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Application News

NDMA impurity in Ranitidine / LCMS™-8060

Quantitative Determination of NDMA Impurity in Ranitidine Drug Products – Examples of Actual Samples Analysis by LCMS-8060 with APCI

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User Benefits

- A high sensitivity MRM based method was established for quantitative determination of NDMA in ranitidine API and drug products on LCMS-8060.
- The method performance such as LOD, LOQ, repeatability and specificity was evaluated in reference to the FDA method published in 2019.

■ Introduction

On 13 September 2019, the US FDA released first alert on the presence of *N*-nitrosodimethylamine (NDMA) impurity, classified as a human carcinogen, in some ranitidine drug products [1]. It was revealed voluntary recalls of 14 lots of ranitidine capsules by Sandoz Inc., in the FDA Updates issued on 24 Sep 2019, due to NDMA impurity found in the products. The US FDA has advised companies to recall ranitidine drugs if testing shows levels of NDMA above the acceptable daily intake, i.e., 96 nanograms per day (ng/day) or 0.32 parts per million (ppm) for ranitidine. In October 2019, the US FDA released testing methods of NDMA impurity in ranitidine solid by LC-HRMS and LC/MS/MS (TQ) method [2]. This Application News describes a high sensitivity and robust LC/MS/MS method used for quantitative determination of NDMA in ranitidine substances and drugs obtained from manufacturers. The sample preparation procedure, system suitability, identification and calculation follows the FDA method with certain modifications [2].

■ Experimental

The NDMA stock solution of 100 µg/mL was prepared in methanol. A calibration series of 1, 5, 20, 50, 100, 200 ng/mL of NDMA were prepared in MeOH/H_2O (5:95, with 0.1% FA). The drug substances and products (API powders, tablet, syrup and injection solution) were obtained from different manufacturers.

Table 1 Analytical conditions of NDMA on LCMS-8060

Column	Shim-pack™ Scepter C18-120 (3.0 X 150 mm, 1.9 µm)
Flow rate	0.5 mL/min
Mobile phase	A: Water with 0.1% formic acid B: Methanol with 0.1% formic acid
Gradient Elution	4%B (0~1.8 min) --> 35% B (4.5 min) --> 95% B (5~12min) --> 4% B (12.1-15 min); Switch to waste: 4.6 min
Oven temp.	45°C
Interface & temp.	APCI, 350°C
MRM (+) of NDMA	75.0>43.1 (quantifier, CE: - 17V) 75.0>58.1 (confirmation, CE: -16V), Int. Ratio: Q/C=100/21
Injection vol.	30 µL

The sample preparation procedure for solid sample is first to crush tablet and weigh an amount equal to 20 mg of ranitidine. Adding 1 mL of MeOH/H_2O (5:95, with 0.1% Formic acid), the mixture was shaken for 30 min at room temperature followed by centrifugation at 15,000 rpm for 10 min. The extract was filtered with 0.22 um PVDF syringe filter and the clear solution was collected in an HPLC sample vial. A triple-quadrupole LCMS-8060 with APCI interface was employed in this work. Details of the system and analytical conditions are compiled into Table 1.

■ Results and Discussion

Working standard and calibration curve

An MRM based method with positive mode using APCI interface was set up for quantitative analysis of NDMA in ranitidine drugs and API substance. Following the FDA reference method [2], an external standard method was established using a quantifier MRM (75.0 > 43.1). The MRM chromatogram of NDMA working standard (1 ng/mL) is shown in **Figure 1**. A calibration curve of NDMA is shown in **Figure 2**.

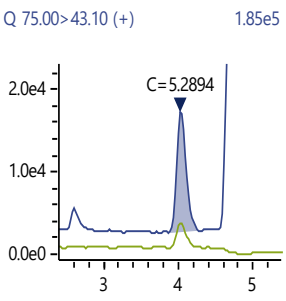

Fig. 1. MRM peak of NDMA, working standard (5 ng/mL) in diluent.

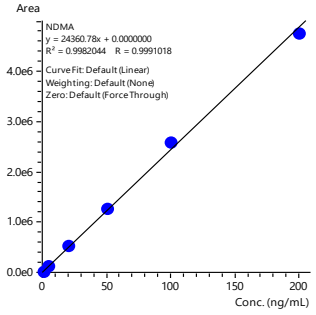

Fig. 2. Calibration curve of NDMA for 1~200 ng/mL with R2 > 0.996

System suitability

The system suitability criterion of the FDA method is based on RSD less than 10% (n=6) for 1 ng/mL working standard. The results shown in Table 2 indicate that the method meets the criterion with a big allowance in two different days' evaluations

Table 2. System suitability for NDMA with 1 ng/mL standard

Data#	Peak Area (Day 1)	Peak Area (Day 2)
1	21,406	20,393
2	19,820	21,895
3	19,548	20,750
4	22,232	19,716
5	19,827	21,892
6	20,217	21,624
Average	20,508	21,045
%RSD	5.22	4.28

Quantitative results of NDMA

Following FDA reference method [2], a typical sequence run includes blank (diluent x 2 injections), working standard (1 ppb x 6 injections) and blank (x 1 injections) before injection of samples. To obtain more accurate results, instead of only working standard (1 ppb x 6 injections), the calibration series (1~200 ppb) were injected before the system suitability testing and analysis of samples. The criterion of identification of FDA reference method is based on RT shift less than 2%, which corresponds to (+/-) 0.08 min.

Table 3. Analysis results of NDMA in various ranitidine samples obtained from manufacturers on LCMS-8060

Sample Description	Ranitidine in Extract (mg/mL)	NDMA Measured (ng/mL)	NDMA (ppm)	RT Shift (%)
Injection (50mg/ 2mL per vial)	12.5	9.3	0.74	0.50
syrup (75mg/5mL per dose)	7.5	81.2	10.83	1.38
API (powders)	20.0	24.8	1.24	-0.34
Tablet 1 (150mg/T)	20.0	221.8	11.09	0.19
Tablet 2 (150mg/T)	20.0	118.8	5.94	1.13
Tablet 3 (150mg/T)	20.0	34.0	1.70	0.38

The results shown in Table 3 were calculated following the formula [2]:

$$NDMA\ impurity\ (ppm) = \frac{A_{spl}}{As} \times C_s \times \frac{1mg}{1 \times 10^6 ng} \times \frac{V}{W} \times 10^6$$

Where

A_{spl} = *Area of NDMA quantifier peak (75.0 > 43.1)*
A_s = *Average area (n = 6) of the NDMA quantifier peak*
C_s = *Conc. of NDMA in the standard solution (ng/mL)*
W = *Weight of drug substance (mg)*
V = *Volume of the diluent in the sample solution (mL)*

The results shown in Table 3 indicate that the NDMA levels in all the samples are higher than the acceptable criterion (0.32 ppm for ranitidine). Figure 3 show a few representative MRM chromatograms of a sequence run including blank, 1 ng/mL standard and actual ranitidine samples.

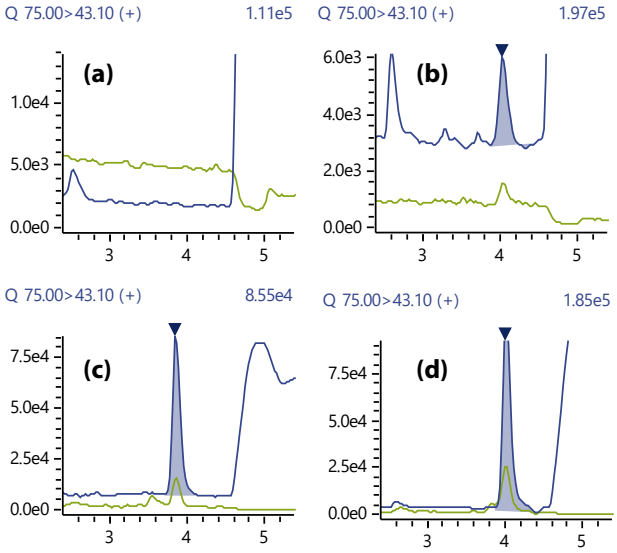

Figure 3. MRM chromatograms of diluent (a), 1 ng/mL std (b), API (c) and Tablet 3 (d).

■ Conclusion

Following the US FDA reference method [2], an MRM quantitation method was set up on LCMS-8060 with APCI interface and applied in determination of NDMA impurity in ranitidine substance and drug products in solid and non-solid forms. NDMA was found in all the samples analyzed and its levels in these samples were higher than the acceptable daily intake (0.32 ppm).

■ References

1. US FDA, Statement alerting patients and health care professionals of NDMA found in samples of ranitidine (13 Sep 2019)
2. US FDA, LC-MS/MS Method for the Determination of NDMA impurity in Ranitidine Drug Substance or Solid Dosage Drug Product (10 Oct 2019)

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