Sicrit technology

Application Note

Sensitive Detection of Nitrosamines for Drug Quality Control using SICRIT® Soft Ionization-MS

Summary

In this study we demonstrate sensitive determination of nitrosamine compounds by GC-soft ionization-MS outperforming GC-MS and LC-MS methods in view of drug quality control.

Introduction

Cancerogenic nitrosamine impurities are of big concern in pharmaceutical quality control. In 2018, FDA and EMA initiated recall of valsartan products of different manufacturers due to NDMA (N-nitrosodimethylamine) impurities and recommended review of manufacturing processes. Recently, both authorities prompted same actions also for ranitidin drugs.

The occurence of nitrosamines in drugs can not be only attributed to byproducts in raw materials but also can be formed during the processing. Thus, the whole manufacturing processes have to be investigated.

As the recalls are associated with serious financial losses, there's a great manufacturer's need of analytical methods for tracing back nitrosamines in their quality assurance.

However, looking at the current analytical techniques, there are challenges in nitrosamine determination for pharma quality control applications.

Hence pharmaceutical quality control and drug purity is mainly done by LC-MS/MS analysis, it would be obvious to include nitrosamine analysis into routine LC-MS drug purity control workflows. But it has been shown, that conventional LC-MS ionization techniques as ESI and APCI are limited in their ionization potential for simultaneous analysis of nitrosamines and the active drug.

In this study we show, that GC-MS coupling on LC-MS instruments using SICRIT® and its broad ionization range presents a well-suited method for simultaneous determination of drug and nitrosamine compounds in one run and thereby clearly facilitating pharmaceutical quality control.

Experimental Setup

In the experimental setup, a GC was coupled to an Agilent Ultivo Triple Quad instrument by SICRIT® Ion source. As GC carrier gas, Helium was used, the plasma source was operated with humidified nitrogen. MS detection was performed in positive MRM mode.

Table 1 - Experimental setup for Nitrosamine analysis.

Samples	Nitrosamine Mix EPA 521, 2 mg/mL in DCM (40035-U, Sigma-Aldrich)
Solvent	MS-grade Hexane (Sigma-Aldrich)
Mass spectrometer	Ultivo LC-TQ (Agilent Technologies)
SICRIT Plasma	1.5 kV, 15 kHz
GC	GC 8860 (Agilent Technologies)
Column	RXI-5ms, 30 m, 0.25 mm ID, 0.25 µm stationary phase (Restek)
Inject volume	2 µL
Split ratio	Splitless
Carrier gas	Helium
Flow rate	2 mL/min
Injector temperature	270°C
Start temperature	35°C, hold for 1.5 min
Temperature ramp	10°C/min (-100°C) 30°C/min (-280°C)
Final temperature	280°C
Transferline temperature	280°C

Results

All compounds of the nitrosamine mix could be separated and ionized as $[M+H]^+$ species. Qualification and quantification was executed using dynamic MRM mode for the transitions stated in Table 2.

Using SICRIT® ionization, the same transitions as known from ESI were used, so method transfer and use of ESI mass spectra data bases are possible.

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Table 2- Investigated nitrosamine components with respective MRM transitions and calculated LODs.

Compound	Abbreviation	Precursor Ion (m/z)	Product Ion (m/z)	Retention Time (min)	Fragmentor (V)	Coll. Energy (V)	Limit of detection (ng/mL]
N-Nitrosodimethylamine	NDMA	75	58	4.03	65	10	1.2
		75	43	4.03	65	17	
Diethylnitrosoamine	NDEA	103	75	6.30	85	8	0.1
		103	47	6.30	85	16	
N-Nitroso-N-methylethylamine	NMEA	89	61	5.21	75	10	0.1
		89	43	5.21	75	10	
N-Nitrosodipropylamine	NDPA	131	89	8.85	70	7	0.4
		131	43	8.85	70	15	
N-Nitrosodibutylamine	NDBA	159	57	10.43	70	7	0.1
		159	41	10.43	70	24	
1-Nitrosopyrrolidine	NPYR	101	55	8.77	55	18	0.4
		101	41	8.77	55	26	
1-Nitrosopiperidine	NPIP	115	69	9.23	85	9	0.5
		115	41	9.23	85	26	

Calibration experiments with diluted standard samples showed excellent sensitivity for all nitrosamine compounds with instrumental LODs in the ppt range (see Figure 1 and Table 2). This high sensitivity confirms the promesing potential of the SICRIT® GC-MS/MS approach.

As mentionend above, for pharmaceutical application comprehensive and universal MS methods for quality control of formulations would be of great advantage.

To examine the applicability of SICRIT® in this context, we did a comparison of LC-ESI-MS and LC-APCI-MS with GC-SICRIT®-MS on example of real samples out of the valsartan manufacturing process.

The results of the comparison are summarized in Figure 2. As known from literature, NDMA could not be ionized with LC-ESI, whereas valsartan was not detectable with LC-APCI. In contrast, GC-SICRIT® showed high ionization efficiency for both compounds, resulting in clearly highest SNR in relation to the absolute amounts on column. This proves GC-SICRIT®-MS to allow sensitive analysis of active drug and nitrosamine impurities in one single run by simply coupling a GC to the LC-MS instrument.

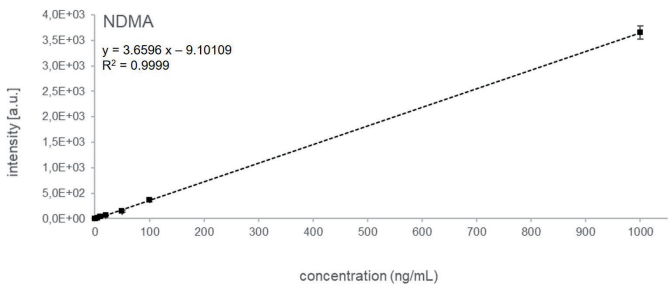

Figure 1 - Calibration of NDMA, obtained on Agilent Ultivo in positive MRM mode.

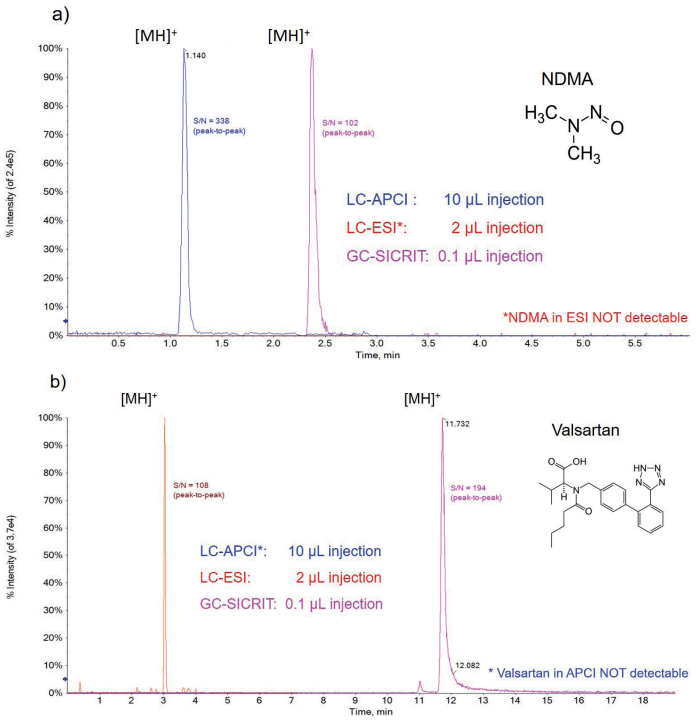

Figure 2 - Evaluation of ionization efficiency of ESI, APCI, and SICRIT for detection of NDMA impurites in valsartan formulation, obtained on SCIEX X500R.

Conclusions

The presented data show sensitive detection of nitrosamine compounds by GC-SICRIT®-MS. Furthermore, the superior ionization potential of SICRIT® allows for analysis of NDMA impurites in valsartan drugs in one single run, which could not be realized with LC-MS methods. In conclusion, GC-SICRIT®-MS is dedicated for universal pharmaceutical quality control by significantly reducing costs and efforts in method development and routine analysis.

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