Challenge

Quality control on trace elemental impurities of sugar solutions used as excipients for pharmaceutical products.

Solution

ICP-OES with exceptionally high sensitivity, high matrix tolerance and an industry leading high-resolution optical system.

Determination of Elemental Impurities in Sorbitol as Pharmaceutical Excipient

Introduction

As all polyols, sorbitol and sorbitol syrup are sugar alcohols or hydrogenated carbohydrates. They are also known as sugar replacers, bulk sweeteners or sugar-free sweeteners. Sorbitol is widely used as a pharmaceutical excipient in direct compression applications to produce tablets, where it provides bulk to the drug products. Especially in modern formulations, like consumer-friendly lozenges or chewable tablets, sorbitol has gained popularity due to its sweet taste and tooth-friendliness. But also in conventional tablets the usage of polyols is increasing.

Pharmaceutical excipients are substances other than the active pharmaceutical ingredient (API) that are intentionally included in an approved drug delivery system or a finished drug product. Therefore, they need to be considered as part of the risk assessment for elemental impurities in final pharmaceutical products. The limits and the type of impurities for each excipient are usually specified in monographs by the issuing Pharmacopoeia. For instance, the European Pharmacopoeia defines the limits for nickel (<1.0 ppm) and lead (<0.5 ppm) in sorbitol products that are used as excipients for the manufacturing of pharmaceuticals.[1]

Since sorbitol is predominantly used in the manufacturing process of tablets for oral administration, class 1 and class 2A trace elemental impurities defined in USP <232> are often analyzed alongside nickel and lead.[2] Due to the release of

USP chapters <232> and <233> as well as the ICH Q3D guidelines, ICP-OES and ICP-MS have found their way as a routine instrumentation into the QC labs of the pharmaceutical industry. [2-4]

Sample transportation into an ICP system requires the dilution of viscous samples such as sorbitol in order to ensure reliable aerosol formation in the spray chamber/nebulizer system. At the same time, sample dilution is desired to be kept at a minimum level in order to not compromise the achievable limits of quantification of the employed method. Hence, aspirating high matrix samples into an ICP requires a robust plasma and a vertically oriented torch system. In this regard, the PlasmaQuant 9100 Elite ICP-OES offers a high-frequency generator in combination with the unique V-Shuttle torch, which can handle high matrix loadings up to saturated salt solutions. This enables the analyst to run small dilution factors. In combination with the high sensitivity of the instrument, low method-specific limits of quantification can be achieved, which is crucial when analyzing trace elements defined in USP regulations. Commonly occurring interferences in ICP-OES are addressed by the high-resolution optical system of the PlasmaQuant 9100 Elite, which allows for an interference-free analysis of trace elements in typical pharmaceutical matrices.

Materials and Methods

Sample preparation

Prior to analysis the sorbitol sample (70%, liquid non-crystallizing) was diluted ten-fold with a 1% (v/v) HNO_3 and 1% HCl (v/v) solution. Calibration was performed as standard addition. The diluted sample was spiked with single standard solutions of arsenic and mercury (Sigma-Aldrich, 1000 mg/L) and a multi-element standard solution (Merck, 1000 mg/L).

Calibration

The spiked concentrations for the applied standard additions calibration are displayed in Table 1. A 7.7% (w/v) D(+)-glucose monohydrate (Merck, ≥ 99%) solution (in 1%(v/v) HNO_3 + 1% HCl (v/v)) was used as blank solution.

Table 1: Concentration levels of standard addition calibration

Element	Unit	Add. Std. 1	Add. Std. 2	Add. Std. 3
As	µg/L	50	100	200
Cd	µg/L	50	100	200
Hg	µg/L	50	100	200
Pb	µg/L	50	100	200
Co	µg/L	50	100	200
Ni	µg/L	50	100	200
V	µg/L	50	100	200

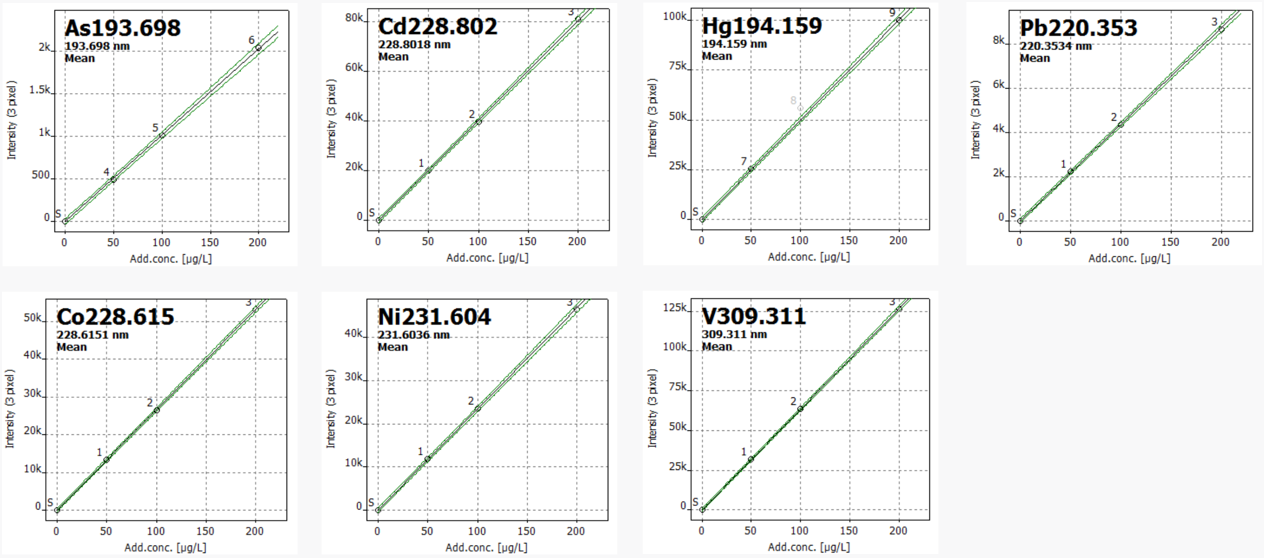


Figure 1: Calibration curves (black) and confidence levels (green)

Instrumentation

Instrument settings

For the analysis a PlasmaQuant 9100 Elite ICP-OES equipped with a standard sample introduction kit was used in combination with a Teledyne Cetac ASX 560 autosampler incl. ENC-560DC enclosure. The detailed system configuration is shown in Table 2.

Table 2: Configuration of the PlasmaQuant 9100 Elite equipped with standard kit

Parameter	Specification
Plasma Power	1350 W
Plasma Gas Flow	14.0 L/min
Auxiliary Gas Flow	0.5 L/min
Nebulizer Gas Flow	0.6 L/min
Nebulizer	Seaspray, 2.0 mL/min, Borosilicate
Spray Chamber	Cyclonic Spray Chamber with Dip Tube,50 mL, Borosilicate
Outer Tube/Inner Tube	Quartz/Quartz
Injector	Quartz, ID: 2 mm
Pump Tubing	PVC (black, black)
Sample Pump Rate	1.0 mL/min
Sample Uptake Delay	120 s
Argon-Humidifier	Yes

Method and evaluation parameters

Table 3: Overview of method-specific evaluation parameters

Element	Line [nm]	Plasma View	Integration Mode	Read Time [s]	Evaluation			
					No. of Pixel	Baseline Fit, Pixel No.	Polyn. Degree	Correction
As	193.698	axial	Peak	10	3	static	auto	-
Cd	228.802	axial	Peak	3	3	ABC[1]	auto	-
Hg	194.159	axial	Peak	10	3	static	auto	-
Pb	220.353	axial	Peak	10	3	ABC	auto	-
Co	228.615	axial	Peak	3	3	ABC	auto	-
Ni	231.604	axial	Peak	3	3	ABC	auto	-
V	309.311	axial	Peak	3	3	ABC	auto	-

[1] Automatic Baseline Correction

Results and Discussion

Low limits of quantification (LOQ) are particularly important for some of the potentially toxic trace elements defined in USP 232, notably arsenic, cadmium, mercury and lead. The LOQ for each target element is reported in Table 4. The method LOQ takes all sample preparation steps into account and represents the limit concentration in the raw sample. In general LOQs significantly below the defined threshold limits within the European Pharmacopoeia (nickel, lead) can be achieved. The sorbitol test specimen showed no considerable levels of elemental impurities. Signals for all investigated elements were found to be below the respective LOQ.

Table 4: Results of sorbitol sample

Element	Line [nm]	Instrument LOQ [µg/L]	Method LOQ [µg/L]	Concentration [µg/L]
As	193.698	9.03	90.3	<LOQ
Cd	228.802	0.66	6.60	<LOQ
Hg	194.159	0.42	4.20	<LOQ
Pb	220.353	1.20	12.0	<LOQ
Co	228.615	1.11	11.1	<LOQ
Ni	231.604	1.05	10.5	<LOQ
V	309.311	0.63	6.30	<LOQ

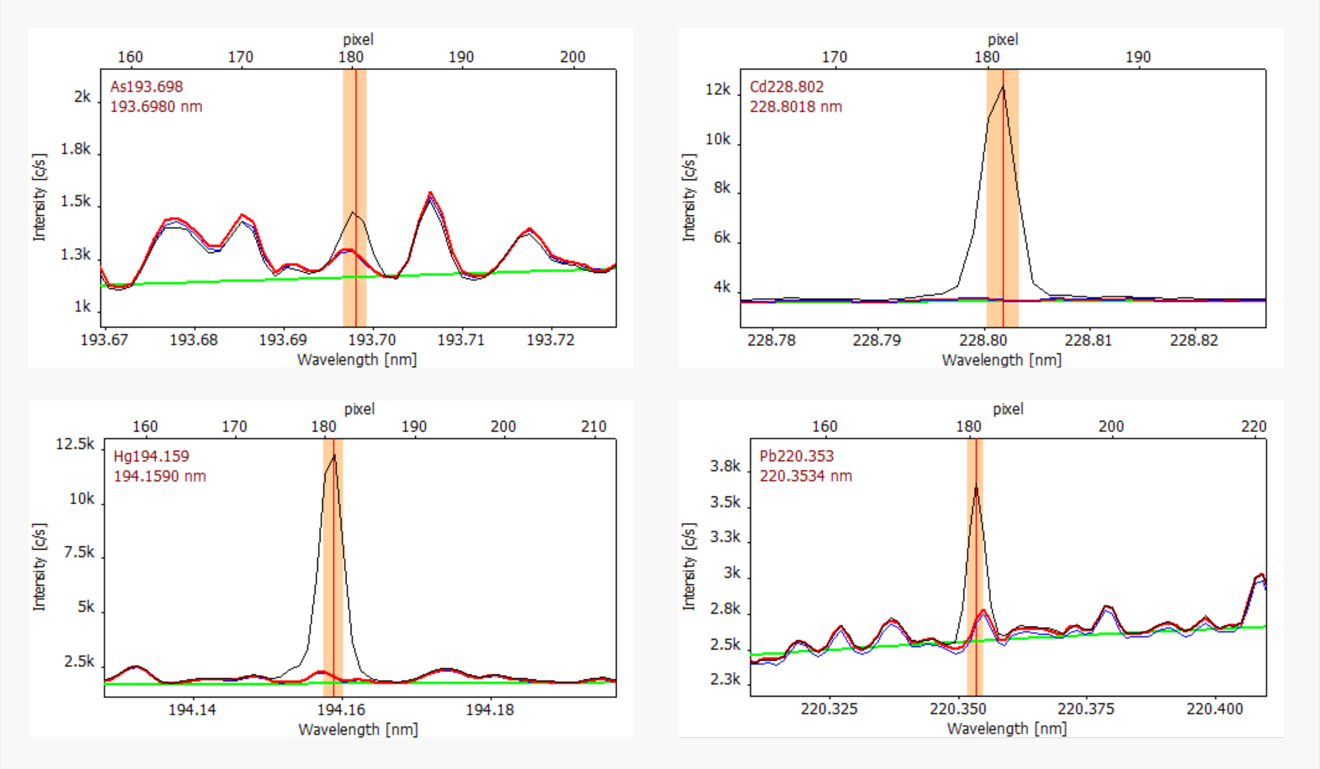
Instrument LOQ – determined in in 7.7 % (w/v) glucose monohydrate solution
Method LOQ – refers to undiluted sample

Validation in terms of accuracy and precision of the applied method was performed via spike recovery testing in the matrix of the tested samples. Here, the sorbitol sample was spiked with a target element concentration of 25 µg/L. The developed method provides excellent accuracy with recoveries ranging from 94% to 101% with a precision of well below 5% RSD. The results for the individual elements are shown in Table 5.

Table 5: Method-specific spike recovery rates in the diluted sorbitol sample

Element	Line [nm]	Measured Concentration [mg/L]	Spiked Concentration [µg/L]	Recovery Rate [%]	RSD [%]
As	193.698	<LOQ	25	99	4.5
Cd	228.802	<LOQ	25	99	0.7
Hg	194.159	<LOQ	25	94	0.4
Pb	220.353	<LOQ	25	101	1.8
Co	228.615	<LOQ	25	100	0.8
Ni	231.604	<LOQ	25	100	1.0
V	309.311	<LOQ	25	99	0.9

A closer look to the recorded high-resolution spectra reveals that all potential spectral interferences are well resolved by the optical system. Representative spectral overlays of all investigated elements are given in Figure 2.



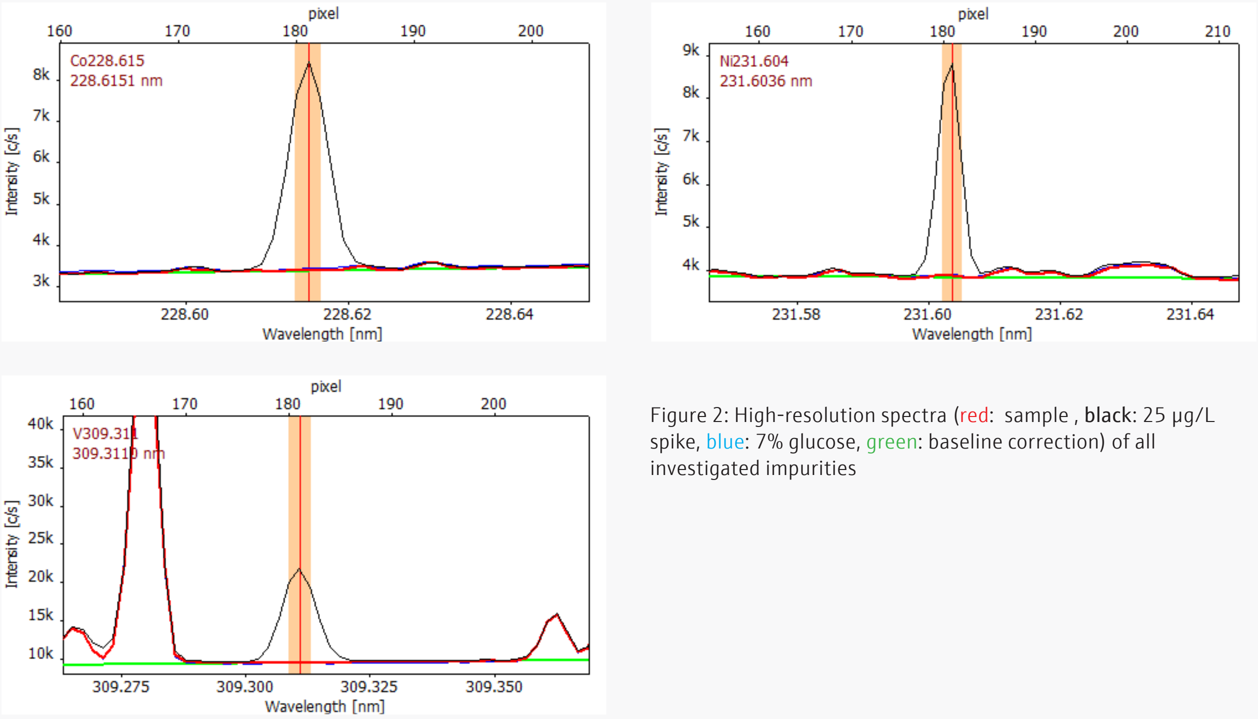


Figure 2: High-resolution spectra (red: sample , black: 25 µg/L spike, blue: 7% glucose, green: baseline correction) of all investigated impurities

Conclusion

In the context of the manufacturing of pharmaceutical products, sorbitol is a commonly used excipient for oral medication. As part of the risk assessment for final pharmaceutical products, also excipients need to be analyzed for trace elemental impurities. The nature of the impurities as well as the respective limits are defined within the according monograph of the issuing Pharmacopoeia. For instance, the European Pharmacopoeia (Ph. Eur.) defines limits for nickel (<1.0 ppm) and lead (<0.5 ppm) in sorbitol.

Additionally, the monograph in the Ph. Eur. contains information about the analytical methods to be used for the determination of these impurities. The described methods are based on time-consuming organic extraction followed by an analysis via atomic absorption spectroscopy (AAS). In contrast to the AAS method the here presented direct analysis of sorbitol by ICP-OES provides the advantage of simplifying and shortening the sample preparation and extending the list of analyzed elements by keeping the measurement time comparably short.

The here presented results demonstrate the enormous application advantages originating from a high-resolution ICP-OES such as the PlasmaQuant 9100 Elite system. The high spectral resolution (2 pm @ 200 nm) allows for using the most sensitive emission lines. In combination with a high sensitivity and a robust plasma that allows for applying lowest dilution factors, exceptional limits of quantification (low µg/L range) can be achieved with high confidence in the obtained results. Additionally, software tools such as the automatic background correction (ABC) significantly reduce the amount of time required for the data evaluation process of the obtained results. The requirements defined in Ph. Eur. are easily achieved with high accuracy and precision by employing the PlasmaQuant 9100 Elite ICP-OES instrument.

References

[1] European Pharmacopeia, European Pharmacopeia, 8.0, 3284 - 3288
[2] General Chapter <232> Elemental Impurities—Limits, USP39. Publishing in Pharmacopeial Forum 42(2) [Mar.–Apr. 2016]
[3] General Chapter <233> Elemental Impurities—Procedures, Second Supplement to USP 38–NF 33, 2015
[4] International Conference on Harmonization, ICH Q3D Step 4 - Guideline for Elemental Impurities (ICH, Geneva, Switzerland, 2014)

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