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Implants for surgery — Calcium phosphates —

Part 3: Hydroxyapatite and beta-tricalcium phosphate bone substitutes

Implants chirurgicaux — Phosphates de calcium —

Partie 3: Substituts osseux à base d'hydroxyapatite et de phosphate tricalcique bêta

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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 13175-3 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 1, *Materials*.

ISO 13175 consists of the following parts, under the general title *Implants for surgery — Calcium phosphates*:

— *Part 3: Hydroxyapatite and beta-tricalcium phosphate bone substitutes*

Introduction

Hydroxyapatite and β-tricalcium phosphate synthetic bone substitutes are now considered as an adequate alternative to autografts and allografts. Indeed, the synthetic origin of these devices guarantees that no transmittable disease will contaminate the patient. Moreover, hydroxyapatite and β-tricalcium phosphate have been shown to be osteoconductive which means that they will promote bone healing at the surface of the material if implanted in a bone site (see References [6] and [7]). Biocompatibility of hydroxyapatite and β-tricalcium phosphate is demonstrated by extensive literature (see Reference [8]).

The devices referred to in this part of ISO 13175 are of three types: synthetic monophasic hydroxyapatite or β-tricalcium phosphate bone substitutes and biphasic hydroxyapatite/β-tricalcium phosphate bone substitutes. The hydroxyapatite/β-tricalcium phosphate ratio influence the dissolution rate of the material: the higher the β-tricalcium phosphate content, the higher the dissolution rate (see References [9] to [11]).

The healing process into the bone substitutes is not only related to the material osteoconductive potential, it is also related to the porosity structure (see References [12] to [16]). It is necessary that macroporosities are large enough and interconnected for bone ingrowth to take place into the whole volume of the implant. Porosities have also an influence on the resorption rate of the ceramic: the higher the number of microporosities, the higher the dissolution rate (see Reference [14]).

As bone substitutes are not intended for bearing heavy loads, their mechanical properties are not essential. However, most of the time blocks have to be reshaped by the surgeon to fit the shape of the bone cavity. The bone substitute shall have sufficient mechanical properties to be machined.

Implants for surgery — Calcium phosphates —

Part 3: Hydroxyapatite and beta-tricalcium phosphate bone substitutes

1 Scope

This part of ISO 13175 specifies requirements for monophasic hydroxyapatite bone substitutes, monophasic β-tricalcium phosphate bone substitutes and biphasic hydroxyapatite/β-tricalcium phosphate bone substitutes in the form of blocks or granules.

This part of ISO 13175 is not applicable to cell-seeded bone void fillers, calcium phosphate cements or bone void fillers containing materials other than hydroxyapatite and β-tricalcium phosphate.

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

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 13320, *Particle size analysis — Laser diffraction methods*[1)]

ISO 13383-1, *Fine ceramics (advanced ceramics, advanced technical ceramics) — Microstructural characterization — Part 1: Determination of grain size and size distribution*[2)]

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

ISO 15901-1, *Pore size distribution and porosity of solid materials by mercury porosimetry and gas adsorption — Part 1: Mercury porosimetry*

ISO 80000-1, *Quantities and units — Part 1: General*

3 Terms, definitions and symbols

3.1 Terms and definitions

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

1) Replaces ISO 13320-1.

2) To be published.

3.1.1
α tricalcium phosphate
α-TCP
chemical compound with a crystallographic structure characterized by ICDD PDF[3] 09-0348

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

3.1.2
β tricalcium phosphate
β-TCP
chemical compound with a crystallographic structure characterized by ICDD PDF 09-0169

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

3.1.3
bone substitute
device intended to fill bony voids or gaps caused by trauma or surgery

3.1.4
hydroxyapatite
HA
chemical compound with a crystallographic structure characterized by ICDD PDF 09-0432 or ICDD PDF 72-1243

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

3.1.5
interconnected pore
pore which communicates with one or more other pores

3.1.6
macropore
pore with one of its dimensions larger than 10 µm

3.1.7
micropore
pore with no dimension larger than 10 µm

3.1.8
porosity
ratio of total pore volume to apparent volume of the block or granule

3.1.9
tetracalcium phosphate
TTCP
chemical compound with a crystallographic structure characterized by ICDD PDF 25-1137 or ICDD PDF 70-1379

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

3.1.10
osteoconductive material
material with the ability to serve as a scaffold on which bone cells can attach, migrate (meaning move or "crawl"), and grow and divide

NOTE 1 to entry: Osteoconductivity is a passive property.

3) International Centre for Diffraction Data Powder Diffraction File.

3.1.11
calcium oxide
CaO
chemical compound with a crystallographic structure characterized by ICDD PDF 4-0777 or ICDD PDF 82-1690

3.1.12
β-tricalcium phosphate density
$d_{\beta TCP}$
theoretical density of dense β-tricalcium phosphate, equal to 3,07 g cm^{-3}

3.1.13
hydroxyapatite density
d_{HA}
theoretical density of dense hydroxyapatite, equal to 3,15 g cm^{-3}

3.2 Symbols

d_r	bulk density of the synthetic bone substitute
d_{th}	theoretical density of the synthetic bone substitute
m	mass of the synthetic bone substitute
V	volume of the synthetic bone substitute

4 Requirements

4.1 Trace elements

The limits of specific trace elements for hydroxyapatite and β-tricalcium phosphate bone substitutes 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.

Table 1 — Limits of specific trace elements

Element	Maximum limit mg/kg
Arsenic	3
Cadmium	5
Mercury	5
Lead	30
Heavy metals	50

Method 1 of the United States Pharmacopeia “Heavy metals <231>” should be used to quantify heavy metals. It is also possible to use one of the methods described above for the quantification of trace elements to assess the heavy metal content by considering that the total amount of heavy metals is the sum of the following elements: lead, mercury, bismuth, arsenic, antimony, tin, cadmium, silver, copper and molybdenum. The method used shall be specified.

Any impurity with a ratio of more than 1 000 mg/kg shall be identified, quantified and its influence on bone healing shall be assessed. The influence of this impurity on biocompatibility shall be assessed according to ISO 10993-1.

Any additional additive shall be identified, quantified and its influence on bone healing and biocompatibility shall be justified or assessed in accordance with ISO 10993-1.

4.2 Qualitative and quantitative determination of crystalline phases

4.2.1 General

Composition and phase purity shall be controlled by the quantification of the phases by X-ray diffraction (XRD) in accordance with ISO 13779-3.

4.2.2 Hydroxyapatite monophasic bone substitutes

Hydroxyapatite mass fraction shall be not less than 95 % of the crystalline phases. The CaO mass fraction shall be not more than 1 % of the crystalline phases.

Hydroxyapatite mass fraction is calculated according to Formula (1):

$$MF_{HA} = 100\% - MF_{\beta TCP} - MF_{\alpha TCP} - MF_{TTCP} - MF_{CaO} \quad (1)$$

where

MF_{HA} is the mass fraction of crystalline HA;

$MF_{\beta TCP}$ is the mass fraction of crystalline β-TCP;

$MF_{\alpha TCP}$ is the mass fraction of crystalline α-TCP;

MF_{TTCP} is the mass fraction of crystalline TTCP;

MF_{CaO} is the mass fraction of crystalline CaO.

The mass fraction of any phase shall be considered as zero if its value is under the detection threshold.

4.2.3 Biphasic bone substitutes

The ratio between hydroxyapatite and β-tricalcium phosphate shall be specified with a tolerance of ± 5 % (absolute) of the mass fraction of crystalline phases.

EXAMPLE A composition of 60 % HA and 40 % TCP means that the composition can be (65 % HA and 35 % TCP) to (55 % HA and 45 % TCP).

Qualitative determination of the mass fraction of other crystalline phases: if α-tricalcium phosphate (α-TCP) can be detected, this information shall be indicated on the report.

4.2.4 β-tricalcium phosphate monophasic bone substitutes

The β-tricalcium phosphate mass fraction shall be not less than 95 % of the crystalline phases.

The β-tricalcium phosphate mass fraction shall be calculated according to Formula (2):

$$MF_{\beta TCP} = 100\% - MF_{HA} \quad (2)$$

The mass fraction of HA shall be considered as zero if its value is under the detection threshold.

Qualitative determination of other crystalline phases: if α-tricalcium phosphate (α-TCP) can be detected, this information shall be indicated on the report.

The presence of other phases shall be assessed by infrared spectroscopy (FTIR) in accordance with ISO 13779-3.

4.3 Form and shape

The physical form of the bone substitute (granules or pre-formed block) shall be specified.

Dimensional specifications shall be given for all device configurations as follows.

— Dimensions for the blocks.

— Dimensions of granulates: the laser diffraction method in accordance with ISO 13320 or sieving method in accordance with ISO 2591-1 shall be used to determine granule dimensions. Parameters D10, D50 and D90 (for laser diffraction) or minimum and maximum dimensions (for sieving) of the granules shall be specified.

The volume of the bone substitute shall be specified on the packaging.

4.4 Porosity

4.4.1 Total porosity ratio

The minimum and maximum porosity ratio of the bone substitute shall be specified. It shall be calculated according to Formula (3):

$$P = 100 - \left(\frac{d_r}{d_{th}} \cdot 100 \right) \tag{3}$$

where

P is the porosity ratio in %.

d_r shall be determined by measuring the dimensions and the mass of a parallelepiped bone substitute having a minimum volume of 2 cm^3. The mass shall be measured with a balance capable of weighing to an accuracy of 0,02 g and the dimensions shall be measured with a vernier calliper capable of measuring to an accuracy of at least 0,02 mm. The volume, V, of the bone substitute shall then be calculated with the measured dimensions and d_r shall then be calculated according to Formula (4):

$$d_r = \frac{m}{V} \tag{4}$$

d_{th} shall be calculated according to Formula (5):

$$d_{th} = \frac{\frac{MF_{HA}}{d_{HA}}}{\frac{MF_{HA}}{d_{HA}} + \frac{MF_{\beta TCP}}{d_{\beta TCP}}} \cdot d_{HAP} + \frac{\frac{MF_{\beta TCP}}{d_{\beta TCP}}}{\frac{MF_{HA}}{d_{HA}} + \frac{MF_{\beta TCP}}{d_{\beta TCP}}} \cdot d_{\beta TCP} \tag{5}$$

If the granules are manufactured by crushing porous blocks, the porosity of granules should be measured on the blocks before crushing by the method described above.

Otherwise, the porosity of granules should be estimated by mercury porosimetry.

4.4.2 Size of micropores and macropores

4.4.2.1 Micropores

To perform the metallographic cuts of the material, it can be necessary in some cases to perform an embedding of the material in a resin before cutting.

The diameter of micropores shall be specified. It shall be determined by measuring the diameter of micropores on SEM photomicrographs of a section of the material by applying one of the methods