Визначення мікроелементів в очних краплях за допомогою NexION ICP-MS

Очні краплі – звичайні ліки, які доступні в аптеках як без рецепта, так і за рецептом в залежності від діючих правил в конкретній країні. Оскільки очні краплі класифікуються як парентеральні ліки і мають відносно великі добові дози, неорганічні компоненти в очних краплях повинні бути присутніми в низьких концентраціях.
В результаті ICPMS є найбільш підходящим методом для визначення мікроелементів в очних краплях.

Міжнародна конференція з гармонізації елементарних домішок Q3D (ICH Q3D) встановила максимально допустимі межі добового впливу (PDE) для елементарних домішок у фармацевтичній продукції. Ці елементи і максимальні межі PDE для перорального, парентерального та інгаляційного впливу наведені в таблиці 1. ICH Q3D також стверджує, що якщо загальний рівень домішок в готовому лікарському препараті менше 30% PDE, препарат безпечний для використання без подальшого контролю.

ПОСИЛАННЯ НА ДЖЕРЕЛО:

https://www.perkinelmer.com/lab-solutions/resources/docs/app_014833_01_nexion_icp-ms-ich-q3d_traceelements_eyedrops.pdf

SocTrade постачає та обслуговує спеціалізоване й аналітичне лабораторне обладнання. Спеціалізоване - означає, що його використовують в межах однієї галузі. Ми дуже сильні в оснащенні лабораторій агро- та харчової продукції, а також лабораторій, що контролюють якість нафтопродуктів. Аналітичне обладнання — універсальне, але більш складне і використовується для високоточних аналізів у науково-дослідних або розвинутих промислових лабораторіях.

За роки роботи в цій порівняно вузькій, але дуже цікавій сфері ми накопичили величезний досвід, яким хочемо ділитися. Тому проводимо кругові випробування, розробляємо нові ДСТУ, співпрацюємо з інститутами, надаючи їм обладнання для дослідницьких і освітніх цілей, беремо участь у лабораторних виставках і конференціях та організовуємо їх. Тобто з ентузіазмом долучаємося до будь-якої діяльності, спрямованої на підвищення рівня контролю якості та природничих наук в Україні.

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APPLICATION NOTE

ICP - Mass Spectrometry

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Determination of Trace Elements in Eye Drops with the NexION ICP-MS

Introduction

Eye drops are commonly used medications which are available both over-the-counter and as prescriptions in various forms. They are used to soothe irritated eyes, treat medical conditions, and provide artificial tears. As a result of these varieties, eye drops are available in different formulations: pure liquids, suspensions, those which contain benzalkonium chloride (a preservative and antimicrobial agent), and combinations of suspensions and benzalkonium chloride. With the exception of artificial tears, many of these formulations are neither soluble in aqueous or organic media.

Because eye drops are classified as a parenteral medication and have relatively large daily doses, the inorganic components in eye drops must be present at low concentrations. As a result, 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. These elements and maximum PDE limits for oral, parenteral, and inhalation exposures are shown in Table 1. ICH Q3D also states that if the total impurity level in a finished drug product is less than 30% of the PDE, the medication is safe for use without further controls being implemented.

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Table 1. Maximum Daily Exposures for Elements Defined in ICH Q3D.

Element	Class	Oral Daily Dose PDE* (µg/day)	Parenteral Daily Dose PDE* (µg/day)	Inhalation Daily Dose PDE* (µg/day)
Cd	1	5	2	2
Pb	1	5	5	5
As (Inorganic)	1	15	15	2
Hg (Inorganic)	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Ir	2B	100	10	1
Pd	2B	100	10	1
Pt	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Ag	2B	150	10	7
Se	2B	150	80	130
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

* PDE = Permissible daily exposure based on a 50 kg person.

It is important when analyzing pharmaceutical materials to maintain compliance with 21 CFR Part 11, which is mandatory for companies and their suppliers that operate in regulated environments to sell products into the United States. This regulation puts forward the criteria for electronic records, electronic signatures, and audit trails to ensure data integrity and reliability during analytical testing. Syngistix™ for ICP-MS Enhanced Security™ software was developed to help companies comply with regulations and sustain best practices delineated in 21 CFR Part 11.

This work discusses the sample preparation and analysis of Class 1, 2, and 3 elements in a variety of eye-drop products with the NexION ICP-MS and Syngistix for ICP-MS Enhanced Security software to aid compliance with 21 CFR Part 11 regulations, following the criteria defined in ICH Q3D.

Experimental

Samples and Sample Preparation

Four different brands of eye drops were purchased locally and can be divided into three categories, as shown in Table 2.

Although eye drops are liquid, only "artificial tears" can be analyzed directly with only dilution. The suspensions are not water-soluble and must be digested, while eye drops containing benzalkonium chloride will have low gold (Au) recoveries unless they are digested. Since artificial tears were not analyzed in this work, all samples were prepared by adding 0.4 g of sample to 2 mL of inverse aqua regia (i.e. 3:1 HNO_3 : HCl) in 50 mL autosampler tubes. The tubes were uncapped and heated to 75 °C for 15 minutes in a water bath. When the heating program finished, the resulting solutions were clear. The samples were allowed to cool and diluted to 50 mL with deionized water for analysis.

Table 2. Characteristics of Eye Drop Samples Tested.

Brand	Characteristic	Daily Dose
1, 2	Benzalkonium Chloride	18 Drops Per Day
3	Solid Suspension	12 Drops Per Day
4	Solid Suspension + Benzalkonium Chloride	12 Drops Per Day

Analyses were performed against two-point external calibrations where the standards were prepared in inverse aqua regia to match the acid concentration of the samples (i.e. 2 mL inverse aqua regia in 48 mL deionized water). Table 3 shows the elements of interest, their analytical masses, as well as the concentrations of the calibration standards for each element.

Instrumental Conditions

All analyses were performed on a NexION ICP-MS using the conditions and parameters in Table 4. Standard sample introduction conditions were used, with all measurements made against external calibration curves. Gallium (Ga), germanium (Ge), indium (In), and terbium (Tb) were used as internal standards. To simplify the analysis, all measurements were made in Collision mode using helium (He) as a cell gas to remove potential interferences.

Table 3. Analyte and Concentrations of Calibration Standards.

Analyte	Mass (amu)	Standard 1 (µg/L)	Standard 2 (µg/L)
Li	7	125	375
V	51	5.00	15.0
Cr	52	550	1650
Co	59	2.50	7.50
Ni	60	10.0	30.0
Cu	63	150	450
As	75	7.50	22.5
Se	78	40.0	120
Mo	95	750	2250
Ru	101	5.00	15.0
Rh	103	5.00	15.0
Pd	105	5.00	15.0
Ag	107	5.00	15.0
Cd	111	1.00	3.00
Sn	118	300	900
Sb	121	45.0	135
Ba	138	350	1050
Os	189	5.00	15.0
Ir	193	5.00	15.0
Pt	195	5.00	15.0
Au	197	50.0	150
Hg	202	1.50	4.50
Tl	205	4.00	12.0
Pb*	206+207+208	2.50	7.50

* The Pb isotopes were summed to account for radioactive decay of higher mass elements.

Table 4. NexION Instrumental Conditions/Parameters.

Parameter	Value
Nebulizer	MEINHARD® Plus Glass Type C
Spray Chamber	Glass Cyclonic, 4 °C
RF Power	1600 W
Sweeps	30
Dwell Time	50-100 ms
Replicates	3
Cell Gas	Helium

Results and Discussion

The concentrations for all elements in all samples analyzed were less than 30% of the maximum PDE for parenteral medications, meaning that controls are not required and that the medications are considered safe, according to ICH Q3D.

Although four different eyedrops were analyzed, for clarity, results for Sample 4 (Table 2) are presented. This medication was a solid suspension which also contained benzalkonium chloride, making it the most challenging sample.

To establish the accuracy of the methodology, analyte spikes at both the low and high calibration levels, as well as at the mid-point of the calibration curve, were added to the samples prior to heating. Adding the spikes at this point and carrying them through the complete sample preparation and analysis proves that analytes are not lost. Figure 1 shows that all recoveries are within 10%, thereby establishing the accuracy of the methodology.

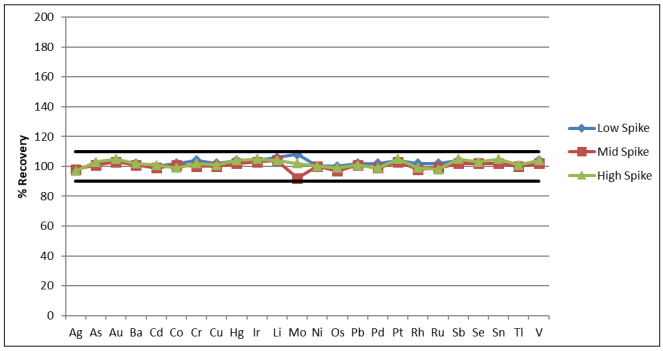

Figure 1. Pre-sample preparation spike recoveries at the low, medium, and high calibration concentrations.

With the accuracy of methodology verified, the stability of the measurements was evaluated by spiking six separate samples at the mid-point concentration on the calibration curve prior to digestion. These samples were then analyzed and showed RSDs less than 3% across the six samples, as shown in Figure 2, demonstrating the stability of the methodology.

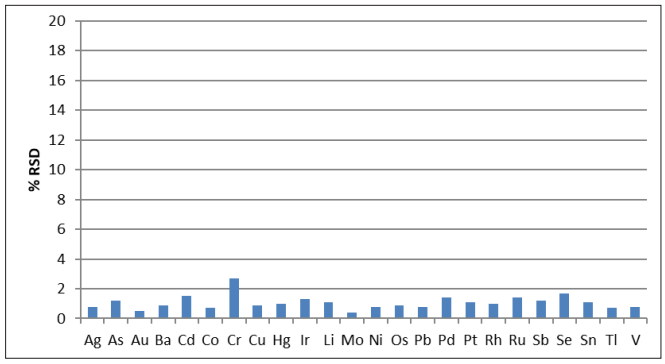

Figure 2. %RSDs of six pre-digestion sample spikes of individual samples.

The day-to-day stability of the methodology was determined by analyzing the same six solutions used for the repeatability test on two different days. With RSDs of the 12 measurements being less than 5% (Figure 3), both the day-to-day stability of the methodology and samples is established, meaning that samples can be prepared a day in advance prior to analysis and still yield correct results.

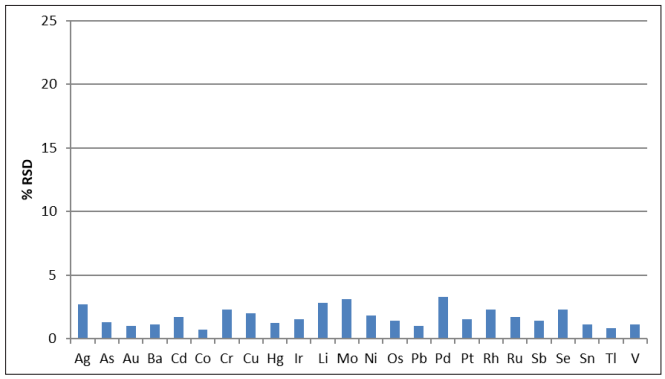

Figure 3. RSDs of six pre-digestion spikes of individual samples analyzed over two days (12 total measurements).

Conclusion

This work has demonstrated the ability of the NexION ICP-MS to successfully measure elemental components in three classes of eye drops: artificial tears, suspensions, and those containing benzalkonium chloride. Although liquids, the eye drops still required digestion in a heating block in reverse aqua regia to dissolve the suspensions and overcome the effects of benzalkonium chloride. The developed methodology (both sample preparation and analytical) demonstrates both accuracy and stability.

References

1. *Guideline for Elemental Impurities: Q3D,* International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2014.

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