



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

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.

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 PQ 9000 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 PQ 9000 Elite, which allows for an interference-free analysis of trace elements in typical pharmaceutical matrices.

Materials and Methods

Sample Preparation

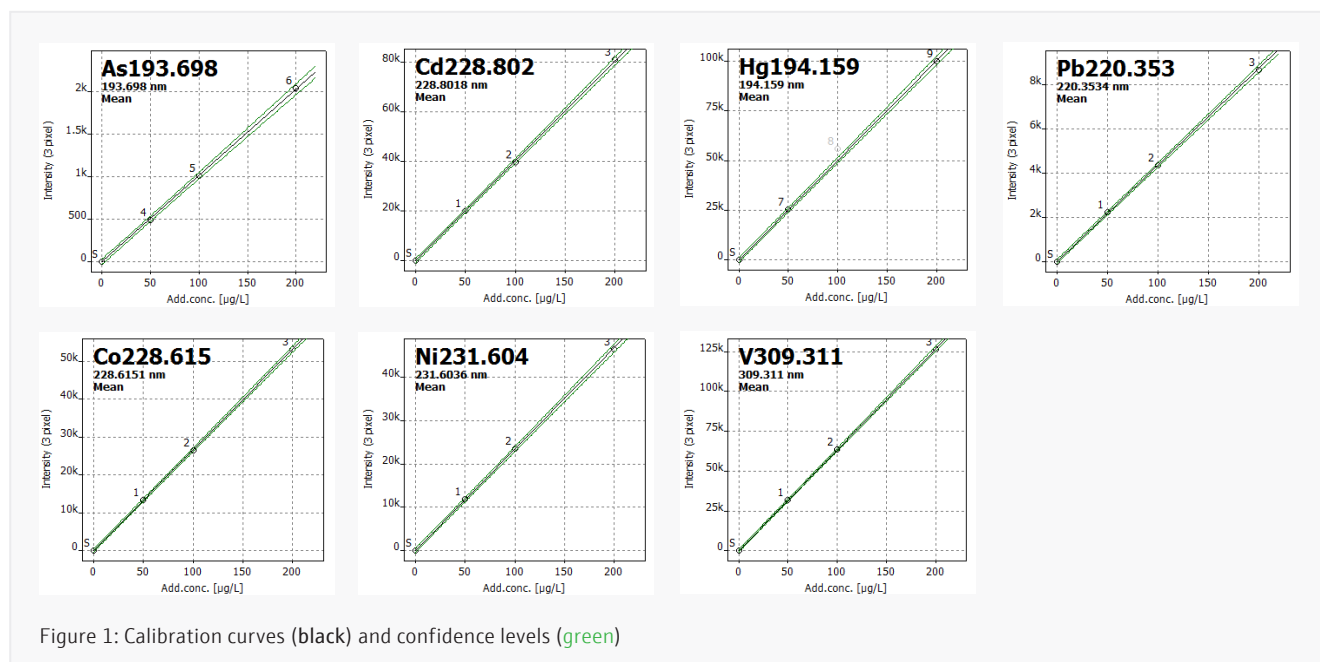
Prior to analysis the sorbitol sample (70%, liquid non-crystallizing) was diluted ten-fold with a 1% (v/v) HNO₃ and 1% HCl (v/v) solution. Calibration was performed as standard addition. The diluted sample was spiked with single standard solutions of arsenic and mercury (Sigma-Aldrich, 1000 mg/L) and 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) HNO₃ + 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 |



Instrumentation

Instrument Settings

For the analysis a PlasmaQuant PQ 9000 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 PQ 9000 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

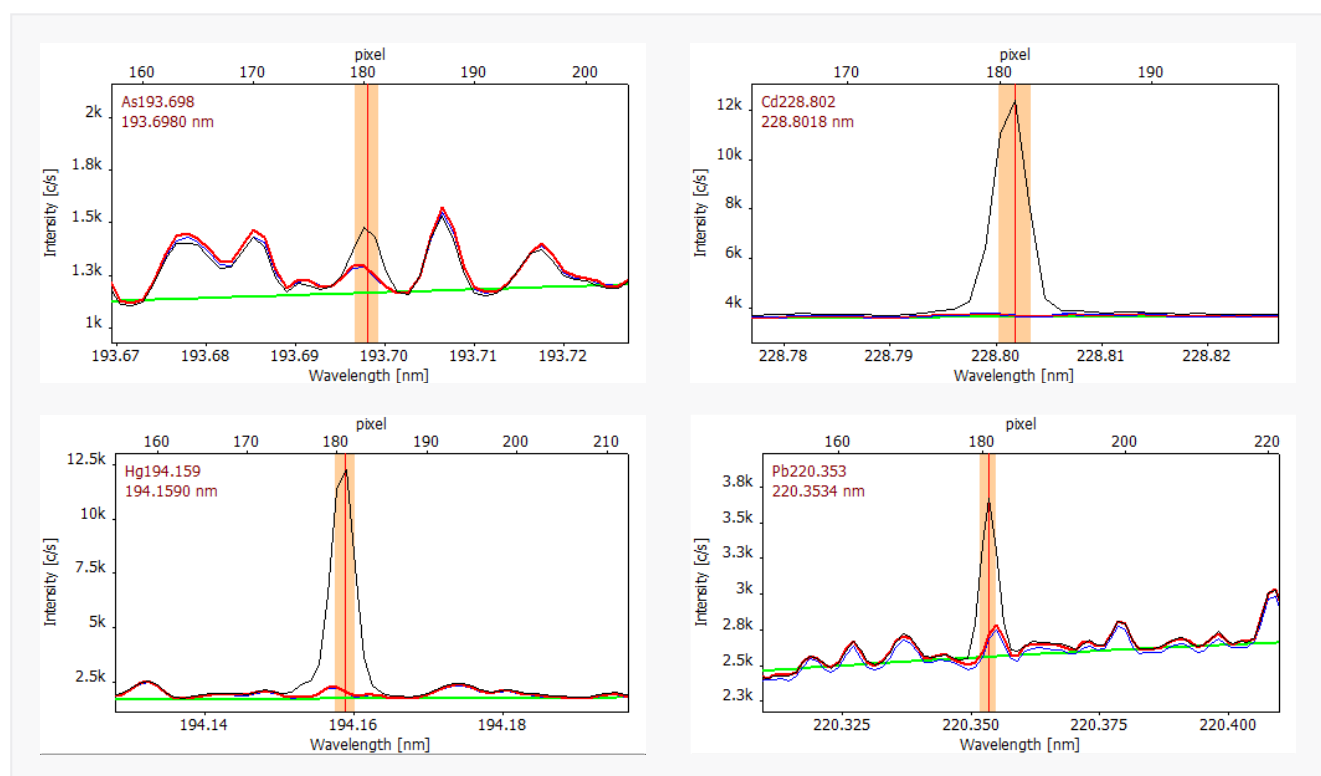
Method LOQ – refers to undiluted sample

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 $\mu\text{g/L}$. 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 [$\mu\text{g/L}$] | 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.



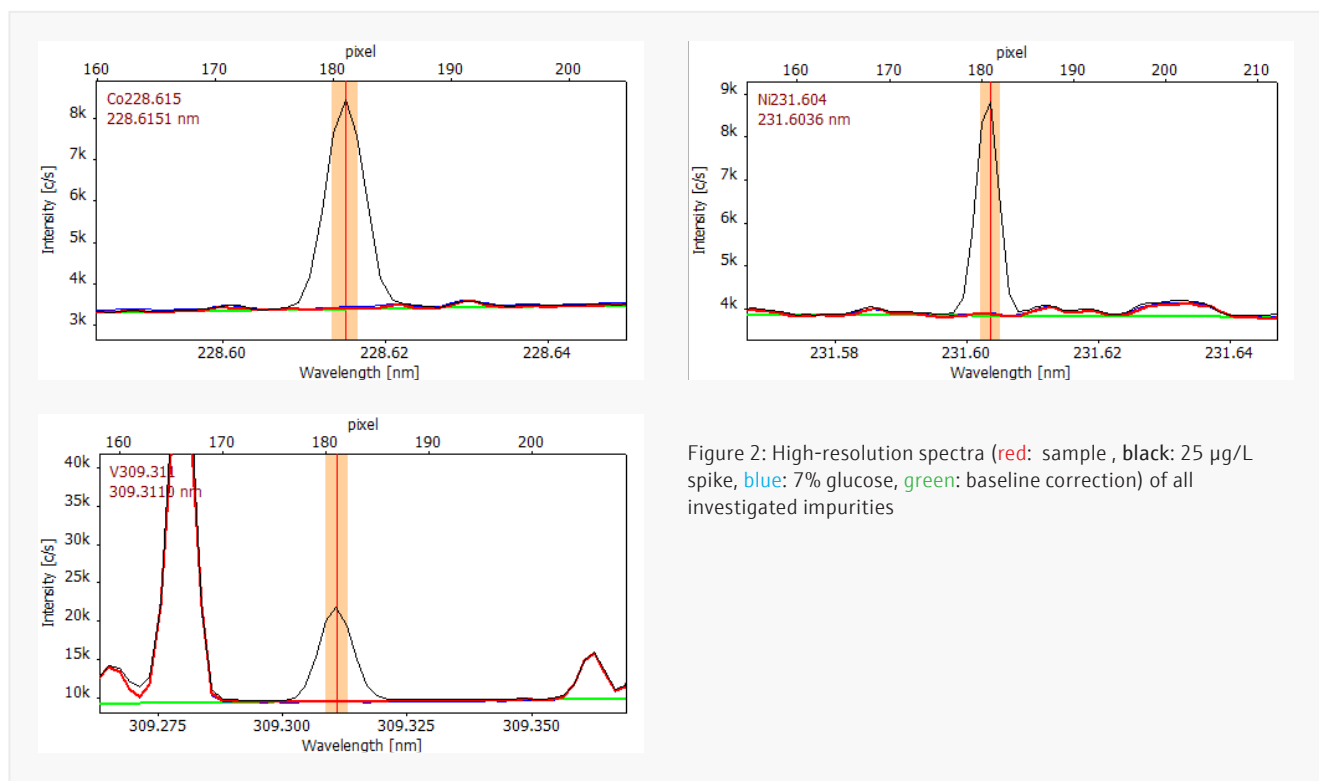


Figure 2: High-resolution spectra (red: sample, black: 25 µg/L spike, blue: 7% glucose, green: baseline correction) of all investigated impurities

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 PQ 9000 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 PQ 9000 Elite ICP-OES instrument.

References

- ¹ European Pharmacopoeia, European Pharmacopoeia, 8.0, 3284 - 3288
- ² General Chapter <232> Elemental Impurities—Limits, USP39. Publishing in Pharmacopoeial 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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