APPLICATION NOTE 65911

Determination of six nitrosamine impurities in angiotensin II receptor blocker drugs by LC-MS/MS

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Goal

This method is to quantitate the following six nitrosamine impurities in Valsartan drug substance and drug product: N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosoethylisopropylamine (NEIPA), N-nitrosodiisopropylamine (NDIPA), N-nitrosodibutylamine (NDBA) and N-nitroso-N-methyl-4-aminobutyric acid (NMBA).

Introduction

Angiotensin II receptor blocker (ARB) drug products are commonly used to treat high blood pressure and heart failure. In July 2018, it was found that some ARB drug products contained carcinogenic nitrosamine impurities[1]. As this incident continues to evolve, it has resulted in numerous recalls and ARB drug shortages in the U.S. The United States Food and Drug Administration USFDA has successfully developed and implemented GC/MS methods to quantitate N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) at trace levels. However, these GC/MS methods cannot yet directly detect N-nitroso-N-methyl-4-aminobutyric acid (NMBA), another nitrosamine impurity that was found in certain ARB drug products by some firms. Additionally, it is speculated that three other nitrosamine impurities may also be present in ARB drugs from reviews of manufacturing processes and published literature sources; namely N-nitrosoethylisopropylamine (NEIPA), N-nitrosodiisopropylamine (NDIPA) and N-nitrosodibutylamine (NDBA). Thus, a single method was developed capable of detecting and quantifying all of the six aforementioned impurities simultaneously. Herein, we report an LC-MS/MS method validated for the simultaneous determination of the six nitrosamine impurities in losartan drug substance and drug product, at sub-ppm levels. The method may also be capable of testing for these six impurities in other ARB drug substances and drug products pending verification and/or validation.

Experimental

The six nitrosamine impurities (NDMA, NDEA, NEIPA, NDIPA, NDBA, and NMBA) are separated from each other, Valsartan drug and drug substance by reverse-phase liquid chromatography. They are then detected by triple stage quadrupole mass spectrometer. High selectivity and sensitivity of detection are achieved by monitoring SRM (selected reaction monitoring) of protonated impurity ions. Quantitation is performed by comparing the peak area of an impurity in extracted ion chromatograms of samples to its standard containing reference standards of all six impurities. All reference standards were purchased from Clearsynith, India.

Table 1. Recommended consumables and reagents.

Recommended consumables and reagents	Part number
Thermo Scientific™ Chromacol™ GOLD-grade Inert 2 mL HPLC vial	2-SVG
Thermo Scientific™ Titan3™ PVDF 0.2 µm syringe filters	42213-PV
HPLC column: Solid core C18 2.6 µm F5 100 Å, 100 x 4.6 mm	
Fisher Scientific™ Fisherbrand™ Borosilicate Glass Test Tubes	11812373
Fisher Scientific™ Water, Optima™ LCMS grade	W6-212
Fisher Scientific™ Formic acid, Optima™ LCMS grade	A117-50
Fisher Scientific™ Methanol, Optima™ LCMS grade	A456-4

Table 2. Instrumentation.

Instrumentation	Part number
Thermo Scientific™ Vanquish™ Flex system consisting of:	
Vanquish System Base	VH-S01-A
Vanquish Binary Pump F	VF-P10-A-01
Sampler FT	VF-A10-A-02
Vanquish Column Compartment	VH-C10-A-02
Active Pre-heater	6732.0110
Thermo Scientific™ TSQ Quantis™ Triple Quadrupole Mass Spectrometer	TSQ02-10001

Mobile phase preparation:

Mobile phase A (0.1% formic acid in water): mix formic acid and water at a volume ratio of 1:1000

Mobile phase B (0.1% formic acid in methanol): mix formic acid and methanol at a volume ratio of 1:1000

Diluent and blank: Methanol

Mixed stock standard preparation:

Prepare a mixed stock standard solution in methanol with the following concentrations.

Table 3. Mixed stock preparation.

Nitrosamine	Conc. (ng/ml)
NDMA	100
NDEA	100
NEIPA	100
NDIPA	100
NDBA	100
NMBA	100

Standard preparation (3.0 ng/mL):

Transfer a 1.5 mL aliquot volume of the mixed stock standard into a 50 mL volumetric flask and dilute to volume with methanol.

Drug substance sample preparation:

Accurately weigh 500 mg of drug substance into a 15 mL glass centrifuge tube. Add 5.0 mL of methanol and mix the solution using a vortex mixer until dissolved.

Drug product sample preparation:

Crush the appropriate number of tablet(s) to obtain a target concentration of 100 mg/mL of API in 5.0 mL of methanol, and transfer into a 15 mL glass centrifuge tube. Add 5.0 mL of methanol and mix for about a minute using a vortex mixer. Shake the sample for 40 minutes using a mechanical wrist action shaker.

After extraction, centrifuge the sample for 15 minutes at 4500 rpm. Filter the supernate using a 0.22 µm PVDF syringe filter, discard the first 1 mL and transfer the filtered sample into an hplc vial for LC/MS analysis.

Injection order:

- Two replicates of Blank at the beginning of a sequence
- Standard solution for six consecutive times before the injection of the first sample
- Standard solution spiked in valsartan sample at LOQ level for recovery calculation at the end of a sequence

Table 4. Chromatographic conditions.

Column temp.	40 °C		
Flow rate	0.6 mL/min		
Mobile phase A	0.1% formic acid in water		
Mobile phase B	0.1% formic acid in methanol		
Gradient	Time (min)	A%	B%
	0.0	90	10
	1.5	90	10
	7.0	45	55
	17.0	45	55
	17.1	10	90
	21.0	10	90
	21.1	90	10
	25.0	90	10
Injection volume	10 µL		
Autosampler temp.	8°C		
Needle wash	80:20, methanol: water with 0.1% formic acid		

Table 5. APCI source conditions.

Ionization	APCI
Sheath gas flow rate	55 arbitrary units
Aux gas flow rate	15 arbitrary units
Sweep gas flow rate	0 units
Corona discharge voltage	2 µA
Capillary temp.	450 °C
Aux gas heater temp.	200 °C

Table 6. MS settings.

S. No.	Compound	Start Time (min)	End time (min)	Precursor (*m/z*)	Product (*m/z*)	Collision energy (V)	RF lens (V)
1	NDMA	0	25	75.01	42.97	16.37	53
2	NDEA	0	25	103.09	75.04	11.19	72
3	NEIPA	0	25	117.10	75.04	9.84	61
4	NDIPA	0	25	131.08	89.13	8.75	62
5	NMBA	0	25	147.03	117.07	5.25	38
6	NDBA	0	25	159.10	103.13	10.94	39

System suitability:

The area of an interference peak for nitrosamine impurities in the blank injection, if present, should be not more than 5% of the peak area in the standard solution.

The %RSD of the peak area for each nitrosamine impurity for the first six injections of standard solution should be not more than 10%.

Observation shared by USFDA method:

- NMBA and NEIPA exist as syn and anti conformers due to the restricted rotation of N-N bond (reference 1, 2), and these conformers can be partially separated by the method's chromatographic conditions.
- The NMBA peak is observed as a doublet at a ratio of approximately 3:1
- Integrate both peaks and use the combined peak area for NMBA.
- Depending on column and concentration of the sample, the NEIPA peak may appear as doublet or a single peak with a tailing shoulder. Include the resolved second peak or the tailing of the main peak when integrating the NEIPA peak(s).
- The retention time difference of any impurity in the analyzed samples should not be more than 2% of the retention time of the corresponding standard in the standard solution.
- Report the nitrosamine impurity content in ppm with three significant figures if the value is ≥ LOD
- Report 'not detected' if no nitrosamine impurity is detected or the value is < LOD

Results and discussion

The TSQ Quantis LC-MS/MS system was successfully able to exceed the desired LOQ as required by the USFDA. Figure 1 shows the system suitability data at LOQ (0.03 PPM w.r.t. sample concentration) for all six impurities. The %RSD is less than 5 for each compound. Figure 2 shows the linearity each impurity ranged from LOQ to 100 PPB (absolute concentration) which is three to ten times lower than LOQ set by USFDA. The additional sensitivity allows greater confidence in being able to detect the presence of nitrosamines at even lower levels if required. Figure 3 shows chromatogram of blank and LOQ sample. The %recovery shown in Figure 4 is well within the acceptance limit (80 to 120%).

A method for the analysis of six nitrosamine impurities in Valsartan active pharmaceutical ingredient (API) samples has been successfully developed with excellent recovery (within 80 to 120%). Linearity for all six impurities has been established lower than the desired LOQ (0.030 PPM with

Table 7. LOQ results for all compounds.

		Limit of quantification (LOQ)			
S. No.	Compound name	With respect to absolute conc. (PPB)	With respect to 100 mg/ml sample conc. (PPM)	Signal to noise ratio at LOQ	Linearity range (PPB)
1	NDMA	1.00	0.0100	65	1.00-100
2	NMBA	1.00	0.0100	218	1.00-100
3	NDEA	0.25	0.0025	643	0.25-100
4	NEIPA	0.25	0.0025	831	0.25-100
5	NDIPA	0.25	0.0025	1016	0.25-100
6	NDBA	0.25	0.0025	123	0.25-100

Compound	Sample ID	Actual RT	Area	Compound	Sample ID	Actual RT	Area
NDBA	SOLVENT_BLANK	N/F	N/F	NDEA	SOLVENT_BLANK	N/F	N/F
NDBA	SOLVENT_BLANK	N/F	N/F	NDEA	SOLVENT_BLANK	N/F	N/F
NDBA	NITRO_MIX_STD_0.03_PPM	14.03	38150	NDEA	NITRO_MIX_STD_0.03_PPM	6.58	19939
NDBA	NITRO_MIX_STD_0.03_PPM	14.03	38147	NDEA	NITRO_MIX_STD_0.03_PPM	6.58	19155
NDBA	NITRO_MIX_STD_0.03_PPM	14.03	37865	NDEA	NITRO_MIX_STD_0.03_PPM	6.58	21044
NDBA	NITRO_MIX_STD_0.03_PPM	14.03	37910	NDEA	NITRO_MIX_STD_0.03_PPM	6.58	18698
NDBA	NITRO_MIX_STD_0.03_PPM	14.02	38765	NDEA	NITRO_MIX_STD_0.03_PPM	6.58	19374
NDBA	NITRO_MIX_STD_0.03_PPM	14.03	36740	NDEA	NITRO_MIX_STD_0.03_PPM	6.59	19083
NDBA	SOLVENT_BLANK	N/F	N/F	NDEA	SOLVENT_BLANK	N/F	N/F
NDBA	SOLVENT_BLANK	N/F	N/F	NDEA	SOLVENT_BLANK	N/F	N/F
	Average	14.03	37929.50		**Average**	6.58	19548.83
	Standard Deviation	0.00	665.35		**Standard Deviation**	0.00	838.37
	%RSD	**0.03**	**1.75**		**%RSD**	**0.06**	**4.29**

Compound	Sample ID	Actual RT	Area	Compound	Sample ID	Actual RT	Area
NDIPA	SOLVENT_BLANK	N/F	N/F	NDMA	SOLVENT_BLANK	N/F	N/F
NDIPA	SOLVENT_BLANK	N/F	N/F	NDMA	SOLVENT_BLANK	N/F	N/F
NDIPA	NITRO_MIX_STD_0.03_PPM	9.25	39236	NDMA	NITRO_MIX_STD_0.03_PPM	2.72	10938
NDIPA	NITRO_MIX_STD_0.03_PPM	9.24	37411	NDMA	NITRO_MIX_STD_0.03_PPM	2.72	11477
NDIPA	NITRO_MIX_STD_0.03_PPM	9.25	38334	NDMA	NITRO_MIX_STD_0.03_PPM	2.72	11658
NDIPA	NITRO_MIX_STD_0.03_PPM	9.25	38851	NDMA	NITRO_MIX_STD_0.03_PPM	2.72	11266
NDIPA	NITRO_MIX_STD_0.03_PPM	9.25	36763	NDMA	NITRO_MIX_STD_0.03_PPM	2.72	11842
NDIPA	NITRO_MIX_STD_0.03_PPM	9.25	38231	NDMA	NITRO_MIX_STD_0.03_PPM	2.73	11781
NDIPA	SOLVENT_BLANK	N/F	N/F	NDMA	SOLVENT_BLANK	N/F	N/F
NDIPA	SOLVENT_BLANK	N/F	N/F	NDMA	SOLVENT_BLANK	N/F	N/F
	Average	9.25	38137.67		**Average**	2.72	11493.67
	Standard Deviation	0.00	914.35		**Standard Deviation**	0.00	344.03
	%RSD	**0.04**	**2.40**		**%RSD**	**0.15**	**2.99**

Compound	Sample ID	Actual RT	Area	Compound	Sample ID	Actual RT	Area
NEIPA	SOLVENT_BLANK	N/F	N/F	NMBA	SOLVENT_BLANK	N/F	N/F
NEIPA	SOLVENT_BLANK	N/F	N/F	NMBA	SOLVENT_BLANK	N/F	N/F
NEIPA	NITRO_MIX_STD_0.03_PPM	8.06	67221	NMBA	NITRO_MIX_STD_0.03_PPM	4.36	47416
NEIPA	NITRO_MIX_STD_0.03_PPM	8.06	68405	NMBA	NITRO_MIX_STD_0.03_PPM	4.36	46286
NEIPA	NITRO_MIX_STD_0.03_PPM	8.06	67259	NMBA	NITRO_MIX_STD_0.03_PPM	4.34	47048
NEIPA	NITRO_MIX_STD_0.03_PPM	8.06	70295	NMBA	NITRO_MIX_STD_0.03_PPM	4.34	45186
NEIPA	NITRO_MIX_STD_0.03_PPM	8.06	68691	NMBA	NITRO_MIX_STD_0.03_PPM	4.34	44960
NEIPA	NITRO_MIX_STD_0.03_PPM	8.06	68047	NMBA	NITRO_MIX_STD_0.03_PPM	4.34	44566
NEIPA	SOLVENT_BLANK	N/F	N/F	NMBA	SOLVENT_BLANK	N/F	N/F
NEIPA	SOLVENT_BLANK	N/F	N/F	NMBA	SOLVENT_BLANK	N/F	N/F
	Average	8.06	68319.67		**Average**	4.35	45910.33
	Standard Deviation	0.00	1136.09		**Standard Deviation**	0.01	1177.92
	%RSD	**0.00**	**1.66**		**%RSD**	**0.24**	**2.57**

Figure 1. System suitability data.

respect to sample). The R2 reported for all compounds is > 0.99. Refer to Figure 2 Linearity Range, LOQ, and S/N ratio at LOQ were reported in table 7.

The LOQ for four compounds (NDEA, NEIPA, NDIPA & NDBA) was established more than four times lower than required. For the rest of the two compounds (NDMA & NMBA), the established LOQ is three-fold lower than required. The %RSD at the desired LOQ (0.030 PPM with respect to API concentration in the sample) was less than 5% for all compounds. The method exceeded the assay requirements as stipulated by the USFDA. %Recovery was performed at 0.03 PPM is well within the permissible limit (80 to 120%).

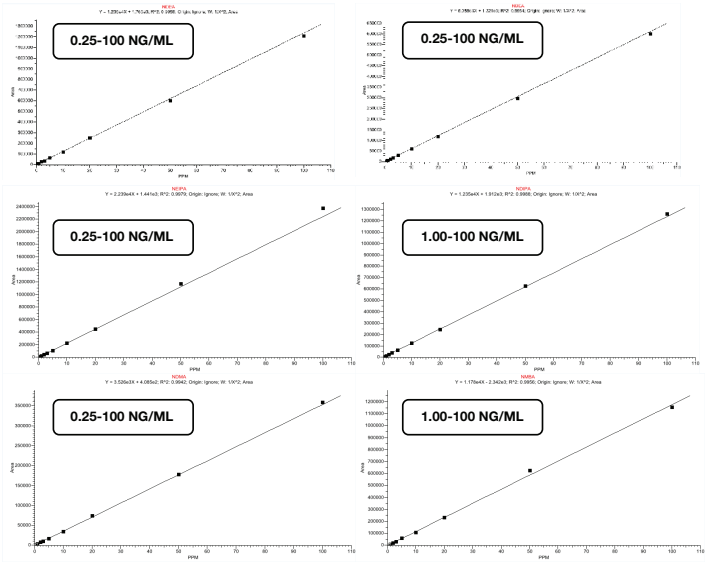

Figure 2. Calibration curves and linearity.

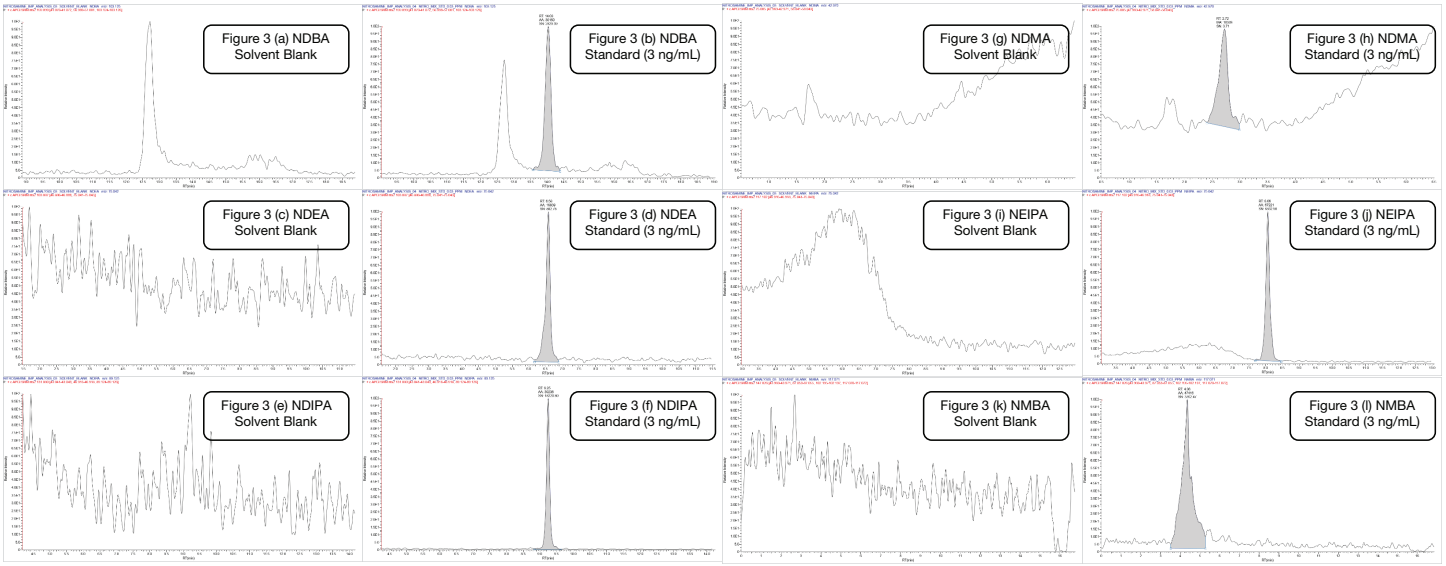

Figure 3. Chromatogram of solvent blank and standard at 0.03 ppm with regard to API sample concentration for NDBA (a-b), NDEA (c-d), NDIPA (e-f), NDMA (g-h), NEIPA (i-j), and NMBA (k-l).

$$\% \text{ Recovery} = \frac{\text{(Calculated Concentration in Sample spiked @0.03PPM w.r.t. API - Calculated concentration of Unspiked API Sample)}}{\text{Calculated concentration in Solvent Standard (0.03PPM)}} \times 100$$

Figure 4. Recovery values.

Compound	Sample ID	Sample Type	Area	Theoretical Amt (ppm)	Calculated Amt (ppm)	Average Conc. with two replicate injections	%Recovery
NDBA	SOLVENT_BLANK	Solvent	N/F	N/A	N/F		
NDBA	NITRO_MIX_STD_0.03_PPM	Cal Std	38150	0.030	0.030		
NDBA	NITRO_MIX_STD_0.03_PPM	Cal Std	38147	0.030	0.030		
NDBA	NITRO_MIX_STD_0.03_PPM	Cal Std	37865	0.030	0.030		
NDBA	NITRO_MIX_STD_0.03_PPM	Cal Std	37910	0.030	0.030		
NDBA	NITRO_MIX_STD_0.03_PPM	Cal Std	38765	0.030	0.031		
NDBA	NITRO_MIX_STD_0.03_PPM	Cal Std	36740	0.030	0.029		
NDBA	SOLVENT_BLANK	Solvent	N/F	N/A	N/F		
NDBA	API_SAC_VAL_SAMPLE	Unknown	5864	N/A	0.005	0.005	
NDBA	API_SAC_VAL_SAMPLE	Unknown	5828	N/A	0.005		
NDBA	API_SAC_VAL_SAMPLE_REC_@0.03_PPM	Unknown	43392	N/A	0.034	0.034	96.67
NDBA	API_SAC_VAL_SAMPLE_REC_@0.03_PPM	Unknown	43300	N/A	0.034		

Compound	Sample ID	Sample Type	Area	Theoretical Amt (ppm)	Calculated Amt (ppm)	Average Conc. with two replicate injections	%Recovery
NDEA	SOLVENT_BLANK	Solvent	N/F	N/A	N/F		
NDEA	NITRO_MIX_STD_0.03_PPM	Cal Std	19939	0.030	0.031		
NDEA	NITRO_MIX_STD_0.03_PPM	Cal Std	19155	0.030	0.029		
NDEA	NITRO_MIX_STD_0.03_PPM	Cal Std	21044	0.030	0.032		
NDEA	NITRO_MIX_STD_0.03_PPM	Cal Std	18698	0.030	0.029		
NDEA	NITRO_MIX_STD_0.03_PPM	Cal Std	19374	0.030	0.030		
NDEA	NITRO_MIX_STD_0.03_PPM	Cal Std	19083	0.030	0.029		
NDEA	SOLVENT_BLANK	Solvent	N/F	N/A	N/F		
NDEA	API_SAC_VAL_SAMPLE	Unknown	1804	N/A	0.000	0.000	
NDEA	API_SAC_VAL_SAMPLE	Unknown	1762	N/A	0.000		
NDEA	API_SAC_VAL_SAMPLE_REC_@0.03_PPM	Unknown	20006	N/A	0.031	0.031	103.33
NDEA	API_SAC_VAL_SAMPLE_REC_@0.03_PPM	Unknown	20444	N/A	0.031		

Compound	Sample ID	Sample Type	Area	Theoretical Amt (ppm)	Calculated Amt (ppm)	Average Conc. with two replicate injections	%Recovery
NDIPA	SOLVENT_BLANK	Solvent	N/F	N/A	N/F		
NDIPA	NITRO_MIX_STD_0.03_PPM	Cal Std	39236	0.030	0.031		
NDIPA	NITRO_MIX_STD_0.03_PPM	Cal Std	37411	0.030	0.029		
NDIPA	NITRO_MIX_STD_0.03_PPM	Cal Std	38334	0.030	0.030		
NDIPA	NITRO_MIX_STD_0.03_PPM	Cal Std	38851	0.030	0.031		
NDIPA	NITRO_MIX_STD_0.03_PPM	Cal Std	36763	0.030	0.029		
NDIPA	NITRO_MIX_STD_0.03_PPM	Cal Std	38231	0.030	0.030		
NDIPA	SOLVENT_BLANK	Solvent	N/F	N/A	N/F		
NDIPA	API_SAC_VAL_SAMPLE	Unknown	1550	N/A	0.001	0.001	
NDIPA	API_SAC_VAL_SAMPLE	Unknown	1527	N/A	0.001		
NDIPA	API_SAC_VAL_SAMPLE_REC_@0.03_PPM	Unknown	39280	N/A	0.031	0.031	100.00
NDIPA	API_SAC_VAL_SAMPLE_REC_@0.03_PPM	Unknown	39362	N/A	0.031		

Compound	Sample ID	Sample Type	Area	Theoretical Amt (ppm)	Calculated Amt (ppm)	Average Conc. with two replicate injections	%Recovery
NDMA	SOLVENT_BLANK	Solvent	N/F	N/A	N/F		
NDMA	NITRO_MIX_STD_0.03_PPM	Cal Std	10938	0.030	0.029		
NDMA	NITRO_MIX_STD_0.03_PPM	Cal Std	11477	0.030	0.030		
NDMA	NITRO_MIX_STD_0.03_PPM	Cal Std	11658	0.030	0.030		
NDMA	NITRO_MIX_STD_0.03_PPM	Cal Std	11266	0.030	0.029		
NDMA	NITRO_MIX_STD_0.03_PPM	Cal Std	11842	0.030	0.031		
NDMA	NITRO_MIX_STD_0.03_PPM	Cal Std	11781	0.030	0.031		
NDMA	SOLVENT_BLANK	Solvent	N/F	N/A	N/F		
NDMA	API_SAC_VAL_SAMPLE	Unknown	N/F	N/A	N/F	0.000	
NDMA	API_SAC_VAL_SAMPLE	Unknown	N/F	N/A	N/F		
NDMA	API_SAC_VAL_SAMPLE_REC_@0.03_PPM	Unknown	11453	N/A	0.030	0.030	98.33
NDMA	API_SAC_VAL_SAMPLE_REC_@0.03_PPM	Unknown	11067	N/A	0.029		

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Compound	Sample ID	Sample Type	Area	Theoretical Amt (ppm)	Calculated Amt (ppm)	Average Conc. with two replicate injections	%Recovery
NEIPA	SOLVENT_BLANK	Solvent	N/F	N/A	N/F		
NEIPA	NITRO_MIX_STD_0.03_PPM	Cal Std	67221	0.030	0.030		
NEIPA	NITRO_MIX_STD_0.03_PPM	Cal Std	68405	0.030	0.030		
NEIPA	NITRO_MIX_STD_0.03_PPM	Cal Std	67259	0.030	0.030		
NEIPA	NITRO_MIX_STD_0.03_PPM	Cal Std	70295	0.030	0.031		
NEIPA	NITRO_MIX_STD_0.03_PPM	Cal Std	68691	0.030	0.030		
NEIPA	NITRO_MIX_STD_0.03_PPM	Cal Std	68047	0.030	0.030		
NEIPA	SOLVENT_BLANK	Solvent	N/F	N/A	N/F		
NEIPA	API_SAC_VAL_SAMPLE	Unknown	N/F	N/A	N/F	0.000	
NEIPA	API_SAC_VAL_SAMPLE	Unknown	N/F	N/A	N/F		
NEIPA	API_SAC_VAL_SAMPLE_REC_@0.03_PPM	Unknown	69289	N/A	0.030	0.030	**100.00**
NEIPA	API_SAC_VAL_SAMPLE_REC_@0.03_PPM	Unknown	67717	N/A	0.030		

Compound	Sample ID	Sample Type	Area	Theoretical Amt (ppm)	Calculated Amt (ppm)	Average Conc. with two replicate injections	%Recovery
NMBA	SOLVENT_BLANK	Solvent	N/F	N/A	N/F		
NMBA	NITRO_MIX_STD_0.03_PPM	Cal Std	47416	0.030	0.031		
NMBA	NITRO_MIX_STD_0.03_PPM	Cal Std	46286	0.030	0.030		
NMBA	NITRO_MIX_STD_0.03_PPM	Cal Std	47048	0.030	0.031		
NMBA	NITRO_MIX_STD_0.03_PPM	Cal Std	45186	0.030	0.030		
NMBA	NITRO_MIX_STD_0.03_PPM	Cal Std	44960	0.030	0.029		
NMBA	NITRO_MIX_STD_0.03_PPM	Cal Std	44566	0.030	0.029		
NMBA	SOLVENT_BLANK	Solvent	N/F	N/A	N/F		
NMBA	API_SAC_VAL_SAMPLE	Unknown	N/F	N/A	N/F	0.000	
NMBA	API_SAC_VAL_SAMPLE	Unknown	N/F	N/A	N/F		
NMBA	API_SAC_VAL_SAMPLE_REC_@0.03_PPM	Unknown	39997	N/A	0.026	0.026	**86.67**
NMBA	API_SAC_VAL_SAMPLE_REC_@0.03_PPM	Unknown	39533	N/A	0.026		

Conclusion

A rapid and sensitive quantitative method is always a major goal for analytical laboratories involved in pharmaceutical analysis. All compounds were well separated with good reproducibility at LOQ. The triple quadrupole mass analyzer TSQ Quantis LC-MS/MS system with Thermo Scientific™ TraceFinder™ software was used for data processing to reduce the processing time thereby resulting in a high throughput method.

High linearity, specificity, recovery and repeatability of the method was established with minimal possible sample preparation time.

This method can be utilized for detection and confirmation of trace amount of nitrosamine impurities in presence of very high concentration of drug substance or drug product. The method has potential to detect trace level compounds at concentration as low as 0.03 PPM with respect to sample.

References and Acknowledgements

1. USFDA method, "Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) Method for the Determination of Six Nitrosamine Impurities in ARB Drugs" https://www.fda.gov/media/125478/download
2. USFDA method, "Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Method for the Determination of NDMA in Ranitidine Drug Substance and Solid Dosage Drug Product." https://www.fda.gov/media/131868/download

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