA	146.07
Valsartan	DS	435.22
Losartan	DS	422.16
Irbesartan	DS	428.23
Ranitidine	DS	314.14

Table 1. Nitrosamine impurities and drug substances (DS) for HPLC separation.

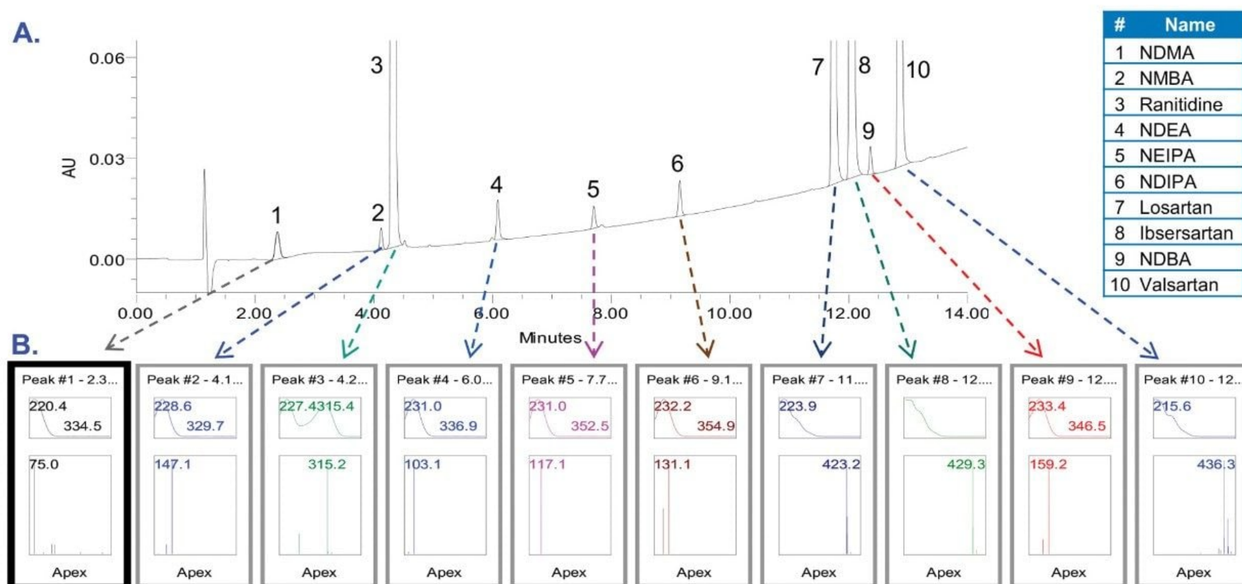

Figure 2. Chromatographic separation of nitrosamine impurities and drug substances on XSelect HSS T3 Column and mass analysis window from Empower 3 Software for peak identity confirmation.

The HSS T3 Column's unique combination of bonding and endcapping also enhances column performance, lifetime, peak shape, loading capacity, method development, selectivity, and stability. The mass spectral data acquired using the ACQUITY QDa Mass Detector confirmed the identity of the impurities and drug substances. Data was analyzed using Empower 3 Chromatography Data System (CDS) Software.

Conclusion

A single HPLC method was successfully developed for the separation and identification of NDMA in ranitidine and nitrosamines in valsartan, losartan and irbesartan drug substances. The separation was performed on the ACQUITY Arc UHPLC System with photodiode array and ACQUITY QDa Mass Detectors. The XSelect HSS T3 Column, a proprietary reversed-phase column, provided excellent retentivity for nitrosamine impurities and a reliable separation for all analytes. The ACQUITY QDa Mass Detectors allowed for a quick confirmation of peak identity by mass detection. This HPLC method is a suitable starting point for the analysis of nitrosamines or similar compounds.

References

1. https://www.uspharmacist.com/article/fda-update-on-recent-voluntary-arb-drug-recalls
2. https://www.fda.gov/news-events/press-announcements/statement-alertingpatients- and-health-care-professionals-ndmafound- samples-ranitidine
3. ICH M7 R1, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, International Conference on Harmonization, March 2018.

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