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Research article

Determination of dimethylamine and nitrite in pharmaceuticals by ion chromatography to assess the likelihood of nitrosamine formation

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ABSTRACT

Since July 2018 several drugs have been recalled due to contamination with *N*-nitrosodimethylamine (NDMA), a probable human carcinogen. Dimethylamine (DMA) and nitrite are precursors in the formation of NDMA. In this study, ion chromatography (IC) methods were developed for the determination of these two precursors in drug substances and drug products. Two methods were developed to determine DMA in two drug products using a cation exchange separation coupled to suppressed conductivity detection. The limit of detection of DMA is < 1 μg/g of active pharmaceutical ingredient (API) for both methods. Nitrite was determined using an anion exchange separation coupled with UV absorbance detection. The limit of detection of nitrite was 0.918 μg/g API. The developed methods were successfully applied to DMA and nitrite determinations in five drug products including metformin, losartan, ranitidine, Nytol, and Benadyrl, and two drug substances (APIs), losartan potassium and metformin hydrochloride. Some samples contained nitrite and DMA at detectable levels. Dimethylamine and nitrite recovery from pharmaceutical samples ranged from 96.0-104 %. The developed methods should be useful for the rapid screening and quantification of nitrite and DMA in pharmaceuticals and in-process samples to assess the likelihood of NDMA formation. The methods for DMA should be applicable to other amines to assess the likelihood of the formation of other nitrosamines in pharmaceutical products.

1. Introduction

In July 2018, the U.S. Food and Drug Administration (FDA) issued a public health alert regarding the presence of *N*-nitrosodimethylamine (NDMA) in products containing valsartan [1]. Additional nitrosamine impurities were subsequently detected in other medicines that belong to the sartan family including *N*-nitrosodiethylamine (NDEA), *N*-nitrosodiisopropylamine (NDIPA), *N*-nitrosoethylisopropylamine (NEIPA), and *N*-nitroso-*N*-methyl-4-aminobutyric acid (NMBA). More recently, NDMA has been reported in ranitidine-, nizatidine-, and metformin-containing drug products [2, 3, 4]. *N*-nitrosodimethylamine is an *N*-nitrosamine, a type of compound that has the generic chemical structure $R_2N–N=O$, a deprotonated amine bonded to a nitroso group. It is a known environmental contaminant found in drinking water, and some foods such as bacon, cheese, and beer due to cooking or fermentation. A positive association between NDMA exposure and cancers was reported [5]. The United States Environmental Protection Agency has classified NDMA as a Group B2 probable human carcinogen [6]. In September 2020, the FDA announced industry guidance to control *N*-nitrosamine impurities in human drugs. The guidance describes conditions that may introduce nitrosamine impurities in pharmaceutical products [7]. The FDA, in collaboration with regulatory counterparts around the world, has set an acceptable daily intake limit for nitrosamines of 0.096 μg/day. The FDA recommends that drugs be recalled by the manufacturer if the drug contains a level of nitrosamine above the acceptable daily intake limit. Drug manufacturers are trying to find out how NDMA is present in such a wide range of medicines and trying to find out how to prevent this contamination. Possible sources include side reactions from drug syntheses, the breakdown of unstable drug compounds, contamination from the manufacturing process, and the conditions under which the compounds are stored and packaged. A recent proposed general information chapter from the United States Pharmacopeia (USP) describes the nitrosamines found in drug substances and drug products, how that they can be formed, and methods for their determination [8]. One possible route to NDMA impurity is the side reaction of one step in the compound's synthesis (Figure 1). In acidic conditions, DMA reacts with nitrites to produce nitrosamines [9]. Dimethylamine is used in the synthesis of many drug substances such as metformin hydrochloride. The nitrosylation of DMA to generate NDMA was used as a model reaction that could rise during API processing.

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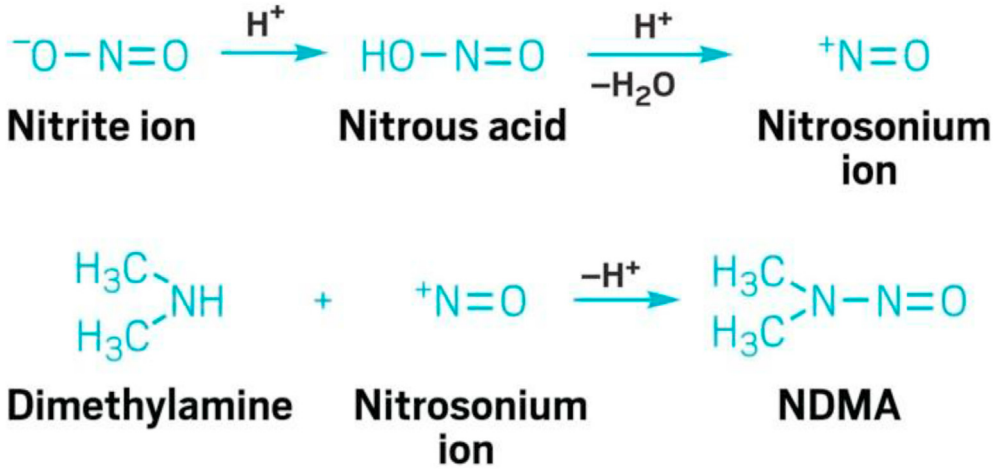

Figure 1. Mechanism for the formation of NDMA from nitrite and dimethylamine.

Simulations based on the published kinetics of secondary amine nitrosylation have shown that higher nitrite levels may result in significant levels of *N*-nitrosamines at low pH or elevated temperature [10]. Therefore, limiting the two precursor compounds in drug substances or products can prevent the potential formation of NDMA and other nitrosamines. In order to devise processes to reduce or eliminate nitrosamine formation, sensitive methods for the determination of DMA, and other amines that are nitrosamine precursors, and nitrite in pharmaceutical products are essential.

Dimethylamine in drug products can be determined by HPLC with fluorescence detection [11]. The method requires a lengthy derivatization process in order to achieve the highest yield. A headspace gas chromatography (GC) method for DMA determination does not require derivatization [12]. However, the GC method requires sample preparation to convert the salt form of the amine to the free base. The method is time-consuming and has a relatively high limit of detection (0.93 mg/L). While there are wet chemical methods for determining nitrite, ion chromatography (IC) is the typical method for nitrite determination, especially when good sensitivity is required.

Ion chromatography is a well-accepted technique for the determination of ions in aqueous solution. For most pharmaceutical samples it requires little or no sample preparation or analyte derivatization. Ion chromatography uses an ion-exchange separation followed typically by conductivity, electrochemical, UV absorption, or mass spectrometry detection. Ion chromatography-based procedures are included in several USP monographs and IC has been applied to all aspects of the manufacturing of pharmaceutical products, including the determination of active pharmaceutical ingredients, counter ions, and ionic drug degradation products and ionic process-related impurities [13].

Recently, IC was used to determine amines that can be nitrosamine precursors in drinking water [14]. In this study, two IC methods were developed to determine DMA in pharmaceutical products. The DMA methods were based on a cation exchange separation coupled with suppressed conductivity detection with the choice of cation-exchange column determined by the pharmaceutical product. We developed another IC method for nitrite. This method was based on an anion exchange separation coupled with UV absorbance detection at 210 nm. The three methods were validated with respect to calibration, detection limit, accuracy, and precision. These methods were successfully applied to seven pharmaceutical samples including metformin, losartan potassium, and ranitidine.

2. Experimental

2.1. Chemicals

Dimethylamine hydrochloride, 99%, was used for preparing DMA stock standard. Sodium nitrite, >99%, was used for preparing nitrite stock standard. Losartan potassium and metformin hydrochloride were used for preparing drug substance samples. All these chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Table 1. MS conditions.

Single quadruple MS conditions					
Ionization interface	Electrospray Ionization (ESI), positive mode				
Sheathe gas pressure	40 psi				
Aux gas pressure	4 psi				
Sweep gas pressure	0.2 psi				
Source voltage	3000 V				
Vaporizer temp.	250 °C				
Ion transfer tube temp.	250 °C				
Chrom. Filter peak width	Off				
Advance Scan mode					
Scan name	Mass list	Scan Time (s)	SIM width (amu)	Ion Polarity	Source CID voltage (V)
Dimethylamine	46	0.5	0.5	Positive	10
Ethylamine	46	0.5	0.5	Positive	10

2.2. Instrumentation

A Dionex ICS-6000 Reagent-free HPIC system composed of a gradient pump module, eluent generator, and conductivity detector was used for all determinations. (Thermo Scientific, Sunnyvale, CA, USA). For nitrite analysis, a diode array detector (Thermo Scientific) was connected in series after the conductivity detector. The system was controlled, and data collected and processed, with Chromeleon 7.2.9 chromatography workstation software.

2.3. Chromatographic conditions

Two methods were developed for DMA analysis. Dimethylamine Method 1: The IC separation used a Dionex IonPac CS16 column (3 × 250 mm) with its guard column (3 × 50 mm) maintained at 20 °C. The eluent was 25 mM methanesulfonic acid (MSA) at 0.5 mL/min for 30 min. Dimethylamine Method 2: The IC separation used a Dionex IonPac CS19 column (2 × 250 mm) with its guard column (2 × 50 mm) maintained at 10 °C. The eluent flow rate was 0.25 mL/min with 3 mM MSA from 0-12 min, followed by a step change to 40 mM MSA from 12-16 min, kept at 40 mM from 16-21 min, and then back to 3 mM from 21-30 min. The injection volume for both methods was 25 μL. For both DMA methods, the MSA eluent was generated automatically using an electrolytic eluent generator equipped with an EGC 500 MSA eluent generation cartridge. Eluent suppression was achieved with a Dionex CDRS 600 (2 mm) electrolytic suppressor operating in the recycle mode. For DMA confirmation by IC-MS, the IC system was coupled to a Thermo Scientific ISQ EC single-quadrupole mass spectrometer equipped with a HESI II probe. Eluent suppression was achieved with a Dionex cation CDRS electrolytic suppressor (2 mm) operating in the external water mode. External water was delivered with the second pump of the ICS-6000 system. Table 1 lists the mass spectrometry conditions.

For nitrite analysis, the IC separation used a Dionex IonPac AS19-4μm column (2 × 250 mm) with its guard column (2 × 50 mm) maintained at 30 °C. The eluent flow rate was 0.25 mL/min with an eluent of 20 mM KOH from 0 to 8 min, followed by a step change to 60 mM KOH from 8-10 min, kept at 60 mM from 10-15 min, and back to 20 mM from 15-30 min. The injection volume was 25 μL. The KOH eluent was generated automatically using an electrolytic eluent generator equipped with an EGC 500 KOH eluent generation cartridge. Eluent suppression was achieved with a Dionex anion ADRS electrolytic suppressor (2 mm) in the recycle mode. The diode array detector followed the suppressor and was set at 210 nm. All columns, suppressors, and eluent generation cartridges were from Thermo Scientific.

2.4. Preparation of standard solutions

To prepare the 1 mg/mL DMA stock solution, 180.9 mg of dimethylamine hydrochloride was dissolved in 100 mL of deionized (DI) water. To prepare the 1 mg/mL nitrite stock solution, 150 mg of sodium nitrite were dissolved in 100 mL of DI water. The standards were prepared in polypropylene bottles and stored at 4 °C. A series of calibration standard solutions were prepared by diluting the stock solution with DI water.

2.5. Preparation of pharmaceutical samples

Pharmaceutical samples used in this study are listed in Table 2. Prepare 1 mg/mL drug substance solutions (Samples 1 and 2) by dissolving 50 mg in 50 mL of DI water. Prepare drug products by dissolving the whole pill into 50 mL (Samples 5 and 7) or 10 mL (Samples 3, 4, and 6) of DI water. This yields a 2.5–10 mg/mL solution based on the API weight. Sonicate in an ultrasonic bath until dissolved and centrifuge the sample extract at 8000 x g for 15 min. Dilute the sample solution to 1 mg/mL with DI water. Filter through a Nalgene 0.45 μm PES syringe membrane filter (Thermo Scientific) prior to IC analysis.

3. Results and discussion

3.1. Ion chromatography method development

Cation exchange chromatography with suppressed conductivity detection (cation IC) is a well-established method to determine μg/L to mg/L concentrations of common cations and many amines. Dimethylamine is a cationic impurity in some pharmaceuticals, and it has been determined in a drug product by cation IC [15]. Of the common inorganic cations, it is potassium that typically elutes close to DMA. Potassium is the counter ion of losartan potassium and is expected to be at a high concentration relative to DMA in losartan samples. Therefore, the method development for DMA in losartan potassium will be more challenging than drug substances and drug products with other counter ions or without a counterion (i.e. the acid form). In order to separate a low amount of DMA from a high amount of potassium we need to select a high capacity cation exchange column. The IonPac CS16 is such a column. Its high capacity allows the separation of short chain amines from common inorganic cations in many sample types. We used the Virtual Column feature of the Chromeleon chromatography workstation software to find conditions where DMA elutes before potassium. This also showed that the resolution for the pair improves at lower eluent concentration and lower column temperature. We chose an eluent concentration of 25 mM MSA and column temperature of 20 °C to achieve a resolution >3 between DMA and potassium in losartan potassium samples, and to keep the run time within 30 min. The developed CS16 column method was successfully applied to other drug products such as Rantidine and Benadyrl. However, when this method was applied to the Metformin drug product, a large peak appeared in the next injection. We believe the large peak is the metformin that was not eluted from the CS16 column during the separation time. We found that this peak was not eluted within 30 min when the eluent concentration was increased to the 100 mM MSA, the maximum concentration the eluent generator can produce. Metformin is a polyamine that has strong interaction with most cation exchange columns. The IonPac CS19 is a column that specifically design for the fast separation of inorganic cations, small polar amines (including alkanolamines and methylamines), and moderately

Table 2. Pharmaceutical samples.

#	Drug Product Name	API	Type	API/pill (mg)	Source	Indication
1	NA	Losartan potassium	Substance	NA	Sigma	NA
2	NA	Metformin hydrochloride	Substance	NA	Sigma	NA
3	Nytol Quickcap	Diphenhydramine HCl	Product	25	OTC	Sleep aid
4	Benadyrl	Diphenhydramine HCl	Product	25	OTC	Allergy
5	Metformin	Metformin hydrochloride	Product	500	Rx	Diabetes
6	Losartan	Losartan potassium	Product	50	Rx	High blood pressure
7	Rantidine	Ranitidine hydrochloride	Product	300	Rx	Diabetes

hydrophobic and polyvalent amines (including biogenic amines and alkyl diamines). Therefore, the CS19 column was chosen for the method development for determining DMA in metformin drug products. Chromeleon Virtual Column shows that DMA and potassium coelute at a column temperature of 30 °C at any eluent concentration. Column temperature needs to be lower or higher than 30 °C in order to achieve separation of this pair. Potassium elutes later than DMA when the column temperature is lower than 30 °C, and elutes earlier than DMA when the column temperature is higher than 30 °C. High potassium was not expected in metformin drug products. Therefore, designing a separation where potassium elutes after DMA was not critical. A lower column temperature is usually not preferred because the total system pressure will be higher and therefore limit the opportunity to use a higher flow rate and decrease analysis time. However, the manufacturer recommends that the column temperature not exceed 30 °C when using the CS19 column as this will reduce its lifetime. Therefore, in this study, we used a column temperature to 10 °C to improve the resolution between DMA and potassium. The resolution of DMA and potassium in metformin samples is > 2.0 at 10 °C. The CS19 method is a 30 min gradient method that separates common cations and DMA at a low eluent concentration of 3 mM MSA that is gradually increased to 40 mM to elute the metformin. Figure 2 shows a separation of DMA and common cations within 30 min using either a Dionex IonPac CS16 (Top) or CS 19 column (Bottom). As this figure shows, DMA is well resolved from other common inorganic cations such as sodium, potassium, and magnesium that can be found in pharmaceuticals.

Anion exchange chromatography with suppressed conductivity detection is a well-established method to determine common anions including nitrite. The main challenge for determining nitrite in hydrochloride drug products is to obtain adequate separation of nitrite from the large of amount of chloride. This can make the quantitative determination of a low concentration of nitrite difficult. Therefore, in this study, UV absorbance detection was used to determine nitrite with good selectivity in pharmaceuticals samples as chloride is not detected. The Dionex IonPac AS19-4μm hydroxide-selective anion-exchange column is a high capacity and high-resolution column, which are critical factors for the determination of nitrite at the low μg/L concentrations in samples containing high concentrations of common anions such as chloride, nitrate, and sulfate. Figure 3 shows a separation of nitrite and other six common anions within 30 min using this column. The top chromatogram displays the suppressed conductivity detection. The bottom chromatogram displays the UV profile of the three analytes that have UV absorbance at 210 nm. As Figure 3 shows, nitrite was resolved from other common inorganic anions. A delay time of 0.25 min is applied to the UV profile to match the CD profile. The delay time is the time required for the analyte to travel from one detector to another when they are in series. Here, the analyte goes through CD cell before going into the absorbance detector.

3.2. Calibration

To cover a wide DMA concentration range in tested samples, the calibration of DMA conductivity response to concentration was investigated in the concentration range of 5–250 μg/L for the CS16 method, and 5–500 μg/L for the CS19 method. Each calibration reference solution was measured in triplicate. The data were best modeled with a quadratic function. The coefficients of determination (r^2) were 0.9999 and 0.9997 respectively for the CS16 and CS19 methods. The linearity of nitrite UV absorbance response to concentration was investigated in the concentration range of 5–500 μg/L. The r^2 was 0.9999.

3.3. Limit of detection (LOD)

The determination of LOD was based on the signal-to-noise (S/N) ratio. Determination of the S/N ratio is performed by comparing measured signal from a standard with a low concentration of analyte with those of blank samples and establishing the minimum concentration at which the analyte can be reliably detected. A S/N = 3 is used for estimating LOD and a S/N = 10 is used for estimating the quantification limit (LOQ) [16]. In this study, the baseline noise was first determined by measuring the peak-to-peak noise in a representative 1-min segment of the baseline where no peaks elute, but close to the peak of interest. The signal was determined from the average height of three injections of standard (1 μg/L). The calculated LOD of DMA was 0.960 and 0.718 μg/L using the CS16 and CS19 columns, respectively. The LOD of DMA is about 1000 times lower than headspace gas chromatography method (930 μg/L) [17]. The reported LOD of DMA is 5.4 μg/L by HPLC with diode array detection after derivatization with halonitrobenzenes, and 0.75 μg/L by hydrophilic interaction chromatography coupled with mass spectrometry detection (HILIC-MS) [11, 18]. The LOD of DMA using our method is close to HILIC-MS method without the need of a high-cost mass spectrometer.

Pharmaceutical samples were prepared at 1 mg/mL. Therefore, the LOD in a pharmaceutical sample translates to 0.960 μg/g API and 0.718

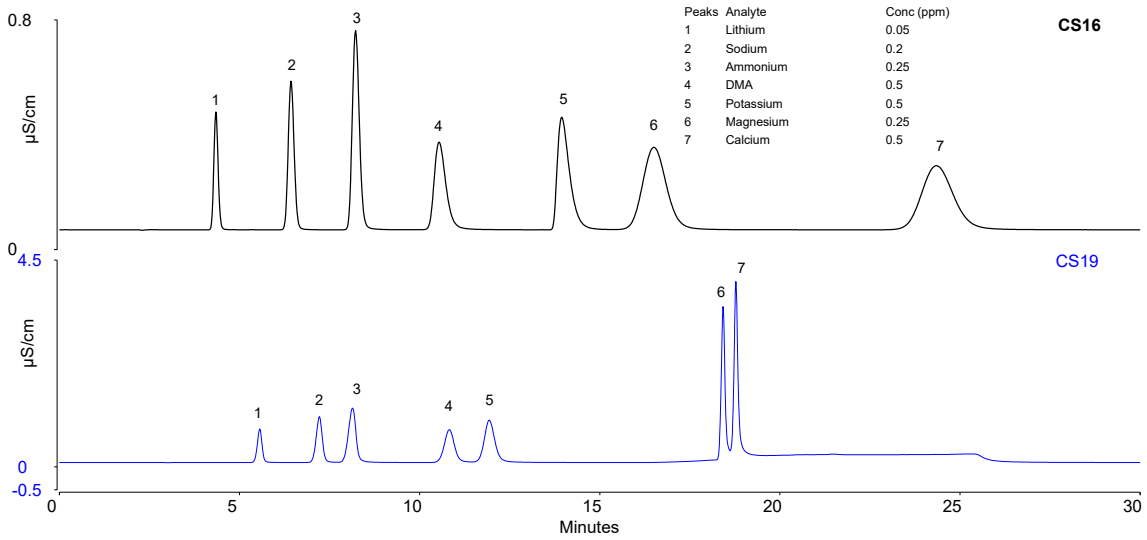

Figure 2. Separation of seven common anions using either a IonPac CS19 or IonPac CS16 column.

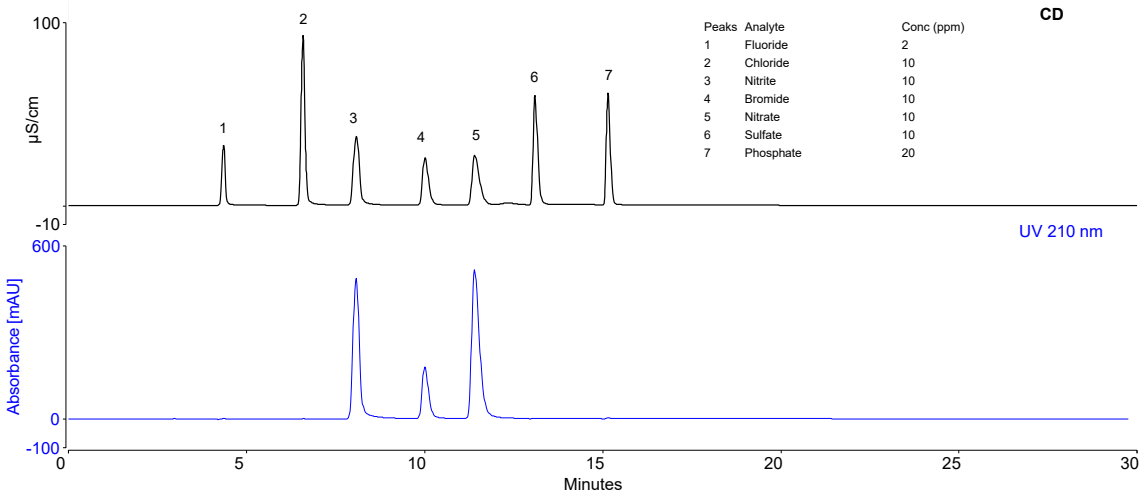

Figure 3. Separation of seven common anions using a Dionex IonPac AS19-4µm column.

µg/g API using the CS16 and CS19 columns, respectively. The calculated LOD of nitrite was 0.918 µg/L, which is about 1000 times lower than spectrophotometry method (930 µg/L) [19]. The LOD of nitrite in a pharmaceutical corresponds to 0.918 µg/g API.

3.4. Sample analysis

Losartan, metformin, and ranitidine are the three drug products that were recalled due to the detection of NDMA in finished products. The amount of DMA and nitrite in products can provide some information to assess the likelihood of nitrosamine formation. Method development for determining DMA and nitrite in pharmaceuticals was initially based on these three drug products. Two of the drug substances (losartan potassium, metformin hydrochloride) were purchased from Sigma-Aldrich and included in the sample list. Two over-the-counter (OTC) drug products (Benadyrl and Nytol) were purchased from a local pharmacy to test whether the developed methods can be applied to general amine-containing drug products. Table 2 lists the information for these seven pharmaceutical samples.

Samples were prepared at 1 mg/mL based on the API weight. Dimethylamine in metformin drug substance (S1) and formulated product (S5) was determined using the CS19 column method and in other samples using the CS16 column method. Nitrite in all samples was determined using the AS19 column method.

The amounts of DMA and nitrite in the seven pharmaceuticals are summarized in Table 3. The highest amount of DMA is detected in sample 2 (metformin hydrochloride drug substance) at 363 ppm (µg/g). Dimethylamine is detected in samples 2–5 in a range from 18.3-48.7 ppm. Dimethylamine is not detected in losartan potassium drug substance (S1) and formulated product (S6). The DMA peak in the detected samples was confirmed by coupling IC with single quadrupole mass spectrometry. DMA and ethylamine have the same ion mass at 46 amu. However, they elute at different retention times on both the CS16 and CS19 columns. Using the conditions reported here, DMA has a retention time of 10.67 min and ethylamine 6.54 min on the CS16 column (11.0 and 9.97 min on the CS19 column). The DMA peak in samples was confirmed by matching both retention time and ion mass. Figure 4 shows an overlay chromatogram of the CD profile (top) and the MS profile (bottom) of Rantidine drug product (S7) demonstrating the detection and confirmation of DMA.

Nitrite was detected in all samples except sample 1 (losartan potassium drug substance). The highest nitrite amount, 95.8 ppm (µg/g), was detected in sample 7 (ranitidine). Nitrite is detected in samples #2- #6 in a range from 4.47-27.4 ppm.

The determination of DMA in losartan potassium is very challenging because potassium is the counter ion of losartan and present at a high concentration relative to DMA. Given this challenge and that we did not detect DMA in either the drug product or drug substance we wanted to confirm the we were not overloading the column, which would cause DMA to have poor or no recovery. Figure 5 shows an overlay of a chromatogram of a losartan drug product sample and that sample spiked with 10 µg/L of DMA. Potassium elutes as a large peak after DMA and therefore it does not interfere with DMA quantification. Dimethylamine is fully recovered, and the size of the peak suggests that the LOD estimated with standards is applicable to samples. The CS16 method can be applied to other drug products in the sample list except metformin. Metformin is a small, hydrophilic, biogenic amine, which has a strong interaction with the CS16 stationary phase. As a result, it cannot be quickly eluted from the CS16 column using the method conditions. The CS19 is a column that is specially designed for this type of amine. Figure 6 shows the determination of DMA in metformin drug product using the CS19 column. Metformin elutes as a large peak at 20–25 min and the analysis can be completed within 30 min. Dimethylamine is well separated from other common cations in the samples.

Table 3. Amount of DMA and nitrite in pharmaceutical samples, ppm (µg/g API).

Sample	DMA	RSD (%) (n = 6)	Nitrite	RSD (%) (n = 6)
1	<LOD	NA	<LOD	NA
2	371	1.8	27.0	2.3
3	27.3	0.6	17.6	2.0
4	48.7	1.1	16.2	2.3
5	42.6	1.8	6.86	2.8
6	<LOD	NA	4.45	2.9
7	18.3	2.4	95.5	1.4

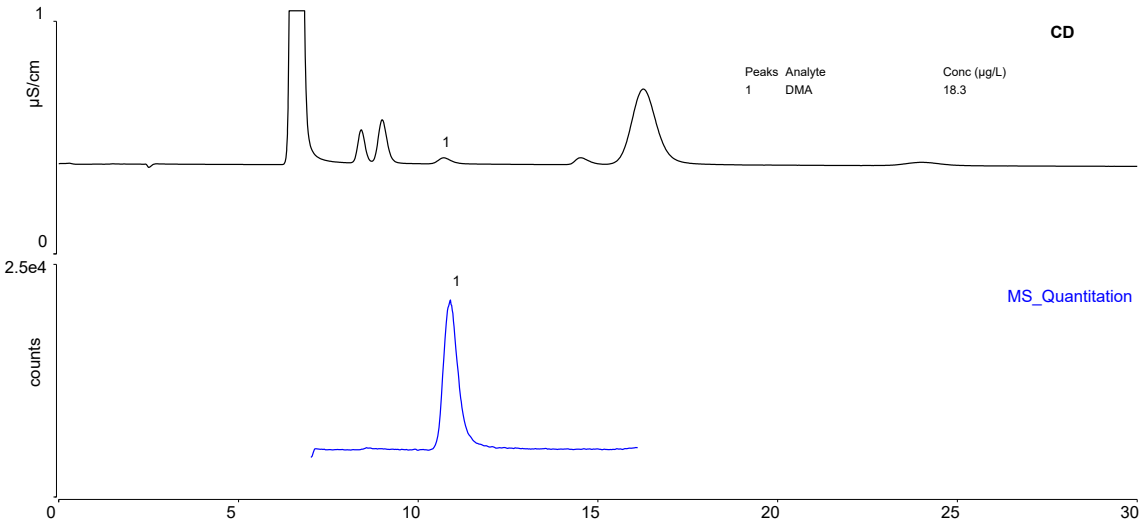

Figure 4. Conductivity profile(top) and MS profile (bottom) of Rantidine drug product (S7).

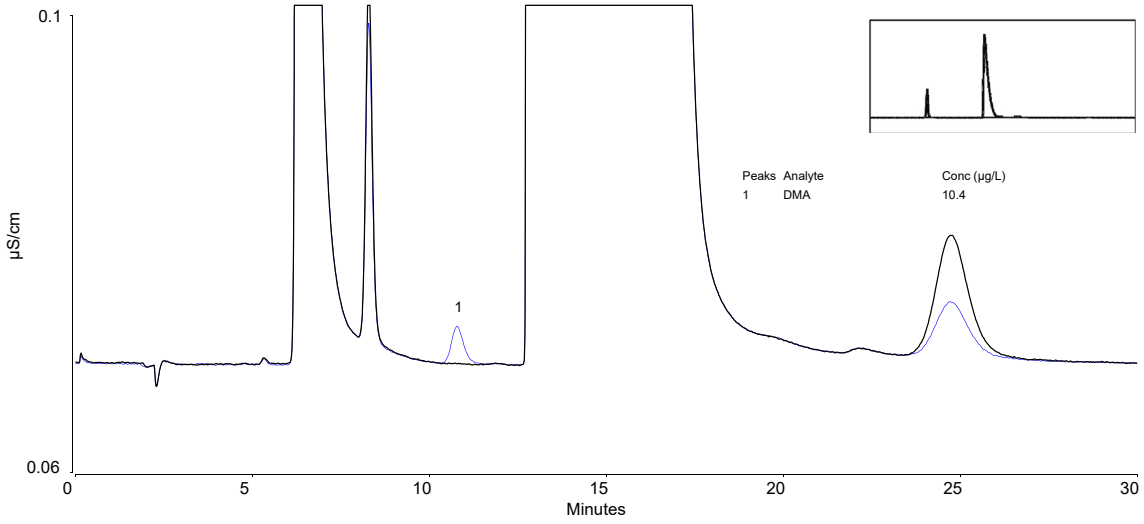

Figure 5. DMA in Losartan drug product (S6) and S6 spike 10 ppb using a Dionex IonPac CS16 column.

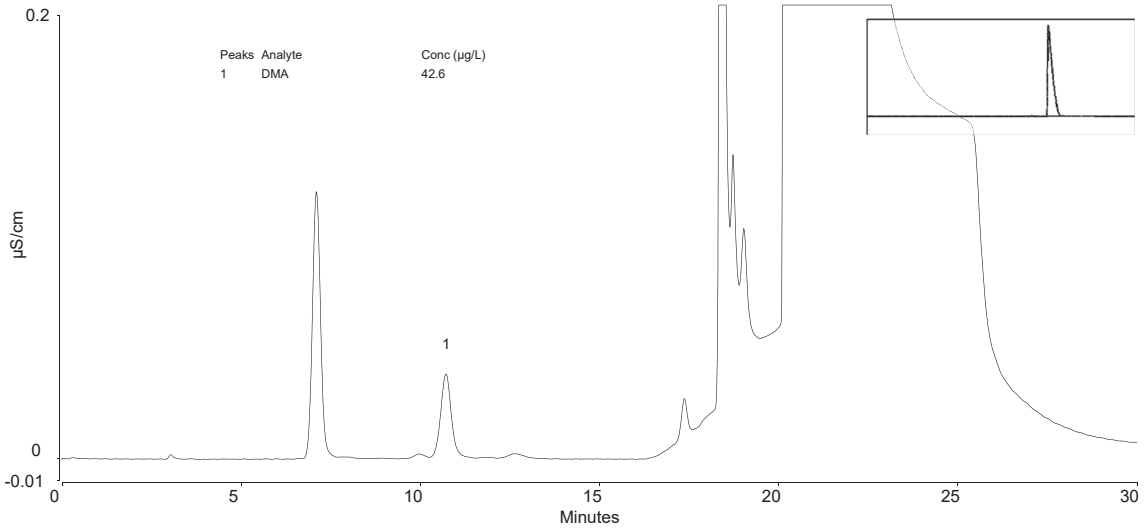

Figure 6. DMA in Metformin drug product (S5) using a Dionex IonPac CS19 column.

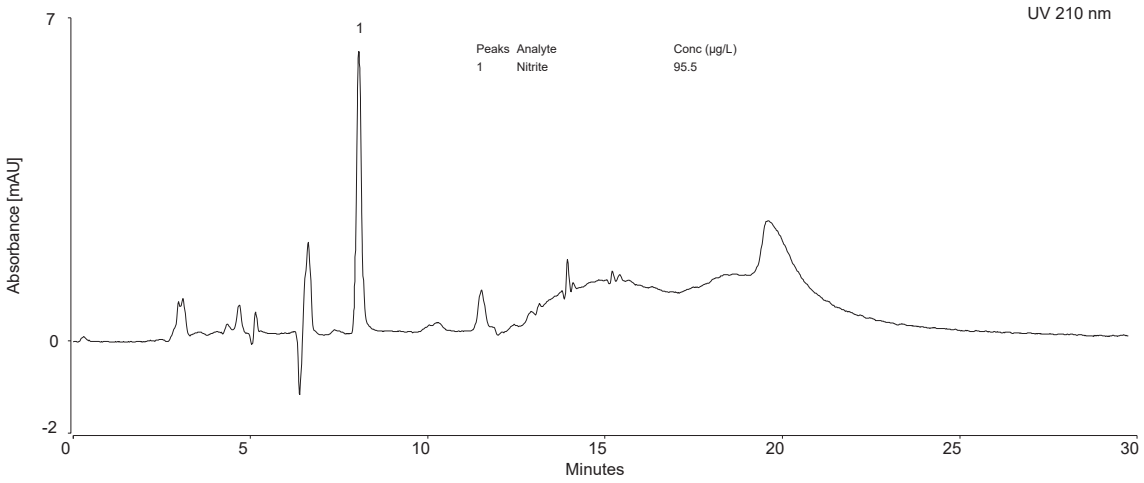

Figure 7. Nitrite in Ranitidine drug product (S7) using a Dionex IonPac AS19 4µm column.

Table 4. Spike recovery of DMA and nitrite in pharmaceutical samples.

Sample	DMA Recovery (%)	RSD (%) (n = 6)	Nitrite Recovery (%)	RSD (%) (n = 6)
1	104	2.6	96.6	1.2
2	96.0	2.3	96.9	2.1
3	100	1.8	101	1.1
4	101	1.7	100	2.7
5	104	1.4	100	2.6
6	104	2.6	98.1	2.6
7	96.3	2.7	100	2.1

Figure 7 shows the determination of nitrite in ranitidine hydrochloride drug product using an IonPac AS19 column. As the figure shows, chloride in ranitidine hydrochloride does not interfere with nitrite quantification. We found this method was applicable to the other six pharmaceutical samples and believe it should be applicable to other pharmaceutical samples.

Using one of the two methods for DMA and the method for nitrite on a given sample can show the possibility of NDMA formation. This does not suggest the sample has NDMA or will develop NDMA, but does suggest a potential for NDMA formation. For example, the 500 mg metformin tablet contains 42.6 µg/g DMA and 6.86 µg/g nitrite. If a product had either DMA or nitrite at the measured LOD and it was converted 100% to NDMA, for most dosages it would exceed the FDA daily limit. Therefore, in our opinion these methods are best used for developing processes that limit the amount of DMA or other amine and nitrite during the synthesis of the API and formulation of the product.

3.5. Method accuracy and precision

Method accuracy was evaluated through recovery studies using spiked pharmaceutical samples. Dimethylamine is spiked into sample at 10 µg/L except sample #2, which was spiked at 100 µg/L. Nitrite was spiked into each sample at 10 µg/L. Table 4 shows recovery of DMA and nitrite spiked into the pharmaceutical samples. The recovery for DMA and nitrite in all the seven samples are in the range of 95.2–104 %. The precision of the DMA method was determined by three injections of the 50 µg/L calibration standard on three separate days. The peak area precision is 1.53 % with retention time precision 0.67 % for DMA using the CS16 column. The peak area precision is 0.65 % with retention time precision 0.07 % for DMA using the CS19 column. The precision of the nitrite method was determined by injections of the 50 µg/L nitrite calibration standard on three separate days. The peak area precision is 0.56 % with retention time precision 0.10 % for nitrite.

4. Conclusions

This study demonstrated that DMA and nitrite, two precursors of NDMA formation, can be determined in pharmaceuticals by IC. Dimethylamine was determined by a cation exchange separation with suppressed conductivity detection using one of two methods, depending on the chemical nature of the drug substance. Nitrite was determined by coupling an anion exchange separation with UV absorbance detection. The limits of detection of DMA and nitrite in pharmaceutical samples are less than 1 ppm (µg/g). Spike recovery experiments showed that these methods are accurate. These methods can be used to measure these NDMA precursors at different stages of the product development and production in order to reduce the potential for NDAM formation. Ion chromatography should be also useful in determining other amines that can be precursors to nitrosamine formation using either one of the two methods described for DMA, or modifications of those methods.

Declarations

Author contribution statement

Jingli Hu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Terri Christison: Performed the experiments.

Jeffrey Rohrer: Conceived and designed the experiments; Wrote the paper.

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Data availability statement

No data was used for the research described in the article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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