

ประกาศกระทรวงอุตสาหกรรม

ฉบับที่ ๓๕๐๑ (พ.ศ. ๒๕๕๑)

ออกตามความในพระราชบัญญัติมาตรฐานผลิตภัณฑ์อุตสาหกรรม

พ.ศ. ๒๕๑๑

เรื่อง กำหนดมาตรฐานผลิตภัณฑ์อุตสาหกรรม

การประเมินทางชีวภาพของเครื่องมือแพทย์

เล่ม 15 : การชี้แจงและการหาปริมาณสารที่สลายได้จากเครื่องมือแพทย์

ที่เป็นโลหะและโลหะเจือ

อาศัยอำนาจตามความในมาตรา ๑๕ แห่งพระราชบัญญัติมาตรฐานผลิตภัณฑ์อุตสาหกรรม พ.ศ. ๒๕๑๑ รัฐมนตรีว่าการกระทรวงอุตสาหกรรมออกประกาศกำหนดมาตรฐานผลิตภัณฑ์อุตสาหกรรมการประเมินทางชีวภาพของเครื่องมือแพทย์ เล่ม 15 : การชี้แจงและการหาปริมาณสารที่สลายได้จากเครื่องมือแพทย์ที่เป็นโลหะและโลหะเจือ มาตรฐานเลขที่ มอก. 2395 เล่ม 15 - 2551 ไว้ดังมีรายการละเอียดต่อท้ายประกาศนี้

ประกาศ ณ วันที่ ๒๕ กรกฎาคม พ.ศ. ๒๕๕๑

สุวิทย์ คุณกิตติ

รัฐมนตรีว่าการกระทรวงอุตสาหกรรม

มาตรฐานผลิตภัณฑ์อุตสาหกรรม

การประเมินทางชีวภาพของเครื่องมือแพทย์

เล่ม 15 : การชี้บ่งและการหาปริมาณสารที่สลายได้ จากเครื่องมือแพทย์ที่เป็นโลหะและโลหะเจือ

มาตรฐานผลิตภัณฑ์อุตสาหกรรมนี้กำหนดขึ้นโดยรับ ISO 10993-15 : 2000 Biological evaluation of medical devices-Part 15 : Identification and quantification of degradation products from metals and alloys มาใช้ใน ระดับเหมือนกันทุกประการ (identical) โดยใช้ ISO ฉบับภาษาอังกฤษเป็นหลัก

มาตรฐานผลิตภัณฑ์อุตสาหกรรมนี้กำหนดวิธีทดสอบเพื่อชี้บ่งและหาปริมาณสารที่สลายได้จากเครื่องมือแพทย์ ที่เป็นโลหะและโลหะเจือที่เกิดจากการเปลี่ยนแปลงทางเคมีซึ่งเป็นการทดสอบโดยภาวะเร่ง โดยกำหนดวิธีทดสอบ 2 วิธี คือ การทดสอบทางเคมีไฟฟ้า (electrochemical test) และการทดสอบโดยการจุ่ม (immersion test) โดยกำหนดเครื่องมือที่ใช้ทดสอบ การเตรียมตัวอย่าง ภาวะทดสอบ วิธีวิเคราะห์ และการรายงานผล

รายละเอียดให้เป็นไปตาม ISO 10993-15 : 2000

Introduction

One of the potential health hazards resulting from medical devices may be due to the interactions of their electrochemically-induced degradation products with the biological system. Therefore, the evaluation of potential degradation products from metallic materials by methods suitable for testing the electrochemical behavior of these materials is a necessary step in the biological performance testing of materials.

The body environment typically contains cations of sodium, potassium, calcium and magnesium and anions of chloride, bicarbonate, phosphate and organic acids generally in concentrations between 2×10^{-3} mol and 150×10^{-3} mol. A range of organic molecules such as proteins, enzymes and lipoproteins is also present, but their concentrations may vary to a great extent. Earlier studies assumed that organic molecules did not exert a significant influence on the degradation of metallic implants, but newer investigations indicate that implant — protein interactions should be taken into account. Depending on a particular product or application, altering the pH of the testing environment may also need to be considered.

In such biological environments, metallic materials may undergo a certain degradation and the different degradation products may interact with the biological system in different ways. Therefore, the identification and quantification of these degradation products is an important step in evaluating the biological performance of medical devices.

Biological evaluation of medical devices —

Part 15: Identification and quantification of degradation products from metals and alloys

1 Scope

This part of ISO 10993 provides guidance on general requirements for the design of tests for identifying and quantifying degradation products from finished metallic medical devices or corresponding material samples finished as ready for clinical use. It is applicable only to those degradation products generated by chemical alteration of the finished metallic device in an *in vitro* accelerated degradation test. Because of the accelerated nature of these tests, the test results may not reflect the implant or material behavior in the body. The described chemical methodologies are a means to generate degradation products for further assessments.

This part of ISO 10993 is not applicable to degradation products induced by applied mechanical stress.

NOTE Mechanically induced degradation, such as wear, may be covered in the appropriate product-specific standard. Where product-group standards provide applicable product-specific methodologies for the identification and quantification of degradation products, those standards should be considered.

Because of the wide range of metallic materials used in medical devices, no specific analytical techniques are identified for quantifying the degradation products. The identification of trace elements ($< 10^{-6}$) contained in the specific metal or alloy is not addressed in this part of ISO 10993, nor are specific requirements for acceptable levels of degradation products provided in this part of ISO 10993.

This part of ISO 10993 does not address the biological activity of the degradation products; see instead the applicable clauses of ISO 10993-1 and ISO 10993-17.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this International Standard. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this International Standard are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 3585, *Borosilicate glass 3.3 — Properties.*

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

ISO 8044, *Corrosion of metals and alloys — Basic terms and definitions.*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing.*

ISO 10993-9, *Biological evaluation of medical devices — Part 9: Framework for identification and quantification of potential degradation products.*

ISO 10993-12, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials.*

ISO 10993-13, *Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymeric medical devices.*

ISO 10993-14, *Biological evaluation of medical devices — Part 14: Identification and quantification of degradation products from ceramics.*

ISO 10993-16, *Biological evaluation of medical devices — Part 16: Toxicokinetic study design for degradation products and leachables.*

3 Terms and definitions

For the purposes of this part of ISO 10993, the terms and definitions given in ISO 8044, ISO 10993-1, ISO 10993-9, ISO 10993-12 and the following apply.

3.1

alloy

material composed of a metallic element with one or more addition(s) of other metallic and/or non-metallic elements

3.2

electrolyte

solution containing ions with the capacity to conduct electric current

3.3

open-circuit potential

potential of an electrode measured with respect to a reference electrode or another electrode when no current flows to or from it

3.4

passive limit potential

E_a

electrode potential of the positive limit of the passive range

See Figure 1.

3.5

breakdown potential

E_p

critical electrode potential above which localized or transpassive corrosion is found to occur

See Figure 1.

4 Degradation test methods

4.1 General

To identify and quantify degradation products from metals and alloys in medical devices, a combination of two procedures is described. The choice of test procedure shall be justified according to the function of the medical device.

The first procedure described is a combination of a potentiodynamic test and a potentiostatic test. The second procedure described is an immersion test.

The potentiodynamic test is used to determine the general electrochemical behavior of the material under consideration and to determine certain specific points (E_a and E_p) on the potential/current density curve.

The immersion test is used to chemically degrade the test material to generate degradation products to be analysed.

If there is the possibility of the loss of a coating from a metallic substrate due to degradation, the potential degradation products from the substrate material shall be considered, as well as the coating itself. In addition, if a metallic substrate coated with a non-metallic material is to be tested, the requirements of ISO 10993-13 and/or ISO 10993-14 shall be considered in order to determine the potential degradation products of the coating.

The identified and quantified degradation products form the basis for evaluation of biological response and, if appropriate, toxicokinetic studies in accordance with ISO 10993-16.

4.2 Prerequisites

The rates of electrochemical degradation reactions are sensitive to small variations in test conditions, instrumentation, sample conditions and preparation. Therefore, electrochemical degradation testing shall be carried out in an appropriately equipped laboratory by experienced and qualified personnel. This includes proper maintenance and calibration of the test equipment. The methods and operating conditions of the equipment shall also be validated.

NOTE Fulfilment of electrochemical test conditions for stability, warm-up time, etc., can be demonstrated by conformance to [1].

5 Reagent and sample preparation

5.1 Sample documentation

The general composition of the material(s) under test shall be documented.

5.2 Test solution (electrolyte)

The test solution (electrolyte) to be used shall be appropriate for the intended use of the medical device. All chemicals shall be of analytical grade and dissolved in water of grade 2 in accordance with ISO 3696.

The first choice for the electrolyte shall be an isotonic aqueous solution of 0,9 % sodium chloride. Other electrolytes may be used, such as artificial saliva or artificial plasma. Examples of alternative compositions are given in annex C.

In the test report the choice of electrolyte shall be justified. If other than an aqueous solution of 0,9 % sodium chloride is used, the pH of the electrolyte shall be specified.

5.3 Preparation of test samples

5.3.1 Test samples

The sensitivity of chemical degradation testing is related to variation in material composition, to material processing and to surface-finishing procedures. The sampling procedure, sample shape and surface preparation are critical. The samples shall be representative of the finished devices.

5.3.2 Sampling

For each chemical test, at least two test samples shall be prepared as specified in ISO 10993-12. If substantial deviations in the test results are found, the reasons for the deviation shall be determined, and more samples shall be tested.

If the metallic sample has anisotropic properties due to manufacturing conditions, tests involving single-surface exposure should include samples cut parallel to both the transverse and longitudinal manufacturing directions.

5.3.3 Sample shape

Standard samples, either circular- or rectangular-section bars or flat coupons, or one single free surface may be used for degradation testing if they are prepared in a manner comparable to the representative medical device. Samples of actual device components may be of any shape and condition, however the testing shall be carried out under well-controlled conditions which shall be reported.

The surface area of the sample exposed to the electrolyte shall be determined to an accuracy of better than 10 % of the total geometrical area to assure an accurate and repeatable determination of the degradation rates.

5.3.4 Sample surface condition

Since the surface condition of a material may affect its electrochemical behaviour, the surface condition of the test sample shall be identical to the finished medical device and shall be described in the test report. For comparing test results of different materials, the surface condition of the test samples shall be the same.

6 Electrochemical tests

6.1 Apparatus

6.1.1 Test cells of borosilicate glass, in appropriate sizes, in accordance with ISO 3585, with a means of controlling the bath temperature within ± 1 °C.

6.1.2 Scanning potentiostat with a potential range ± 2 V and a current output range from 10^{-9} A to 10^{-1} A.

6.1.3 Potential-measuring instrument with a high input impedance ($>10^{11}$ Ω) and a sensitivity and accuracy to detect a change of 1 mV over a potential range between ± 2 V.

6.1.4 Current-measuring instrument capable of measuring a current to $\pm 1\%$ of the absolute value over a current range between 10^{-9} A and 10^{-1} A.

6.1.5 Working electrode (test sample).

6.1.6 Counter-electrode(s) such as platinum (grid, plate, or wire) or vitreous carbon with an area at least 10 times that of the working electrode.

6.1.7 Reference electrode.

6.1.8 pH-meter with a sensitivity of $\pm 0,1$.

A schematic diagram of the electrochemical measurement circuit which may be used as a system with variable potential is given in annex A.

A schematic drawing of an electrolytic cell is given in annex B.

6.2 Sample preparation

Mount the test sample in a watertight electrode holder so that only the test surface is in contact with the electrolyte. Take care to avoid the creation of conditions where crevice corrosion can occur due the formation of a crevice between the mounting and the sample. Before testing, clean the specimen ultrasonically for 10 min to 15 min in ethanol, carefully rinse with water of grade 2 in accordance with ISO 3696 and immediately transfer into the test cell.

6.3 Test conditions

Fill the test cell with the test solution (electrolyte). If the electrochemical behaviour is temperature-sensitive in the range of 10 °C to 50 °C, maintain the electrolyte cell at (37 ± 1) °C. Reduce the oxygen level in the electrolyte by bubbling oxygen-free nitrogen or argon at a rate of approximately $100 \text{ cm}^3\text{-min}^{-1}$ for not less than 30 min prior to the start of the test. The electrolyte shall be agitated either by the bubbling gas or mechanical means to avoid concentration gradients. If gas agitation is used, take care not to have any gas bubbles adhering to the active test surface.

Magnetic stirrers often interfere with electrochemical test cells. If they are used, their effect on the test cell shall be determined as part of the validation of test equipment, see 4.2.

6.4 Potentiodynamic measurements

Measure the open-circuit potential not less than 2 h after the immersion of the working electrode. This potential shall be the starting potential for potentiodynamic measurements. The sweep rate shall be $1,0 \text{ mV}\cdot\text{s}^{-1}$, except in tests where the sweep rate has little effect, where the test may be accelerated by increasing the sweep rate to $10 \text{ mV}\cdot\text{s}^{-1}$. Record the potential/current density curve up to a maximum of 2000 mV or a maximum current density of $1,0 \text{ mA}\cdot\text{cm}^{-2}$, whichever comes first, to evaluate the transpassive range of the sample (see Figure 1). To ensure consistency, reverse the scan and continue back at least to the open-circuit potential. Then repeat the test back to 2000 mV or $1,0 \text{ mA}\cdot\text{cm}^{-2}$. If the curves are not reproducible, then continue cycling 5 to 10 times. If consistent potential/current density curves are not achieved after 5 to 10 cycles, investigate possible causes such as test set-up, electrode function, innate material properties, etc. The log current density/potential curves should also be recorded (see Figure 2). Record the breakdown potential (E_p) from the last cycle taken (see Figure 1).

Noble metals may behave differently from passivating metals during an electrochemical test. Therefore, take care in determining the breakdown potential (E_p) for different metal systems.

6.5 Potentiostatic measurements

This method permits qualitative and quantitative determination of degradation products which might be dissolved in the electrolyte.

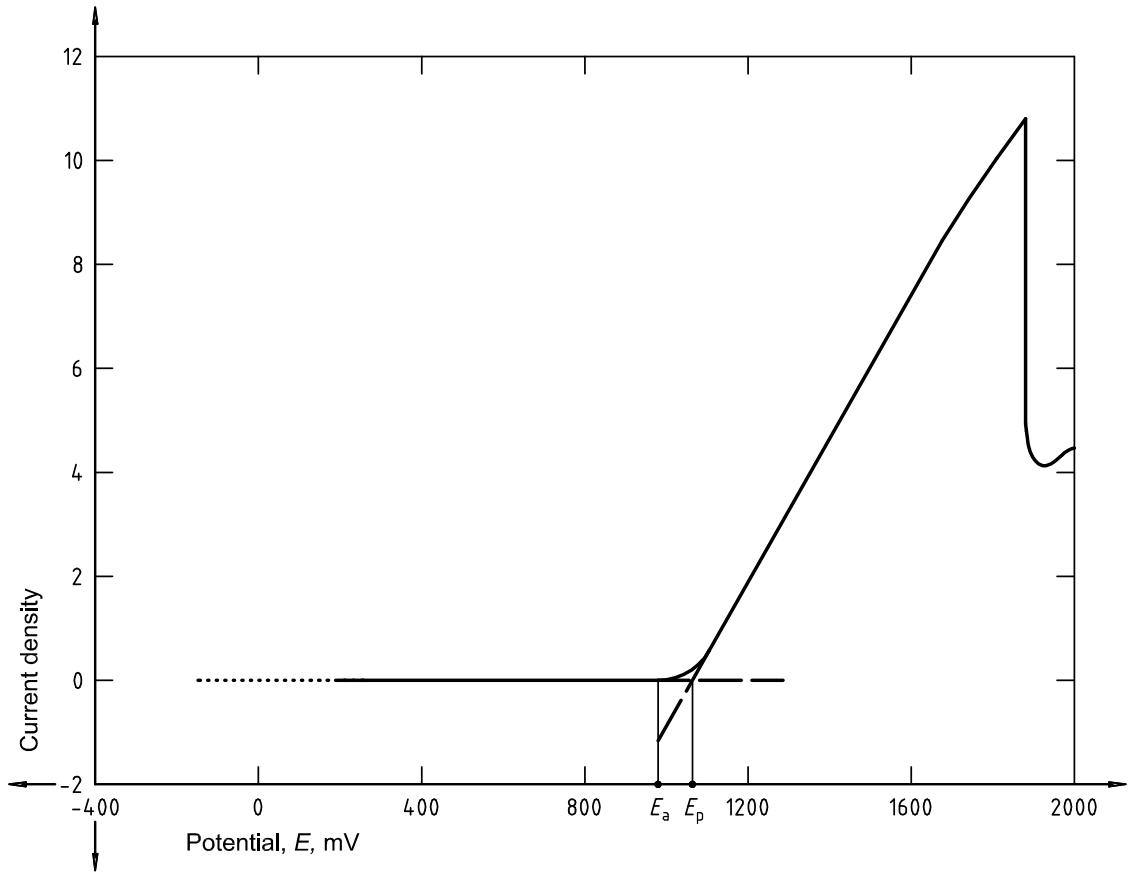
Hold a new test sample at a constant electrode potential during the test time, and record the current density/time curve. The potential used to determine the degradation products shall be the breakdown potential (E_p) + 50 mV. Depending upon the material studied, the polarization duration shall be either 1 h or 5 h and shall be reported. Measure and record the volume of the electrolyte for use in future calculations.

7 Immersion test

7.1 Apparatus

7.1.1 Test cells of borosilicate glass, of appropriate sizes, in accordance with ISO 3585, with a means of controlling the bath temperature within ± 1 °C.

7.1.2 pH-meter with a sensitivity of $\pm 0,1$.



NOTE E_p is determined by extrapolation of the linear part of the oxidation curve to zero current density.

Figure 1 — Plot of current density versus potential, showing the start of corrosion current at E_a and breakdown potential, E_p

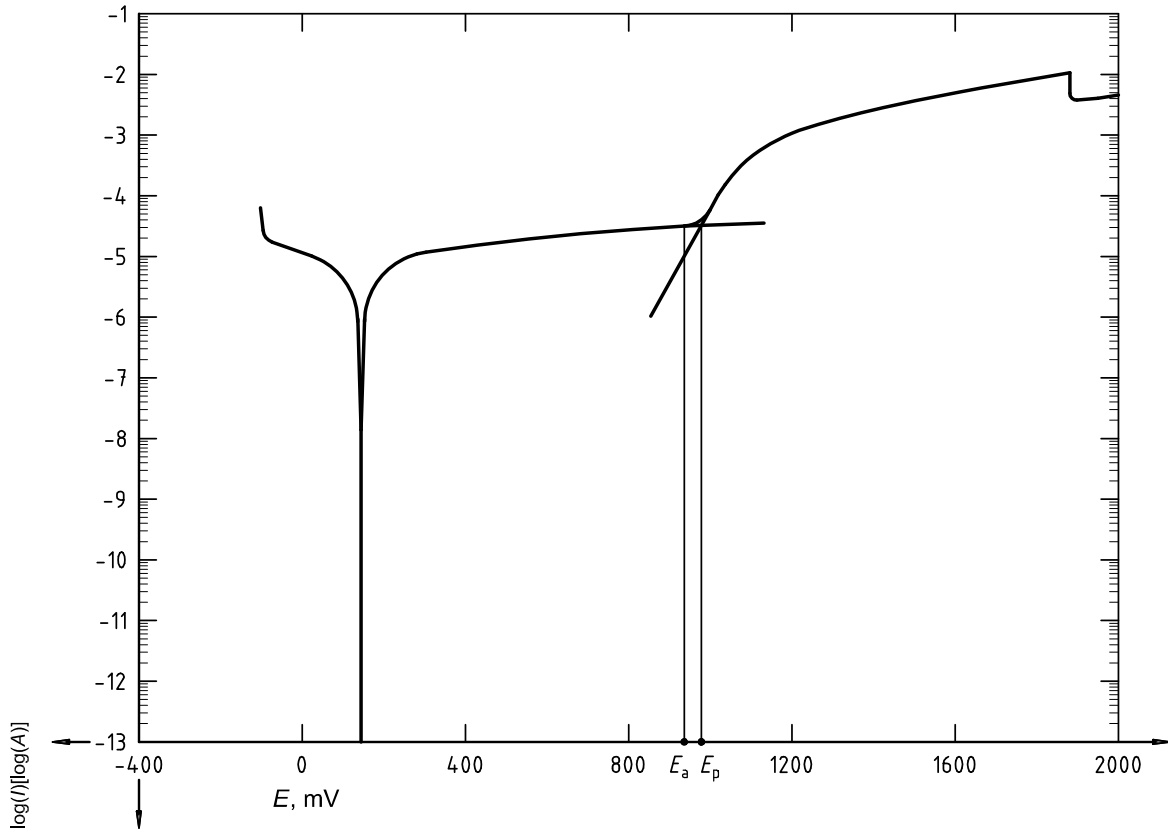


Figure 2 — Log current density versus potential plot showing the breakdown potential, E_p , at the inflection point of the curve

7.2 Sample preparation

The test sample shall be placed in a separate glass container. The size of the glass container should be selected so that an electrolyte volume of less than 1 ml/cm² of sample surface shall completely cover the sample(s).

Do not compromise the data through biological contamination. For example, the electrolyte may need to be prepared under aseptic conditions.

NOTE The surface area and volume of electrolyte should be sufficient for the intended method of analysis (see clause 8).

Care should be taken such that the samples do not touch the glass surface except in a minimum support line or point. If the test sample is small, the proper surface area/volume ratio may not be attainable with a single test sample. Therefore, if the test sample must be made up of two or more pieces, the pieces shall not touch each other.

7.3 Immersion test procedure

Measure the pH of the electrolyte containing the test sample at the start of the test. Then tightly close the test cell to prevent evaporation and maintain at $(37 \pm 1) ^\circ\text{C}$ for $(7 \pm 0,1)$ days. Then remove the sample and measure the pH of the residual electrolyte.

8 Analysis

Observe and record the condition of the test sample under low-power microscopy ($> 50\times$) and report any significant changes to the surface. More detailed analysis of the surface may be undertaken if appropriate.

After each experiment, perform a qualitative and quantitative analysis of the electrolyte using a method of adequate sensitivity (at least $1,0 \times 10^6$ by atomic absorption, ICP, or mass spectroscopy for example). Report compositional constituents detected above the limits of quantification. If potentially biologically hazardous constituents are identified but not quantified, other analytical analyses may be necessary. In addition, any deposits on the counter-electrode shall be accounted for in the analysis.

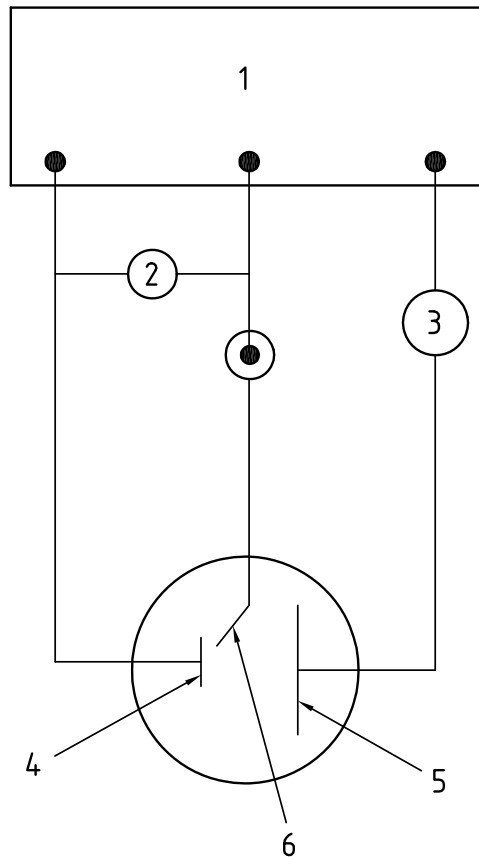
9 Test report

The test report shall contain at least the following details:

- a) complete identification of the test sample, including the chemical composition;
- b) ratio of the exposed surface area of the sample to the volume of the electrolyte;
- c) composition and pH (with an uncertainty of $\pm 0,1$) of the electrolyte and a description of the natural or reference electrode for the electrochemical test;
- d) composition and initial and final pH of the electrolyte for the immersion test;
- e) temperature of the electrolyte;
- f) current density vs. potential curve(s), optionally the log (current density) vs. potential curve for comparison;
- g) open-circuit potential;
- h) breakdown potential E_p and the current density at the breakdown potential;
- i) sweep rate;
- j) current density vs. time curve(s) and total test time;
- k) brief comments on the curves (e.g. hysteresis, peaks);
- l) description of any significant changes of the sample surface and/or of the electrolyte;
- m) results of analysis of degradation elements in the electrolyte, including degradation rate, reported in micrograms per square centimetre per hour ($\mu\text{g}/\text{cm}^2/\text{h}$) for the electrostatic test or per seven days ($\mu\text{g}/\text{cm}^2/7$ days) for the immersion test;
- n) method of chemical analysis of electrolyte;
- o) type of reference electrode [all potentials should be referenced to the normal hydrogen electrode (NHE)];
- p) name of investigator;
- q) date(s) of investigation;
- r) signature of the investigator.

Annex A
(informative)

Schematic diagram of the electrochemical measuring circuit



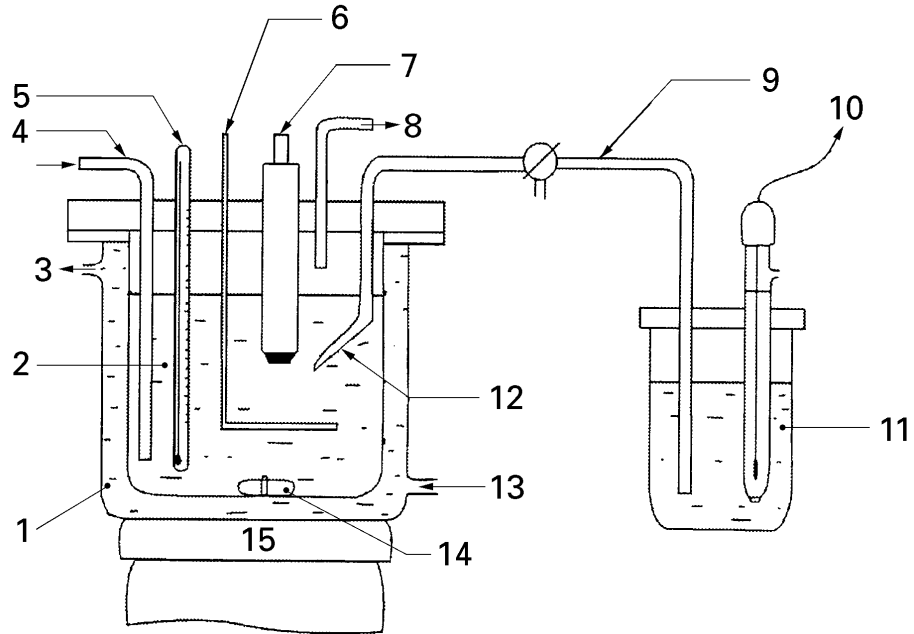
Key

- 1 Potentiostat
- 2 Potential measurement
- 3 Current measurement
- 4 Working electrode
- 5 Counter-electrode
- 6 Reference electrode

Figure A.1 — Schematic diagram of the electrochemical measuring circuit

Annex B
(informative)

Schematic drawing of an electrolytic cell



Key

- | | | | |
|---|---------------------------|----|----------------------------------|
| 1 | Constant-temperature cell | 9 | Electrolytic bridge |
| 2 | Electrolyte | 10 | Reference electrode |
| 3 | Water outlet | 11 | Saturated KCL solution |
| 4 | Gas inlet | 12 | Luggin capillary |
| 5 | Thermometer | 13 | Constant-temperature water inlet |
| 6 | Counter-electrode | 14 | Magnetic stirring bar |
| 7 | Working electrode | 15 | Magnetic stirrer |
| 8 | Gas outlet | | |

Figure B.1 — Schematic drawing of an electrolytic cell

Annex C (informative)

Examples of alternative electrolytes for the electrochemical tests

C.1 General

All chemicals shall be of analytical grade and dissolved in high purity water, grade 2 in accordance with ISO 3696. Care shall be taken to avoid precipitation when preparing these solutions.

C.2 Artificial saliva (see [2])

Na ₂ HPO ₄	0,260 g/l
NaCl	0,700 g/l
KSCN	0,330 g/l
KH ₂ PO ₄	0,200 g/l
NaHCO ₃	1,500 g/l
KCl	1,200 g/l

C.3 Artificial plasma (see [2])

NaCl	6,800 g/l
CaCl ₂	0,200 g/l
KCl	0,400 g/l
MgSO ₄	0,100 g/l
NaHCO ₃	2,200 g/l
Na ₂ HPO ₄	0,126 g/l
NaH ₂ PO ₄	0,026 g/l

Bibliography

- [1] ASTM G 5-94, *Reference Test Method for Making Potentiostatic and Potentiodynamic Anodic Polarization Measurements.*
- [2] AFNOR NF 91-141G 5-94, *Biodegradability of dental metal alloys — Standardization of electrochemical test.*
- [3] ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances using health-based risk assessment.*
- [4] ISO 10271, *Dental metallic materials — Corrosion test methods.*