INTERNATIONAL STANDARD

ISO 4802-2

Second edition
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Glassware — Hydrolytic resistance of the interior surfaces of glass containers —

Part 2: Determination by flame spectrometry and classification

Verrerie — Résistance hydrolytique des surfaces internes des récipients en verre —

Partie 2: Détermination par spectrométrie de flamme et classification

Reference number
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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 4802-2 was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection equipment for medical and pharmaceutical use*.

This second edition cancels and replaces the first edition (ISO 4802-2:1988), which has been technically revised.

ISO 4802 consists of the following parts, under the general title *Glassware — Hydrolytic resistance of the interior surfaces of glass containers*:

— *Part 1: Determination by titration method and classification*

— *Part 2: Determination by flame spectrometry and classification*

Introduction

This part of ISO 4802 is largely based on a method of test approved by the International Commission on Glass (ICG), Technical Committee 2, *Chemical Durability and Analysis,* for measuring the hydrolytic resistance of the interior surfaces of glass containers.

This part of ISO 4802 contains a classification which is related to but not equivalent to the classification set up in ISO 4802-1 for the titration method.

Glassware — Hydrolytic resistance of the interior surfaces of glass containers —

Part 2:
Determination by flame spectrometry and classification

1 Scope

This part of ISO 4802 specifies:

a) methods for determining the hydrolytic resistance of the interior surfaces of glass containers when subjected to attack by water at (121 ± 1) °C for (60 ± 1) min. The resistance is measured by determining the amount of sodium and other alkali metal or alkaline earth oxides in the extraction solution using flame atomic emission or absorption spectrometry (flame spectrometry);

b) a classification of glass containers according to the hydrolytic resistance of the interior surfaces determined by the methods specified in this part of ISO 4802.

The test method specified in this part of ISO 4802 might not be applicable to containers whose surfaces have been treated with silicon (e.g. containers that are ready for direct filling).

2 Normative references

The following referenced documents are indispensable for the application 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 385, *Laboratory glassware — Burettes*

ISO 719, *Glass — Hydrolytic resistance of glass grains at 98 °C — Method of test and classification*

ISO 720, *Glass — Hydrolytic resistance of glass grains at 121 °C — Method of test and classification*

ISO 1042, *Laboratory glassware — One-mark volumetric flasks*

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

ISO 3819, *Laboratory glassware — Beakers*

ISO 9187-1, *Injection equipment for medical use — Part 1: Ampoules for injectables*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
ampoule
small, normally flat-bottomed container having stems in many different forms

NOTE Ampoules are thin-walled and have a capacity normally up to 30 ml. They are intended to be closed, after filling, by flame sealing.

3.2
bottle
flat-bottomed container, made from moulded glass

NOTE Bottles are normally thick-walled and have a capacity usually of more than 50 ml. They may be of circular or other geometric cross-section. Bottles are sealed with a closure made from a material other than glass, and not by flame-sealing.

3.3
brimful capacity
volume of water required to fill a container, placed on a flat, horizontal surface

3.4
container
article made from glass to be used as primary packaging material intended to come into direct contact with the pharmaceutical preparations

EXAMPLE Bottles, vials, syringes, ampoules and cartridges, see also Figure 1.

NOTE These containers are made from borosilicate or soda-lime-silica glass.

3.5
filling volume
the defined volume of water to fill the test specimen

NOTE For the determination of the filling volume, see 7.2. The filling volume is a test specific quantity that is used to compare container sets from different sources or lots. It has no relation to the nominal product volume.

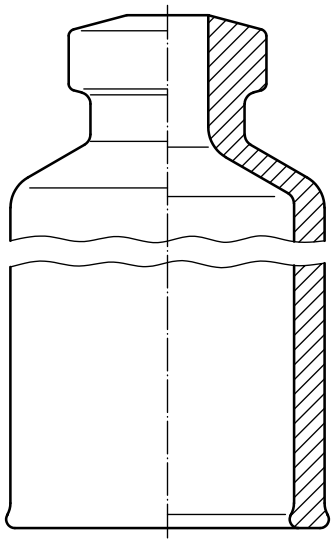
3.6
borosilicate glass
silicate glass having a very high hydrolytic resistance due to its composition containing significant amounts of boric oxide

NOTE 1 Borosilicate glass contains a mass fraction of boric oxide between 5 % and 13 %. This glass type may also contain aluminium oxide and/or alkaline earth oxides.

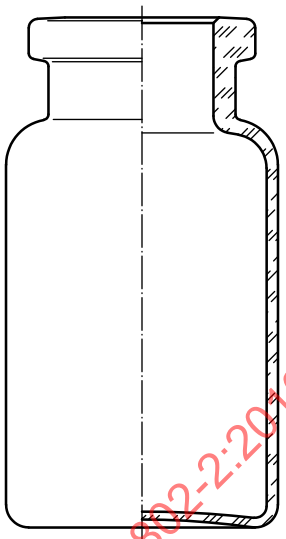
NOTE 2 Neutral glass is a borosilicate glass having a very high hydrolytic resistance and a high thermal shock resistance. When tested according to ISO 720, it meets the requirements of class HGA 1. Containers properly made from this glass comply with hydrolytic resistance container class HC_F 1 of this part of ISO 4802.

3.7
soda-lime-silica glass
silicate glass containing a mass fraction up to approximately 15 % of alkali metal oxides – mainly sodium oxide – and a mass fraction up to about 15 % of alkaline earth oxides, mainly calcium oxide

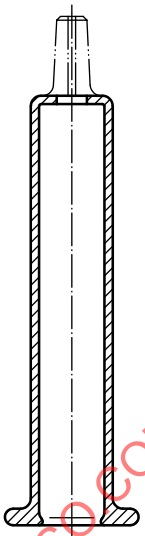
NOTE Containers made from this glass will have a moderate hydrolytic resistance due to the chemical composition of the glass, and comply with hydrolytic resistance container class HC_F 3.



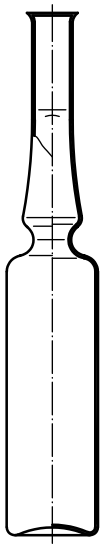
a) **Example of a glass cylinder for pen-injectors** (see ISO 13926-1)



b) **Example of an injection vial made of glass tubing** (see ISO 8362-1)



c) **Example of a glass barrel** (see ISO 11040-4)



d) **Example of a stem cut ampoule with constriction** (see ISO 9187-1)

Figure 1 — Examples of containers

3.8
surface treatment
treatment of the internal surface of glass containers with reagents in order to achieve a de-alkalized surface and to produce a significantly lower release of alkali metal ions (and alkali earth metal ions)

NOTE Surface treatment is used, for example, in order to change a soda-lime-silica glass container of hydrolytic resistance class HC_F 3 to a container of hydrolytic resistance class HC_F 2 container. Treated containers are rinsed before use.

3.9
vial
small, flat-bottomed container, made from tubing or from moulded glass

NOTE Vials are normally thick-walled and have a capacity up to 100 ml. They are normally sealed with a closure made from a material other than glass, and not by flame-sealing.

4 Principle

This method of test is a surface test applied to glass containers as produced and/or as delivered.

The containers to be tested are filled with specified water to a specified capacity. They are loosely capped and then heated under specified conditions. The degree of the hydrolytic attack is measured by flame spectrometric analysis of the extraction solutions.

5 Reagents

During the test, unless otherwise stated, use only reagents of recognised analytical grade.

5.1 **Test water**, complying with the requirements specified in ISO 3696 for grade 2 water or better.

5.2 **Hydrochloric acid**, solution, c(HCl) ≈ 2 mol/l.

5.3 **Hydrochloric acid**, solution, c(HCl) ≈ 6 mol/l (≈ 1 + 1).

5.4 **Hydrofluoric acid**, c(HF) ≈ 22 mol/l (i.e. ≈ 400 g HF/l solution).

5.5 **Distilled water** or **water of equivalent purity** (grade 3 water complying with the requirements specified in ISO 3696).

5.6 **Spectrochemical buffer solution** (caesium chloride solution, CsCl).

Dissolve 80 g of caesium chloride in approximately 300 ml of test water (5.1), add 10 ml of hydrochloric acid (5.3) and transfer to a 1 000 ml volumetric flask (6.3). Dilute to the mark with the test water (5.1) and mix.

5.7 **Stock solutions**.

5.7.1 Dry sodium chloride, potassium chloride and calcium carbonate at (110 ± 5) °C for 2 h. Prepare aqueous stock solutions, using the test water (5.1), directly from the chlorides and from the calcium carbonate, after dissolving in the minimum amount of hydrochloric acid so that all solutions have concentrations of 1 mg/ml, calculated as sodium oxide, potassium oxide and calcium oxide.

5.7.2 Commercially available standard solutions may also be used.

5.8 **Standard solutions**.

5.8.1 Prepare standard solutions by diluting the stock solutions (5.7) with the test water (5.1) to obtain concentrations suitable for establishing the reference solutions in an appropriate manner, e.g. with concentrations of 20 µg/ml of sodium oxide, potassium oxide and calcium oxide.

5.8.2 Commercially available standard solutions may also be used.

5.9 **Reference solutions**.

The reference solutions for establishing the calibration graph (set of calibration solutions) shall be prepared by diluting suitable concentrated standard solutions (5.8) with the test water (5.1). They should normally cover the optimum working ranges of the specific elements according to the instrument used for the measurement. Typical concentration ranges of the reference solutions are

— for determination by flame atomic emission spectroscopy (FAES) of sodium oxide and potassium oxide: up to 10 µg/ml;

— for determination by flame atomic absorption spectrometry (FAAS) of sodium oxide and potassium oxide: up to 3 µg/ml;

— for determination by flame atomic absorption spectrometry (FAAS) of calcium oxide: up to 7 µg/ml.

For the measurement of containers of hydrolytic resistance container classes HC_F 1, HC_F 2 or HC_F B (borosilicate or highly resistant glasses), the reference solutions shall be used without addition of the spectrochemical buffer solution (5.6).

Nevertheless, when the test is run for arbitration purposes it is recommended that the spectrochemical buffer solution also be added to these container classes.

For the measurement of containers of hydrolytic resistance container classes HC_F 3 or HC_F D (soda-lime-silica glasses), the reference solutions shall contain a volume fraction of 5 % of the spectrochemical buffer solution (5.6).

6 Apparatus

Ordinary laboratory apparatus, and those specified in 6.1 to 6.6.

6.1 Autoclave or **steam sterilizer**, capable of withstanding a pressure of at least 250 kPa (2,5 bar) and of carrying out the heating cycle specified in 8.3. It shall be capable of maintaining a temperature of (121 ± 1) °C, equipped with a calibrated thermometer or a calibrated thermocouple recorder, a pressure gauge and a vent-cock.

When necessary and appropriate, the autoclave vessel and ancillary equipment shall be thoroughly cleaned before use using the test water (5.1) in order to avoid contamination that can influence the test results.

6.2 Burettes, having a suitable capacity according to the analytical procedure to be used and complying with the requirements specified for class A burettes in ISO 385 and made of glass of hydrolytic resistance grain class HGA 1 as specified in ISO 720[1)] or ISO 719.

6.3 One-mark volumetric flasks, having a capacity of 1 000 ml and complying with the requirements specified for class A one-mark volumetric flasks in ISO 1042.

6.4 Water bath, capable of being heated to approximately 80 °C.

6.5 Flame atomic absorption (FAAS) or **flame atomic emission (FAES) instrument**.

FAAS instruments shall be equipped with line sources for sodium, potassium and calcium; they shall be equipped with air/propane or air/acetylene gas supplies and burners for measuring sodium and potassium, and with a nitrous oxide/acetylene gas supply and burner for measuring calcium.

FAES instruments shall be equipped with air/propane or air/acetylene gas supplies and burners for measuring sodium and potassium.

6.6 Beakers, having a suitable capacity and complying with the requirements specified in ISO 3819.

Before use, each new beaker shall be pretreated by subjecting it to the autoclaving conditions described in 8.3.

1) Glass of hydrolytic resistance grain class ISO 719-HGB 1 adequately meets the requirements of class HGA 1 specified in ISO 720.

7 Sample preparation

7.1 Sample size

For each container capacity to be tested, the number of containers to be measured separately is specified in Table 1.

Table 1 — Number of containers for the determination of the hydrolytic resistance by flame spectrometry methods

Capacity of container [volume corresponding to filling volume (see 7.2)] ml	Number of containers to be measured separately	Additional containers for desired preliminary measurements
$\leqslant 2$	20	2
$> 2 \leqslant 5$	15	2
$> 5 \leqslant 30$	10	2
$> 30 \leqslant 100$	5	1
> 100	3	1

7.2 Determination of the filling volume

7.2.1 Flat-bottomed containers $\leqslant$ 20 mm bore diameter (except ampoules, syringes and cartridges)

Select six containers (having a capacity $\leqslant$ 100 ml) or three containers (having a capacity $>$ 100 ml) at random from the sample lot and remove any dirt or packaging debris by shaking the containers. Allow the dry containers to reach room temperature. Weigh each of the empty containers to the nearest 0,01 g for containers having a nominal volume $\leqslant$ 30 ml, and to the nearest 0,1 g for containers having a nominal volume $>$ 30 ml. Place the containers on a horizontal surface and fill them nearly to the top with distilled water (5.5), avoiding overflow and introduction of air bubbles. Adjust the liquid levels to the brimful line using distilled water (5.5). The meniscus shall be equal to the upper edge of the bore.

Weigh the filled container to the nearest 0,01 g for containers having a nominal volume $\leqslant$ 30 ml, and to the nearest 0,1 g for containers having a nominal volume $>$ 30 ml. Calculate the mass of water, in grams, contained within the container.

Calculate the mean value of the results from six containers and express the result in millilitres of water; this value is the mean brimful capacity of the containers.

Calculate 90 % of this mean brimful capacity to one decimal place. This volume is the filling volume for the particular sample lot.

7.2.2 Flat-bottomed containers $>$ 20 mm bore diameter

Proceed as described in 7.2.1 but cover each container with a strike-plate (for measuring the brimful capacity of small and other bottles). The strike-plate shall be made of rigid, inert, transparent material of any convenient shape, but with a central hole approximately 5 mm in diameter. The strike-plate shall be large enough to fit snugly on and completely cover the sealing surface of the container for which the brimful capacity is to be measured.

Calculate 90 % of this mean brimful capacity to one decimal place. This volume is the filling volume for the particular sample lot.

7.2.3 Round-bottomed containers

Select six containers (having a capacity $\leqslant$ 100 ml) or three containers (having a capacity $>$ 100 ml) at random from the sample lot and remove any dirt or packaging debris by shaking the containers. Allow the dry containers to reach room temperature. Fix each container vertically in an appropriate device and determine the brimful capacity in accordance with 7.2.1.

Then calculate 90 % of the mean brimful capacity to one decimal place. This volume is the filling volume for the particular sample lot.

7.2.4 Lipped containers

Wrap adhesive plastic tape around the rim of the containers such that the tape around the lip is level with the rim. Weigh the container, then fill and reweigh as described in 7.2.1.

7.2.5 Ampoules

Place at least six dry ampoules on a flat, horizontal surface and fill them with distilled water (5.5), at room temperature, from a burette (6.2), until the meniscus of the water reaches point h_6 of ISO 9187-1, where the body of the ampoules declines to the shoulder (see Figure 2). Read the capacities to two decimal places and calculate the mean value.

This volume, expressed to one decimal place, is the filling volume and shall be filled in all ampoules of the same lot.

7.2.6 Syringes and cartridges

Select six syringes or cartridges. Close the small opening (mouth of cartridges and needle and/or Luer cone of syringes) using an inert material (e.g. Tip Cap). Determine the mean brimful volume in accordance with 7.2.1.

Then calculate 90 % of the mean brimful capacity to one decimal place. This volume is the filling volume.

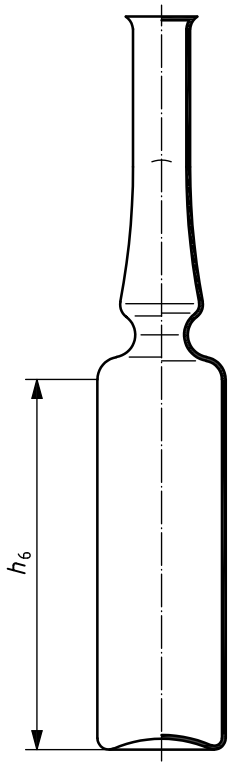


Figure 2 — Filling volume of ampoules (up to h_6)

8 Procedure

8.1 General

This procedure shall be completed within one working day.

8.2 Cleaning of samples

The following cleaning process for each container shall be completed within 30 min.

Remove from all open samples any packaging debris or dirt which has collected during storage and transport. Rinse each sample thoroughly at least twice with the distilled water (5.5) at ambient temperature, then allow to stand, filled with the distilled water. Immediately before testing, empty the samples, rinse once with the distilled water and then once with the test water (5.1).

Closed ampoules shall not be rinsed before testing.

NOTE For opening by flame, closed ampoules can be warmed, e.g., in a water bath or air-oven at about 40 °C for approximately 2 min before opening, or cut and broken at the height of the sealing point.

8.3 Filling and heating

Fill each container, selected for the sample size in accordance with 7.1 and cleaned in accordance with 8.2, to the filling volume with the test water (5.1) by means of suitable volumetric measuring devices.

Each container, including ampoules, shall be loosely capped with an inert material, for example with inverted beakers (6.6) of such a size that the bottoms of the beakers fit snugly down on the rims of the sample. Ampoules capped with clean aluminium foil is another example.

Ensure that the foil does not release measurable ions into the test water.

Place the samples, gathered in groups in Petri dishes or in the beaker, on the rack in the autoclave (6.1), containing distilled water (5.5) at ambient temperature, and ensure that they are held above the level of the water in the vessel.

Insert the end of a calibrated thermal device in a filled container through a hole of approximately the diameter of the thermocouple and connect it to an external measuring device. If the container is too small to insert a thermocouple, apply a thermocouple in a suitable, similar container. Close the autoclave door or lid securely but leave the vent-cock open. Start automatic recording of the temperature versus time and heat the autoclave at a regular rate such that steam issues vigorously from the vent-cock after 20 min to 30 min, and maintain a vigorous evolution of steam for a further 10 min. Close the vent-cock and raise the temperature from 100 °C to 121 °C at a rate of 1 °C/min within 20 min to 22 min. Maintain the temperature at (121 ± 1) °C for (60 ± 1) min from the time when the holding temperature is reached. Cool down to 100 °C at a rate of 0,5 °C/min, venting to prevent formation of a vacuum, within 40 min to 44 min.

NOTE 1 For autoclaves using a steam generator it is not necessary to maintain the temperature for 10 min at 100 °C.

CAUTION — For security reasons (boiling retardation) do not open the autoclave before the water in the containers has reached a temperature of 95 °C**.**

NOTE 2 Experience has shown that the rate of heating to 121 °C, the holding temperature of (121 ± 1) °C and the rate of cooling to 100 °C are critical. Deviations from the specified conditions can produce variable results even to the extent of invalidating them.

Remove the hot samples from the autoclave and cool to room temperature within 30 min. Start with the determinations after cooling. Special care shall be taken in cooling down large capacity containers as thermal drops larger than 40 °C may cause the fracture of the glass by thermal shock.

8.4 Analysis of the extraction solutions

8.4.1 Containers of hydrolytic resistance container classes HC_F 1, HC_F 2 and HC_F B or those known to be made from borosilicate glass

NOTE Normally these containers do not release potassium or calcium in a significant amount and only sodium is to be determined. Carry out preliminary measurements of the potassium and calcium oxide concentrations on one of the extraction solutions. If, for one container type, the concentration of potassium oxide is less than 0,2 µg/ml, and if the concentration of calcium oxide is less than 0,1 µg/ml, the remaining extraction solutions of this container type need not be analysed for these ions.

Aspirate the extraction solution from each sample directly into the flame of the atomic absorption or atomic emission instrument (6.5), and determine the concentrations of sodium oxide (and potassium oxide and calcium oxide, if present) by reference to calibration graphs produced from the aqueous reference solutions (5.9) of suitable concentration.

8.4.2 Containers of hydrolytic resistance container classes HC_F 3 and HC_F D, or those known to be made from soda-lime-silica glass

8.4.2.1 Preliminary determinations

Add to one container, from each container type, a volume of the spectrochemical buffer solution (5.6) equivalent to 5 % of the filling volume.

Cap narrow-necked containers with a piece of inert plastic film and mix the liquid well by shaking. Mix the liquids in other containers by using stirrers.

NOTE 1 Ensure that the plastic film does not release the ions to be determined.

Aspirate the extraction solution into the flame of the instrument (6.5) and determine first the approximate sodium oxide concentration, then the exact potassium oxide and the calcium oxide concentration. When the potassium oxide concentration is less than 0,2 µg/ml, the remaining solutions of this container type need not be analysed for potassium oxide.

According to the instrument conditions, the sodium oxide concentration may be above the optimum working range. For FAAS techniques this normally takes place for concentrations greater than 3 µg/ml of sodium oxide. In these cases, dilute the extraction solution for the final measurements so that the sodium oxide concentration becomes less than 3 µg/ml.

Take care that dilution to concentrations less than 3 µg/ml of sodium oxide is done carefully. The volumes shall be measured to two decimal places and the measurement and dilution shall be done in very carefully cleaned apparatus.

If dilution is necessary, prepare such a diluted solution from an original extraction solution, and add the spectrochemical buffer solution (5.6) [5 % (volume fraction)].

NOTE 2 Experience shows that calcium oxide and potassium oxide can be accurately measured from undiluted solutions.

8.4.2.2 Final determination

If dilution is unnecessary, add a volume of the spectrochemical buffer solution (5.6) equivalent to 5 % of the filling volume as described in 8.4.2.1, mix well and determine sodium oxide and calcium oxide (and potassium oxide, if present) by reference to calibration graphs. They shall be produced from the aqueous reference solutions (5.9) and shall contain a volume fraction of 5 % of the spectrochemical buffer solution (5.6).

For the determination of the calcium oxide concentration with the FAAS method, the nitrous oxide/acetylene flame shall be used.

If dilution is necessary, determine sodium oxide, calcium oxide and potassium oxide, if present, following the procedures as described before. The measuring solutions shall contain a volume fraction of 5 % of the spectrochemical buffer solution (5.6).

Ensure that any dilution (because of sodium oxide concentration and/or caesium chloride addition) is taken into consideration in the calculations.

Concentration values $< 1{,}0$ µg/ml should be expressed to two decimal places, values $\geqslant 1{,}0$ µg/ml to one decimal place.

8.5 Testing to determine whether the containers have been surface-treated

NOTE The hydrolytic resistance of the interior surface of vials and bottles made from soda-lime-silica glass can be considerably increased by treating these surfaces during the course of production. Ampoules made from borosilicate glass tubing are not normally subjected to an internal surface treatment because their high chemical resistance is dependent upon the chemical composition of the glass as a material (see Clause 3).

If it is necessary to determine whether or not a container has been surface-treated, the samples previously tested shall be used.

Fill the samples with a mixture of one volume of hydrofluoric acid (5.4) and nine volumes of hydrochloric acid (5.2) to the brimful point. Allow the filled samples to stand at ambient temperature for 10 min, then empty the solution very carefully. Rinse the samples three times with distilled water (5.5), then at least twice with test water (5.1). Then test the samples as specified in 8.3, and 8.4.

CAUTION — Hydrofluoric acid is extremely aggressive. Even tiny quantities can cause life-threatening injuries.

If the results are considerably higher than those obtained from the original surfaces (about five to ten times), the samples shall be considered to have been surface-treated.

9 Expression of results

9.1 Calculation

Calculate the mean value of the concentration of individual oxides (8.4) found in each of the samples tested in micrograms of the individual oxides per millilitre of the extraction solution, and as the sum of the individual oxides in micrograms of sodium oxide per millilitre of the extraction solution. Use the following conversion factors:

1 µg of potassium oxide $\triangleq$ 0,658 µg of sodium oxide

1 µg calcium oxide $\triangleq$ 1,105 µg of sodium oxide

NOTE This hydrolytic resistance container class HC_F obtained by the flame spectrophometric method is comparable with the class HC_T obtained in accordance with ISO 4802-1, although the individual test values are not equivalent. Therefore, conversions from this part of ISO 4802 to ISO 4802-1 are not permitted.