



Designation: F2224 – 09 (Reapproved 2020)

Standard Specification for High Purity Calcium Sulfate Hemihydrate or Dihydrate for Surgical Implants¹

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1. Scope

1.1 This specification covers material requirements for unfabricated and fabricated forms of hydrated calcium sulfate intended for surgical implants. Fabricated forms may include pressed and cast surgical implants in various geometric shapes. The calcium sulfate hemihydrate in the unfabricated form can be converted with the addition of water or other water-containing solutions to a fabricated calcium sulfate dihydrate form.

1.2 The requirements of this specification apply to calcium sulfate combined with two molecules of water or two calcium sulfate molecules sharing one water molecule.

Approximate chemical formulae:

Calcium Sulfate Dihydrate
 $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$

Calcium Sulfate Hemihydrate
 $\text{CaSO}_4 \cdot 1/2\text{H}_2\text{O}$ or $\text{CaSO}_4 \cdot \text{H}_2\text{O} \cdot \text{CaSO}_4$

1.3 This specification specifically excludes calcium sulfate anhydrite and calcium sulfate forms that contain additives such as reinforcing phases, medicaments, biological agents, and so forth.

1.4 The presence of processing aids does not exclude a product from the physical and mechanical requirements of this specification.

1.5 Some provisions of Specification C59/C59M and Test Methods C472 apply. Special requirements that are detailed in this specification are included to characterize the material which will be used in surgical implants.

1.6 The biological response to calcium sulfate in bone tissue has been well characterized by a history of clinical use (1-14)² and by laboratory studies (15-18).

1.7 The following precautionary caveat pertains only to the test method portion, Sections 4, 5, and 6, of this specification.

¹ This specification is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.13 on Ceramic Materials.

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² The boldface numbers in parentheses refer to the list of references at the end of this standard.

This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.

1.8 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 ASTM Standards:³

- C59/C59M Specification for Gypsum Casting Plaster and Gypsum Molding Plaster
- C472 Test Methods for Physical Testing of Gypsum, Gypsum Plasters, and Gypsum Concrete
- F648 Specification for Ultra-High-Molecular-Weight Polyethylene Powder and Fabricated Form for Surgical Implants
- F756 Practice for Assessment of Hemolytic Properties of Materials
- F763 Practice for Short-Term Screening of Implant Materials
- F813 Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices
- F895 Test Method for Agar Diffusion Cell Culture Screening for Cytotoxicity
- F981 Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Insertion into Bone
- F1088 Specification for Beta-Tricalcium Phosphate for Surgical Implantation
- F1635 Test Method for *in vitro* Degradation Testing of Hydrolytically Degradable Polymer Resins and Fabricated Forms for Surgical Implants

³ For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

2.2 Other Documents:

BS 6463-102: 2001 Quicklime, Hydrated Lime and Natural Calcium Carbonate—Part 102: Methods for Chemical Analysis⁴

US Pharmacopeia XXIV (USP 24) NF-19⁵

CFR Title 21, Part 820 Quality System Requirements⁶

Food Chemical Codex (FCC)⁷

European Pharmacopeia⁸

ISO 10993-1 Biological Evaluation of Medical Devices⁹

3. Terminology

3.1 Definitions:

3.1.1 *calcium sulfate anhydrite*—a chemical substance having approximate molecular formula of CaSO_4 .

3.1.2 *calcium sulfate dihydrate*—a chemical having the approximate molecular formula of $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$. This substance is also known as gypsum.

3.1.3 *calcium sulfate hemihydrate*—a chemical substance having approximate molecular formula of $\text{CaSO}_4 \cdot 1/2\text{H}_2\text{O}$ or $\text{CaSO}_4 \cdot \text{H}_2\text{O} \cdot \text{CaSO}_4$. The mineral name of this substance is bassanite and the substance is also known as Plaster of Paris in the clinical literature.

3.1.4 *processing aids*—any constituent intentionally used in the processing of the raw material to fulfill a certain technological purpose during treatment or processing. Some examples would be: binders, lubricants, compaction aids, disintegrants, plasticizers, defloculants, wetting agents, water retention agents, antistatic agents, antifoam agents, foam stabilizers, chelating or sequestering agents, phase stabilizers, and so forth.

3.1.4.1 *Discussion*—Use of a processing aid may result in the unintentional but technically unavoidable presence of residues of the substance or its derivatives in the final product.

3.1.5 *set time*—for a mixture of calcium sulfate hemihydrate and an aqueous solution, set time is defined as the elapsed time between the onset of mixing and the development of sufficient mechanical properties to meet a specific criteria (for example, hardness or resistance to indentation).

4. Chemical Requirements

4.1 Calcium sulfate for surgical implants (raw material) shall have a purity of not less than 98 % for calcium sulfate (absent of water) when measured by USP 24 NF 19. (This purity measurement method may not be applicable to the fabricated forms containing substantial quantities of additives.)

⁴ Available from the British Standards Institution, c/o IHS Engineering/IHS International, 15 Inverness Way East, Englewood, CO 80112, <http://www.global.ihs.com>.

⁵ Available from U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852, <http://www.usp.org>.

⁶ Available from U.S. Government Printing Office Superintendent of Documents, 732 N. Capitol St., NW, Mail Stop: SDE, Washington, DC 20401, <http://www.access.gpo.gov>.

⁷ Available from National Academies Press, 500 Fifth St., NW, Lockbox 285, Washington, DC 20055, <http://www.nap.edu>.

⁸ Available from EDQM, European Pharmacopeia, Council of Europe, B.P. 907, F-67029, Strasbourg, France, <http://www.edqm.eu>.

⁹ Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, <http://www.ansi.org>.

4.2 The total concentration of heavy metals (for example, lead, arsenic, cadmium, antimony, bismuth, and mercury) in the calcium sulfate raw material shall be limited to less than 10 ppm. Other trace elements, such as iron, may also affect implant performance and should be kept to a minimum. For example, for calcium sulfate to meet USP grade, the iron concentration should not be higher than 100 ppm. Methods for measuring these trace elements are described in Specification **F1088** (Coupled Plasma—Atomic Absorption Spectrometry), the United States Pharmacopeia (USP), European Pharmacopeia, or Food Chemical Codex (FCC). A second method that may be used to analyze acid insoluble impurities is described in BS 6463-102.

4.2.1 When calcium sulfate dihydrate is converted into calcium sulfate hemihydrate, the mass of the material is reduced by approximately 15 % due to dehydration. Depending on the conversion process, the quantities (total mass) of most or all of the trace elements present in the dihydrate are not affected. Therefore, the concentration of those trace elements in the resulting hemihydrate material can be expected to increase by approximately 15 %. This should be taken into account when setting acceptance criteria for a calcium sulfate dihydrate raw material that will be used to produce a hemihydrate final product that is expected to conform to this specification.

5. Physical and Mechanical Characterization

5.1 The following physical and mechanical characterization may be applicable to calcium sulfate for surgical implant applications in either the fabricated form or intra-operative fabricated form. When characterization test results are reported in labeling, the test methods associated with these results shall be referenced. Labeling can be defined as but is not limited to the product label, brochures, technical monographs, and other related documentation.

5.2 *Set Time*—If set time is an applicable property, it should be reported along with the method by which it was determined in order to inform the final user. Test Methods **C472** as described in Specification **C59/C59M** can be used to define a typical set time. The actual method used for set time determination shall be described or referenced in labeling.

5.3 *Compressive Strength*—Calcium sulfate dihydrate in a fabricated final form is intended to be used in non-load bearing applications. If applicable to implant performance, documentation of typical compressive strength and the methods used to determine it should be reported in order to inform the final user. Test Methods **C472** as described in Specification **C59/C59M** can be used for the typical compression strength determination. The actual method used shall be described or referenced in labeling.

5.4 *In vitro Degradation*—For calcium sulfate dihydrate in a fabricated final form, weight loss from dissolution may be reported. If reported, the method used should be described or referenced. Additional information is given in Appendix **X1.4**.

6. Test Specimen Fabrication

6.1 Prepare test specimens from material(s) produced according to the same manufacturing procedures and processes employed in fabricating the implant device.

7. Quality Program Requirements

7.1 The manufacturer shall conform to Quality Systems Regulations (see Title 21, part 820, of the U.S. Code of Federal Regulations) or its equivalent.

8. Keywords

8.1 bone; calcium sulfate; gypsum; implant; plaster

APPENDIX

(Nonmandatory Information)

X1. RATIONALE

X1.1 The biocompatibility of calcium sulfate may depend upon processing conditions and source material, both which may not be identified by the compositional requirements of this specification. The biocompatibility of these products should be ensured by a combination of preclinical testing and process controls. Material derived under the desired process conditions should be tested in accordance with the recommendations of Practices F756, F763, F813, and F981; Test Methods F895 and F1635; Specification F648; and ISO 10993-1, and manufacturing controls put in place to ensure that process variations outside of acceptable tolerances do not occur. Substantial changes in process conditions or source material parameters will necessitate additional biocompatibility or preclinical functional testing to ensure maintenance of an acceptable tissue response.

X1.2 X-ray powder diffraction (XRD) analysis of the material provides differentiation between calcium sulfate dihydrate and calcium sulfate hemihydrate. The International Centre for Diffraction Data (ICDD) designation of calcium sulfate hemihydrate for surgical implants is ICDD # 41-0224 (Bassanite, syn). A typical calcium sulfate dihydrate XRD pattern will show the peaks from ICDD #s 33-0311 (Gypsum, syn), 37-1496 (Anhydrite syn), and 41-0224 (Bassanite, syn).

X1.3 The setting time measurement in Section 5 is useful for the calcium sulfate hemihydrate since the hemihydrate must be hydrated to a calcium sulfate dihydrate before surgical use. Likewise, the calcium sulfate hemihydrate and dihydrate raw material powders do not have the compressive strength or degradation attributes that are needed for surgical applications without being converted by hydration to calcium sulfate dihydrate or with the dihydrate form pressed into a geometric shape.

X1.4 The mechanism of resorption of calcium sulfate *in vivo* is complex and involves both physical dissolution and cell mediated resorption. As a result, *in vitro* dissolution experiments should not be expected to accurately predict *in vivo* resorption rates. In addition, it has been shown that the choice of simulated body fluid can radically alter *in vitro* resorption rates. For example, calcium sulfate dihydrate pellets immersed in a phosphate buffered saline solution (PBS) can develop a shell of recrystallized hydroxyapatite on their surface which significantly slows the process of dissolution (19). This behavior has not been observed *in vivo*. Similarly, the use of distilled or deionized water for *in vitro* testing has been shown to accelerate the rate of degradation relative to rates observed clinically and in pre-clinical animal studies (19).

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