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Implants for surgery — Homopolymers, copolymers and blends on poly(lactide) — In vitro degradation testing

Implants chirurgicaux — Homopolymères, copolymères et mélanges sur poly(lactide) — Essais de dégradation in vitro

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Contents

Page

Foreword ... **iv**
Introduction ... **v**
1 Scope ... **1**
2 Normative references ... **1**
3 Terms and definitions ... **2**
4 Degradation evaluation ... **3**
4.1 General ... 3
4.2 Apparatus and reagents ... 4
4.3 Real-time degradation — Sample conditioning procedure ... 5
4.3.1 Sample loading and placement ... 5
4.3.2 Control of temperature ... 5
4.3.3 Control of buffer solution ... 5
4.3.4 Sample retrieval ... 5
5 Physical, chemical and mechanical tests ... **6**
5.1 General ... 6
5.2 Loss of sample mass ... 6
5.2.1 Apparatus ... 6
5.2.2 Number of test samples ... 6
5.2.3 Procedure ... 7
5.2.4 Reusability of test specimens ... 7
5.3 Evaluation of molar mass ... 8
5.3.1 Via inherent viscosity ... 8
5.3.2 Via gel permeation chromatography/size exclusion chromatography ... 8
5.4 Mechanical tests ... 8
5.4.1 General ... 8
5.4.2 Conditioning of test samples ... 8
5.4.3 Test methods ... 9
5.5 Additional evaluation methods for consideration ... 9
6 Test termination ... **9**
7 Test report ... **10**
Annex A (informative) **Nomenclature of absorb, degrade and related terms** ... **12**
Annex B (informative) **Additional analytic methods for consideration** ... **13**
Bibliography ... **14**

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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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 150, *Implants for surgery,* Subcommittee SC 1, *Materials.*

This second edition cancels and replaces the first edition (ISO 13781:1997) and ISO 15814, which have been technically revised.

The main change compared to the previous edition is as follows:

— the principle contents of ISO 15814 are incorporated into this document.

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Introduction

With the development of absorbable polymers for use in implantable devices, there is a need to define standard test methods to evaluate the behaviour of bulk material or devices under simulated physiological environments. On the other hand, the behaviour of absorbable materials and devices *in situ* depends on the conditions in which the material is implanted. These conditions differ, so that the site-specific behaviour of the material or device can differ. The interpretation of *in vitro* test results therefore needs to be considered carefully, taking into account any correlation of test results under *in vitro* and *in vivo* conditions. Only functional *in vivo* tests with the final product can answer actual degradation behaviour *in situ*.

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Implants for surgery — Homopolymers, copolymers and blends on poly(lactide) — In vitro degradation testing

1 Scope

This document describes methods for the determination of chemical and mechanical changes in poly(lactide)-based homopolymers, copolymers and/or blends induced under *in vitro* degradation testing conditions. This document covers polymers based on L-lactide, D-lactide, and/or D, L-lactide monomeric units.

The purpose of this document is to compare and/or evaluate materials or processing conditions. This document also describes the fundamental physical and mechanical evaluations needed for an *in vitro* degradation characterization of an absorbable poly(lactide) or other hydrolysable material or device.

This document is applicable to poly(lactide)-based homopolymers, copolymers and/or blends in bulk or processed forms and used for the manufacture of surgical implants, including finished products (packaged and sterilized implants).

The test methods specified in this document are also intended to determine the *in vitro* degradation rate and related changes in material properties of polylactide-based copolymers and/or blends with various other comonomers, such as glycolid, trimethylene, carbonate and/or ε-caprolactone. Unless otherwise validated for a specific device, these *in vitro* methods cannot be used to definitively predict device behaviour under *in vivo* conditions.

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 178, *Plastics — Determination of flexural properties*

ISO 180, *Plastics — Determination of Izod impact strength*

ISO 527-1, *Plastics — Determination of tensile properties — Part 1: General principles*

ISO 527-2, *Plastics — Determination of tensile properties — Part 2: Test conditions for moulding and extrusion plastics*

ISO 527-3, *Plastics — Determination of tensile properties — Part 3: Test conditions for films and sheets*

ISO 604,*Plastics — Determination of compressive properties*

ISO 1628-1, *Plastics — Determination of the viscosity of polymers in dilute solution using capillary viscometers — Part 1: General principles*

ISO 1805, *Fishing nets — Determination of breaking force and knot breaking force of netting yarns*

ISO 2062, *Textiles — Yarns from packages — Determination of single-end breaking force and elongation at break using constant rate of extension (CRE) tester*

ISO 6721-2, *Plastics — Determination of dynamic mechanical properties — Part 2: Torsion-pendulum method*

ISO 13934-1, *Textiles — Tensile properties of fabrics — Part 1: Determination of maximum force and elongation at maximum force using the strip method*

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ISO 14130, *Fibre-reinforced plastic composites — Determination of apparent interlaminar shear strength by short-beam method*

ISO 16014-1, *Plastics — Determination of average molecular mass and molecular mass distribution of polymers using size-exclusion chromatography — Part 1: General principles*

ISO 16014-2, *Plastics — Determination of average molecular mass and molecular mass distribution of polymers using size-exclusion chromatography — Part 2: Universal calibration method*

ISO 16014-3, *Plastics — Determination of average molecular mass and molecular mass distribution of polymers using size-exclusion chromatography — Part 3: Low-temperature method*

ISO 16014-4, *Plastics — Determination of average molecular mass and molecular mass distribution of polymers using size-exclusion chromatography — Part 4: High-temperature method*

ISO 16014-5, *Plastics — Determination of average molecular mass and molecular mass distribution of polymers using size-exclusion chromatography — Part 5: Method using light-scattering detection*

ASTM D2990,*Standard test methods for tensile, compressive, and flexural creep and creep-rupture of plastics*

ASTM D5296, *Test method for molecular weight averages and molecular weight distribution of polystyrene by high performance size-exclusion chromatography*

ASTM F1635-16, *Standard test method for in vitro degradation testing of hydrolytically degradable polymer resins and fabricated forms for surgical implants*

ASTM F2902-16, *Standard guide for assessment of absorbable polymeric implants*

3 Terms and definitions

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

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

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

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

NOTE A discussion regarding the basis for some of the terms and definitions in this clause is available in Annex A.

3.1
absorbable polymer
non-endogenous (foreign) polymeric material that is capable of passing through or being assimilated by cells and/or tissue over time

3.2
absorption
act of a non-endogenous (foreign) material or substance passing through or being assimilated by cells and/or tissue over time

3.3
blend
physical mixture of two or more different thermoplastic polymers and/or *copolymers* (3.4)

3.4
copolymer
polymer synthesized by polymerizing two or more monomer units together

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3.5
***in vitro* degradation**
loss of mechanical properties and/or chemical integrity through chemical changes induced by a simulated physiological environment

3.6
poly(D,L-lactide)
polymer synthesized with approximately equimolar concentrations of D-lactide and L-lactide monomeric units

3.7
poly(L-lactide)
polymer synthesized exclusively from L-lactide monomeric units

3.8
sample
finite subset, object or individual of a group, class or population whose properties or characteristics are studied to gain information regarding the whole

3.9
specimen
specific portion or quantity of a sample utilized to obtain a single measurement of a property or characteristic

4 Degradation evaluation

4.1 General

Appropriate *in vitro* characterization of the degradation of an absorbable polymeric material monitors the progressive loss of both sample mass and molar mass (i.e. molecular weight) from ongoing exposure to a physiologically relevant environment. Such an environment provides fluid and thermal conditions that generate an *in vitro* degradation rate that approximates the rate observed *in vivo*. Such an *in vitro* degradation characterization also monitors the loss of device-relevant mechanical properties over time. Thus, unless justified otherwise, such a material or device degradation characterization shall include a systematic monitoring of the loss of sample mass (see 5.2), molar mass (via inherent viscosity and/or GPC/SEC, see 5.3) and at least one mechanical property that can be considered relevant to the characteristics and intended use of the device (see 5.4).

The degradation rate of an absorbable material or device can be affected by sample dimensions and other manufacturing/processing parameters (e.g. fibre draw ratio). As the shape and the structure of the test sample can have a strong influence on the degradation kinetics, where applicable, the initial test sample should be comparable to the intended product in shape and structure (i.e. fibre, film, plate, rod, bulk material or other relevant form, as appropriate). The test sample may be a finished product or a test coupon fabricated to emulate the relevant physical and/or mechanical properties of the intended product.

Evaluation of samples representative of the finished product shall be conducted following terminal sterilization at a level that meets or exceeds anticipated commercial exposure.

While the described general degradation evaluations and related tests can be useful toward characterizing a finished product, they are not necessarily adequate to address all device-specific issues. For example, a device that undergoes *in vivo* loading can degrade significantly faster than an identical device implanted in an unloaded application. Thus, a device that is intended to undergo *in vivo* loading should be additionally evaluated *in vitro* under real-time degradation conditions that approximate the anticipated mechanical loading, including, if applicable, cyclic loading, shear, creep loading, with further guidance available in ASTM F2902-16, 6.2.2.2.

The initial values for all tests shall be determined directly before starting the degradation test (time zero). All subsequent tests shall be carried out on degraded samples at each test interval. The presence

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