



# Analysis of Nitrosamines in Ranitidine by GC-TEA

## Overview

This application note describes the analysis of nitrosamine contamination in Ranitidine tablets.

## Background

Ranitidine was widely used to treat heartburn and other gastrointestinal conditions, with typical daily dosages ranging from 75 mg to 300 mg. In 2019, N-Nitrosodimethylamine (NDMA), a probable human carcinogen, was detected in ranitidine products, leading to widespread recalls and heightened scrutiny of nitrosamine impurities in pharmaceuticals. The acceptable daily intake limit for NDMA in pharmaceutical products is 96 nanograms. Monitoring NDMA levels in ranitidine is essential to maintain patient safety and comply with regulatory standards.

## Analytical Method

### Automated Total Nitrosamine Analysis (ATNA)

The ATNA system was employed to screen for nitrosamines in the metformin samples. ATNA uses a non-targeted approach to detect the NO functional group, which is common to all nitrosamines.

### Calculations for Tablet Quantity

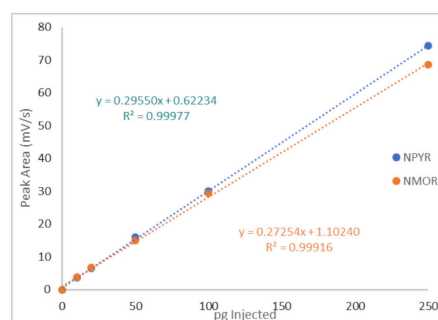
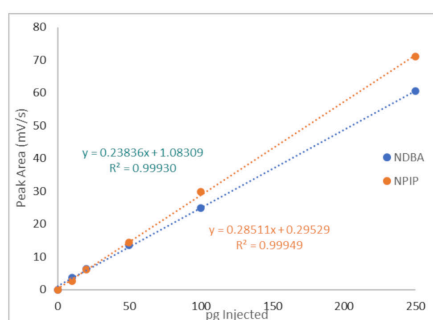
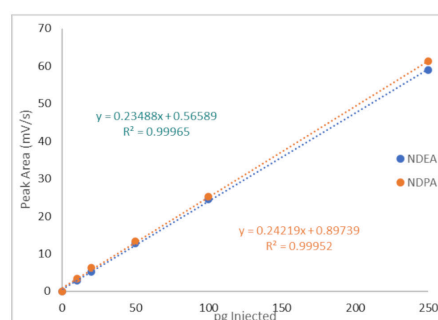
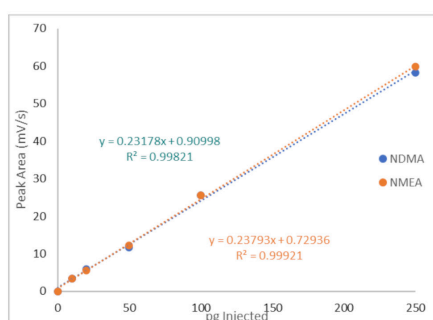
Determining the appropriate quantity of tablets to test depends on the sensitivity of the GC-TEA system for each nitrosamines. For instance, in Ranitidine, given a maximum daily dosage of 600mg, the FDA sets the NDMA daily limit at 96ng. The GC-TEA can detect 40pg of NDMA on column. We inject 0.5µl of the methanol extracted sample.

With the standard extraction procedure (10 tablet with 5ml of solvent), the threshold becomes 488ng in 5ml which equates to, 97.6pg per µl or 48.8pg in 0.5µl injection.

These calculations ensure the analysis aligns with the limits of detection (LOD) for each nitrosamine, with a daily exposure limit of 96ng or greater, and the maximum prescribed dosage.

# Analytical Method

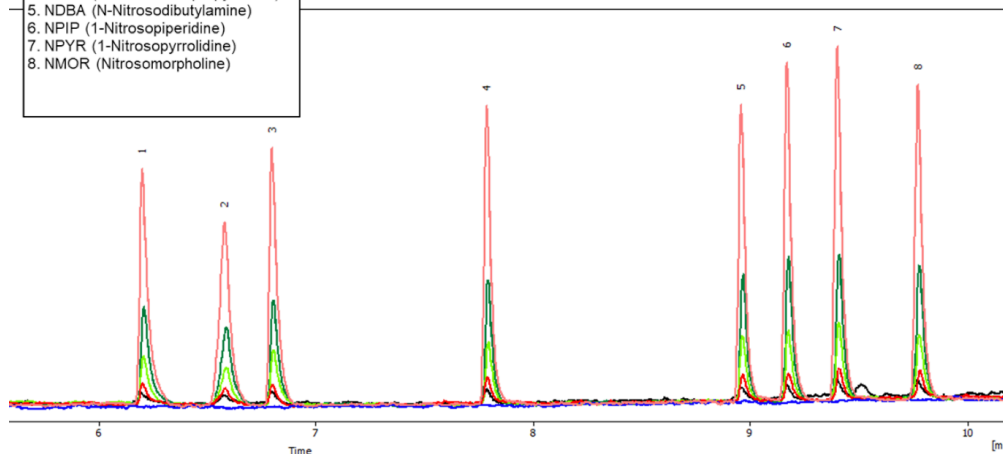
## GC-TEA Calibration Curves



Calibration: 10pg on-column is 0.5µL injection of a 20ng/mL standard (20ppb per component) Signal:Noise – 5:1 on smallest peak

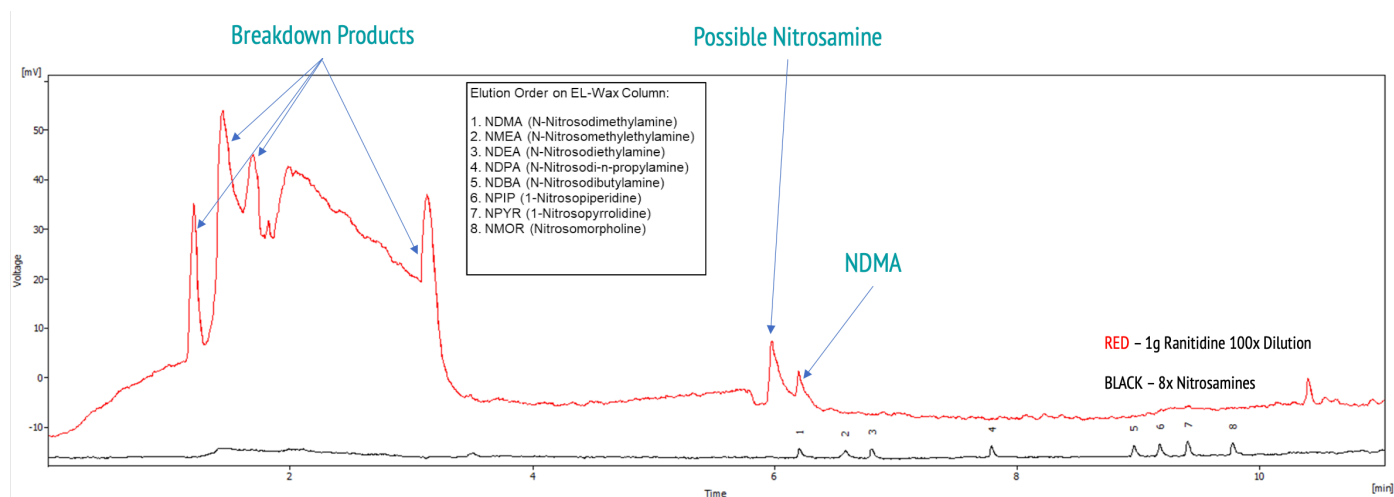
Elution Order on EL-Wax Column:

1. NDMA (N-Nitrosodimethylamine)
2. NMEA (N-Nitrosomethylethylamine)
3. NDEA (N-Nitrosodiethylamine)
4. NDPA (N-Nitrosodi-n-propylamine)
5. NDBA (N-Nitrosodibutylamine)
6. NPIP (1-Nitrosopiperidine)
7. NPYR (1-Nitrosopyrrolidine)
8. NMOR (Nitrosomorpholine)



PINK – 250pg On-column  
GREEN – 100pg On-column  
GREEN – 50pg On-column  
RED – 20pg On-column  
BLACK – 10pg On-column  
BLUE – 0pg On-column

1g of a Ranitidine sample was extracted with 5mL methanol. This was further diluted 100-fold. 0.5µL splitless injection



## Results

It is clear that NDMA is present at a concentration in excess of the acceptable threshold for NDMA. However, since the GC-TEA is giving a response only for the nitrosamine molecule, the other peaks present early in the chromatogram suggests the presence of nitrosamines that are less stable than NDMA and have fallen apart within the GC inlet.

If this analysis was being performed by a GC-MSMS analysis, the user would be completely unaware of the presence of these other nitrosamine-related as there is no analytical standard for them.

## Conclusion

The GC-TEA system provides a sensitive means of quantitating real life samples to demonstrate regulatory compliance for the presence of specific nitrosamines in pharmaceutical samples.

## Product Information

The part numbers listed below include all the components required to integrate the Thermal Energy Analyzer (TEA) with your existing Gas Chromatography (GC) system.

PN: 32000810 - TEA 810 - 230V50Hz

PN: 32020300 - 810 Pyrolyser Interface Kit

PN: 32001060 - 230V Ozone Destroyer (for TEA)

PN: 32020200 - NCDSi Dry Scroll Pump w/ Silencer

If you do not currently have a GC system and require one, we recommend our 200 Series GC. For more information about this GC solution, please visit <https://www.ellutia.com/200-series-gas-chromatograph>



To learn more about Ellutia's TEA, please visit:  
<https://www.ellutia.com/800-series-tea-detector>

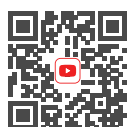


Colston House, 200 Lancaster Way Business Park, Ely, Cambridgeshire, CB6 3NX, UK

Tel: +44 (0)1353 669916 Web: [www.ellutia.com](http://www.ellutia.com)

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Registered Address Colston House, 200 Lancaster Way Business Park, Ely, Cambridgeshire, England, CB6 3NX



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