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Glass syringes — Determination of extractable tungsten

Seringues en verre — Dosage du tungstène extractible

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Foreword

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This document was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Glass syringes are typically produced from glass tubing via a hot-forming process.

One important step of this process is the cone formation and more importantly its opening with a pin that has the form of a filament and that is made of material resistant to high temperatures such as ceramics, tungsten and other.

This process is valid for the different syringe cone configurations such as Luer cone, Luer lock and also for staked needle syringes.

In the case of tungsten pins, tungsten residuals will form on the inner surface of the cone. These residues can affect the effectivity of the drug product e.g. causing aggregation of protein-based drugs. For this reason, the level of soluble tungsten residues needs to be controlled in certain applications.

Glass syringes — Determination of extractable tungsten

1 Scope

This document specifies an analytical method to quantitatively determine the water-soluble amount of tungsten (W) from the inner surface of glass syringes.

The method can be applied to Luer cone, staked needle or Luer lock syringes.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 3696, *Water for analytical laboratory use — Specification and test methods*

ISO 11885, *Water quality — Determination of selected elements by inductively coupled plasma optical emission spectrometry (ICP-OES)*

ISO 17294-2, *Water quality — Application of inductively coupled plasma mass spectrometry (ICP-MS) — Part 2: Determination of selected elements including uranium isotopes*

3 Terms and definitions

No terms and definitions are listed in this document.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

4 Principle

This test method is intended to be used to determine the water-soluble tungsten content of glass syringes as produced and/or as delivered. The syringes to be tested are filled with water to their nominal volume. They are tightly capped and then extracted by ultrasonic treatment [(75 ± 5)°C, (60 ± 1) min]. The amount of extracted tungsten is determined by analysing the aqueous extracts with inductively coupled plasma (ICP) mass or optical emission spectrometry (ICP-MS or ICP-OES).

5 Reagents

5.1 Test water, in accordance with ISO 3696 grade 2 or better.

5.2 Silicone oil polydimethylsiloxane.

5.3 Nitric acid (HNO_3), 65 % mass fraction, suprapure quality or better.

5.4 Ammonium hydroxide solution (NH_4OH), 25 % mass fraction, suprapure quality or better.

5.5 Diluent, 5 % mass fraction in HNO_3 by dilution of 5.3 with test water or 0,5 % mass fraction NH_4OH by dilution of 5.4 with test water.

5.6 Stock solution, 1 000 mg/l tungsten standard solution, ICP-MS grade, (e.g. in 5 % HNO_3 or 0,5 % NH_4OH).

5.7 Second stock solution, from another supplier or another lot.

5.8 Standard solutions, for ICP measurement (calibration and internal to be defined).

6 Apparatus

6.1 Ultrasonic bath, able to hold a temperature of (75 ± 5) °C for 60 min, provide a frequency of 45 kHz and a specific power of at least 16 W/l.

6.2 Pipettes, suitable for measuring the nominal volume, (e.g. 1 000 µl), suitable for measuring the volume of stock solution for spiking syringes (5 µl), suitable for preparing the calibration solutions.

6.3 Sample tubes, polypropylene (PP), volume 15 ml.

6.4 ICP-mass spectrometer (ICP-MS) or ICP-optical emission spectrometer (ICP-OES), suitable to determine tungsten in aqueous solutions with appropriate limit of detection (e.g. 50 ng/ml or less in a diluted extract).

7 Sample preparation

7.1 General

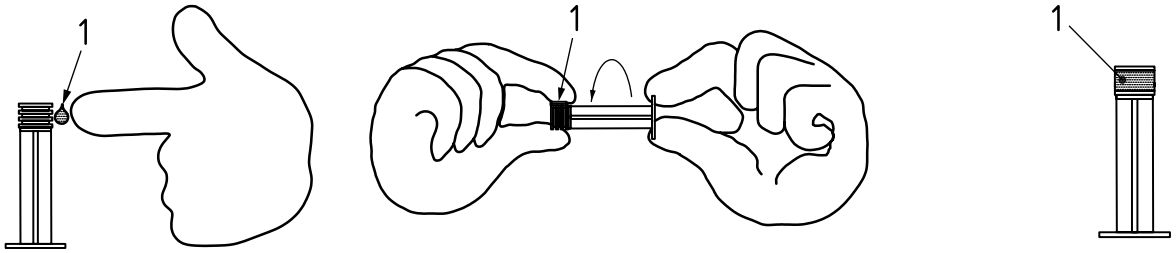
Due to the properties of the formation mechanism of tungsten residues in glass syringes, the variability of the extractable tungsten level within a series of syringes may be high. Taking this into account, a quantity of not less than 60 syringes per lot is recommended to be analysed. Each of the articles shall be identical in size and shape.

Depending on the nature of the syringes to be tested, the inner wall of the syringe glass barrel may need to be siliconized to allow the plunger rod movement.

7.2 Siliconization

For siliconization, a rubber stopper is mounted on a plunger rod. The side surface of the rubber stopper is then manually wetted with a small quantity of silicone oil [see Figure 1 a) and Figure 1 b)]. The quantity of silicone oil shall be calculated to apply a silicone amount of (9 ± 3) mg/cm^2 on the inner glass surface of the syringe. The silicone oil shall not reach the front surface of the rubber stopper [(see Figure 1 c)].

The plunger is then inserted into the syringe and moved several times upwards and downwards to distribute the silicone oil over the inner surface of the syringe, taking care of avoiding the contamination of the funnel with silicone oil. In case of siliconized syringes, this step is not necessary.



a) Manual application of a silicone droplet onto the side surface of the rubber stopper

b) Distribution of silicone onto the rubber stopper by turning the mounted plunger rod

c) Final siliconized rubber stopper

Key

1 silicone oil

Figure 1 — Siliconization of the inner surface of the syringe barrel

7.3 Filling

7.3.1 General

The filling volume is the nominal volume of the syringe, (e.g. 1,0 ml for a 1 ml syringe). In case of syringes with different nominal volumes, care should be taken that extraction is focused on the cone area. The minimum volume should be 1 ml, except of 0,5 ml syringes.

7.3.2 Determination of the filling level

Fill the reference syringe with the exact filling volume of test water. Therefore, pipette the exact volume of test water (1,0 ml in case of 1 ml syringes) into a small cup (e.g. 2 ml vial). Aspirate the complete volume through the needle or the Luer channel into the syringe without capturing any air. Remove accidentally captured air bubbles by turning the syringe tip upwards and pushing the plunger rod carefully. Close the syringe with a tip cap or a needle shield, which is filled with test water. Mark the resulting filling level (position of the stopper) with a permanent marker. Then transfer this filling level from the reference syringe to the syringes to be tested by suitable means, e.g. by a ruler or a stencil, see Figure 2. Other methods ensuring the extraction efficiency and repeatability of the quantity of extraction media may be used, this should be validated by, e.g. using the spiking procedure in Annex A.

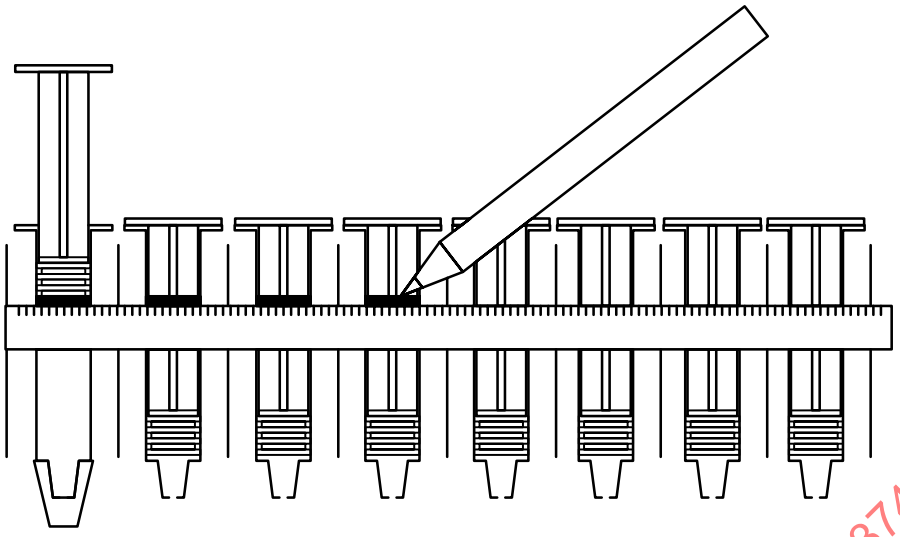


Figure 2 — Transfer of the filling level marks to the syringes to be tested

7.3.3 Filling of the syringes to be tested

Aspirate the test water through the syringe cone to tightly beneath the mark without capturing any air bubbles. Fill the tip cap/needle shield with test water and close the syringe with it. The excessive liquid shall be removed with a paper towel.

8 Extraction by ultrasonics

The extraction by ultrasonics shall be carried out twice on each test specimen with test water (5.1). Warm the ultrasonic bath beforehand to (75 ± 5) °C and make sure that the water level of the bath is correct. Put the syringes vertically (tip down) in a rack and then put it into the ultrasonic bath. Start the sonication process for 60 min at (75 ± 5) °C; 45 kHz specific power of at least 16 W/l.

When the extraction is finished, take out the rack from the ultrasonic bath (use oven gloves).

Gently dry every syringe, outside and inside up to the stopper, with paper towel.

Take the syringe, turn it tip cap facing up. Tap the tip cap to move the bubble towards the flow channel, screw the plunger rod on the stopper, pull the plunger to remove the water from the tip channel and then take off the tip cap. In case of needle shielded syringes pull the plunger to create a vacuum in the syringe and take off the rigid needle shield.

Flush the extraction solution into the sample tubes.

Rinse the syringes twice by aspirating 1 ml of purified water into each syringe and flush it into the same sample tube which contains the extraction solution. The volume of the first extract is 3,0 ml in case of a 1 ml syringe.

A second extraction shall be done with the same test syringes reproducing the same process from the beginning (filling of the syringes).

The second extraction solution is flushed into the same tube that contains the first extraction. The final volume after 2 extractions is in total 6,0 ml of extracted solution in case of a 1 ml syringe. In case of larger nominal volumes, the final volume should be as small as possible.

If a larger volume is necessary for analysis, enhance the dilution up to factor 10. For the dilution, the same diluent should be used as for the calibration standards. The concentration of standards and the final samples shall be comparable, (e.g. both 5 % HNO_3 or 0,5 % NH_4OH).

9 Analysis

9.1 General

The extracts shall be analysed for tungsten with ICP-MS or ICP-OES, in accordance with ISO 17294-2 and ISO 11885, respectively. For measurement with ICP techniques, an internal elemental standard (e.g. Tl, Re, Ir) shall be used.

The matrix of the sample solutions shall be matched with the calibration solutions.

9.2 ICP-MS

Set up the instruments according to the manufacturer's instruction using the masses 182, 183 and 184 for tungsten.

The internal standard (e.g. Tl, Re, Ir) should be added to the sample either directly or online.

For direct addition, a concentration of 50 ng/ml is recommended. When using an online addition system, the stock concentration shall be as high, that it gives 50 ng/ml in the nebulizer system.

Aspirate the set of calibration solutions and adjust zero. Aspirate the set of calibration solutions, prepared by dilution of standard solution with either 5 % nitric acid or 0,5 % NH_4OH and prepare a linear calibration, which covers the whole concentration range of the sample solutions, (e.g. 5-10-20-50-100 ng/ml).

9.3 ICP-OES

Set up the instruments according to the manufacturer's instruction using a wavelength of 207,912 nm or 220,449 nm for tungsten, with an appropriate correction for background absorption effects.

Aspirate the set of calibration solutions and adjust zero. Aspirate the set of calibration solutions, prepared by dilution of standard solution with either 5 % nitric acid or 0,5 % NH_4OH and prepare a linear calibration that covers the whole concentration range of the sample solutions.

9.4 Quality control

9.4.1 Measurement with ICP-MS or ICP-OES

To control accuracy of ICP results, the measurement of a blank solution and an independent standard solution is recommended. The standard can be prepared, e.g. from a second tungsten stock solution. The recovery for the independent standard solution should be between 90 % and 110 %.

9.4.2 Extraction efficiency

For control of accuracy of extraction, tungsten-free syringes shall be spiked with tungsten standard solutions of known concentration, e.g. according to Annex A. The extraction efficiency of the method shall not be lower than 75 %. The precision ($n \geq 3$) shall be no larger than 20 %.

9.5 Expression of the results

The concentration of extractable tungsten measured in the diluted extracts shall be multiplied by the dilution factor. The concentration value in ng/ml is then calculated to the absolute amount in ng per syringe.

10 Test report

The test report shall include the following information:

a) a reference to this document, i.e. ISO 3749:2022;

b) the result parameter name “extractable tungsten”;

c) the average of the results, calculated per syringe (e.g. [ng/syringe]);

d) the standard deviation of the results;

e) the number of syringes extracted;

f) the extraction volume;

g) the detection method (ICP-MS or ICP-OES).