Vol. 12, No. 2, 2021
ISSN 2233-4203/ e-ISSN 2093-8950
ARTICLE www.msletters.org | Mass Spectrometry Letters

Screening of Nitrosamine Impurities in Sartan Pharmaceuticals by GC-MS/MS

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Received in April 22, 2021; Revised May 11, 2021; Accepted May 18, 2021
First published on the web June 30, 2021; DOI: 10.5478/MSL.2021.12.2.31

Abstract : Probable human carcinogenic compounds nitrosamines, have been detected as by-product impurities in sartan pharmaceuticals in recent years which has drawn worries for medication safety. To provide a sensitive and effective method for the quality control of sartan pharmaceuticals, this study established a feasible gas chromatography–tandem mass spectrometry (GC–MS/MS) method for simultaneous determination of 13 nitrosamines. The target analytes were separated on a DB-WAX Ultra Inert column (30 m × 0.25 mm; i.d., 0.25 μm) and were then subjected to electron impact ionization in multiple reaction monitoring mode. The established method was validated and further employed to analyze authentic samples. Limits of detection (LODs) and limits of quantification (LOQs) of the 13 nitrosamines were 15-250 ng/g and 50-250 ng/g, respectively, which also exhibited intra-day and inter-day accuracies of 91.4-104.8%, thereby satisfying validation criteria. Five nitrosamines, viz., *N*-nitrosodiethylamine, *N*-nitrosodimethylamine, *N*-nitrosodiphenylamine, *N*-nitrosomorpholine, and *N*-nitrosopiperidine were detected at concentrations above their LODs in 68 positive samples out of 594 authentic samples from seven sartans.

Keywords : angiotensin II type 1 receptor blockers, carcinogens, gas chromatography, mass spectrometry, nitrosamines

Introduction

Nitrosamines, analog compounds that include the same *N*-nitroso core structure (–N–N=O), are considered probable human carcinogens; these compounds are generally found in industrial manufacturing processes and environments.[1] In common industries, such as the food, cigarette, cosmetics, dye, pesticide, polymer, rubber, steel, and pharmaceutical sectors, nitrosamines are present as by-product impurities in the final products or as waste released into the environment.[2] The formation of a nitrosamine involves a series of complex reactions. While the mechanism of formation remains unclear, it is understood to involve nitrosation by nitrite, which, in turn, is affected by various factors, including the employments of amines, nitrates, and nitrites, as well variations of reaction conditions (such as pH, content, and concentration of the precursors).[3,4] The oxidation of unsymmetrical dimethylhydrazine (UDMH) and the chlorination of nitrites can also lead to the formation of nitrosamines.[5]

The evaluated excess lifetime cancer risk posed by nitrosamines is 10^{-5}–10^{-6} in the 0.7–100 ng/L concentration range for drinking water.[6,7] Since nitrosamines probably pose cancer risks to humans, several have been regulated by the international organizations or countries. For example, *N*-nitrosodiethylamine (NDEA) and *N*-nitrosodimethylamine (NDMA) have been categorized as Group 2A substances (probably carcinogenic to humans) by the World Health Organization (WHO), Group 1B substances (presumed to have carcinogenic potential for humans) in the European Union, and Group 2B substances (probable human carcinogens) in the USA. In addition, *N*-nitrosodipropylamine (NDPA), *N*-nitrosomethylethylamine (NMEA), *N*-nitrosomorpholine (NMOR), and *N*-nitrosopiperidine (NPIP) are categorized as Group 2B substances (possibly carcinogenic to humans) by the WHO.[7,8]

NDMA, an impurity present in valsartan, was detected and reported by Spain in 2018, which was announced via the PIC/S Rapid Alert System. Initially, this unexpected impurity was ascribed to a change in the manufacturing process of valsartan active pharmaceutical ingredient (API) by a Chinese pharmaceutical company.[9,10] Subsequently, more countries have reported the cases of nitrosamine-contaminated sartan medicines.[11-13] From these reports, the nitrosamine contamination of sartan medicines has become an urgent issue in the world-wide quality control of pharmaceuticals.

Sartans are classified as angiotensin II receptor type 1 antagonists and are widely used to treat cardiovascular

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diseases, such as hypertension, heart failure, and myocardial infarction.[14,15] While minor impurities, such as the degraded fragments of the target compounds, are produced within the synthesis of sartan APIs, nitrosamines are not generally expected to be produced following the methods applied for synthesizing sartan API.[16-18] Unfortunately, some alterations to the synthetic protocols have led to the formation of nitrosamines. For example, the solvent used in the recovery process can lead to the formation of nitrosamines. The aprotic polar solvent used to manufacture sartans, especially dimethylformamide (DMF), is recycled and quenched with sodium nitrite ($NaNO_2$) to remove residual azide formed through the use of anhydrous zinc chloride ($ZnCl_2$) and sodium azide (NaN_3), which leads to the formation of NDMA.[19,20]

Since nitrosamines are probably carcinogenic to humans, establishing an analytical method for the detection of nitrosamines in pharmaceutical products has become an important objective. Literatures have reported methods for determining nitrosamines based on liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS).[21,22] On contrast, several research teams have developed analytical methods for few nitrosamines based on gas chromatography–mass spectrometry GC–MS and GC–MS/MS methods.[23,24] This study aimed to develop a GC–MS/MS method of larger coverage for the screening of 13 nitrosamines in sartan medicines. The established method was validated and further employed to analyze authentic sartan medicines.

Materials and Methods

Chemicals and reagents

N-Nitrosodibutylamine (NDBA), NDEA, NDMA, NDPA, NDMA-d_6, and NDPA-d_{14} were purchased from AccuStandard (CT, USA). *N*-Nitrosoethylisopropylamine (NEIPA), *N*-nitrosodiisopropylamine (NDiPA), and NMOR were purchased from BOC Sciences (NY, USA), Chem Service (PA, USA), and Sigma-Aldrich (MO, USA), respectively. *N*-Nitrosodiphenylamine (NDPhA) and NPIP were purchased from Supelco (PA, USA). *N*-Nitrosodiisobutylamine (NDiBA), *N*-nitrosodicyclohexylamine (NDCHA), *N*-nitrosodiisononylamine (NDiNA), NMEA, *N*-nitrosodiethylamine-d_4 (NDEA-d_4), and *N*-nitrosodiphenylamine-d_{10} (NDPhA-d_{10}) were acquired from TRC (ON, Canada). Chromatography-grade methanol was obtained from Sigma-Aldrich (MO, USA). The chemical structures of the 13 nitrosamines analyzed in this study are shown in Fig. 1. A total of 594 authentic samples of seven sartans, viz. azilsartan medoxomil (19 final products), candesartan cilexetil (4 APIs and 6 final products), irbesartan (35 APIs and 28 final products), losartan (68 APIs and 198 final products), olmesartan medoxomil (8 APIs and 18 final products), telmisartan (18 final products), and valsartan (65 APIs and 127 final products), were collected by local public health bureaus in Taiwan and analyzed in this study.

Instrumentation and chromatographic conditions

The experiments were conducted on a GC–MS/MS system in which a 7890B GC instrument was coupled to a 7000C triple quadrupole mass spectrometer, both from Agilent Technologies (Santa Clara, CA, USA). Data acquisition and processing were performed using Agilent Mass Hunter Quantitative Analysis B.06.00 and Mass Hunter Qualitative software. Chromatography was performed using an Agilent Technologies DB-WAX Ultra Inert column (30 m × 0.25 mm; i.d., 0.25 μm), with the performance of an Agilent J&W HP-5MS column (30 m × 0.25 mm; i.d., 0.25 μm) and an Agilent DB-624 column (60 m × 0.25 mm; i.d., 1.40 μm) was also examined. The carrier gas (helium) was set to a constant flow rate of 1 mL/min. The GC operating parameters were as follows: pulsed splitless injection mode, inlet temperature 250°C, and interface temperature 250°C. The GC temperature program was set as follows: the initial temperature of 80°C was held for 3.0 min, after which it was raised to 250°C at 20°C/min and held for 3 min. A sample injection volume of 2 μL was applied. The total chromatographic run time was 14.5 min. The mass spectrometer was operated in electron impact (EI) ionization mode under the following conditions: ionization energy 70 eV, ion source temperature 230°C, and 1st & 2nd quadrupole temperature 150°C. Analytes were monitored in multiple reaction monitoring (MRM) mode. The MRM parameters, including the MRM transitions, quantifiers, qualifiers, and collision energies, are provided in Table 1.

Standard solution preparation

Stock solutions of the 13 nitrosamines and four internal standards (ISs) were prepared in methanol at concentrations of 1000 μg/mL. The IS stock solution was diluted with methanol to prepare 200 ng/mL IS solutions. Calibration curves for the nitrosamines were prepared at seven points in the 1–50 ng/mL concentration range, including the IS of equivalent 20 ng/mL. All the stock and working solutions were stored at -30°C. All reagents were brought to controlled room temperature prior to use.

Sample preparation

Sartan matrices (100 mg; API or ground tablet powder), IS solutions (500 μL; 200 ng/mL), and 4.5 mL of methanol were transferred to a 15-mL centrifuge tube and mixed well to form a homogeneous solution. It should be noted that methanol was replaced with the standard solution of interest for validation purposes. Each solution was sonicated for 30 min and then filtered through a 0.22-μm polyvinylidene fluoride (PVDF) filter. The filtrate was collected as the sample solution and subjected to analysis in this study.

Method validation

Linearity and sensitivity

Linearity was assessed by least-squares linear regression analysis of the calibration curves. The calibration curves were constructed by plotting the peak area ratio of the

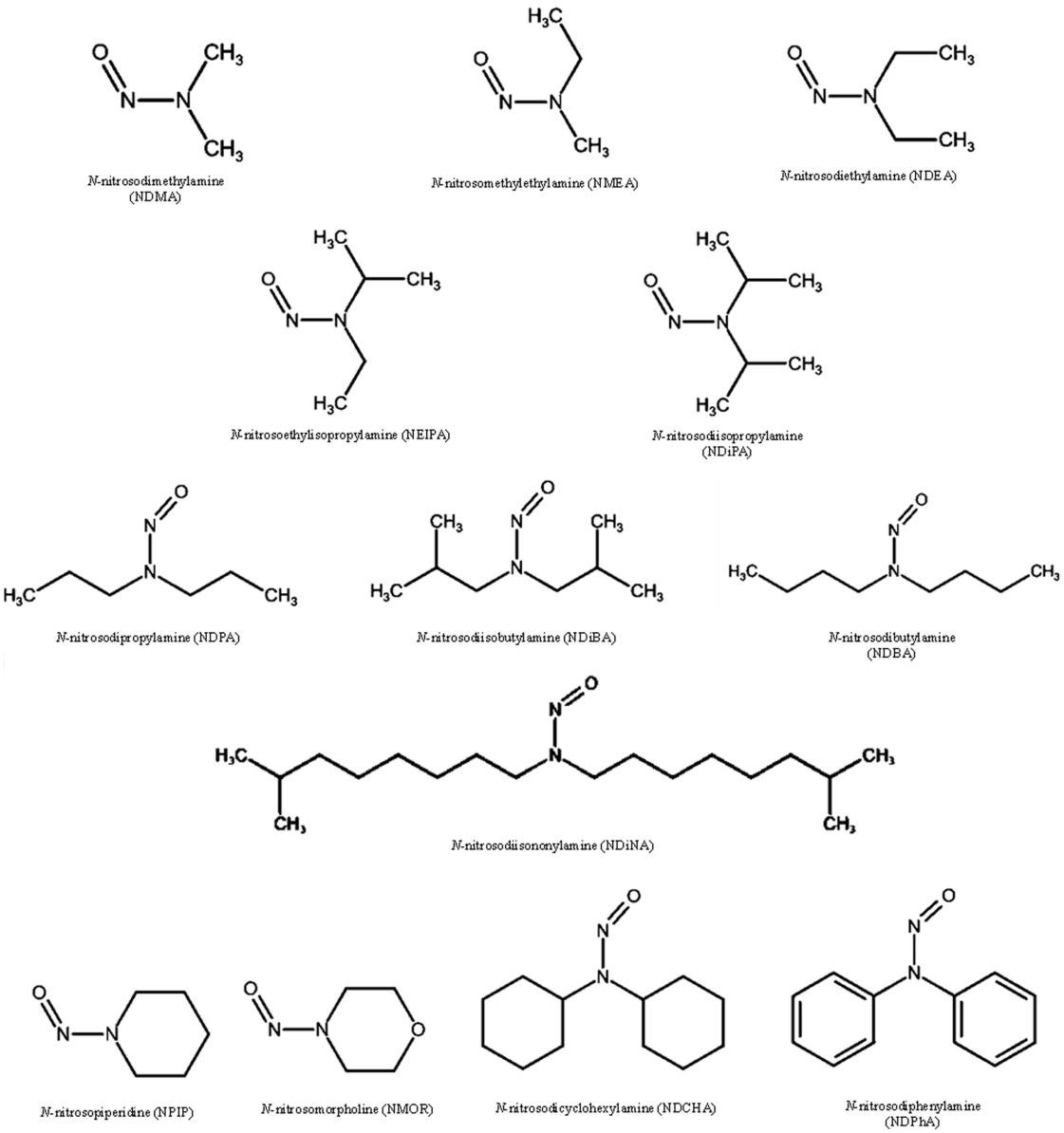


Figure 1. Chemical structures of the 13 nitrosamines.

standard solution vs. IS determined by the analysis of 13 standard solutions with concentration range of 1–50 ng/mL. The acceptable value for the correlation coefficient (r) was 0.995 and above. The limits of detection (LOD) and quantification (LOQ) were selected as indices of sensitivity and evaluated following the validation protocol of the International Council for Harmonisation (ICH).[25] The LOD and LOQ were determined based on signal-to-noise (S/N) ratios of 3 and 10, respectively, whereas ± 20% was set as the ion-ratio criterion.

Accuracy and precision

Prior to any assessment, the sartan matrices were examined to ensure that no nitrosamines were present as interferents. Accuracy, expressed as recovery (%), was determined through quality control (QC) based on intra-day and inter-day target analyte testing following the ICH procedure.[25,26] The QC criteria are referenced to those of the Taiwan Food and Drug Administration (TFDA): for 1-10 ng/mL, recoveries of 60-125% and an RSD < 30%; for 10-100 ng/mL, recoveries 70-120% and an RSD of 20%. Accuracy (%) was assessed by comparing the concentration of the analyte determined in the matrix (A) with the concentration of the standard solution (B) as follows: [A]/[B] × 100%. Precision (RSD in %) was assessed at three concentrations (5, 25, and 50 ng/mL) on the same day (n = 3) and over three consecutive days (n = 9).

Table 1. MRM parameters for the 13 nitrosamines and four ISs.

Analyte	Retention time (min)	MRM transition (*m/z*)	Dwell time (ms)	CE (eV)
NDMA	5.004	74 > 42 [a] 74 > 44	80	20 13
NMEA	5.556	88 > 71 [a] 88 > 42	45	2 15
NDEA	5.875	102 > 85 [a] 102 > 56	45	2 15
NEIPA	6.225	116 > 99 [a] 116 > 44	55	2 12
NDiPA	6.470	130 > 88 [a] 130 > 42	55	2 10
NDPA	7.113	130 > 113 [a] 130 > 43	40	2 13
NDiBA	7.278	115 > 84 [a] 103 > 57	40	2 8
NDBA	8.412	116 > 99 [a] 158 > 99	100	2 5
NPIP	8.643	114 > 84 [a] 114 > 97	55	10 5
NMOR	9.139	116 > 86 [a] 116 > 56	55	2 13
NDiNA	11.606	169 > 99 [a] 281 > 225	100	12 12
NDCHA	12.638	210 > 128 [a] 210 > 111	150	5 2
NDPhA	13.141	169 > 168 [a] 169 > 167	65	18 30
NDMA-d_6	4.996	80 > 46 [a]	80	18
NDEA-d_4	5.873	106 > 88 [a]	45	2
NDPA-d_{14}	7.049	110 > 78 [a]	40	2
NDPhA-d_{10}	13.123	179 > 177 [a]	80	18

[a] quantifier; CE: collision energy; MRM: multiple reaction monitoring

Results and Discussion

GC–MS/MS method development

As part of the optimization process, the efficacy of different columns was investigated in order to determine which was the most suitable for the chromatographic analysis of the target analytes. Several columns have reportedly been used to detect nitrosamines in non-water matrices. Santillana et al. reported a GC–MS method for the detection of eight nitrosamines in polymer teats and soothers by applying an Agilent DB-624 column in which the overall run time of the method was 30 min.[27] The U.S. FDA has specified GC–MS and GC–MS/MS methods for the detection of nitrosamines in valsartan that use Agilent DB-WAX and VF-WAXms columns with overall run times for both methods of less than 20 min.[28,29] In the current study, the three columns described in the "Instrumentation and chromatographic conditions" section were examined. The 13 nitrosamines (50 μg/mL in methanol) were separately analyzed in full scan mode using the three columns and the temperature program reported in the literature for the chromatographic separation of the target analytes.[29] Nevertheless, the reference method was not entirely suitable for this study because a larger number of nitrosamines was investigated; several analytes did not appear in the chromatogram within the run time, and the entire analysis process was inefficient, with loosely dispersed chromatographic peaks. Hence, the method was adjusted to improve the peak profile, with most analytes finally separated by applying the temperature program described in "Instrumentation and chromatographic conditions" section. However, discrepancies of the individual columns were observed in the chromatographic separations, which are ascribable to the polarity difference among the target analytes and columns. NDMA and NMEA were coincident with the solvent peak (3 min) using the HP-5MS column, owing to the high polarity of both analytes, while the remaining 11 nitrosamines exhibited split peaks. On the other hand, NDiNA, NDCHA, NDELA, and NDiPLA were not detected using the DB-624 column, whereas the peaks for the remaining nine nitrosamines were asymmetric. In contrast, the DB-WAX Ultra Inert column demonstrated good resolution (more than 0.1 min between adjacent analytes) and symmetric peaks for all 13 nitrosamines. Based on these results, DB-WAX Ultra Inert column was adopted for further method development.

The MS/MS conditions were optimized in order to select the best precursor and product ions for each analyte based on the ions collected in full scan mode (in the 50–300 *m/z* range). The ionization energy was appropriately set in order to optimally fragment each analyte since the ionization energy would affect screening efficacy and target analyte quantification. The lower ionization energy 40 eV has been reportedly used to determine multiple nitrosamines.[29] Therefore, the ionization energy was initially set at 40 eV in this study. However, the scale of this energy level was found to be insufficient to fragment those nitrosamines with larger molecular weights. Consequently, the ionization energy was adjusted to the higher level 70 eV; at this energy level, all 13 nitrosamines were successfully ionized to generate fragments suitable for MRM mode. The MRM parameters for the 13 nitrosamines and 4 ISs are listed in Table 1, whereas the total ion chromatograms (TICs) of GC analysis and MRM chromatograms for mass fragment are displayed in Figure 2 and Figure 3, respectively. Although the qualifiers and quantifiers of the analytes were determined according to the relative intensities of the precursor and product fragments, specific scenarios needed to be considered. For example, the matrix can contribute ions to the analytes in MRM mode. In this study, the matrix interfered with the 210 > 193 *m/z* qualifier ions

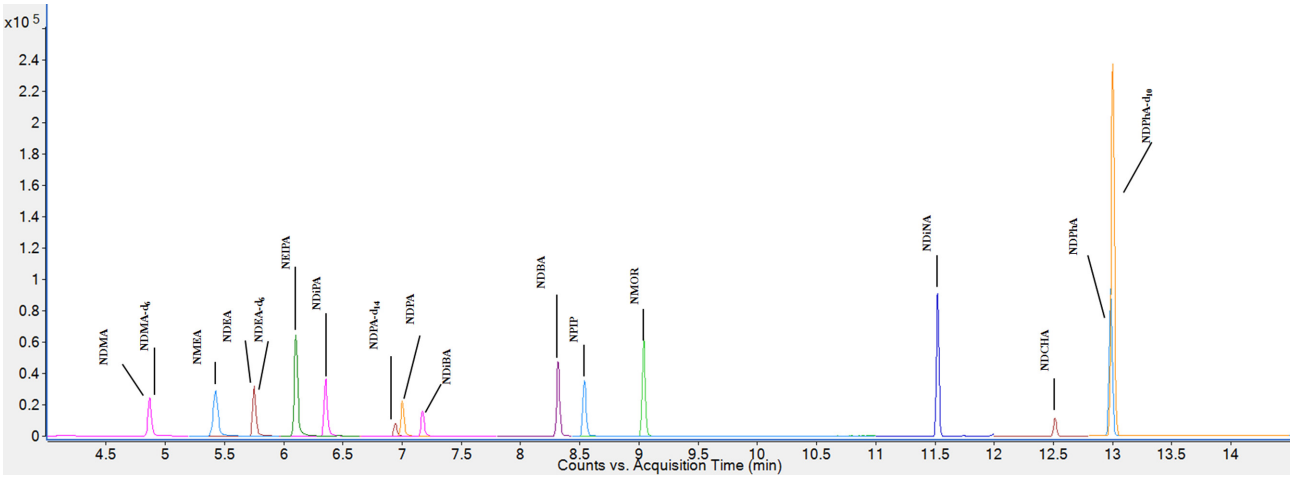


Figure 2. Total ion chromatogram of the 13 nitrosamines (25 ng/mL) and four ISs (20 ng/mL).

for NDCHA; hence, to avoid incorrect assignments, the 210 > 111 (*m/z*) qualifier ions were used instead, which helped to diminished interference from the matrix.

Method validation

Linearity and sensitivity

The calibration curves for the 13 nitrosamines were assessed in the 1-50 ng/mL concentration range, with the criterion of correlation coefficient (*r*) for each analyte set to 0.995 and above. The *r* values for all 13 nitrosamines exceeded 0.995 (data shown in Table S1 of supplemental data), revealing sufficient linearity in the concentration range and indicating that the ISs used are suitable for the quantification of the target analytes by applying the developed method. The LOD and LOQ for each nitrosamine in each sartan matrix, including the APIs and final products, were determined and the data are listed in Table 2. The lower limits were achieved for most analytes during qualification and quantification; however, the matrices significantly hindered quantification ions of analytes at low concentrations, which affected the determination of LOD and LOQ. This hindering effect is attributable to the components of the matrices of final products, such as the excipients, whereas few hindering effects were observed for the API matrices. Among all matrices, that of the losartan final product hindered most analytes, including NDMA, NMEA, NDPA, NDiBA, NMOR, and NDCHA. To diminish the hindering effects of the matrices on LOD determination, solid phase extraction (SPE) was applied to purify the samples. Several cartridges (Agilent Bond Elut C18, 50 mg, 40 µm, 3 mL; Oasis MCX Vac, 60 mg, 30 µm, 3 mL; Oasis HLB Vac, 60 mg, 30 µm, 3 mL) and elution conditions were examined; however, no remarkable improvement was observed owing to poor recoveries, which made improving the LODs of the analytes difficult.

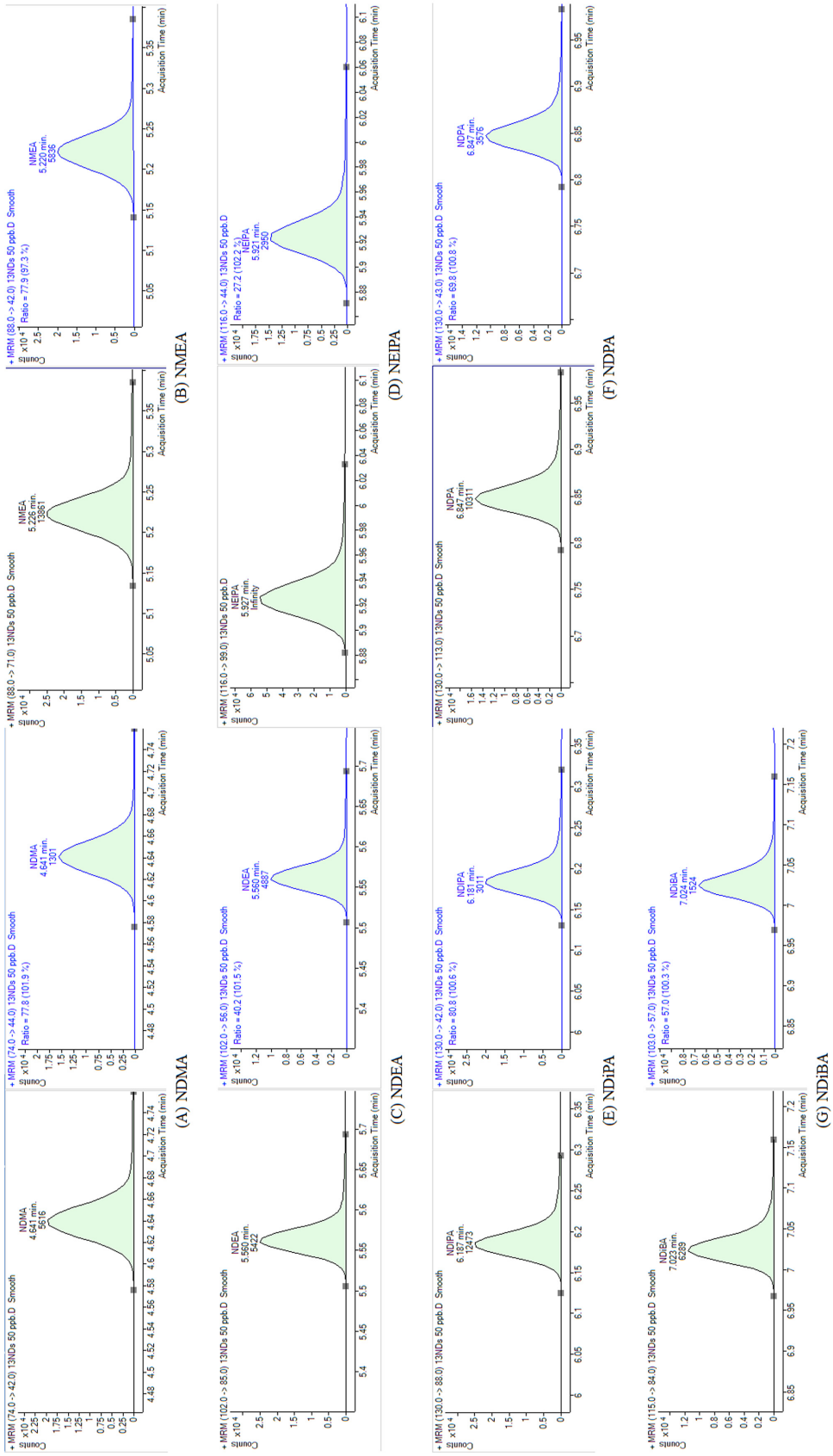
GC–MS and GC–MS/MS methods have been developed for determining nitrosamines in sartans. The U.S. FDA established a GC–MS/MS method for determining five nitrosamines for which LODs of 1–10 ng/g were observed for sartan APIs and 2–16 ng/g for sartan final products. Furthermore, LOQs were observed to range from 5 to 25 ng/g in sartan APIs and from 8 to 40 ng/g in sartan final products.[29] Health Canada announced a GC–MS/MS method for detecting NDMA and NDEA in sartan APIs, with LODs of 2 ng/g for both nitrosamines, and LOQs of 5.4 ng/g and 7.3 ng/g, respectively.[30] Compared to the methods reported in the literature, the GC–MS/MS method developed in this study is effective for a larger variety of analytes and displays sufficient sensitivity for the detection and determination of nitrosamines in sartans.

Accuracy and precision

The intra-day accuracies for the 13 analytes in the sartan APIs were determined to be 97.0-103.5% with precisions of 0.5-9.7%, whereas these values were 91.4-104.2% and 1.2-7.9% for the sartan final products, respectively. The 13 analytes in the sartan APIs exhibited inter-day accuracies of 97.8-104.8% with precisions of 1.5-12.2%, whereas the sartan final products exhibited values of 92.9-103.3% and 1.6-7.1%, respectively. Therefore, the accuracies and precisions of the 13 analytes in the sartan matrices, including the APIs and the final products, are compliant with the criteria set in "Accuracy and precision" section (all data were shown in Table S2 and S3 of supplemental data).

Application to authentic samples

The validated method was further applied to analyze the sartan samples collected from the pharmacies and pharmaceutical manufacturers. A total of 594 authentic samples from seven sartans were analyzed, the results of which are summarized in Table 3. Five nitrosamines,



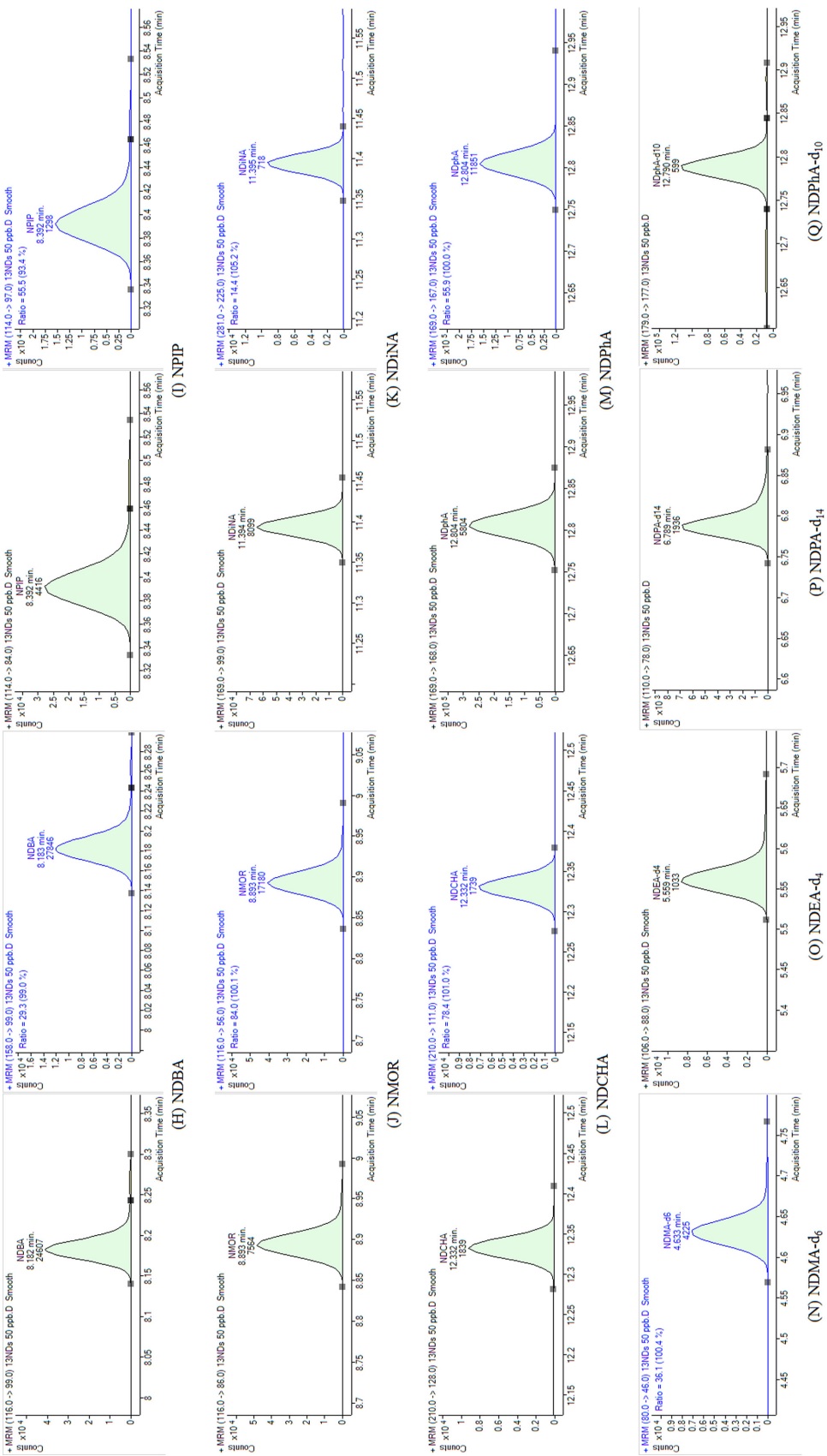


Figure 3. Chromatograms of transition ions for 13 nitrosamines (qualifier in left and quantifier in right) and four ISs (quantifier only) under MRM mode.

Table 2. LODs and LOQs for the 13 nitrosamines (APIs).

Analyte	Matrix									
	Candesartan cilexetil		Irbesartan		Losartan		Olmesartan medoxomil		Valsartan	
	LOD (μg/g)	LOQ (μg/g)	LOD (μg/g)	LOQ (μg/g)	LOD (μg/g)	LOQ (μg/g)	LOD (μg/g)	LOQ (μg/g)	LOD (μg/g)	LOQ (μg/g)
NDMA	0.025	0.05	0.025	0.05	0.025	0.05	0.25	0.25	0.025	0.05
NMEA	0.025	0.05	0.025	0.05	0.025	0.05	0.025	0.05	0.015	0.05
NDEA	0.025	0.05	0.025	0.05	0.025	0.05	0.015	0.05	0.025	0.05
NEIPA	0.025	0.10	0.025	0.10	0.015	0.10	0.015	0.10	0.025	0.15
NDiPA	0.015	0.05	0.015	0.05	0.015	0.05	0.025	0.05	0.015	0.05
NDPA	0.25	0.25	0.025	0.05	0.025	0.05	0.025	0.05	0.015	0.05
NDiBA	0.05	0.10	0.05	0.10	0.05	0.10	0.10	0.10	0.05	0.10
NDBA	0.015	0.05	0.015	0.05	0.015	0.05	0.015	0.05	0.025	0.05
NPIP	0.015	0.05	0.025	0.05	0.015	0.05	0.025	0.05	0.025	0.05
NMOR	0.025	0.05	0.025	0.05	0.015	0.05	0.025	0.05	0.025	0.05
NDiNA	0.025	0.05	0.025	0.05	0.025	0.05	0.025	0.05	0.025	0.05
NDCHA	0.025	0.05	0.025	0.05	0.025	0.05	0.025	0.05	0.025	0.05
NDPhA	0.015	0.05	0.015	0.05	0.015	0.05	0.05	0.05	0.015	0.05

Note: Five sartan APIs merchandised in Taiwan were tested.

Table 2. (Continued, final products)

Analyte	Matrix													
	Azilsartan medoxomil		Candesartan cilexetil		Irbesartan		Losartan		Olmesartan medoxomil		Telmisartan		Valsartan	
	LOD (μg/g)	LOQ (μg/g)	LOD (μg/g)	LOQ (μg/g)	LOD (μg/g)	LOQ (μg/g)	LOD (μg/g)	LOQ (μg/g)	LOD (μg/g)	LOQ (μg/g)	LOD (μg/g)	LOQ (μg/g)	LOD (μg/g)	LOQ (μg/g)
NDMA	0.30	0.30	0.025	0.05	0.05	0.05	0.25	0.25	0.25	0.25	0.10	0.15	0.025	0.05
NMEA	0.025	0.05	0.015	0.05	0.025	0.05	0.025	0.05	0.10	0.10	0.025	0.05	0.025	0.05
NDEA	0.05	0.05	0.025	0.05	0.025	0.05	0.025	0.05	0.015	0.05	0.025	0.05	0.025	0.05
NEIPA	0.05	0.10	0.05	0.10	0.025	0.10	0.05	0.10	0.05	0.15	0.05	0.10	0.05	0.10
NDiPA	0.025	0.05	0.015	0.05	0.025	0.05	0.025	0.05	0.025	0.05	0.05	0.05	0.025	0.05
NDPA	0.025	0.05	0.05	0.05	0.025	0.05	0.15	0.15	0.15	0.15	0.05	0.10	0.015	0.05
NDiBA	0.25	0.25	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.10	0.15	0.05	0.05
NDBA	0.025	0.05	0.015	0.05	0.015	0.05	0.015	0.05	0.015	0.05	0.025	0.05	0.025	0.05
NPIP	0.025	0.05	0.015	0.05	0.015	0.05	0.015	0.05	0.025	0.05	0.025	0.05	0.025	0.05
NMOR	0.025	0.05	0.05	0.05	0.015	0.05	0.05	0.05	0.025	0.05	0.05	0.05	0.025	0.05
NDiNA	0.015	0.05	0.015	0.05	0.015	0.05	0.015	0.05	0.025	0.05	0.05	0.10	0.025	0.05
NDCHA	0.025	0.05	0.025	0.05	0.025	0.05	0.25	0.25	0.25	0.25	0.025	0.15	0.05	0.05
NDPhA	0.015	0.05	0.025	0.05	0.015	0.05	0.015	0.05	0.015	0.05	0.025	0.05	0.025	0.05

including NDMA, NDEA, NDPhA, NMOR, and NDIP were detected at concentrations above their LODs in 68 positive samples of losartan, irbesartan, and valsartan. Among the samples, the valsartan products included 57 positive samples (duplicated samples excluded) with the highest nitrosamine contents (NDMA, 99,790 ng/g). In addition, these positive samples were found to contain multiple targets, with NDEA detected most frequently in these samples. On the basis of these results, we conclude that the developed method is a sensitive and effective technique for monitoring and quantifying multiple nitrosamines in sartans.

Table 3. Nitrosamines detected in authentic sartan samples.

Target	Item	Sartan		
		Valsartan (192 pcs)	Losartan (266 pcs)	Irbesartan (63 pcs)
NDMA	Positive samples (pcs)	54	0	0
	Detection rate (%)	28.1	-	-
	Content (μg/g)	0.06-99.79	ND	ND
NDEA	Positive samples (pcs)	11	4	5
	Detection rate (%)	5.7	1.5	7.9
	Content (μg/g)	0.11-8.84	0.07-0.20	0.10-0.14
NDPhA	Positive samples (pcs)	1	1	1
	Detection rate (%)	0.5	0.4	1.6
	Content (μg/g)	0.12	0.10	0.06
NMOR	Positive samples (pcs)	2	0	0
	Detection rate (%)	1.0	-	-
	Content (μg/g)	0.16	ND	ND
NPIP	Positive samples (pcs)	2	0	0
	Detection rate (%)	1.0	-	-
	Content (μg/g)	0.12	ND	ND

Conclusion

In this study, we successfully developed a GC–MS/MS method for monitoring and determining 13 nitrosamines in sartans. The method was validated and satisfactorily applied to analyze authentic samples. Therefore, the developed method can be used for quality-monitoring purposes during the manufacture of sartan pharmaceuticals.

Acknowledgments

This work was supported by the Food and Drug Administration, Ministry of Health and Welfare in Taiwan, R.O.C.

Supplementary Information

Supplementary Information is available at https://drive.google.com/file/d/1Q4BG0FwkaUrgXcqG3afYbOlYXqeIrqOM/view?usp=sharing.

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