SHIMADZU

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An Alternative Approach for NDMA Quantification in Metformin Final Product by LC/MS 2050 Single Quadrupole

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1. Introduction

Metformin is the most widely prescribed drug for the treatment of type 2 diabetes mellitus, However, dimethylamine (DMA) is used as starting material in its synthetic route, which is a direct precursor for the synthesis of N-nitrosodimethylamine (NDMA).[1]

Herein, an analytical methodology using MS single quadrupole (Shimadzu), capable of quantifying NDMA in the finished product of Metformin, was developed with good sensitivity and repeatability.

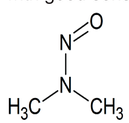


Figure 1. Molecular structure of NDMA

2. Methods

Analytical chromatography was performed using an LC-MS (Nexera X3 - LCMS-2050, Shimadzu®, Japan) with the following conditions of HPLC and MS (Table 1 and 2, respectively).

Table 1. Method parameters of LC system.

Column	PN: 227-31012-05; Shim-pack Scepter C18-120, 1.9um, 2.1x100 mm
Mobile Phase	A – 0.3% Formic acid in H_2O B – 0.3% Formic acid in methanol.
Flow and Column Temp.	0.4 mL/min - 40 °C
Injection Volume	50µL

Figure 2. LCMS 2050 single quadrupole.

Table 2. Method parameters of MS system.

Interface Voltage	5 kV
Interface	ESI +
Nebulizing Gas Flow	2 L/min
Heating Gas Flow	5 L/min
Drying Gas Flow	3 L/min
Dessolvation Temp.	400 °C
DL Temp.	150 °C

Table 3. Quantitative information of analytes.

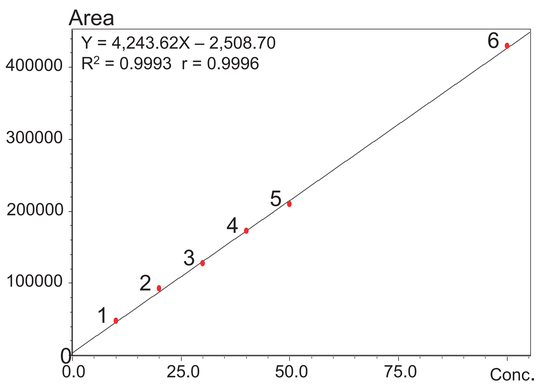
Analyte	Precursor (SIM)	Mode	Wavelenght (nm)
NDMA	75.0	Positive (+)	-
Metformin Chlorohydrate	-	-	254

3. Results

The linearity test was performed using NDMA samples with concentrations in the range of 10 to 100 ppb (six points). As a diluent for each point of the calibration curve, a methanolic solution of Metformin Hydrochloride was used at a concentration of 1 ppm.

The methodology presented satisfactory linearity results (R^2>0.99), even in the presence of the drug as matrix. Furthermore, the relative standard deviation (RSD) of a triplicate injection of the same 10 ppb sample vial was 2.5%. The Shim-pack Scepter C_{18} column (Shimadzu®, Japan) proved to be efficient by promoting complete separation between the active pharmaceutical ingredient (IFA), which is present in high concentrations, and NDMA, thus facilitating the construction and handling of the selector valve program between the MS and the discard.

This type of selection program has a great importance in pharmaceutical methods due to the high concentration of IFA in its samples, thus preserving MS and its consumables. Figures 3 and 4, Table 4 and Graphic 1 contain the results obtained.



Graphic 1. Calibration curve of NDMA with range of 10-100ppb.

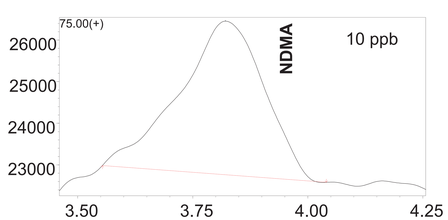


Figure 3. Limit of quantification injection.

Table 4. Flow selection program between waste and detector.

Time	Valve Position
0.01	Waste
2.90	MS
6.00	Waste

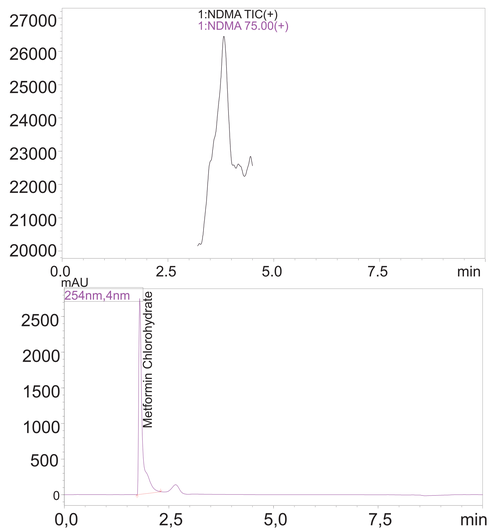


Figure 4. Chromatographic separation observed between NDMA (above) and Metformin Hydrochloride (below) in the LOQ sample.

4. Conclusion

Using the LCMS-2050 system, it was possible to develop a sensitive and reproducible methodology for quantitative analysis of NDMA in Metformin Hydrochloride final product. It was possible to reach quantification limits lower than those stipulated by Anvisa[2] (Brazilian regulatory institution – 38 ppb), regarding the maximum permitted daily intake of this impurity.

References

•[1] *Ministério da Saúde*. Relação Nacional de Medicamentos Essenciais, Rename 2022. Brasília, DF: Ministério da Saúde, 2022.

•[2] *ANVISA*, 2023a. Guia sobre o Controle de Nitrosaminas em Insumos Farmacêuticos Ativos e Medicamentos. Guia nº 50/2021 – versão 3.

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