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Nitrosamines in Pharmaceutical Products

Anatune Nitrosamines Round Table Discussion 2020 Discussion 6th February 2020

The group of potential carcinogens known as nitrosamines represent one of the biggest challenges to the pharmaceutical industry today. The widely publicised discovery of N-nitrosodimethylamine (NDMA) in pharmaceutical products has led to wide-scale product recall.

This leaflet aims to provide a brief overview of the issue, what pharmaceutical companies are doing to address it and some of the best known techniques to measure for nitrosamines on the market today.

Getting to grips with the issue:

In October 2019, it was widely reported that regulators around the world, in particular the European Medicines Agency (EMA) were preparing to respond to new discoveries of products containing NDMA. After learning from customers about the severity of the issue, Anatune invited key members from three of the major pharmaceutical companies to discuss the implications of the issue, regularity and where each was in the early stages of their method development.

Representatives from AstraZeneca, GSK and Pfizer shared information with the intention of reaching a general consensus on the main analytical challenges that need to be overcome. Anatune's status as experts in automation put them in good position to help with concerns around throughput and data quality that were suspected to be major issues. By taking out manual sample preparation risk of false positives is greatly reduced.

False Positives: Potentially rectified by avoiding manual sample preparation and high-end selective Mass Spectrometry. Anatune has shown high contamination from Nitrile gloves and contamination can also come from pasture pipette tips.

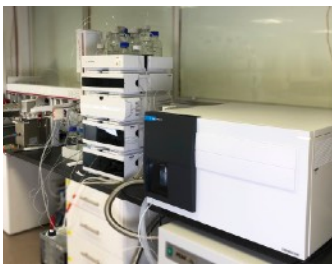
Ion Suppression: An issue due to the high level of excipients present in drug products. This can lead to poor detection limits.

Key focus on Nitrosamines: NDMA, NDEA, NDIPA, NDEIPA, NMBA, NMPA.

Unstable API: The ability to prepare samples just in time greatly reduces any risk of inaccurate results to instability.

Solving the Problem

There are generally two methods in common use at the moment. An LC-MS/MS method using mixing sonication and centrifugation represents about 50% of the market. This one is favourable because it makes testing for NMBA much easier.



GC-MS analysis makes up the other 50%. Using Headspace GC with accurate mass measurement has been Anatune's focus using the GC/Q-TOF.

LC-MS/MS

INSTRUMENTATION

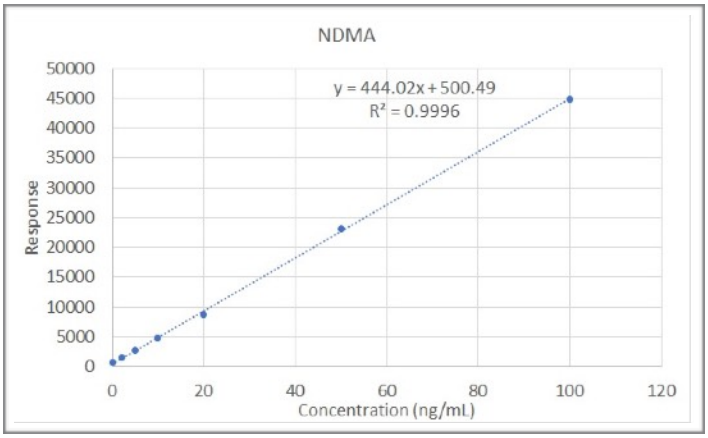
GERSTEL Dual head MultiPurpose Sampler (MPS) Robotic/Robotic Pro 2M rail. GERSTEL QuickMix, Anatune CF200 Robotic centrifuge. Agilent 1260 HPLC, Agilent 6470 Triple Quadrupole

METHOD

Linearity experiments ranging from 2 ppb to 100 ppb (seven point) for N-Nitrosodimethylamine and, N-Nitroso-diethylamine (NDMA and NDEA) in the presents of drug product.

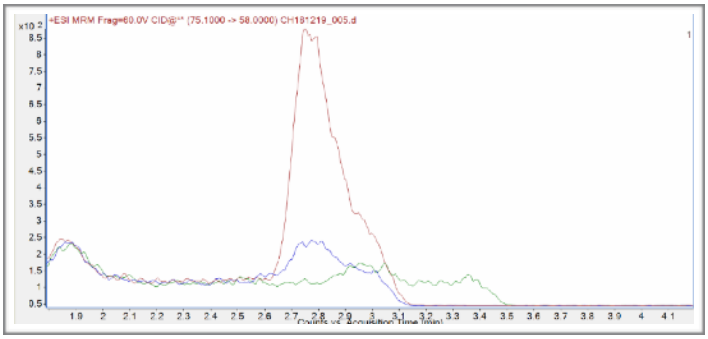
After adding tablet to a 10 mL vial, the sample preparation was fully automated. 6 mL of water was added, an addition of nitrosamine standard (volume depending on concentration) was spiked into this solution. Solution was mixed for a period of time using the Quickmix and centrifuged using the automated CF200. An 50 µL aliquot was injected into a 10µL loop (with rheodyne) on the MPS rail and the LC-MS/MS was triggered for analysis.

RESULTS



Showing Linearity of NDMA (range from 2ppb to 100 ppb

A similar correlation coefficient of 0.9991 was obtained for NDEA. NDMA was the least sensitive nitrosamine.



Showing blank tablet (green), 2 ppb (blue) and 20 ppb spike NDMA (red). The peak at 2.8 minutes is NDMA.

GC/Q-TOF

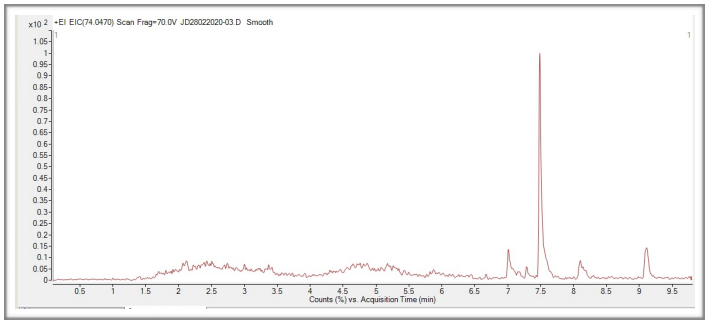
INSTRUMENTATION

GERSTEL Dual head MultiPurpose Sampler (MPS) Robotic/Robotic Pro 1.6M rail. GERSTEL Headspace analysis. GERSTEL quickMIX Anatune CF200 Robotic Centrifuge. Agilent GC/Q-TOF 7250

METHOD

After adding the tablet to a 10 mL vial, the sample preparation was fully automated. 6 mL of 1-Methyl-2-pyrrolidinone (NMP) was added, an addition of nitrosamine standard (volume depending on concentration) was spiked into this solution. Solution was mixed for a period of time using the Quickmix and headspace analysis was performed. We are currently evaluating if centrifuging the solution improves analytical method.

RESULTS



Extracted ion chromatogram of NDMA at 7.5 minutes

Conclusion

This is a big issue, but the pharmaceutical companies are responding quickly and thoroughly in the spirit of collaboration

While there are many complexities surrounding nitrosamine analysis, we've developed methods which can avoid false positives, help deal with ion suppression and sample degradation while detecting all the key nitrosamines in question.

Contact

If you're concerned by this issue and want to find out how to prevent it becoming a problem, we'd love to hear from you.

Email us on enquiries@anatune.co.uk or call our Cambridge office on
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