Electronic Supplementary Material (ESI) for Analytical Methods.

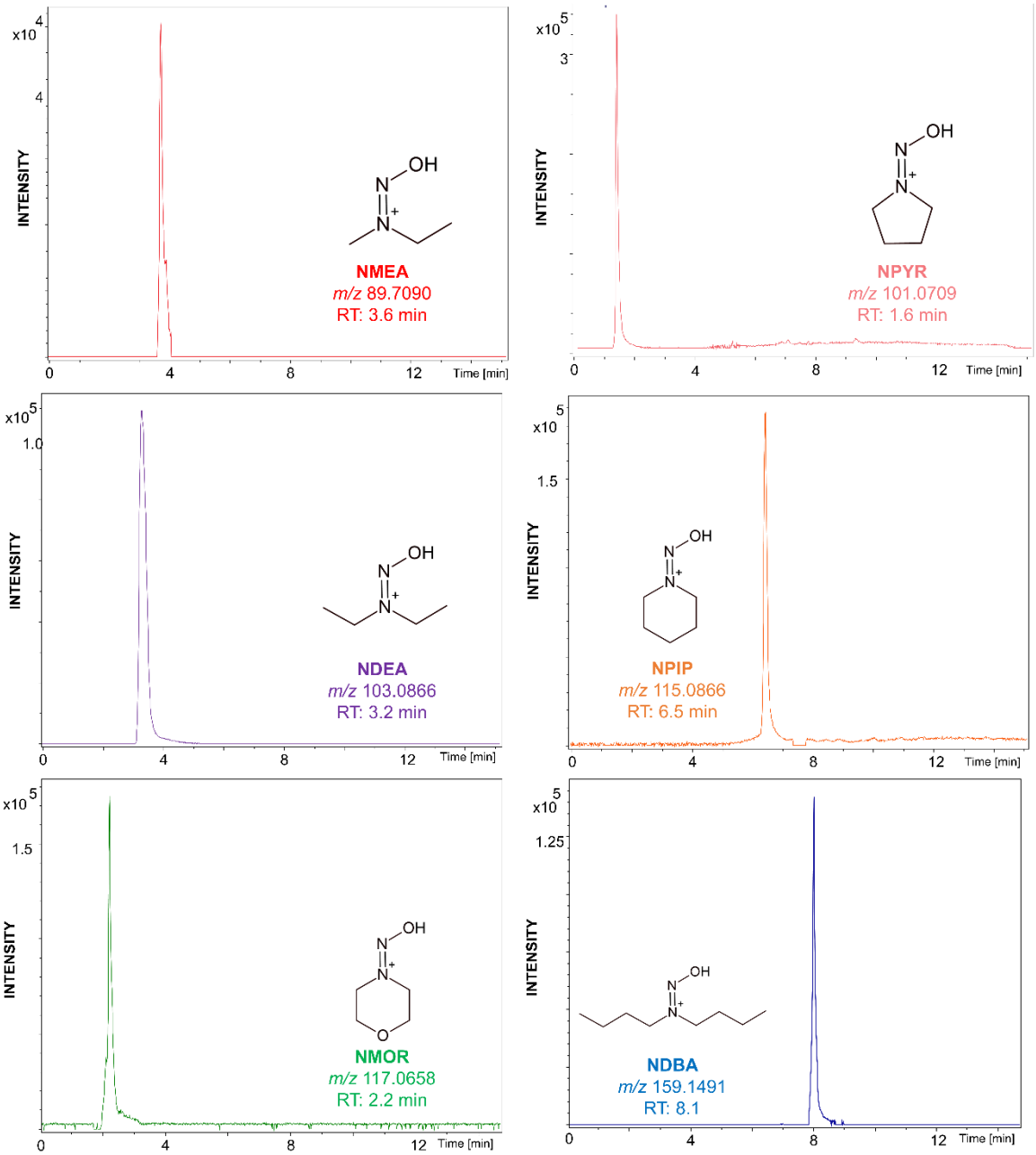

# DEVELOPMENT OF A RELIABLE METHOD FOR N-NITROSAMINES IN MEDICINES DETERMINATION BY DISPOSABLE PIPETTE EXTRACTION AND HPLC-MS ANALYSIS

**Almir Custodio Batista Junior[1], Yuri Arrates Rocha[1], Gabriela Guimarães Souza[1], Andréa Rodrigues Chaves[1*]**

[1] Federal University of Goiás, Chemistry Institute, Goiânia, Goiás 74690-900, Brazil

*andrea_chaves@ufg.br

## ELETRONIC SUPLEMENTARY INFORMATION




**RT:** Retention time; **NMEA:** N-nitroso-N-methylethylamine; **NPYR:** N-nitrosopyrrolidine; **NDEA:** N-nitrosodiethylamine; **NPIP:** N-nitrosopiperidine; **NMOR:** N-nitrosomorpholine; **NDBA:** N-nitroso-N-dibutylamine.

**Figure S1**: Extracted Ion Chromatogram for each N-nitrosamine analyzed by HPLC-MS

**Table S1:** Sorbents specifications obtained via its certificate of analysis.

| Extraction phase | Pore size (Å) | Pore Volume (mL $g^{-1}$) | Surface Area ($m^2$ $g^{-1}$) | Particle size (µm) |
|---|---|---|---|---|
| C8 | 60 | 0.8 | 500 | 40-63 |
| C18 | 60 | 0.8 | 500 | 40-63 |
| $NH_2$ | 70 | 0.8 | 499 | 47-60 |
| PH | 73 | 0.8 | 462 | 54 |
| HLB | 80-200 | 1.5 – 2.6 | 700-1025 | 35-45 |
| CN | 70 | 0.8 | 500 | 47-60 |
| ENVI-CARB | - | - | - | - |

**Table S2:** Experiments performed on the central composite design.

| Experiment | Block | pH | DC | ET / s |
|---|---|---|---|---|
| 1 | 1 | 6.0 | 6 | 20.0 |
| 2 | 1 | 6.0 | 10 | 60.0 |
| 3 | 1 | 8.0 | 6 | 60.0 |
| 4 | 1 | 8.0 | 10 | 20.0 |
| 5 (C) | 1 | 7.0 | 8 | 40.0 |
| 6 (C) | 1 | 7.0 | 8 | 40.0 |
| 7 | 2 | 6.0 | 6 | 60.0 |
| 8 | 2 | 6.0 | 10 | 20.0 |
| 9 | 2 | 8.0 | 6 | 20.0 |
| 10 | 2 | 8.0 | 10 | 60.0 |
| 11 (C) | 2 | 7.0 | 8 | 40.0 |
| 12 (C) | 2 | 7.0 | 8 | 40.0 |
| 13 | 3 | 5.3 | 8 | 40.0 |
| 14 | 3 | 8.6 | 8 | 40.0 |
| 15 | 3 | 7.0 | 5 | 40.0 |
| 16 | 3 | 7.0 | 11 | 40.0 |
| 17 | 3 | 7.0 | 8 | 7.0 |
| 18 | 3 | 7.0 | 8 | 72.0 |
| 19 (C) | 3 | 7.0 | 8 | 40.0 |

| | | | | | |
|---|---|---|---|---|---|
| | 20 (C) | 3 | 7.0 | 8 | 40.0 |

**DC:** Desorption cycles; **ET:** Equilibrium time.

**Table S3:** Comparation between the formulations of the commercial medicines.

| Commercial Medicine | Excipients |
|---|---|
| **LOSARTAN POTASSIUM** | Lactose monohydrate, microcrystalline cellulose, starch, silicon dioxide, croscarmellose sodium, magnesium stearate, titanium dioxide, macrogol, hypromellose. |
| **VALSARTAN** | Microcrystalline cellulose, silicon dioxide, lactose monohydrate, crospovidone, polyvinyl alcohol, magnesium stearate, titanium dioxide, macrogol, talc, iron oxide. |
| **IBUPROFEN** | Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, stearyl sodium, hypromellose, titanium dioxide, macrogol, ethyl alcohol. |

**Table S4:** Analytical greenness metric for the proposed DPX method

| Criteria | | Score | Weight |
|---|---|---|---|
| **1** | Sample preparation placement | 1.00 | 1 |
| **2** | Hazardous materials | 0.33 | 5 |
| **3** | Sustainability, renewability, and reusability of materials | 0.25 | 2 |
| **4** | Waste | 0.62 | 4 |
| **5** | Size economy of the sample | 1.00 | 2 |
| **6** | Sample throughput | 0.64 | 3 |
| **7** | Integration and automation | 0.25 | 2 |
| **8** | Energy consumption | 1.00 | 4 |
| **9** | Post-sample preparation configuration for analysis | 0.25 | 2 |
| **10** | Operator's safety | 0.75 | 3 |