# ICP-MS Computer Controlled Determination of some Trace Elements in Pharmaceutical Containers and Substances

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*The objective of our study has been the determination of eight trace elements in eight pharmaceutical matrices in order to ensure a complete quality control and patient safety. The paper presents computer-controlled ICP-MS methods for determination of cadmium, nickel and lead in different substances (magnesium stearate, stearic acid, talc, sugar, lactose and starch), respectively for vanadium, titanium, chromium, barium and aluminum in various containers (polyethylene, polyethylene terephtalate). Different methods for sample preparation were established, depending on the matrix nature. Microelement concentrations have been measured with ICP-MS equipment (Elan DRC-e, Perkin Elmer). Performance parameters of the methods have been effectuated according to the validation protocol from American Pharmacopeia. Moreover, an automatic Linux network-based backup system was put in place to prevent data loss for critical analyses and to ensure data security. Linearity was established for the range of concentrations between 1-800 ppb, specific for each element ($R^2$=0.9923-0.9998). Limits of detection (0.00024-0.00390 ppm) and limits of quantification (0.00048-0.00780 ppm) have been determined according to the isotope mass. The accuracy of methods, effectuated on samples spiked with known amounts of inorganic impurities, was between 97.1-98.8%. The method precision for each element and respectively for each matrix was satisfactory, in relation to values prescribed for this technique. Results are in concordance with the requirements imposed by the most recent European and British Pharmacopeia editions, regarding the limits and type of the element for the quality control of the containers and pharmaceutical substances. The presented ICP-MS methods allow for the accurate determination of quantitative trace elements in the pharmaceutical field.*

*Keywords: ICP-MS, pharmaceutical substances, containers*

The integration of Romania in the European Union leads, in the pharmaceutical domain too, to a process of harmonization with European Parliament and European Council directives and guides concerning the quality, safety and efficacy of drugs. A mandatory requirement concerning the control of drug quality refers to impurity detection and measurement, especially concerning impurities with potentially high toxic effects, or those that may interfere with therapeutic effects.

Given the potentially sensitive nature of quality control information in the pharmaceutical domain, data backup and security procedures become essential components of any analysis system. Since all instrument control and data processing in the ICP-MS equipment used, the ELAN DRC-e ICP-Mass Spectrometer, are computer controlled, computer security and backup may become a liability in case of failure. An automatic Linux based backup system was established in order to prevent data loss for critical analyses.

Many cations have a significantly toxic action due to their ability to replace essential metals in metalo-enzymes. There are especially severe requirements for evaluating impurities in drugs, with low admissibility thresholds, especially for toxic impurities – such as determining chromium 0.05 ppm, vanadium 0.1 ppm, lead 0.5 ppm, cadmium 0.6 ppm, etc., for pharmaceutical substances and for pharmaceutical containers alike. In order to obtain correct results in such situations one must make use of modern equipment and efficient methods.

One of the techniques imposed by European regulation in determining inorganic impurities is the inductively coupled plasma spectrometry. Within this technique, ICP-MS has the advantage of approaching analytical problems unable to be adressed by other techniques, due to its unique qualities, such as computer-controlled optimizations, multielement capability, high sample throughput, low detection limits, wide dynamic range, etc. Various applications of ICP-MS are quoted in the literature in fields as diverse as the environment [1], clinical / biological [2], geological [4], semiconductors [5], nuclear [6]. In the pharmaceutical field there is a limited amount of data regarding the ICP-MS technique [7]. The determination of metals in various pharmaceutical matrices has used other techniques such as: flame atomic absorption spectrometry, graphite furnace absorption spectrometry, inductively coupled plasma atomic emission spectrometry etc [8, 9, 10].

The current paper presents established ICP-MS methods of determining cadmium, nickel and lead in various substances such as magnesium stearate, stearic acid, talc, sugar, lactose and starch, respectively for vanadium, titanium, chromium, barium and aluminum in various containers such as polyethylene and polyethylene terephtalate.

## Experimental part

*Processing probes:*

1. Pharmaceutical substances:

a) sugar, lactose and starch: dilution 1:25 with 0.2% nitric acid;

b) talc: reflux with 0.5 M hydrochloric acid, 2.5:25 ratio, during 30 min;

c) magnesium stearate and stearic acid: digestion with concentrated nitric acid – hydrochloric acid 0.5:10:2 ratio, using a sample preparation with microwave in closed flasks

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**Table 1**
OPTIMAL OPERATING CONDITIONS FOR ELAN DRC-e

| No. | Parameter | Selected optimal values |
|---|---|---|
| 1 | RF power for ICP | 1250.00 watts |
| 2 | Nebulizing gas flow | 0.96 L/min |
| 3 | Auxiliary gas flow | 1.20 L/min |
| 4 | Ion lens | 8.20 (Autolens) |
| 5 | Integration time | 1000 m/s |
| 6 | Dwell time | 50 m/s |
| 7 | No. of sweeps / read | 20 |
| 8 | Mode detector | Dual |
| 9 | No. of replicates | 3 |

(Perkin Elmer) and a digestion program in two steps. Resulting solutions transfer to graded balloons of 50 mL and water is added until the volume is reached.

2. Pharmaceutical containers from different materials:

a) polyethylene: reflux with 0.1 M hydrochloric acid, 10:25 ratio, during one hour;

b) polyethylene terephtalate: heating to 50°C with 0.1 M hydrochloric acid, in 10:25 ratio, for five hours.

All dilutions were prepared with acids of Ultrapur Merck quality and transferred immediately from graded glass balloons in plastic flasks.

In order to check the accuracy we have applied the same methods of probe processing on probes which were spiked with known quantities of inorganic impurities in concentrations stipulated by the strictest admissibility limit.

*Equipment*

We have applied the analytical technique of inductively coupled plasma mass spectrometry, using ICP-MS equipment, model ELAN DRC-e, Perkin Elmer. The configuration was designed to measure trace elements in complex matrices. The Dynamic Reaction Cell Technology (DRC) allows the polyatomic influences to be completely eliminated and prevents the formation of new interferences, thus ensuring the possibility of detection at ultratrace level, even for difficult matrices.

Optimal operating conditions for this work are presented in table 1.

## Results and discussions

The successful usage of ICP-MS to determine trace elements in pharmaceutical substances and containers is conditioned by several specific aspects, such as establishing an adequate method for probe processing to allow for the precise determination at trace level of the interference of cations that are present in large quantities as well as polyatomic spectral interferences etc.

We have selected processing methods as simple as possible in order to ensure high reproducibility. For sugar, lactose and starch we preferred a direct dilution of the probe, while for talc and polyethylene a short term reflux. For magnesium stearate and stearic acid we have established a method of acid digestion according to an optimum program of decomposition. In order to simplify the mineralization process we have applied the digestion technique using a microwave oven.

We have removed possible interferences by using specific probe processing methods for respective matrices, the selection of the isotope with an area of zero possible interference and connecting the Dynamic Reaction Cell (DRC-e).

The method performance parameters were conducted according to stipulations of the validation protocol of analysis method in the pharmaceutical domain. According to the presentation in the American Pharmacopeia (USP-29), this protocol stipulates the realization of the detection limit, the quantification limit, linearity and linearity range, specificity (selectivity), accuracy and precision. In addition to these, we realized the parameter of "system stability", a criterion which is only required by users of the ICP-MS technique.

Detection limits and quantification limits are presented in table 2.

One can see in table 2 that low values which were obtained are close to those stipulated by the producer Perkin Elmer SCIEX. The low values of the detection limit and the quantification limit allow for the use of a larger dilution factor in probe processing, which leads to a decrease of the effect of the respective matrix.

The linearity and linearity domains are presented in table 3. For each element we realized the linearity on the 50-150% domain of the admissibility limit stipulated by the European Pharmacopeia 5. We have prepared 5 reference solutions from several elements according to requirements stipulated in the pharmaceutical monograph. The values of the correlation coefficients are included in the interval 0.9923-0.9998, above the minimum value of 0.990 which is admitted in international regulations concerning this performance criterion.

**Table 2**
DETECTION LIMITS AND QUANTIFICATION LIMITS FOR THE DETERMINATION OF SOME TRACE ELEMENTS IN PHARMACEUTICAL CONTAINERS AND SUBSTANCES

| No. | Element | Selected mass | Detection limit (ppm) | Quantification limit (ppm) |
|---|---|---|---|---|
| 1 | Chromium | 52 | 0.0006 | 0.0012 |
| 2 | Vanadium | 51 | 0.0015 | 0.0030 |
| 3 | Titanium | 47 | 0.0039 | 0.0078 |
| 4 | Aluminum | 27 | 0.0029 | 0.0058 |
| 5 | Barium | 138 | 0.0005 | 0.0010 |
| 6 | Cadmium | 111 | 0.0006 | 0.0012 |
| 7 | Nickel | 60 | 0.0002 | 0.0004 |
| 8 | Lead | 208 | 0.0003 | 0.0006 |

In order to demonstrate the system stability at a given time interval in the analysis from the initial standardization we used a standard solution of the initial calibration curve which was reanalyzed as a check standard. We decided that after 5 probes to check system stability. The value of the reanalyzed standard is 184.684 ppb (Al), which means -3.2% compared to the theoretical value, thus being within the interval of +/-10% admitted for concentrations larger than 1ppb.

The selectivity of the methods is ensured by the ability of the ELAN DRC-e equipment to monitor a single ion with a specific mass/charge ratio and by the presence of the Dynamic Reaction Cell.

The values obtained at accuracy evaluation are presented in table 4. These were computed as an average of recoveries for reference solutions which contain the respective element in admissible concentrations for the

**Table 3**
LINEARITY FOR THE DETERMINATION OF STUDIED TRACE ELEMENTS

| No. | Concentration (ppb) | | | Average intensity (cps) | | |
|---|---|---|---|---|---|---|
| I | Chromium | Vanadium | Titanium | Chromium | Vanadium | Titanium |
| 1 | 5.00 | 10.00 | 100.00 | 3633.33 | 8584.00 | 7049.66 |
| 2 | 9.31 | 19.46 | 195.04 | 5299.00 | 15072.00 | 12508.66 |
| 3 | 18.51 | 39.01 | 389.39 | 8533.00 | 28017.33 | 23019.00 |
| 4 | 28.00 | 58.88 | 584.84 | 11581.66 | 40976.33 | 33026.66 |
| 5 | 37.59 | 78.68 | 783.85 | 14565.33 | 53759.33 | 43341.00 |
| $R^2$ | 0.9930 | 0.9994 | 0.9991 | | | |
| II | Lead | Cadmium | Nickel | Lead | Cadmium | Nickel |
| 1 | 10.00 | 6.00 | 1.00 | 152250.43 | 11678.83 | 1722.16 |
| 2 | 28.654 | 14.908 | 1.089 | 310789.63 | 27949.05 | 2776.4 |
| 3 | 48.801 | 29.716 | 4.066 | 499362.01 | 53949.57 | 6248.32 |
| 4 | 69.355 | 41.637 | 5.741 | 700643.02 | 74613.44 | 8212.75 |
| 5 | 96.853 | 59.228 | 9.121 | 943103.99 | 104482.83 | 11305.78 |
| $R^2$ | 0.9986 | 0.9998 | 0.9923 | | | |
| III | Aluminum | Barium | - | Aluminum | Barium | - |
| 1 | 100.000 | 25.000 | - | 25853.667 | 15444.749 | - |
| 2 | 198909 | 49.032 | - | 50327.333 | 28115.000 | - |
| 3 | 387.277 | 98.869 | - | 88935.660 | 54711.300 | - |
| 4 | 583.285 | 198.531 | - | 127842.330 | 107465.070 | - |
| 5 | 785.387 | 393.964 | - | 168676.330 | 2033965.180 | - |
| $R^2$ | 0.9991 | 0.9996 | | | | |

**Table 4**
ACCURACY IN DETERMINING THE STUDIED TRACE ELEMENTS IN PHARMACEUTICAL SUBSTANCES AND CONTAINERS

| No. | Element | Measured concentration (ppm) | Theoretical concentration (ppm) | Recovery (%) |
|---|---|---|---|---|
| 1 | Chromium | 0.0449 | 0.0463 | 97.1 |
| 2 | Vanadium | 0.0952 | 0.0975 | 97.6 |
| 3 | Titanium | 0.9531 | 0.9735 | 97.9 |
| 4 | Aluminum | 0.9527 | 0.9682 | 98.4 |
| 5 | Barium | 0.4904 | 0.4963 | 98.8 |
| 6 | Cadmium | 2.9151 | 2.9716 | 98.1 |
| 7 | Nickel | 0.8910 | 0.9120 | 97.7 |
| 8 | Lead | 0.4694 | 0.4776 | 98.3 |

**Table 5**
PRECISION OF DETERMINATION METHODS FOR LEAD, CADMIUM AND NICKEL IN PHARMACEUTICAL SUBSTANCES

| No. | Substance | Probe | Concentration (ppm) | | |
|---|---|---|---|---|---|
| | | | Lead | Cadmium | Nickel |
| 1 | Magnesium stearate | P1 | 0.28887 | 0.00096 | 3.01873 |
| 2 | | P2 | 0.23851 | 0.0000 | 2.73290 |
| 3 | | P3 | 0.28515 | 0.00088 | 2.70267 |
| 4 | | P4 | 0.22060 | 0.00000 | 2.76859 |
| 5 | | P5 | 0.28052 | 0.00018 | 2.69733 |
| 6 | | P6 | 0.20640 | 0.0000 | 2.75205 |
| 7 | | Average value | 0.25360 | - | 2.77870 |
| 8 | | s | 0.03582 | - | 0.12077 |
| 9 | | RSD% | 14.12 | * | 4.34 |
| 10 | Stearic acid | P1 | - | - | 1.03826 |
| 11 | | P2 | - | - | 0.76284 |

| | | | | | |
|---|---|---|---|---|---|
| 12 | | P3 | - | - | 0.81777 |
| 13 | | P4 | - | - | 0.76231 |
| 14 | | P5 | - | - | 0.81099 |
| 15 | | P6 | - | - | 0.76916 |
| 16 | | Average value | - | - | 0.82690 |
| 17 | | s | - | - | 0.10641 |
| 18 | | RSD% | - | - | 12.86 |
| 19 | Talc | P1 | 0.1552 | 0.001727 | 0.2137 |
| 20 | | P2 | 0.1561 | 0.001430 | 0.1717 |
| 21 | | P3 | 0.1504 | 0.001658 | 0.2136 |
| 22 | | P4 | 0.1520 | 0.001340 | 0.1675 |
| 23 | | P5 | 0.1503 | 0.001629 | 0.2099 |
| 24 | | P6 | 0.1513 | 0.001191 | 0.1636 |
| 25 | | Average value | 0.1525 | 0.0015 | 0.1900 |
| 26 | | s | 0.00250 | 0.00021 | 0.02471 |
| 27 | | RSD% | 1.641 | 14.014 | 13.002 |
| 28 | Sugar | P1 | 0.04439 | - | - |
| 29 | | P2 | 0.04898 | - | - |
| 30 | | P3 | 0.04297 | - | - |
| 31 | | P4 | 0.05084 | - | - |
| 32 | | P5 | 0.04564 | - | - |
| 33 | | P6 | 0.05638 | - | - |
| 34 | | Average value | 0.04810 | - | - |
| 35 | | s | 0.00503 | - | - |
| 36 | | RSD% | 10.41 | - | - |
| 37 | Starch | P1 | 0.08260 | - | 0.02850 |
| 38 | | P2 | 0.09168 | - | 0.02525 |
| 39 | | P3 | 0.08455 | - | 0.02080 |
| 40 | | P4 | 0.08488 | - | 0.02561 |
| 41 | | P5 | 0.08472 | - | 0.02134 |
| 42 | | P6 | 0.08356 | - | 0.02507 |
| 43 | | Average value | 0.08530 | - | 0.02440 |
| 44 | | s | 0.00323 | - | 0.00289 |
| 45 | | RSD% | 3.78 | - | 11.8 |

* Was not computed because values were very low.

**Table 6**
PRECISION OF DETERMINATION METHODS FOR CHROMIUM, VANADIUM AND TITANIUM IN PHARMACEUTICAL CONTAINERS

| No. | Substance | Probe | Concentration (ppm) | | |
|---|---|---|---|---|---|
| | | | Chromium | Vanadium | Titanium |
| 1 | Polyethylene | P1 | 0.05665 | 0.02583 | 0.04890 |
| 2 | | P2 | 0.05348 | 0.02625 | 0.03013 |
| 3 | | P3 | 0.06055 | 0.02725 | 0.04000 |
| 4 | | P4 | 0.05528 | 0.03429 | 0.03101 |
| 5 | | P5 | 0.06301 | 0.02993 | 0.04007 |
| 6 | | P6 | 0.05657 | 0.03477 | 0.03009 |
| 7 | | Average value | 0.06000 | 0.02956 | 0.04000 |
| 8 | | s | 0.00353 | 0.03 | 0.01000 |
| 9 | | RSD% | 6.10 | 14.24 | 14.27 |

lowest threshold stipulated in international regulation. We have opted for this method for two reasons: the lack of certified reference materials for each type of pharmaceutical substance or container that was studies, and the lack of interference in the analyzed probes, which is due to the performance of the ELAN DRC-e equipment, which uses special interference minimization technologies (the Dynamic Reaction Cell – a patent of Perkin Elmer, Auto Lens, etc).

Results demonstrate that insignificant metal quantities were lost during the process of sample preparation.

Quantifying the precision of determination methods for trace lead, cadmium and nickel in pharmaceutical substances is detailed in table 5, and for chromium, vanadium, titanium, barium and aluminum in tables 6 and 7. The relative standard deviation was computed for each method on 6 determinations for a homogenous probe.

The resulting values are in conformity with stipulated values for this technique for low element concentrations.

All log and analysis information produced by the ELAN DRC-e ICP-Mass Spectrometer computer system was stored on a dedicated hard disk drive by a Linux-based procedure. The Linux system accesses and stores the data from shared folders, by a backup script. Backup information is also archived, and additional encryption procedures may be put into place if necessary.

**Table 7**
PRECISION OF DETERMINATION METHODS FOR ALUMINUM AND BARIUM IN PHARMACEUTICAL CONTAINERS

| No. | Substance | Probe | Concentration (ppm) | |
|---|---|---|---|---|
| | | | Aluminum | Barium |
| 1 | Polyethylene terephtalate | P1 | 1.04543 | 0.22423 |
| 2 | | P2 | 0.83500 | 0.29143 |
| 3 | | P3 | 0.97674 | 0.22117 |
| 4 | | P4 | 0.85327 | 0.29324 |
| 5 | | P5 | 0.96979 | 0.22022 |
| 6 | | P6 | 0.798697 | 0.286703 |
| 7 | | Average value | 0.91001 | 0.26007 |
| 8 | | s | 0.09751 | 0.03765 |
| 9 | | RSD% | 10.68 | 14.7 |
| 10 | Polyethylene | P1 | 1.23631 | - |
| 11 | | P2 | 1.19548 | - |
| 12 | | P3 | 1.20688 | - |
| 13 | | P4 | 1.16196 | - |
| 14 | | P5 | 1.23100 | - |
| 15 | | P6 | 1.23380 | - |
| 16 | | Average value | 1.21091 | - |
| 17 | | s | 0.02906 | - |
| 18 | | RSD% | 2.4 | - |

## Conclusions

This article presents a study concerning the use of ICP-MS technique for quality control in the pharmaceutical domain.

-Methods were established for determining cadmium, nickel and lead in various substances such as magnesium stearate, stearic acid, talc, sugar, lactose and starch, respectively for vanadium, titanium, chromium, barium and aluminum in various containers such as polyethylene and polyethylene terephtalate.

-Methods were established for processing probes according to matrix types.

-The established methods were validated. The resulting values for detection limits, quantification limits, linearity, precision and accuracy demonstrate that these methods are in conformity with performance criteria established by the American Pharmacopeia.

Results are compatible with requirements indicated by the most recent editions of the European and British Pharmacopeias regarding limits and element type in quality control for pharmaceutical substances and containers. The ICP-MS methods allow for the quantitative determination of trace elements in the pharmaceutical domain.

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