LC-MS/MS Method for the Determination of NDMA Impurity in Ranitidine

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Application #AN7060

Ranitidine is a popular prescriptive drug used to decrease the amount of acid created by the stomach and is included on the World Health Organisation's 'Model List of Essential Medicines'.

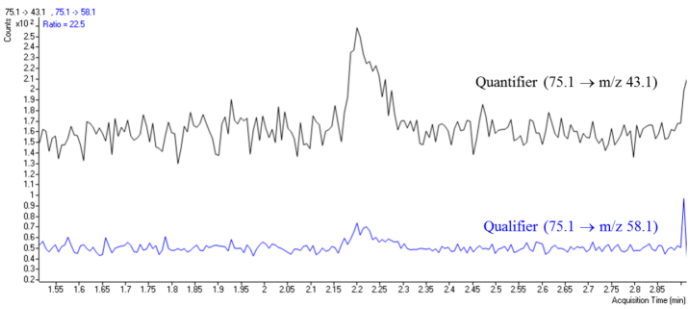
The U.S. Food and Drug Administration has announced that low-levels of the impurity N-nitroso-di-methylamine (NDMA) have been detected in some medicines containing ranitidine. NDMA is classified as a 'probable human carcinogen' based on results from laboratory tests. It is also a known environmental contaminant that can be found in water and foods such as dairy products, vegetables and meat.

Further to the Liquid Chromatography High Resolution Mass Spectrometry (LC-HRMS) method detailed in ACE application note #AN7030 (FDA method FY19-177-DPA-S), the FDA have developed an LC-MS/MS method, based on a triple quadrupole mass spectrometer (QQQ), for the determination of NDMA in ranitidine drug substance and drug product. The QQQ platform is more widely available and this method can be used as an alternative or confirmatory method to the LC-HRMS approach. This method uses the ACE Excel 3 C18-AR, 50 x 4.6 mm column (EXL-119-0546U).

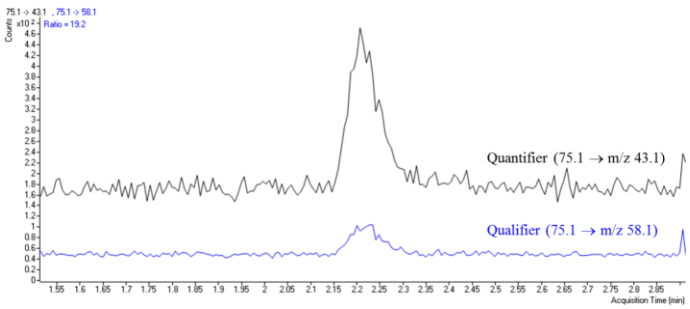
For further information regarding the method, visit https://www.fda.gov/media/131868/download

NDMA Impurity, Example Chromatograms

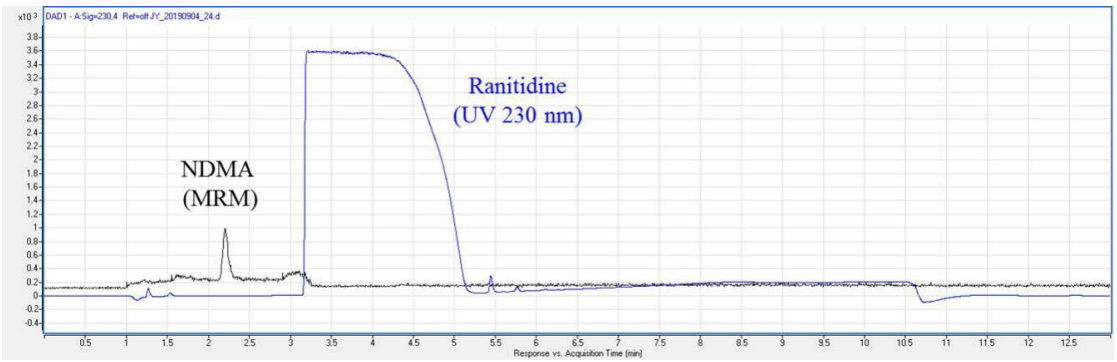
NDMA LOD (0.3 ng/mL Standard)



NDMA LOQ (1.0 ng/mL Standard)



Overlapped MRM and UV Chromatograms of Ranitidine Drug Product



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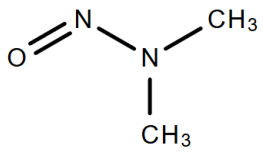
Conditions

Column:	ACE Excel 3 C18-AR
Dimensions:	50 x 4.6 mm
Part Number:	EXL-119-0546U
Mobile Phase:	A: 0.1% formic acid in water B: 0.1% formic acid in methanol

Time (mins)	%B
0	5
1.0	5
3.0	20
7.0	100
9.0	100
9.1	5
14.0	5



N-nitroso-di-methylamine (NDMA)

Flow Rate:	0.6 mL/min
Injection:	10 µL
Column Temperature:	30 °C
Autosampler Temperature:	4 - 8 °C
Detection:	Agilent 6420 Triple Quad LC-MS system with APCI source, MRM, positive ion mode

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Method for the Determination of NDMA in Ranitidine Drug Substance and Solid Dosage Drug Product. *U.S. Food and Drug Administration*, FY20-006-DPA-S (Data copied 13 November 2019). https://www.fda.gov/media/131868/download