INTERNATIONAL STANDARD

ISO 4802-1

Second edition
2010-04-01

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

Part 1: Determination by titration method and classification

Verrerie — Résistance hydrolytique des surfaces internes des récipients en verre —
Partie 1: Détermination par analyse titrimétrique et classification

Reference number
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ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

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Contents

Page

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 4802-1 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 4802-1:1988), 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.

The European Pharmacopoeia Commission has adopted the principle of the determination by titration and has set up a classification for glass containers for injectable preparations which is now included in this part of ISO 4802. In addition, this part of ISO 4802 contains a classification of containers other than for injectable preparations.

According to many results of international interlaboratory tests this part of ISO 4802 specifies the test conditions in more detail than the European Pharmacopoeia in order to increase the reproducibility of the test results. In particular, the autoclaving cycle is described in detail. The principle of the test method described in this part of ISO 4802 is, however, in full compliance with the corresponding test method of the European Pharmacopeia[11].

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

Part 1: Determination by titration method and classification

1 Scope

This part of ISO 4802 specifies:

a) a method for determining the hydrolytic resistance of the interior surfaces of glass containers when subjected to attack by water at 121 °C ± 1 °C for 60 min ± 1 min. The resistance is measured by titration of a known aliquot portion of the extraction solution produced with hydrochloric acid solution, in which case the resistance is inversely proportional to the volume of acid required;

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.

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 648, *Laboratory glassware — Single-volume pipettes*

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 1773, *Laboratory glassware — Narrow-necked boiling 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
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.

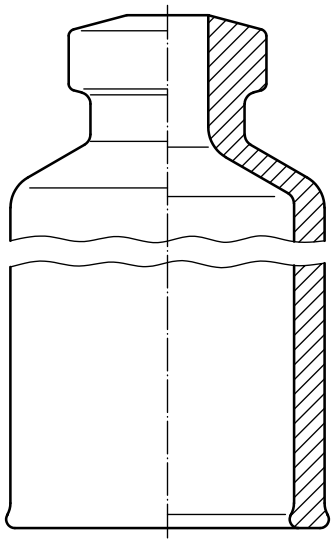
3.6
borosilicate glass
silicate glass having a very high hydrolytic resistance due to its composition, containing significant amounts of boric oxide

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

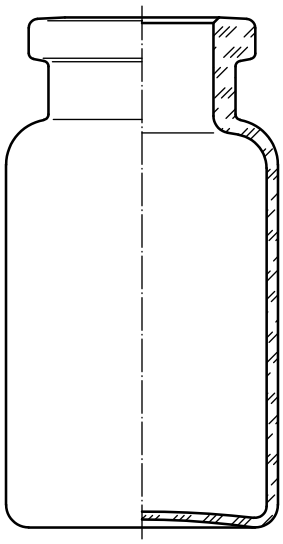
NOTE 2 Neutral glass is a borosilicate glass having a very high hydrolytic resistance and a high thermal shock resistance. When tested in accordance with ISO 720 it meets the requirements of class HGA 1. Containers properly made from this glass comply with hydrolytic resistance container class HC_T 1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

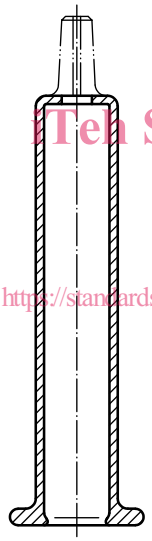
NOTE Containers made from this glass have a moderate hydrolytic resistance due to the chemical composition of the glass, and comply with hydrolytic resistance container class HC_T 3.



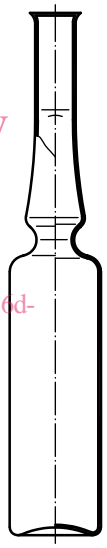
a) **Example of a glass cylinder for pen–injectors** (see ISO 13926-1)



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_T 3 to a container of hydrolytic resistance class HC_T 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 titration 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.

The test water can be produced, e.g. by double distillation or reverse osmosis.

Such test water can normally be stored for 24 h in a stoppered flask without change of the pH value. In case of longer storage, the water shall be freed from dissolved gases, such as carbon dioxide, by boiling for at least 15 min in a boiling flask of fused silica or borosilicate glass. The boiling flask shall be pretreated once as specified in 8.3 before it is used for the first time.

Performed correctly and tested immediately before use, this test water will produce an orange-red (not a violent-red or yellow) colour when four drops of the methyl red indicator solution (5.5) are added to 50 ml of the test water. This is the neutral point of methyl red corresponding to pH 5,5 ± 0,1.

The water, so coloured, may also be used as the reference solution (see 8.4).

5.2 Hydrochloric acid, standard volumetric solution, c(HCl) = 0,01 mol/l.

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

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

5.5 Methyl red, indicator solution.

Dissolve 25 mg of the sodium solution salt of methyl red ($C_{15}H_{14}N_3NaO_2$) in 100 ml of the test water (5.1).

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

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 of 50 ml, 25 ml, 10 ml or 2 ml, 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.

The capacity of the burettes shall be chosen according to the expected consumption of hydrochloric acid (5.2).

6.3 Conical flasks, having a capacity of 100 ml and 250 ml and complying with the requirements of ISO 1773.

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

IMPORTANT — If it is intended to use these flasks for other purposes, before being re-used in accordance with this part of ISO 4802, the flasks shall be properly cleaned (e.g. by treatment with hydrochloric acid and/or by autoclave cleaning).

6.4 Pipettes, having a suitable capacity and complying with the requirements specified for class A pipettes described in ISO 648.

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

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.

7 Sample preparation

7.1 Sample size

The number of containers to be tested depends on the capacity of the container, the volume of extraction solution necessary for one titration and the number of titration results required. It shall be calculated according to the requirements given in Table 1.

Table 1 — Number of containers for the determination of the hydrolytic resistance by titration

Capacity of container [volume corresponding to filling volume (see 7.2)] ml	**Minimum number of containers for one titration**	**Volume of extraction solution for one titration** ml	**Number of titrations**
⩽ 3	10	25,0	1
> 3 ⩽ 30	5	50,0	2
> 30 ⩽ 100	3	100,0	2
> 100	1	100,0	3

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