Challenge

Determination of trace element impurities in eye drops and contact lens solutions.

Solution

A simple and effective method for routine preparation and analysis of pharmaceutical samples according to ICH Q3D and USP 232, 233 regulations using PlasmaQuant MS Q.

Metals Content in Eye Drops and Contact Lens Solutions by ICP-MS

Introduction

Eye medications are used to diagnose, treat, and prevent eye diseases. Most eye medicines need a prescription. However, artificial tears to lubricate the eye and ocular decongestants to decrease redness are available as over-the-counter eye drops. Eye drops are most often saline solutions including medications to treat various conditions of the eye. Sometimes, they contain no medication and are meant to lubricate the eyes or to rinse out foreign bodies. Artificial tears have various formulations and viscosities. Some may contain bicarbonate ions, and varying viscosity as well as tonicity. Except for artificial tears, many of these formulations are neither soluble in aqueous nor organic media.

A contact lens solution is designed to rinse, store and clean the contact lenses. It also kills bacteria, prevents bacteria growth and keeps the contact lenses safe when they come into contact with the eyes. Solutions come in many different formulas, all aimed to accommodate slightly different needs, but mostly they all do a very similar job. Classified as parenteral medication and relatively large daily doses, the inorganic components in these pharmaceutical products must be present at low concentrations. Therefore, ICP-MS is the most appropriate technique for the determination of trace elements in eye drops.

The International Conference on Harmonization Guideline for Elemental Impurities Q3D (ICH Q3D) (1) has established maximum permitted daily exposure (PDE) limits for elemental impurities in pharmaceutical products. Table 1 shows PDE limits for oral, parenteral, and inhalation exposures of all interesting

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elements. Besides that, ICH Q3D also states that if the total elemental impurity level from all sources in the drug product is expected to be consistently less than 30 percent of the PDE, then additional controls are not required.

This application note demonstrates the performance of the PlasmaQuant MS Q for the analysis of Class 1, 2 and 3 elements in a variety of eye drop and contact lens solutions according to USP 232, 233 regulations (2-3).

Table 1: Permitted Daily Exposure (PDE) for elemental impurities

Element	Class	Oral PDE [µg/day]	Parental PDE [µg/day]	Inhalation PDE [µg/day]
Cadmium	1	5	2	2
Lead	1	5	5	5
Arsenic (inorganic)	1	15	15	2
Mercury (inorganic)	1	30	3	1
Cobalt	2A	50	5	3
Vanadium	2A	100	10	1
Nickel	2A	200	20	5
Thallium	2B	8	8	8
Gold	2B	100	100	1
Palladium	2B	100	10	1
Iridium	2B	100	10	1
Osmium	2B	100	10	1
Rhodium	2B	100	10	1
Ruthenium	2B	100	10	1
Selenium	2B	150	80	130
Silver	2B	150	10	7
Platinum	2B	100	10	1
Lithium	3	550	250	25
Antimony	3	1200	90	20
Barium	3	1400	700	300
Molybdenum	3	3000	300	30
Copper	3	3000	300	30
Tin	3	6000	600	60
Chromium	3	11000	1100	3

Materials and Methods

Samples and reagents

Two commercially available eye drops and two contact lens solutions were locally purchased and present two different types of matrices classified, as shown in Table 2.

Table 2: Characteristics of eye drops and contact lens solution tested

Sample	Type	Characteristics	Daily dose / Rinse volume
1 and 2	Eye drops	Hyaluronic acid	10 drops per day
3 and 4	Contact lens solution	Polyhexanide biguanide EDTA NaCl KCl	2 g in each case

Even though eye drops and contact lens solutions are liquid and water-soluble, a direct analysis can be performed only with dilution. However, and because of matrix effects observed for both products, a digestion procedure was performed. All samples were prepared by weighing 0.4 g of sample and adding 2 mL of reverse aqua regia (3:1 - HNO_3: HCl) into 50 mL autosampler plastic tubes. The tubes were uncapped and heated to 75 ºC for 15 minutes in a heater block. When the heating program finished, the resulting solutions were allowed to cool down and filled to the 50 mL mark with ultrapure water prior to the analysis by ICP-MS.

The samples were measured, using an external calibration approach using calibration solutions prepared in the same diluent as the samples (2 mL reverse aqua regia in 48 mL ultrapure water). The calibration solutions contained all 24 of the elements listed in Table 1 to be checked for PDE (in µg/g) using the latest USP <232> version, Elemental Impurities - Limits document (Mar-Apr 2016) (2). The calibration range for all elements is shown in Table 3 and is in accordance with the calculated J value.

Table 3: Calibration concentration of standards used

Element	Calibration Std1 at 0.5J [µg/L]	Calibration Std2 at J [µg/L]	Calibration Std3 at 1.5J [µg/L]
Cadmium	1	2	3
Lead	2.5	5.0	7.5
Arsenic (inorganic)	7.5	15.0	22.5
Mercury (inorganic)	1.5	3.0	4.5
Cobalt	2.5	5.0	7.5
Vanadium	5	10	15
Nickel	10	20	30
Thallium	4	8	12
Gold	25	50	75
Palladium	2.5	5	7.5
Iridium	2.5	5	7.5
Osmium	2.5	5	7.5
Rhodium	2.5	5	7.5
Ruthenium	2.5	5	7.5
Selenium	40	80	120

Silver	5	10	15
Platinum	2.5	5	7.5
Lithium	62.5	125	187.5
Antimony	22.5	45	67.5
Barium	175	350	525
Molybdenum	375	750	1125
Copper	75	150	225
Tin	150	300	450
Chromium	275	550	825

Instrumentation

A PlasmaQuant MS Q ICP-MS with Analytik Jena ASPQ 3300 autosampler was used for the analysis of 24 elements specified in the USP <232> and ICH Q3D. The operating conditions are summarized in Table 4 for two different integrated Collision Reaction Cell (iCRC) gas modes (Helium and Hydrogen). Internal standardization was applied using Sc, Y, Tb, and Bi at 20 µg/L added on-line via a Y-piece.

Table 4: PlasmaQuant MS Q settings and method parameters for eye drop and contact lens solutions analysis

Parameter	Settings
Plasma gas flow	9.0 L/min
Auxillary gas flow	1.20 L/min
Nebulizer gas flow	0.98 L/min
Plasma RF power	1.30 kW
Sampling depth	5.0 mm
Spray chamber type and temperature	Quartz glass Scott-type with Peltier chiller, 4°C
Pump rate / Tubing	10 rpm – black/black PVC tubing for sample; orange/green for internal standards
Sampling uptake time	60 s
iCRC	H_2 – 140 mL/min He – 120 mL/min
Stabilization delay	20 s
Dwell time	10 - 20 ms
Scan mode	Peak hopping, 1 pt./peak
No. of scans per replicate	20
No. of replicates per sample	5
Acquisition time	300 s

Results and Discussion

Limits of detection and sample results

Low limits of detection are particularly crucial for some of the potentially toxic trace elements defined in USP <232>, notably As, Cd, Hg, and Pb. Table 5 reports the method detection limit (MDL), and concentrations in all samples analyzed, which were less than 30% of maximum PDE for parenteral medications, meaning no further controls are required, and all products are safe, according to ICH Q3D.

Table 5: MDL and sample concentrations

Element	MDL [µg/L]	Control threshold, 30% PDE, [µg/L]	Sample 1 [µg/L]	Sample 2 [µg/L]	Sample 3 [µg/L]	Sample 4 [µg/L]
^{7}Li	0.20	187.5	<MDL	<MDL	0.29	<MDL
^{51}V	0.06	7.5	<MDL	<MDL	2.0	2.1
^{52}Cr	0.49	825	<MDL	<MDL	1.2	0.70
^{59}Co	0.01	3.75	<MDL	<MDL	<MDL	0.01
^{60}Ni	0.05	15	0.07	<MDL	0.10	0.41
^{65}Cu	0.16	225	<MDL	<MDL	0.17	<MDL
^{75}As	0.01	11.25	<MDL	0.04	0.12	0.10
^{78}Se	0.06	60	<MDL	< MDL	0.10	0.18
^{98}Mo	0.02	1125	<MDL	0.08	1.2	0.14
^{101}Ru	0.02	7.5	<MDL	<MDL	<MDL	<MDL
^{103}Rh	0.01	7.5	<MDL	0.01	0.02	<MDL
^{105}Pd	0.01	7.5	<MDL	0.25	< MDL	<MDL
^{107}Ag	0.01	7.5	<MDL	0.03	< MDL	<MDL
^{111}Cd	0.001	1.5	0.001	<MDL	0.01	0.01
^{118}Sn	0.18	450	<MDL	<MDL	0.43	< MDL
^{121}Sb	0.07	67.5	<MDL	<MDL	1.6	0.27
^{137}Ba	0.11	525	<MDL	<MDL	0.36	<MDL
^{189}Os	0.25	7.5	<MDL	<MDL	<MDL	<MDL
^{193}Ir	0.01	7.5	<MDL	<MDL	0.03	0.02
^{195}Pt	0.007	7.5	<MDL	<MDL	<MDL	<MDL
^{197}Au	0.06	75	<MDL	2.4	0.79	0.27
^{202}Hg	0.03	2.25	<MDL	0.13	0.05	<MDL
^{205}Tl	0.01	6	<MDL	<MDL	0.07	0.03
^{206,7,8}Pb	0.004	3.75	<MDL	<MDL	0.06	0.05

The method detection limits were measured under routine laboratory conditions and are well below the target limits of each element. The MDL is based on the measurement of 12 blank solutions measured on two non-consecutive days and is defined as three times the standard deviation of the 12 blank measurements.

Spike recovery – accuracy

By following USP <232> guidelines, spike recoveries are used to assess ICP-MS accuracy. Figure 1 shows spike recoveries for all samples at both levels, 0.5J and 1.5J, which were spiked before the heating stage.

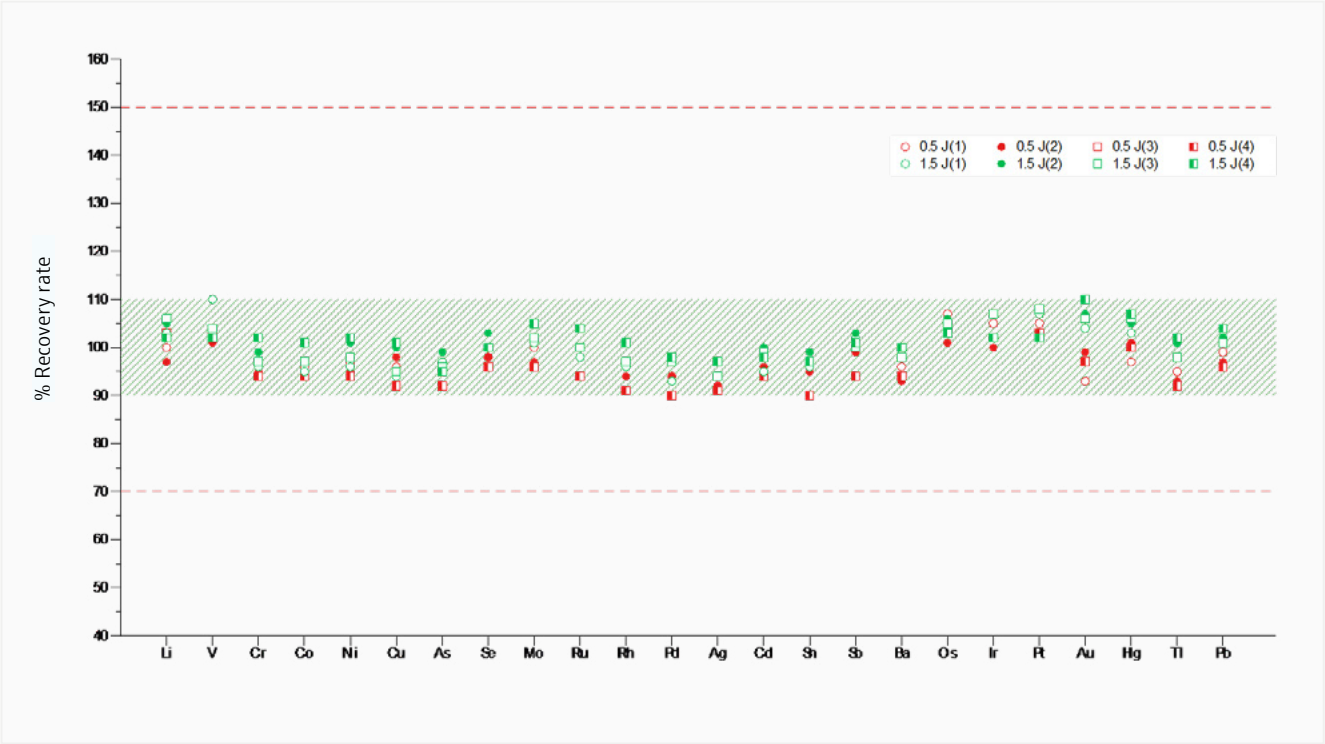

Figure 1: Recovery rate (in %) for 0.5J and 1.5J spike levels for all samples tested

The acceptance criteria defined in USP <233> for this kind of test are recoveries within 70 and 150 % range. Figure 1 clearly shows that these criteria were easily met using the PlasmaQuant MS Q with average recoveries ranging from 90 to 110 %. This proves that the analytes remained in solution in all four sample solutions tested.

Stability – repeatability

Six independent aliquots of each sample, spiked with concentration J prior to digestion, were used to check the repeatability of the measurements. These independent aliquots were also analyzed on 2 different days (12 measurements) as shown in Figure 2. RSDs of less than 3% were achieved on both days for most of the elements, demonstrating the stability of the method.

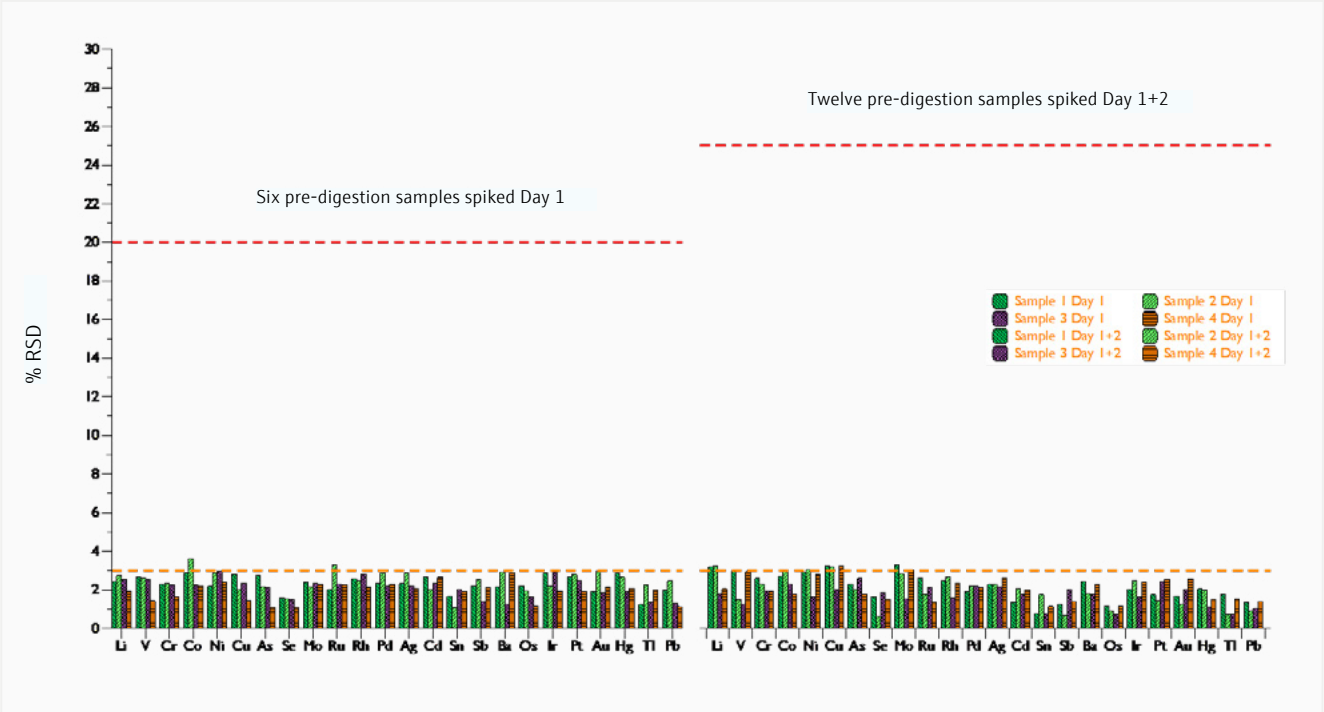

Figure 2: RSDs of six pre-digestion of all four samples analyzed in two different days. Criterium of 20% for day one and 25% for day-to-day stabilities accordingly to USP <232>

Conclusion

The PlasmaQuant MS Q is well suited for the determination of trace elemental impurities in eye drops and contact lens solutions. This was proven by method validations that tested the efficiency to meet the target values and performance criteria as defined in the ICH guidelines and USP Chapters <232> <233>.
This application note describes a simple and effective method for the analysis of pharmaceutical materials by ICP-MS in combination with the required digestion in a heating block in reverse aqua regia to dissolve the suspensions and overcome matrix effects.

The PlasmaQuant MS Q includes unique and patented technologies that significantly lower running costs and provide ease-of-use without compromising performance. These include the Eco Plasma, the only plasma system that runs on <11 L/min of argon gas without compromising plasma robustness or analyte sensitivity. The integrated Collision Reaction Cell is a powerful yet simple to use interference management system that removes spectroscopic interferences on essential pharmaceutical elements, including Cr, As, Se, V, and Cu.

References

[1] Guideline for Elemental Impurities: Q3D, International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2014.
[2] General Chapter <232> Elemental Impurities—Limits, USP39. Publishing in Pharmacopeia Forum 42(2) [Mar.–Apr. 2016]
[3] General Chapter <233> Elemental Impurities—Procedures, Second Supplement to USP 38–NF 33, 2015

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