INTERNATIONAL STANDARD

ISO 8536-6

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Infusion equipment for medical use —

Part 6:
Freeze drying closures for infusion bottles

Matériel de perfusion à usage médical —
Partie 6: Bouchons à lyophilisation pour flacons de perfusion

Reference number
ISO 8536-6:1995(E)

Contents

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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.

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.

International Standard ISO 8536-6 was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection equipment for medical use*.

ISO 8536 consists of the following parts, under the general title *Infusion equipment for medical use*:

— *Part 1: Infusion glass bottles*

— *Part 2: Closures for infusion bottles*

— *Part 3: Aluminium caps for infusion bottles*

— *Part 4: Infusion sets for single use*

— *Part 5: Burette type infusion sets*

— *Part 6: Freeze drying closures for infusion bottles*

— *Part 7: Caps made of aluminium-plastics combinations for infusion bottles*

Annexes A, B, C, D, E and F form an integral part of this part of ISO 8536.

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Infusion equipment for medical use —

Part 6:
Freeze drying closures for infusion bottles

1 Scope

This part of ISO 8536 specifies the design, dimensions, material, performance, requirements and test for the type of closure for infusion bottles, as described in ISO 8536-1, which is used in connection with the freeze drying (or lyophilization) of drugs and biological materials.

Closures which form the subject of this part of ISO 8536 are intended for single use only.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this part of ISO 8536. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this part of ISO 8536 are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 48:1994, *Rubber, vulcanized or thermoplastic — Determination of hardness (hardness between 10 IRHD and 100 IRHD).*

ISO 3302:1990, *Rubber — Dimensional tolerances for use with products.*

ISO 7864:1993, *Sterile hypodermic needles for single use.*

ISO 8536-1:1991, *Infusion equipment for medical use — Part 1: Infusion glass bottles.*

ISO 8536-2:1992, *Infusion equipment for medical use — Part 2: Closures for infusion bottles.*

ISO 8536-3:1992, *Infusion equipment for medical use — Part 3: Aluminium caps for infusion bottles.*

ISO 8871:1990, *Elastomeric parts for aqueous parenteral preparations.*

3 Definitions

For the purposes of this part of ISO 8536, the following definitions apply.

3.1 freeze drying; lyophilization: Process by which drying is obtained by sublimation of the solvent in the frozen state.

3.2 freeze drying closure: Closure which enables the drying of a frozen good in a vacuum chamber.

It is put in place on top of a glass container after filling, leaving sufficient openings for the sublimation process under vacuum. At the end of the drying process it can be fully inserted into the glass container by hydraulic or mechanical means in the vacuum chamber.

4 Design aspects

4.1 The plug part shall provide slits, channels or other appropriate means, in conjunction with protruding or locating elements at the outer diameter, which enable insertion in a drying (halfway) position during the sublimation process.

4.2 The design of the locating elements to hold the freeze drying closure firmly in the sublimation position shall not generate too high a resistance when the closure is fully inserted.

4.3 The design of the flange part in conjunction with the plug design shall permit both the reconstitution of the freeze-dried product with the appropriate solvent and the removal of the dissolved product by means of a piercing device, without excessive piercing force and without generating an excessive number of rubber fragments.

4.4 The freeze drying closure shall be designed and manufactured in such a way that the removal of the reconstituted product with a hypodermic needle can be visually controlled in order to minimize the amount of residual product.

4.5 The freeze drying closure shall be made from the formulation originally tested and approved by the end-user.

The manufacturer of the freeze drying closure shall certify identity as well as conformance to previously agreed functional parameters or compendium requirements.

4.6 The design of the freeze drying closure should allow easy cleaning.

4.7 Figure 1 illustrates the general design of a freeze drying closure, the dimensions of which are given in clause 5.

5 Dimensions

5.1 The dimensions of freeze drying closures shall be as given in table 1.

5.2 If not otherwise specified, general dimensional tolerances shall be in accordance with ISO 3302.

Table 1 — Dimensions of freeze drying closures

Dimensions in millimetres

Nominal size	d_1 ± 0,2	d_2 [1] ± 0,1	h_2 ± 0,3	h_3 min.	h_4 min.
32	30,8	23,6	4	4	3,7
28	27,1	19,6	3,4	4	2,2

1) The value of d_2 is applied in that area which is defined by h_3.

5.3 If spacers are located on the top of the flange, they shall not interfere with the marks for the injection site. The height of the spacers shall not exceed 0,3 mm.

On the top surface there may be marks or indentations.

5.4 If the flange of the closure has a slightly conical shape in order to facilitate production, the difference in diameter shall not exceed 0,8 mm. The tolerances of the trimmed edge of the flange shall comply with the overall tolerances specified for the flange diameter.

5.5 All edges of the closure may be rounded.

6 Designation

A freeze drying closure for infusion bottles shall be designated by the words "freeze drying closure", the number of this part of ISO 8536, followed by the nominal size of the closure:

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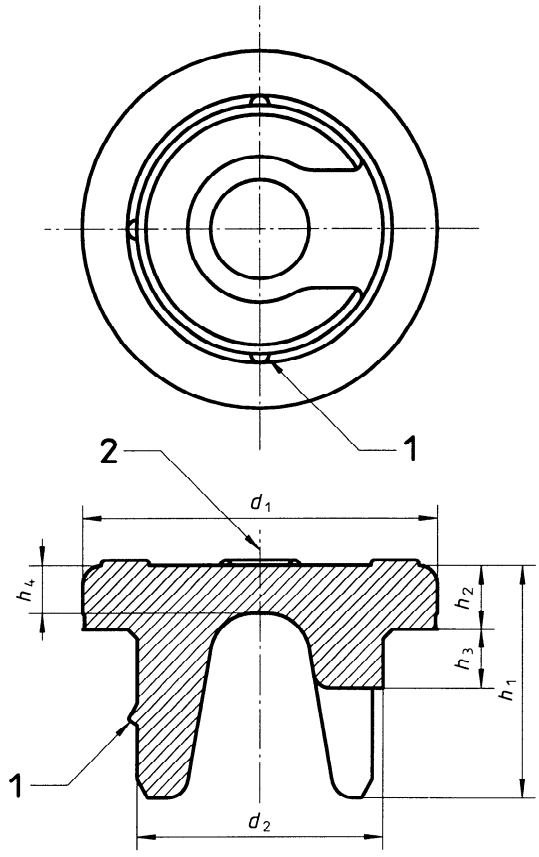
7 Requirements

7.1 Materials

The elastomeric materials used to manufacture freeze drying closures shall meet the general requirements specified in ISO 8536-2.

NOTE 1 It is current practice to prefer elastomeric materials which use straight or halogenated butyl rubbers as a base polymer, since this class of materials exhibits an excellent barrier function against water vapour and gas transmission.



1 Locating element

2 Spacers

NOTE — The total height of the freeze drying closure, h_1, may vary and is subject to mutual agreement between manufacturer and user.

Figure 1 — Closure example

7.2 Physical requirements and performance

NOTE 2 Requirements for dimensions are specified in clause 5.

7.2.1 Hardness

When tested by the method given in ISO 48 using test plates supplied by the manufacturer, the hardness shall not differ from the value stated by the manufacturer by more than ± 5 IRHD.

7.2.2 Fragmentation (coring)

When tested for fragmentation in accordance with annex A, not more than 20 fragments per 10 piercings shall be observed.

7.2.3 Penetration force

When tested for penetration in accordance with annex B, the force needed to penetrate the closure shall not exceed 80 N, and the average value shall be not more than 75 N.

7.2.4 Sealability and spike retention

When tested in accordance with annex C, satisfactory penetration shall be achieved in all cases. No signs of leakage shall appear between the spike and the closure during 4 h, nor shall the spike be pulled from the closure during this time period.

7.2.5 Closure/container integrity and self-sealing

When tested in accordance with annex F, no methylene blue solution shall leak into the interior of the infusion bottle.

7.2.6 Resistance to ageing

The minimum shelf-life of the closure should be agreed upon between closure manufacturer and user.

NOTES

3 The resistance to ageing depends on the actual circumstances of storage and handling. A guide to storage of vulcanized rubber is laid down in ISO 2230, *Vulcanized rubber — Guide to storage.*

4 The useful lifetime of the closure in contact with the pharmaceutical product is part of the compatibility tests to be carried out by the user.

7.2.7 Mechanical stability of freeze drying closures in evaporation position

When freeze drying closures are put in place for the lyophilization process and the container is exposed to transport processes, they should exhibit sufficient shock and vibration resistance that under regular processing conditions they do not fall off nor become distorted.

7.2.8 Residual moisture

The rubber manufacturer shall give a recommendation at what time and temperature (time/temperature profile) the user can reduce residual moisture from freeze drying closures to a level acceptable for his application.

Annex E describes a method for the determination of residual moisture.

NOTE 5 Freeze drying closures can pick up water during shipping, storage, washing and steam sterilization cycles which it is difficult to remove in a subsequent drying cycle. As a consequence, the freeze drying closures are usually loaded with residual moisture. Depending upon the mass of the freeze-dried product and the degree of its sensitivity to water, the residual moisture in the rubber material can spoil the freeze-dried preparation during storage.

7.3 Chemical requirements

The chemical limits specified in table 2 shall be met.

8 Biological requirements

The freeze drying closure shall not release any substances which may adversely affect the therapeutic effectiveness of the injectable products, including those substances which may exhibit toxic, pyrogenic or haemolytic reactions.

Reference shall be made to biological tests, e.g. as described in the United States Pharmacopoeia, European Pharmacopoeia or other Pharmacopoeias, or related regulations of health authorities.

9 Samples

9.1 Sample size

The closures to be tested shall be taken from a sample collected as specified in ISO 8871.

If not otherwise specified, the following number of samples is needed:

— nominal size 32: 200 pieces,

— nominal size 28: 200 pieces.

9.2 Sample preparation

Samples for the tests in annexes A, B and C shall be preconditioned as specified by ISO 8536-2:1992, subclause 6.2 and cooled for at least 2 h at room temperature.

10 Labelling

The packaged freeze drying closures shall be labelled in accordance with the designation specified in clause 6.

Table 2 — Chemical limits for freeze drying closures for infusion bottles

Test	Requirement	Test as described in ISO 8871:1990, annex
Reducing matter (oxidizables)	$\leqslant$ 7 ml of $c(KMnO_4)$ = 2 mmol/l per 20 ml	C
Heavy metals calculated as Pb^{2+}	$\leqslant$ 10 µg Pb^{2+}/10 ml	D
Ammonium (calculated as NH_4^+)	$\leqslant$ 20 µg NH_4^+/10 ml	E
Acidity/alkalinity	$\leqslant$ 1 ml of c(HCl) or c(NaOH) = 5 mmol/l per 20 ml	G
Residue on evaporation (total solids)	$\leqslant$ 4 mg/100 ml	H
Volatile sulfides (at pH $\approx$ 2)	coloration of lead acetate paper $\leqslant$ 50 µg Na_2S/20 cm^2 rubber surface	J
Zinc (calculated as Zn^{2+})	$Zn^{2+} \leqslant$ 30 µg/10 ml	K
Conductivity	$\leqslant$ 40 µs/cm	L
Turbidity	not exceeding opalescence suspension number 3	M

Annex A
(normative)

Determination of fragments

A.1 General

The purpose of the test is to measure the relative coring tendencies of different rubber closures. The values obtained can be significantly affected by many factors, such as prior processing of the closures, crimping device type, sealing force, spike design, its sharpness and spike lubrication.

It is, therefore, necessary to control these variables in order to obtain comparable results. For this reason, the closures to be tested shall be compared to known samples.

A.2 Principle

A number of closures is pierced under defined conditions with a spike as specified in annex D. The closure fragments caused by this operation are collected and counted by visual examination without magnifying aids.

A.3 Apparatus

A.3.1 20 infusion bottles, complying with ISO 8536-2.

A.3.2 Hand-operated capping device and **aluminium caps** with a central hole which fit the infusion bottles to be used in the test.

A.3.3 Membrane filter set.

A.3.4 A steel spike as specified in annex D.

A.4 Procedure

A.4.1 Degrease the test spike (A.3.4) by means of acetone or methylisobutylketone, and dip it into distilled water. Inspect the spike before and during use: it shall have its original sharpness and shall not be damaged.

A.4.2 Select 20 infusion bottles (A.3.1) in a size matching the closure, preconditioned according to 9.2.

Place n ml of water in each of these bottles, where n is 50 % of the nominal volume of the bottles.

Place a closure of the type to be tested on each of 10 bottles, and a closure with known fragmentation properties on each of the remaining 10 bottles.

Seal all bottles with an aluminium cap (A.3.2) using the hand-operated capping device.

Arrange the bottles in two rows as shown in figure A.1.

A.4.3 Hold the spike vertically by hand and pierce closure No. 1 within the marked area, leaving bottle No. 1 standing firmly in a vertical position. Shake the bottle for a few seconds and withdraw the spike.

After each piercing repeat the procedure described in A.4.1.

A.4.4 Repeat the procedure described in A.4.3 using closure No. 11 fitted on bottle No. 11 (i.e. the first closure/bottle combination in the second row).

A.4.5 Repeat all of the procedures described in A.4.3 and A.4.4, using, alternatively, bottles from the two rows, until all of the closures have each been pierced once.

A.4.6 Remove the closures to be tested from the bottle (first row). Put the contents of all the bottles from the first row through one membrane filter. Ensure that no fragments remain in the bottle. Count and record the number of rubber fragments on the filter visible with the naked eye under normal conditions at a distance between eye and filter of 25 cm.

It is assumed that fragments having a diameter larger than 50 µm are seen with the naked eye.

For further identification the fragments may be examined with a microscope in order to determine their sizes and nature.

A.4.7 Repeat the procedure described in A.4.6, using the bottles with closures having known fragmentation properties.

A.5 Expression of results

The recorded numbers of fragments per 10 piercings for the two series shall be reported.

A.6 Validity

The results obtained on the test closures shall be considered invalid if the results on the known closures lack consistency with previous results; the reason for such inconsistency shall be detected.

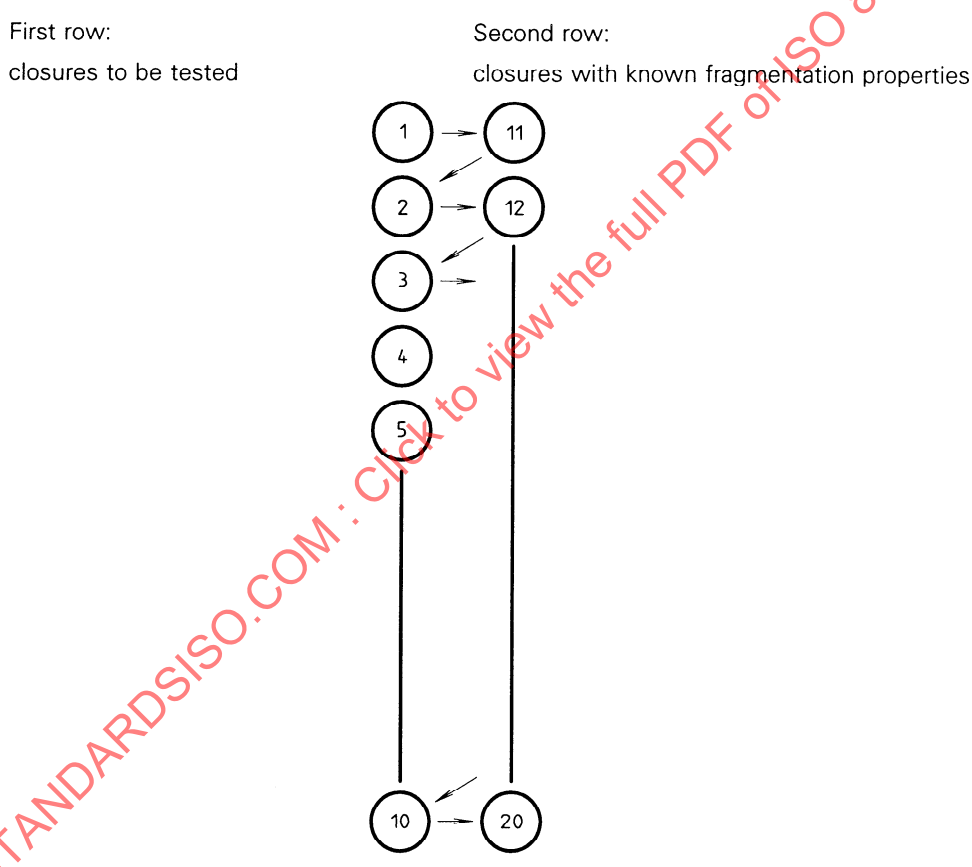


Figure A.1 — Test sequence for fragmentation test

Annex B
(normative)

Determination of penetration force

B.1 Principle

Measurement of the force required to pierce the closure with a spike as specified in annex D.

B.2 Apparatus

B.2.1 **Piercing device** which satisfies the following requirements.

The spikes, when clamped in this device, can be moved perpendicularly at a speed of 200 mm/min. The force exerted backwards on the spike during such movement is indicated or registered with an accuracy of ± 2 N.

An infusion bottle can be placed in the device in axial alignment, allowing central piercing of the closure on this bottle.

B.2.2 **Two steel spikes** as specified in annex D.

NOTE 6 The spikes are designated as S1 and S2.

B.3 Preparation

B.3.1 Take a sample of 10 closures from the type or lot to be tested. Take a sample of 10 closures from a lot or type known to yield satisfactory results in practice.

B.3.2 Prepare 20 infusion bottles according to ISO 8536-1 of any size, half-filled with water. Close 10 infusion bottles with preconditioned closures according to 9.2 of the type to be tested (T) and 10 bottles with the closures of known quality (C).

B.3.3 Fix the closures with aluminium caps according to ISO 8536-3.

B.4 Procedure

B.4.1 Degrease spike S1 with acetone exerting the utmost care not to blunt it and clamp spike S1 in the piercing device.

Take one bottle of type T. Remove the cap so as to have free access to the closure. Place the bottle in the testing device in such a way that the closure will be perforated perpendicularly and centrally.

Operate the device at the specified speed and register the force exerted immediately before penetration takes place.

Restore the clamp into the original position and remove the bottle.

B.4.2 Repeat steps B.4.1, taking a bottle of type C.

B.4.3 Repeat steps B.4.1 and B.4.2, taking bottles of type T and type C alternately, until five bottles of each type have been tested.

B.4.4 Repeat steps B.4.1 to B.4.3 using, however, spike S2.

B.5 Expression of results

B.5.1 Calculate average values, AT and AC, for all bottles of type T and type C respectively.

B.5.2 Calculate the difference between the highest and lowest values in each of these series (RT and RC respectively).

B.5.3 If RT and/or RC is larger than 50 N and the second part of the collected closure samples is still available, then repeat the whole experiment, using this second part of the closure samples.

B.5.4 If the repetition still fails to result in RT and RC being lower than 50 N, then repeat the whole experiment, using two new spikes.

B.5.5 If the average value AC is not in accordance with the expectation based on experience, then repeat the whole experiment, using new reference closures as well as new spikes.

Annex C
(normative)

Spike retention/sealability

C.1 Preparation

Take 10 bottles of 50 ml or 125 ml in accordance with ISO 8536-1. Fill the bottles with the nominal volume of water, close them with the preconditioned closures according to 9.2 and secure with aluminium caps as specified in ISO 8536-3:1992, type A.

C.2 Procedure

C.2.1 Place a new spike vertically on the centre of the uncovered part of an unperforated closure fitted to a bottle as prepared in C.1.

C.2.2 Apply a vertical force to the spike. Increase this force until a satisfactory penetration has occurred or up to the highest manually achievable value.

C.2.3 If a satisfactory penetration is achieved, then fix the bottle vertically with the bottom end up, and attach a total mass of approximately 0,5 kg to the spike. Leave it in this situation for 4 h, observe and note any signs of liquid leaking along the spike during this period.

C.3 Expression of results

C.3.1 Report the number of cases in which no satisfactory penetration was obtained and the number of cases in which leakage along the spike occurred during the observation period.

C.3.2 Report the number of cases with satisfactory penetration, in which leakage along the spike during the observation period has occurred.

C.3.3 Report the number of cases where the spike was not in place after 4 h under stress.

Annex D
(normative)

Closure piercing device

NOTE 7 Since there is currently no plastics reference spike available, the use of the steel spike in figure D.1 is recommended. The values obtained may not correlate with those obtained with plastics spikes.

Dimensions in millimetres

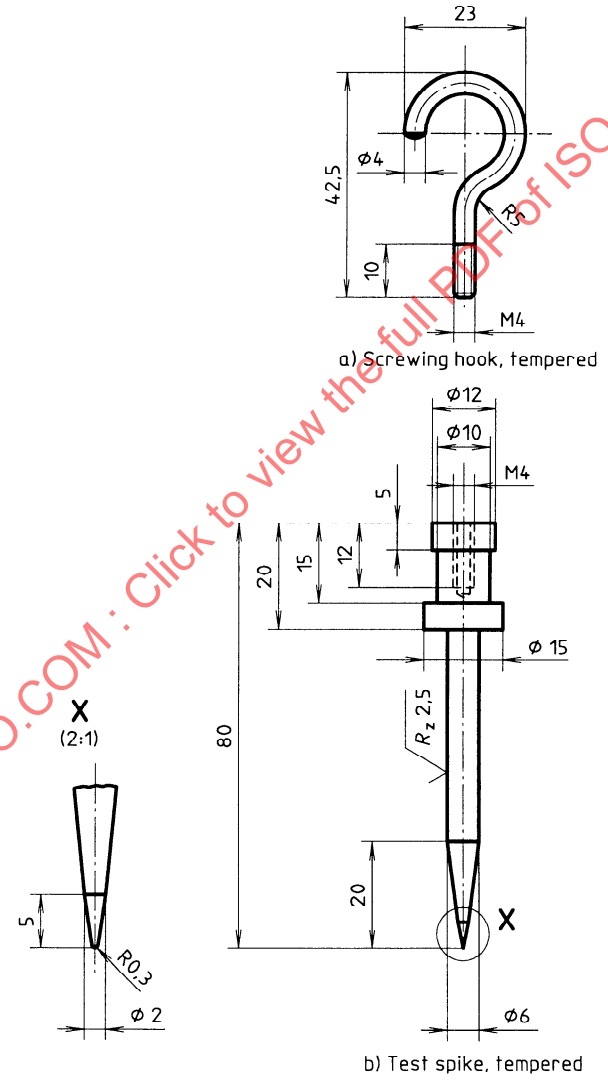


Figure D.1 — Test spike

Annex E
(normative)

Determination of residual moisture

E.1 Principle

The elastomeric material to be tested is heated in a nitrogen stream in a drying pistol. The evaporated water is passed into a titration cell where the amount of water is determined coulometrically.

E.2 Apparatus

E.2.1 Karl-Fischer coulometric device.

E.2.2 Drying pistol with a heating system to adjust temperatures between 110 °C and 150 °C.

E.2.3 Nitrogen supply with a molecular sieve cartridge.

NOTE 8 Choose nitrogen with a low moisture content.

E.2.4 Stainless steel weighing boat.

E.2.5 Analytical balance accurate to 0,1 mg.

E.2.6 Reagents as specified in the measurement system manual.

E.2.7 Sodium tartrate with defined water content (standard).

E.2.8 Check solution: 1 % (*V/V*) water in organic solvent.

E.3 Procedure

E.3.1 Apparatus preparation

Set up the apparatus as indicated in the instruction manual. Adjust the drying pistol to 140 °C ± 2 °C and flush it with nitrogen at a suitable rate.

Check the apparatus in particular for

— low blank drift,

— correct determination of check solution,

— constant slope of the cumulative graph water/time when running a blank during at least 80 min,

— correct determination of water in sodium tartrate.

NOTE 9 Checking once a day is recommended.

E.3.2 Sample preparation

E.3.2.1 General

Use pincers or disposable gloves in handling the closures.

Maintain the untreated closures in their original packing and keep treated closures in airtight vessels with as small as possible a headspace.

Treat closures in a standard laboratory atmosphere [temperature 23 °C ± 2 °C, relative humidity (50 ± 10) %].

E.3.2.2 Preparing elastomeric material for determination

Collect at least 10 closures and cut from each closure at least one segment from the top flange along a perpendicular plane such that the segment length is approximately 9 mm (see figure E.1).

Put all these segments in the weighing boat, taking segments from all closures. Weigh to an accuracy of 0,1 mg. The suitable amount of elastomeric material depends on water content and the determination unit which is used (see E.5).

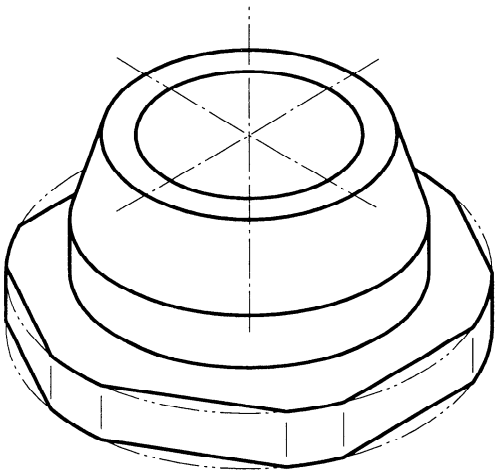


Figure E.1 — Cutting segments from closure

E.3.3 Determination

Put the segments into the drying pistol immediately after weighing and start the determination.

Record the values obtained as a cumulative curve of water versus time for at least 90 min. Repeat the test with new samples.

E.4 Calculation and expression of results

E.4.1 Extrapolation

Figure E.2 shows schematically the cumulative curve as recorded during determination.

For extrapolation, take the values at 90 min, 85 min, 80 min, 75 min and 70 min.

Read the primary results as micrograms of water from the curve by extrapolation as shown in figure E.2.

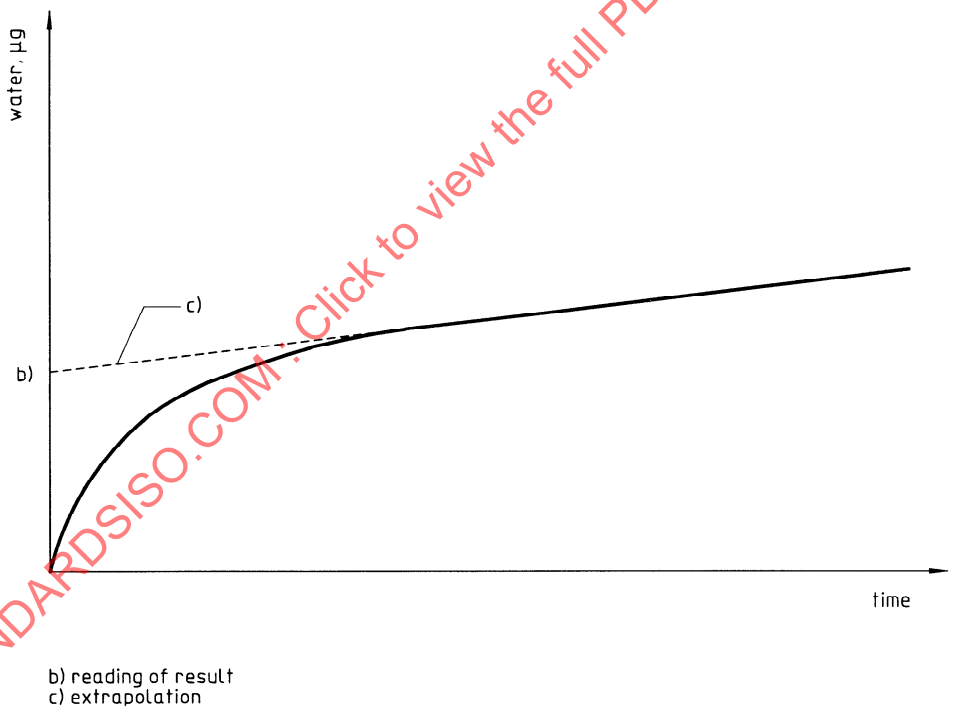


Figure E.2 — Cumulative curve:water/time

E.4.2 Expression of results

The amount of water, μ, shall be indicated as % (*V/V*) moisture related to rubber segments in the drying pistol:

$$\mu = \frac{V}{m \times 10}$$

where

V is the water, in micrograms;

m is the mass of rubber segments in the drying pistol, in milligrams.

E.5 Comments and limitations

E.5.1 Persistent slope decrease at the end part of the curve may be the result of the following factors:

— apparatus drift, including residual moisture in the carrier gas;

— side reactions with volatile ingredients or decomposition products from the material tested;

— slow diffusion from the inner area of the rubber particles tested.

Back-extrapolation will compensate for the effects of drift and other influences.

Slow diffusion is countered by minimizing the thickness of the material tested.

E.5.2 The mass of the probe normally should be between 200 mg and 400 mg, as a function of an expected moisture content between 0,5 mg and 3 mg.

These conditions will allow meaningful calculation of moisture contents between 0,1 % and 1,5 %.