INTERNATIONAL STANDARD

ISO 13779-6

First edition
2015-01-15

Corrected version
2016-09-15

Implants for surgery — Hydroxyapatite —

Part 6: Powders

Implants chirurgicaux — Hydroxyapatite —

Partie 6: Poudres

Reference number
ISO 13779-6:2015(E)

ISO copyright office
Ch. de Blandonnet 8 • CP 401
CH-1214 Vernier, Geneva, Switzerland
Tel. +41 22 749 01 11
Fax +41 22 749 09 47
copyright@iso.org
www.iso.org

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.

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 meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT), see the following URL: Foreword — Supplementary information.

The committee responsible for this document is ISO/TC 150, *Implants for surgery*, Subcommittee SC 1, *Materials.*

ISO 13779 consists of the following parts, under the general title *Implants for surgery — Hydroxyapatite*:

— *Part 1: Ceramic hydroxyapatite*

— *Part 2: Coatings of hydroxyapatite*

— *Part 3: Chemical analysis and characterization of crystallinity and phase purity*

— *Part 4: Determination of coating adhesion strength*

— *Part 6: Powders*

This corrected version of ISO 13779-6:2016 incorporates the following change:

— In A.8, the last line of formula for the value ka_1 has been corrected and added.

Introduction

No known surgical implant material has ever been shown to be completely free of adverse reactions in the human body. However, long term clinical experience of the use of the material referred to in this part of ISO 13779 has shown that an acceptable level of biological response can be expected, if the material is used in appropriate applications.

This part of ISO 13779 describes specifications for hydroxyapatite raw material powders used to obtain high-quality medical devices. However, the quality of the final device depends on the manufacturing process and it is recognized that a separate performance standard can be necessary for each end-use product.

Implants for surgery — Hydroxyapatite —

Part 6: Powders

1 Scope

This part of ISO 13779 specifies requirements for hydroxyapatite powders used as a raw material for the manufacturing of surgical implants or coating of surgical implants.

This part of ISO 13779 does not apply to hydroxyapatite coatings, ceramic hydroxyapatite, glass ceramics, α- and β-tricalcium phosphate, or other forms of calcium phosphate.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 2591-1, *Test sieving — Part 1: Methods using test sieves of woven wire cloth and perforated metal plate*

ISO 13779-3, *Implants for surgery — Hydroxyapatite — Part 3: Chemical analysis and characterization of crystallinity and phase purity*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 24235, *Fine ceramics (advanced ceramics, advanced technical ceramics) — Determination of particle size distribution of ceramic powders by laser diffraction method*

European Pharmacopoeia 5.0: Tribasic calcium phosphate

3 Terms and definitions

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

3.1
atomisation
<spray drying> process for producing more or less spherical agglomerates of powder particles (atomized powders) by spraying a suspension of particles followed by immediate drying

3.2
α tricalcium phosphate
α-TCP
chemical compound with a crystallographic structure characterized by ICDD PDF 09-0348 (see Bibliography)

Note 1 to entry: The chemical formula is $Ca_3(PO_4)_2$.

Note 2 to entry: International Centre for Diffraction Data Powder Diffraction File (ICDD PDF).

3.3
β tricalcium phosphate
β-TCP
chemical compound with a crystallographic structure characterized by ICDD PDF 09-0169 (see Bibliography)

Note 1 to entry: The chemical formula is $Ca_3(PO_4)_2$.

Note 2 to entry: International Centre for Diffraction Data Powder Diffraction File (ICDD PDF).

3.4
calcination
thermal treatment of the powder in order to remove volatile impurities or to change the density or specific surface area of the powder

3.5
calcium oxide
CaO
chemical compound with a crystallographic structure characterized by ICDD PDF 4-0777 or 82-1690 (see Bibliography)

Note 1 to entry: International Centre for Diffraction Data Powder Diffraction File (ICDD PDF).

3.6
crystallinity ratio
ratio between the mass fraction of crystalline hydroxyapatite and the total mass fraction of hydroxyapatite (crystalline and amorphous)

3.7
$\boldsymbol{D_{50}}$
particle diameter corresponding to 50 % of the cumulative undersize volume distribution

Note 1 to entry: On a volumetric basis size distribution, 50 % of the particles is smaller than D_{50}.

3.8
$\boldsymbol{D_{10}}$
particle diameter corresponding to 10 % of the cumulative undersize volume distribution

Note 1 to entry: On a volumetric basis size distribution, 10 % of the particles is smaller than D_{10}.

3.9
$\boldsymbol{D_{90}}$
particle diameter corresponding to 90 % of the cumulative undersize volume distribution

Note 1 to entry: On a volumetric basis size distribution, 90 % of the particles is smaller than D_{90}.

3.10
foreign phase
crystalline phase other than hydroxyapatite

3.11
grinding
process for reducing the size of the raw powder particles

3.12
hydroxyapatite
HA
chemical compound with a crystallographic structure characterized by ICDD PDF 09-0432 or 72-1243 (see Bibliography)

Note 1 to entry: The chemical formula is $Ca_{10}(PO_4)_6(OH)_2$.

Note 2 to entry: International Centre for Diffraction Data Powder Diffraction File (ICDD PDF).

3.13
hydroxyapatite ceramic
hydroxyapatite which has been sintered into a body of high crystallinity

3.14
hydroxyapatite coating
hydroxyapatite which has been deposited onto the surface of a metallic or non-metallic substrate

Note 1 to entry: Material deposition can be obtained either by means of a thermal spray process which produces a ceramic-type coating or by means of a solution-based technique which may deposit hydroxyapatite directly or may require thermal or other treatment to convert it into a crystalline form.

3.15
pressing
process for producing green (before sintering) ceramics under pressure causing the consolidation of powders to the shape of the die used

3.16
sintering
process for production of ceramics in which the application of heat promotes the coalescence of ceramic grains and causes a significant reduction of particle surface area and bulk volume to achieve densification and consequent increase in mechanical properties

3.17
specific surface area
total surface area of the powder particles per unit of mass, $m^2\ g^{-1}$

3.18
tetracalcium phosphate
TTCP
chemical compound with a crystallographic structure characterized by ICDD PDF 25-1137 or 70-1379 (see Bibliography)

Note 1 to entry: The chemical formula is $Ca_4(PO_4)_2O$.

Note 2 to entry: International Centre for Diffraction Data Powder Diffraction File (ICDD PDF).

4 Requirements

4.1 General

The minimum requirements for the hydroxyapatite powder are established in 4.2 to 4.7.

According to the use of the hydroxyapatite powder, other characterization tests can be useful and should be conducted (see Annex A).

4.2 Calcium to phosphorus molar ratio (Ca/P)

The content of calcium and phosphorus of the hydroxyapatite powder shall be determined in accordance with ISO 13779-3.

A calcium to phosphorus molar ratio, Ca/P, of $1{,}66 \leq Ca/P \leq 1{,}71$ is suitable to fit the requirements of ISO 13175-3, ISO 13779-1, and ISO 13779-2.

4.3 Trace elements

The limits of specific trace elements for hydroxyapatite powders are given in Table 1.

Either inductively coupled plasma/atomic emission spectrometry (ICP/AES), inductively coupled plasma/mass spectroscopy (ICP/MS), atomic absorption spectroscopy (AAS), or the method specified in ISO 13779-3 shall be used to quantify trace elements. The method used shall be specified and validated.

The maximum allowable limit of the sum of all heavy metals shall be 30 mg/kg. Method A (§ 2.4.8.) described in European Pharmacopoeia for tribasic calcium phosphate <1052> shall be used to quantify heavy metals. It is also possible to use one of the methods described above for the quantification of trace elements considering that the total amount of heavy metals is the sum of the following elements:

— lead;

— mercury;

— bismuth;

— arsenic;

— antimony;

— tin;

— cadmium;

— silver;

— copper;

— molybdenum.

The method used shall be specified.

Any chemical element except for calcium, phosphorus, hydrogen, and oxygen likely to be present with a mass fraction more than 500 mg/kg shall be identified. Identification of these elements shall be based on a risk analysis of the process of the manufacturer of the powder, performed according to ISO 14971. These elements shall be quantified and if present with a mass fraction more than 500 mg/kg, the element content shall be indicated on the certificate of compliance of the batch.

Table 1 — Limits of specific trace elements

Element	Maximum limit mg/kg
Arsenic	3
Cadmium	5
Mercury	5
Lead	30
Total heavy metals	30

Total heavy metals specified in Table 1 is more restrictive than in other parts of ISO 13779 or ISO 13175-3 as it is considered that a raw material shall have a higher purity than the finished product to take into account possible pollution by the process.

4.4 Qualitative and quantitative determination of foreign phases

Crystallinity ratio determination shall be performed in accordance with ISO 13779-3.

Quantification of foreign phases shall be performed in accordance with ISO 13779-3. If the crystallinity ratio of the raw powder is ≥ 95 %, it is not necessary to perform calcination of the sample before the quantification of foreign phases. Otherwise, the sample shall be calcined for 15 h at (1 000 ± 25) °C before the quantification of foreign phases.

The CaO content shall be not more than 1 %. The sum of α-TCP, β-TCP, TTCP, and CaO content shall be not more than 5 % (α-TCP, β-TCP, TTCP, or CaO content shall be considered as zero if their value is below the detection threshold). The detection threshold for each phase (α-TCP, β-TCP, TTCP, and CaO) shall be not more than 1 %.

Some crystalline foreign phases such as carbonated apatite and hydrogenophosphate phases may be present in the hydroxyapatite powder and will not be detected by X-ray diffraction as per ISO 13779-3 after calcination at 1 000°C. For qualitative determination of the foreign phases including carbonated apatite and hydrogenophosphate phases, a method is proposed in A.3.

4.5 Powder morphology

The nature of the powder (ground or atomized) shall be specified.

The powder morphology shall be described and documented by optical microscopy (OM) or scanning electron microscopy (SEM) pictures at different scales.

4.6 Granulometry

D_{10}, D_{50}, and D_{90} shall be specified.

If laser diffraction is used, it shall be in accordance with ISO 24235. If a sieving method is used, it shall be in accordance with ISO 2591-1. If another method is used, it shall be specified and justified.

4.7 Calcination loss

Define the calcination loss only for powders which have a crystallinity ratio ≤ 95 % when tested in accordance with ISO 13779-3.

Calcination loss shall be specified for a treatment of 1 h at (1 000 ± 25) °C. It shall be determined by weighing 10 g of powder before and after calcination for 1 h at (1 000 ± 25) °C. After cooling, powder shall be removed from the oven at a temperature between 50 °C and 100 °C. Perform the reweighing as soon as the powder temperature returns to room temperature. The balance used shall be capable of weighing the test portion to an accuracy of 0,05 g or better.

5 Manufacturing design requirement

The homogeneity of each batch of powder shall be validated.

A risk analysis of the powder manufacturing process shall be performed in accordance with ISO 14971 before the validation protocols have been defined. This analysis shall be conducted in a way to determine potential failures during the manufacturing process, taking into consideration the different steps of the manufacturing process.

Worst cases for process validation shall be determined with the help of the risks analysis.

The validation plan shall be established and approved before proceeding.

6 Certificate of compliance

Each batch of powder shall be delivered with a certificate of compliance indicating at least the acceptance criterion, the value measured (or detection limit) on the batch, and the uncertainty of at least the following parameters:

— calcium to phosphorus molar ratio (Ca/P) (see 4.2);

— trace elements, including trace elements in excess of 500 mg/kg with their mass fraction (see 4.3);

— foreign phases content (see 4.4);

— critallinity ratio (see 4.4);

— ground or atomized state of the powder (see 4.5);

— granulometry (see 4.6);

— calcination loss at 1 000 °C (see 4.7).

The certificate of compliance shall contain the reference of the powder, the powder batch number, and the reference to the present standard.

Annex A
(informative)

Other possible characterization tests

A.1 General

Depending on the use of the hydroxyapatite powder, other characterization tests can be useful and should be conducted.

A.2 Foreign-coloured particles

No foreign particles should be found in the hydroxyapatite powder.

It can be determined by visual inspection after spreading the powder on a white surface of at least 100 cm^2.

A.3 Infrared spectroscopy

Fourier Transformation Infrared Spectroscopy (FTIR) should be conducted on an HA powder sample. All functional groups of HA should be detected. At least the presence of the functional groups of oxyapatite, nitrate, carbonate, and hydrogen-phosphate impurities should be assessed. The presence of any of these impurities should be documented and justified.

A detailed method for FTIR analysis is described in Reference [16].

A.4 Powder flow

Powder flow should be specified, especially for plasma spraying or pressing applications of the powder. It should be determined as specified in ASTM D6393 by indicating the Carr compressibility index (this index not only characterize the compressibility of the powder but also the powder flow) (see Reference [15]) or as specified in ISO 4490. The method used should be specified.

A.5 Tap density

Tap density should be specified for atomized powders. It should be determined as specified in ISO 787-11 or ISO 23145-1. The method used should be specified.

A.6 Specific surface area

Specific surface area should be specified especially for powder intended for sintering applications. It should be determined using the BET method as specified in ISO 18757.

A.7 Dissolution

Dissolution of HA powder should be assessed in accordance with ASTM F1926.

The test should be repeated six times. Average and standard deviation should be calculated for initial and final dissolution rate. Initial and final pH should be recorded.

A.8 Solubility product, K_{SP}

The determination of the solubility product (K_{SP}) at 37 °C on the hydroxyapatite powder should be performed. The saturated solutions with respect to hydroxyapatite powder are obtained by dissolution of 400 mg of hydroxyapatite powder in 20 ml of aqueous solutions of phosphoric acid (5,026 mmol/dm^3) for 60 days at (37,0 ± 0,1) °C in a continuously shaken water bath. The thermodynamic solubility product, K_{SP}, of hydroxyapatite is defined as

$$K_{SP} = \left[Ca^{2+}\right]^5 \left[PO_4{}^{3-}\right]^3 \left(\frac{K_e}{10^{-pH}}\right)^7 \left(\frac{Ka_1{}^3 Ka_2{}^3}{K_e{}^6}\right)$$

K_{SP} is calculated from measured equilibrium calcium and phosphate concentrations and pH values as input data. Calcium and phosphate concentrations should be determined after filtration at 0,2 µm, either by inductively coupled plasma/atomic emission spectrometry (ICP/AES), inductively coupled plasma/mass spectroscopy (ICP/MS), atomic absorption spectroscopy (AAS), or the method specified in ISO 13779-3. The method should be specified and validated.

Values for K_e, Ka_1, Ka_2, and Ka_3 are as follows.

— water ionic product

$H_3O^+ + OH^- \leftrightarrows 2H_2O$ $\qquad K_e = \left[OH^-\right]\left[H_3O^+\right] = 10^{-14}$

— acidic constants of the triacid H_3PO_4

$H_3PO_4 + H_2O \leftrightarrows H_2PO_4{}^- H_3O^+$ $\qquad Ka_3 = \dfrac{\left[H_2PO_4{}^-\right]\left[H_3O^+\right]}{\left[H_3PO_4\right]} = 7{,}5\times10^{-3}$

$H_2PO_4{}^- + H_2O \leftrightarrows HPO_4{}^{2-} H_3O^+$ $\qquad Ka_2 = \dfrac{\left[HPO_4{}^{2-}\right]\left[H_3O^+\right]}{\left[H_2PO_4{}^-\right]} = 6{,}2\times10^{-8}$

$HPO_4{}^{2-} + H_2O \leftrightarrows PO_4{}^{3-} H_3O^+$ $\qquad Ka_1 = \dfrac{\left[PO_4{}^{3-}\right]\left[H_3O^+\right]}{\left[HPO_4{}^{2-}\right]} = 4{,}8\times10^{-13}$

The test should be repeated six times. Average K_{SP}(HA) and standard deviation should be calculated.

The mean value obtained with the six samples should be compared with the mean value obtained after six measurements of a pure fully crystallized hydroxyapatite reference powder.

NOTE The mean value and standard uncertainty of the 12 replicate determinations (n = 12) of SRM #2910a reference powder tested by NIST according to the present method are: K_{SP}(HA) = (2,03 ± 0,04) × 10^{-59}.