Designation: F451 – 16

Standard Specification for Acrylic Bone Cement[1]

This standard is issued under the fixed designation F451; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This specification covers self-curing resins used primarily for the fixation of internal orthopedic prostheses. The mixture may be used in either the predough or dough stage in accordance with the manufacturer's recommendations.

1.2 Units of premeasured powder and liquid are supplied in a form suitable for mixing. The mixture then sets in place.

1.3 While a variety of copolymers and comonomers may be incorporated, the composition of the set cement shall contain poly(methacrylic acid esters) as its main ingredient.

1.4 This specification covers compositional, physical performance, and biocompatibility as well as packaging requirements. The biocompatibility of acrylic bone cement as it has been traditionally formulated and used has been reported in the literature (**1**, **2**).[2]

1.5 The values stated in SI units are to be regarded as standard. No other units of measurement are included in this standard.

1.6 *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 and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*[3]

D638 Test Method for Tensile Properties of Plastics

D695 Test Method for Compressive Properties of Rigid Plastics

D1193 Specification for Reagent Water

D3835 Test Method for Determination of Properties of Polymeric Materials by Means of a Capillary Rheometer

F619 Practice for Extraction of Medical Plastics

F748 Practice for Selecting Generic Biological Test Methods for Materials and Devices

F749 Practice for Evaluating Material Extracts by Intracutaneous Injection in the Rabbit

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

2.2 *ANSI/ADA Standard:*

No. 15 Specification for Acrylic Resin Teeth[4]

3. Terminology

3.1 *Definitions of Terms Specific to This Standard:*

3.1.1 *doughing time*—the time after commencement of mixing at which the mixture ceases to adhere to a standard probe (see 7.5).

3.1.2 *exothermic or maximum temperature*—the maximum temperature of the mixture due to self-curing in a standard mold (see 7.6).

3.1.3 *extrusion*—the rate of flow of the material through a standard orifice under load (see 7.8.1).

3.1.4 *intrusion*—the distance of flow of the mixture into a standard mold under load (see 7.8.3).

3.1.5 *setting time*—the time after commencement of mixing at which the temperature of the curing mass equals the average of the maximum and ambient temperatures (see 7.7).

3.1.6 *unit*—one package or vial of premeasured powder component and one package or vial of premeasured liquid component.

[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 F04.11 on Polymeric Materials.

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

[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.

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

4. Physical Requirements

4.1 *Liquid:*

4.1.1 *Appearance*—The liquid shall be free of extraneous particulate matter or obvious visual contaminants in its container.

4.1.2 *Stability*—After being heated for 48 h at 60 ± 2°C, the viscosity of the liquid shall not increase by more than 10 % of its original value (see 7.3).

4.1.3 *Sterility*—The liquid, as poured from its container, shall pass the tests described in "Sterility Tests—Liquid and Ointments" (7.4) **(3)**.

4.2 *Powder:*

4.2.1 *Appearance*—The powder shall be pourable and free of extraneous materials, such as dirt or lint (7.2.2).

4.2.2 *Sterility*—The powder, as poured from its package, shall pass the tests described in "Sterility Tests—Solids" (7.4) **(2)**.

4.3 *Powder-Liquid Mixture:*

4.3.1 If the mixture is to be used in its predough stage, the material shall conform to the properties given in Table 1.

4.3.2 If the mixture is to be used in its dough stage, the material shall conform to the properties given in Table 1.

4.3.3 If the mixture can be used in either its predough or dough stages, separate units must be tested for compliance with 4.3.1 and 4.3.2.

4.4 *Cured Polymer*—The material after setting shall conform to the properties given in Table 2.

5. Weights and Permissible Variations

5.1 Weight and volume measurements shall be made on the respective powder and liquid components of five units (see 3.1). These units may be subsequently utilized in any of the nonsterile tests of this specification.

5.2 The weights, or volume of the powder and liquid components, or both, shall not deviate by more than 5 % from those stated on the package (9.2.2), of each of five units.

6. Sampling

6.1 Units of powder and liquid shall be procured to provide sufficient material for all the tests of this specification. The units shall be obtained from regular retail distribution channels. Provided no repeat tests are required, this will amount to between seven and ten units.

6.2 It will only be necessary to maintain sterility in tests described in 7.4. All other tests described in this specification need not be conducted under sterile conditions.

TABLE 1 Requirements for Powder Liquid Mixture

Property	Extrusion, Viscosity Tests	Dough Usage, Intrusion Tests
Max Dough Time, min.	5.0	5.0
Setting Time Range, min.	5 to 15	5 to 15
Temperature, max., °C	90	90
Intrusion, min., mm	...	2.0

TABLE 2 Requirements for Cured Polymer After Setting

Property	Requirement
Compressive Strength, min., MPa	70

7. Test Methods and Sample Size

7.1 Maintain all equipment, mixing surfaces, and materials at 23 ± 2°C at least 2 h prior to testing and conduct all tests at 23 ± 2°C and 50 ± 10 % relative humidity unless otherwise specified.

7.2 *Inspection*—Use visual inspection in determining compliance to the requirements outlined in 4.1.1, 4.2.1, 8.1 and 8.2.

7.2.1 The liquid component of two separate units shall comply with the requirements of 4.1.1 and 8.1.

7.2.2 The powder component of two separate units shall comply with the requirements of 4.2.1 and 8.1.

7.3 *Liquid Component Viscosity*—Record the viscosity change of two separate units (4.1.2) before and after the heating exposure by timing the flow of the liquid level between the 0 and 5 mL marks of a 10 mL measuring pipet. Calculate the percent change as follows:

$$\% \text{ Change} = \frac{t_a - t_b}{t_b} \times 100 \quad (1)$$

where:

t_b = flow time before heating, and
t_a = flow time after heating exposure (4.1.2) of 60 ± 2°C for 48 h in the dark in a closed container.

7.3.1 An alternative method for viscosity may be used if it can be demonstrated to yield similar results. Both shall comply to the less than 10 % change specified (4.1.2).

7.4 The components of the two units shall be tested for sterility in accordance with the test methods described in U.S. Pharmacopoeia, "Sterility Tests" **(3)**.

7.5 *Doughing Time:*

7.5.1 *Environment*—All equipment, mixing surfaces, and material (unit size) shall be maintained at 23 ± 1°C at least 2 h prior to testing and tests shall be conducted at 23 ± 1°C. The relative humidity shall be 50 ± 10 %.

7.5.2 Mix all the powder and liquid of a single unit together as directed by the manufacturer's instructions (see 8.2). Start a stop watch at the onset of combining the liquid to the powder and read all subsequent times from this stop watch. Approximately 1.5 min after the onset of mixing, gently probe the mixture with a non-powdered surgically gloved (latex) finger. Take visual notice as to the formation of fibers between the surface of the mix and the finger as it leaves the surface. Repeat this process from that time on at 15 s intervals with a clean portion of the glove until the gloved finger separates cleanly. Denote the time at which this is first observed as the doughing time. Mix the mixture between determinations to expose fresh material for each probing.

7.5.3 Determine the average doughing time from two separate units.

7.5.4 The two values found shall agree within 30 s of each other, otherwise repeat the test on two additional units. Report the average of all four tests and the range of values.

7.5.5 Report the doughing time to the nearest 15 s as the average of all determinations. Maximum and minimum values of doughing times measured shall not differ by more than ±1½ min from the average.

7.5.6 Report the brand of non-powdered surgical glove used for dough time determinations. It is necessary that the type of glove be described in detail, including manufacturer, when the dough time is reported.

7.6 *Exothermic Temperature*—Within 1 min after doughing time, gently pack approximately 25 g of the dough described in 7.5 into the mold described in Fig. 1. This mold shall be made of polytetrafluoroethylene (PTFE), poly(ethyleneterephthalate), polyoxymethylene, high density polyethylene, or ultra-high molecular weight polyethylene (UHMWPE) and be equipped with a No. 24 gage wire thermocouple, or similar device, positioned with its junction in the center of the mold at a height of 3.0 mm in the internal cavity. Immediately seat the plunger with a C-clamp or suitable press to produce the 6.0 mm specimen height. Upon producing plunger seating, remove the excess material and the C-clamp or press for the remainder of the procedure. Continuously record the temperature with respect to time from the onset of mixing the liquid and the powder until cooling is observed, Fig. 2. Report the maximum temperature recorded to the nearest 1°C. This should not exceed the value given in Table 1.

7.6.1 The maximum temperature shall be the average of two separate determinations reported to the nearest 1°C.

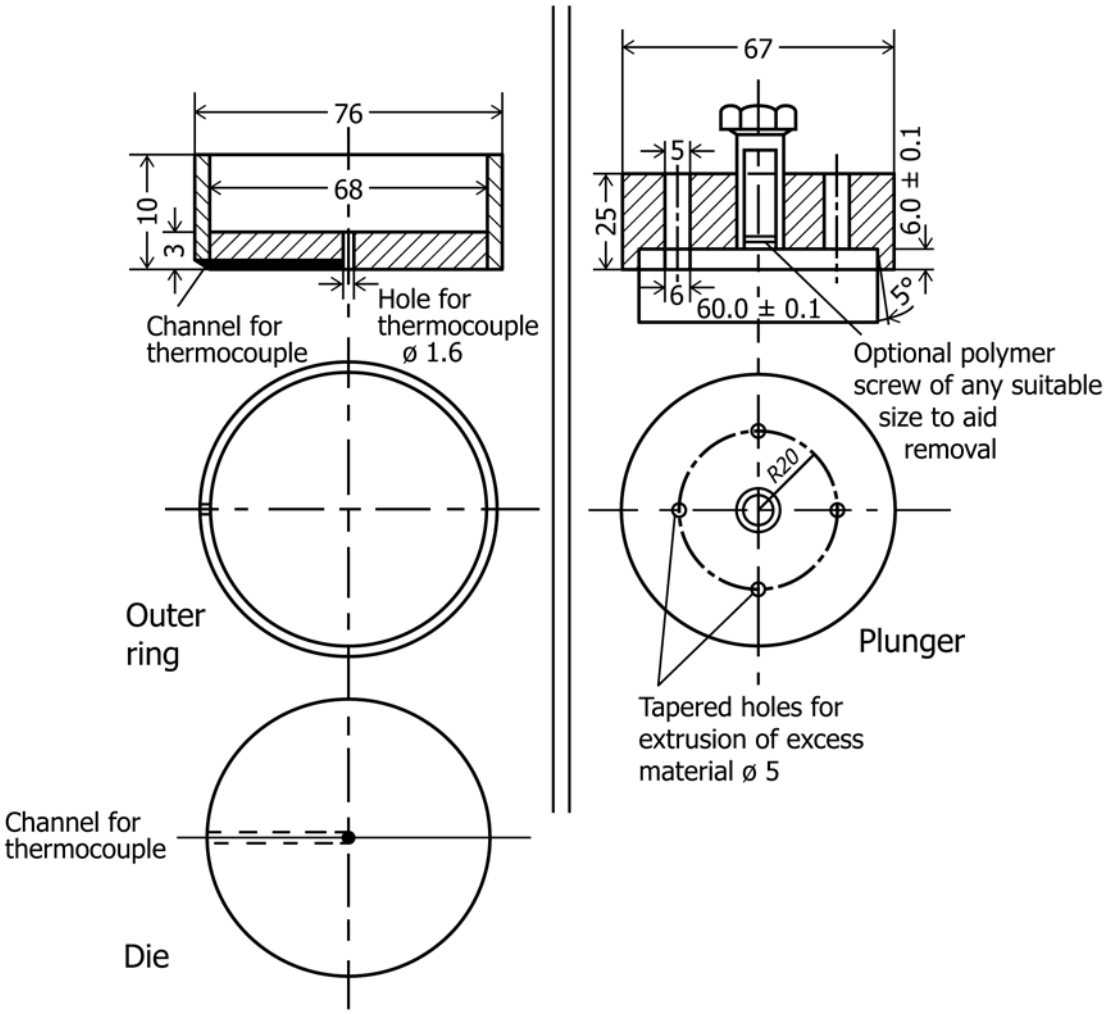
7.6.2 If the difference between the maximum temperature for the two determinations is greater than 5.0°C, repeat the test on two additional units and report the average of all four runs to the nearest 1°C. Individual maximum and minimum values for maximum temperature shall not differ by more than ±4°C of the average value of all determinations.

7.7 *Setting Time*—From the continuous time versus temperature recording of 7.6, the setting time (T_{set}) is the time when the temperature of the polymerizing mass is as follows:

$$(T_{max} + T_{amb})/2 \quad (2)$$

where:

T_{max} = maximum temperature, °C, and
T_{amb} = ambient temperature of 23 ± 1°C.



NOTE 1—Dimensions in millimetres and ±0.2 unless otherwise specified. Material for all components: Polytetrafluoroethylene, poly(ethyleneterephthalate), polyoxymethylene, high density polyethylene, or ultra-high molecular weight polyethylene (UHMWPE).

FIG. 1 Exothermic Heat Mold

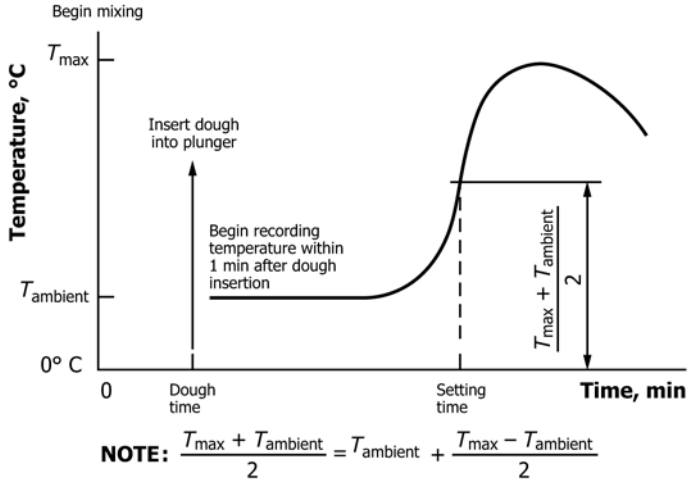


FIG. 2 Continuous Temperature Record

7.7.1 Report the setting time to the nearest 5 s.

7.7.2 Make two separate determinations of the setting time.

7.7.3 The two values should agree within 1 min of each other, otherwise repeat the test on two additional units and report the average of all runs.

7.7.4 Report the setting time to the nearest 15 s as the average of all determinations.

7.8 *Flow Properties and Viscosity Determination*—The manufacturer must specify whether the cement may be used in its pre-dough or dough state, or both. The determination of its usage dictates which of the following tests the cement should comply with. If the mixture is to be utilized in the pre-dough stage, use the extrusion viscosity test (7.8.1 and/or 7.8.2) and Table 1. If the mixture is to be utilized in the dough stage, use the intrusion test (7.8.3) and Table 1. If the mixture is to be used as a dual usage cement, then both the extrusion (7.8.1 and/or 7.8.2) and intrusion (7.8.3) tests must be performed.

7.8.1 *Extrusion, Capillary Viscosity:*

7.8.1.1 *Apparatus:*

(1) Capillary Rheometer—Any capillary rheometer is satisfactory in which acrylic bone cement can be forced from a reservoir through a capillary die and in which temperature, applied force, output rate, and barrel and die dimensions can be controlled and measured accurately. Equipment that provides a constant shear rate has been shown to be equally useful. The capillary die of the rheometer shall have a smooth straight bore that is held within ±0.0076 mm (±0.0003 in.) in diameter and shall be held to within ±0.025 mm (±0.001 in.) in length. The bore and its finish are critical. It shall have no visible drill or other tool marks and no detectable eccentricity.

(2) Due to the extreme sensitivity of flow data to the capillary dimensions, it is important that the capillary dimensions are measured with precision and reported. The length to diameter ratio shall normally be between 20 and 40. Larger ratios and ratios less than that suggested require applying large corrections to the data (**4**, **5**). In addition, the ratio of the reservoir diameter to capillary diameter should be between 3 and 15. See Test Method D3835 for further details of capillary rheometers.

7.8.1.2 *Calibration*—Perform the test with a certified standard viscosity fluid approximating that expected for bone cement (50 N·s/m^2 to 500 N·s/m^2). Determine the viscosity of the standard fluid and the percent error from its specified value. Report this error along with the viscosity of the tested cements.

7.8.1.3 *Corrections*—Bone cement is a non-Newtonian fluid, the data may be reported as corrected data. For example, true shear rates, corrected for non-Newtonian flow behavior, and true shear stress, corrected for end effects or kinetic energy losses, may be calculated. In such cases, the exact details of the mode of correction must be reported. Some correction factors which may apply are:

(1) Piston friction,
(2) Plunger back flow,
(3) Cement compressibility,
(4) Barrel back pressure,
(5) Capillary entrance effects (Bagley correction) (**6**), and
(6) Rabinowitsch shear rate correction (**7**).

7.8.1.4 *Procedure:*

(1) Select conditions of temperature and shear stress or shear rate in accordance with expected usage so that the flow rate will fall within desired limits.

(2) Inspect the rheometer and clean it if necessary. Ensure that previous cleaning procedures and usage have not changed the dimensions or caused scratches or defects in the capillary or apparatus. Make the necessary measurements on the apparatus for future calculations. Prepare the apparatus for running the test.

(3) Mix one or more complete unit(s) of powder and liquid in the recommended manner. Start a stopwatch at the onset of mixing and read all subsequent times from this watch. After complete mixing, transfer the cement to the thermally equilibrated reservoir and eject any entrapped air or excess bone cement.

(4) Start the apparatus at a time not greater than 2½ min from the start of mixing and continue operating until the estimated dough time or the viscosity exceeds 500 N·s/m^2.

(5) Disassemble the apparatus quickly before the cement sets and clean the apparatus of all remaining cement.

7.8.1.5 *Calculations:*

(1) Perform the calculation for viscosity of the cement at time intervals of 15 s from the start to finish of test run. Use the following equations:

$$\text{Shear Stress, Pa} = \frac{Pr}{2L} = \frac{Fr}{2\pi R^2 L} \quad (3)$$

$$\text{Shear Rate, s}^{-1} = \frac{4Q}{\pi r^3} = \frac{4V}{\pi r^3 t} \quad (4)$$

$$\text{Viscosity, Pa·s} = \frac{P\pi r^4}{8LQ} = \frac{Fr^4 t}{8R^2 LV} \quad (5)$$

where:

P = pressure by ram, Pa,
F = force on ram, N,
r = radius of capillary, m,
R = radius of barrel, m,
L = length of capillary, m,
Q = flow rate, m^3/s,
V = volume extruded, m^3, and
t = extrusion time, s.

(2) These equations yield true shear rate and true viscosity for Newtonian fluids only; for non-Newtonian fluids, such as bone cement, the apparent shear rate and viscosity are obtained.

7.8.1.6 *Report*—The report of the flow properties of the cement shall include:

(1) Description of the rheometer used.

(2) Temperature at which the data were obtained.

(3) The capillary diameter and length to diameter ratio of the capillary.

(4) The shear rate at which the test was performed.

(5) Viscosity versus observation time for three runs.

(6) Statement as to whether any correction factors (7.8.1.3) were applied.

7.8.2 *Extrusion, Rotational Shear Viscosity:*

7.8.2.1 *Apparatus—Rotational Shear Rheometer*—Any parallel plate rotational shear rheometer that can use 4 cm diameter plates, 1000 µm gap and maintain a temperature of 23 ± 0.5ºC is satisfactory.

7.8.2.2 *Calibration*—Calibrate the rheometer according to the manufacturer's specifications.

7.8.2.3 *Procedure:*

(1) Mount a parallel plate geometry on the top fixture. A disposable plate system may be used. A stainless steel 4 cm diameter plate is recommended. A removable bottom plate can be added to facilitate sample removal.

(2) Control the temperature of the rheometer so that at least one of the plates is at 23 ± 0.5 ºC.

(3) Move the plates apart to allow sample loading.

(4) Mix the cement according to the manufacturer's specifications. Start a laboratory timer from the start of mixing.

(5) After the requisite mixing procedure is complete, place a sufficient quantity of bone cement between the plates so as to completely fill the gap between the plates and no bubbles in excess of 1 mm are visible. Reduce the gap height between the plates to 1000 µm. Scrape away excess cement.

(6) Start a steady shear experiment at 0.5 s^{-1}, monitoring the shear viscosity as a function of time at a sampling rate of 0.5 Hz or better. Note the elapsed time from the start of mixing to when the first data point is obtained.

(7) Collect data until the viscosity reaches 1000 Pa·s. Stop the test and remove the cement before it completely hardens.

(8) It is recommended that three runs are conducted per cement formulation.

7.8.2.4 *Report*—The report of the flow properties of the cement shall include:

(1) Description of the rheometer used.

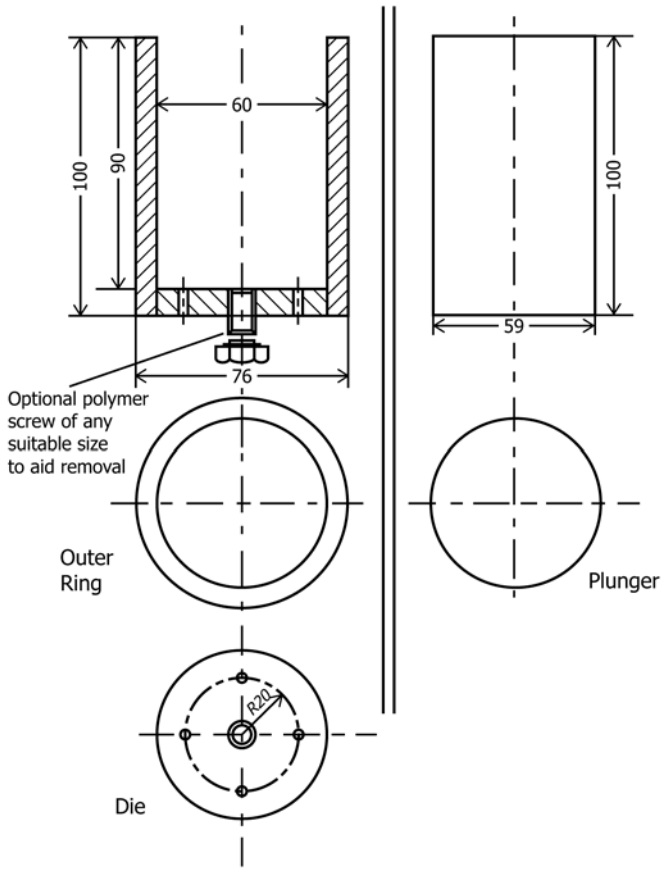
(2) The shear viscosity as a function of time from the start of mixing. The reported instrument time points will need to be shifted by the elapsed time measured in 7.8.2.3(*6*).

7.8.3 *Intrusion:*

7.8.3.1 The mold necessary for this test shall be made of polytetrafluoroethylene (PTFE), poly(ethyleneterephthalate), polyoxymethylene, high density polyethylene, or ultra-high molecular weight polyethylene (UHMWPE) and is shown in Fig. 3.

7.8.3.2 Following the set, remove the specimen and measure the average height of the intrusion into all four of the 1.0-mm diameter holes of the die to the nearest 0.5 mm.

7.8.3.3 Run this test once. If the requirement is not met, it must be met so in a repeat test.



NOTE 1—Dimensions in millimetres; 4 holes in bottom to be 1.00 ± 0.05. Tolerance on all other dimensions ±0.2. Material for all components: Polytetrafluoroethylene, poly(ethyleneterephthalate), polyoxymethylene, high density polyethylene, or ultra-high molecular weight polyethylene (UHMWPE).

FIG. 3 Intrusion Mold

7.9 *Compressive Strength*—The test specimens shall be cylinders 12 mm high and 6 mm in diameter. The ends of the specimens shall be flat and smooth and shall be parallel to each other and at right angles to the long axis of the cylinder. An apparatus found convenient for forming these test cylinders is shown in Fig. 4. An apparatus containing additional or fewer holes may be used as long as adequate spacing between holes is maintained. A mold release agent or silicone spray may be sparingly applied to facilitate specimen removal.

7.9.1 Place the specimen mold on a flat glass or smooth metal plate and slightly overfill using one unit of mixed cement of standard proportions at the commencement of dough time. Press a second flat glass or smooth metal plate on top of the mold. Hold the mold and plates firmly together with a small C-clamp. Then, 1 h later, surface the ends of the cylinder plane at right angles to the axis. The ends of the specimens may be ground flat to the axis by use of a small amount of 240-mesh silicon carbide powder and water. Draw the molds containing the specimens back and forth across the plate coated with the abrasive and water. After surfacing, remove the specimens from the mold. The specimens should be visually examined for surface defects. A surface defect is defined as a surface discontinuity greater than 500 microns in major diameter. Acceptable specimens for testing shall appear to be uniform and meet the dimensional requirements of 7.9. A minimum of five specimens shall be selected from the remaining acceptable specimens and tested. Report the results of all specimens tested.

7.9.2 The time lapse between the start of mixing and the measurement of the compressive strength testing shall be 24 ± 2 h. Storage of the specimens before testing shall be at 23 ± 2 °C and 50 ± 10 % relative humidity. Run specimens on any universal testing machine equipped to record load versus deformation. Employ a deformation cross head speed of 20 to 25.4 mm/min. Test the specimens without use of any type of pad between the specimen and the platens of the machine. The failure load shall be the load at the 2.0 % offset (2.0 % proof stress), upper yield point, or at fracture, whichever occurs first (Fig. 5).

7.9.2.1 The load at 2.0 % offset is the load at the intersection of the load deformation curve and a straight line parallel to the Hookean portion of the curve (See Fig. X1.1 in Test Method D695) but offset along the deformation axis by 2.0 % of the test's gauge length (specimen's height).

7.9.2.2 Calculate the compressive strength as the failure load divided by the calculated cross-sectional area.

7.9.2.3 Report the compressive strength of the material as the average of the compression strengths of the specimens tested in 7.9.2 to the nearest 1 MPa (145 psi). A minimum of five specimens is required.

7.10 *Stability Testing*—The shelf life stability of bone cement powder-liquid systems shall be evaluated using the test methods listed in Table 3.

7.11 *Precision and Bias*—Since 1976, the original Specification F451 methodologies have reportedly been routinely utilized by the various manufacturers. With the exception of the viscosity method of 7.8.1, which is based on another accepted ASTM document (Test Method D3835), each test methodology in Section 7 contains its own statement of reporting acceptable levels of performance, reproducibility, and precision. Therefore, no interlaboratory studies have been performed by the Committee F04.

8. Packaging

8.1 Materials shall be supplied in properly sealed containers made of materials that shall not contaminate or permit contamination of the contents. The containers shall be packaged so as to prevent damage or leakage during shipping and storage. Materials must be packaged to permit sterile transfer of contents to the sterile field.

8.2 The contents shall be easily accessible, easy to open, and convenient to mix in the operating room. Entire package contents (both powder and liquid) must be mixed to achieve recommended proportions.

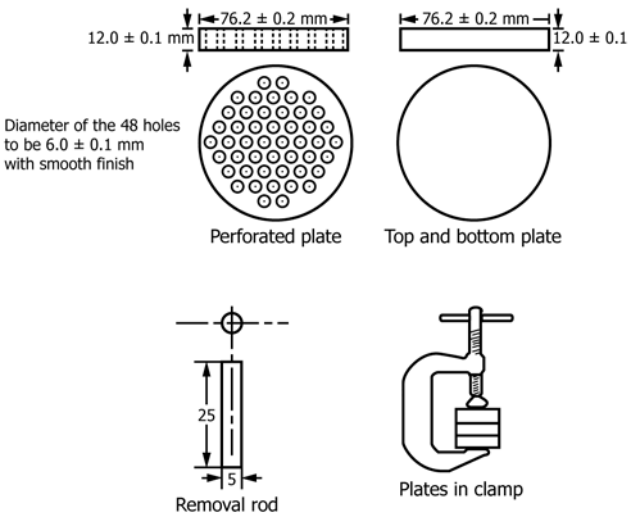


FIG. 4 Compression Specimens Mold

NOTE 1—Material for Perforated Plate: Stainless Steel, Aluminum, Polytetrafluoroethylene, high density polyethylene, or ultra-high molecular weight polyethylene (UHMWPE).

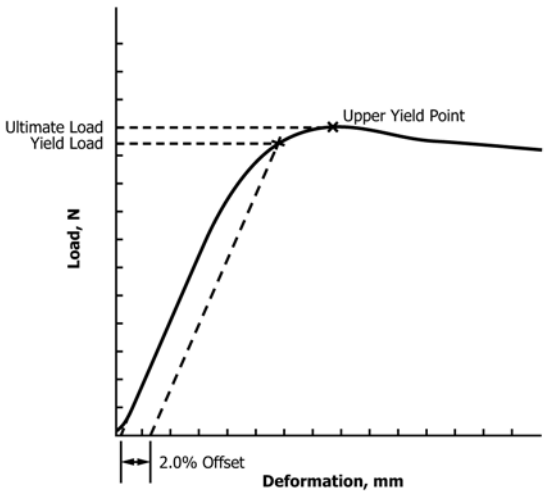


FIG. 5 Failure Load Criteria

TABLE 3 Requirements for Stability Testing

Test Type	Test Description	Test Material
Viscosity	7.3	Liquid Component
Residual Peroxide	Annex A1, or equivalent	Powder Component
Dough Time	7.5	Curing Cement
Set Time	7.7	Curing Cement
Compressive Strength	7.9	Cured Cement
Tensile Strength	D638	Cured Cement
Leachable Monomer	Annex A2, or equivalent	Cured and Curing Cement

9. Labeling

9.1 Labeling on these cements must be in conformance with the Federal Food, Drug, and Cosmetic Act, Code of Federal Regulations, and other pertinent laws and regulations.

9.2 The following minimal information must appear on the container label.

9.2.1 It shall be clearly stated or color coded, or both, if the mixture is intended for usage in the pre-dough, dough, or dual usage state.

9.2.2 The weight or volume, or both, of the liquid and powder components must be stated.

9.2.3 Constituents of the powder and liquid shall be clearly stated in terms of weight or volume percent. This information shall include the generic names of polymers, copolymers, chemical initiators, stabilizers, cross-linking agents, and any other ingredients, such as radiopacify agents, gels, fillers, or antibiotics.

9.2.4 A statement that the contents are sterile and that the sterility shall be guaranteed only if the containers are undamaged.

9.2.5 The following warning shall appear on the label: (*a*) Flammable liquid; (*b*) Store below 25°C, and (*c*) Protect from light.

9.2.6 A statement to the effect that federal law restricts this device for sale by or on the order of a physician should be displayed.

9.2.7 The manufacturer and distributor shall be identified.

9.2.8 Each individual component of the package unit must be clearly identified as to batch or lot number.

9.3 The following information shall appear on the product insert labeling accompanying each package.

9.3.1 Adequate and accurate instruction shall be given for handling the components and preparing the cement. Instructions shall include a directive to mix all of the powder with all the liquid of a single unit. Procedures required to mix the materials, along with recommended mixing utensils, shall be given.

9.3.2 Proper technique for administration and recommended procedures for using the cement, including any special precautions, shall be indicated.

9.3.3 Toxic, hazardous, or irritating characteristics associated with the handling and use of the components and cement shall be indicated.

9.3.4 A statement shall be included that states that high temperatures of either the ambient surroundings or material will cause shorter doughing and setting times, while low temperatures of either the ambient surroundings or material will increase doughing and setting times. In addition, if the instructions for use (IFU) have an allowable temperature range, a chart showing handling (that is, doughing and setting) time versus temperature should be provided for the allowed range of temperature (for example, 16 to 26°C).

9.3.5 The ranges of doughing and setting times as measured at 23 ± 1°C (7.5 and 7.7) shall be clearly stated. If a range of temperatures has been identified, then testing at the lower and upper temperature limits and any intermediate increments should be performed and the results reported in the IFU.

10. Biocompatibility

10.1 The biocompatibility of acrylic bone cement has been reported in the literature (**1**, **2**). The material has been shown to produce a well characterized level of biological response following long-term clinical use and laboratory studies. The results of these studies and the clinical history indicate an acceptable level of biological response in applications in which the material has been utilized. When new applications of the material, or significant modification to the material, or its physical forms are being contemplated, the recommendations of Practice F748 and testing as described in Practices F619, F749, F756, F763, F813, F895, and F981 should be considered.

11. Keywords

11.1 acrylic bone cement; compression strength; doughing time; exothermic temperature; extrusion; intrusion; poly(methacrylic acid esters); setting time

ANNEXES

(Mandatory Information)

A1. DETERMINATION OF TOTAL DIBENZOYL PEROXIDE (BPO) CONTENT

A1.1 Weigh 2.0 ± 0.1 g of polymer and transfer to a 250 mL flask, recording the weight to the nearest 0.0001 g.

A1.2 Add 100 mL of reagent grade acetone to the flask, and mix the contents immediately.

A1.3 Add a magnetic stir bar and stir at room temperature for 1 h or until all polymer is dissolved. Cover or stopper the flask while stirring.

A1.4 Prepare a 50 % (w⁄w) aqueous solution of potassium iodide.

A1.5 Add 5 mLl of glacial acetic acid and 3 mL of the 50 % (w/w) aqueous potassium iodide solution and let stand (covered) for 1 min.

A1.5.1 If the potassium iodide solution appears yellowish, a fresh solution should be prepared and used.

A1.6 Titrate the mixture with 0.01 N sodium thiosulfate solution to a yellow-free end point.

A1.7 Break up any precipitated clumps of polymer with a glass rod and continue the titration until the end point persists for 1 min.

A1.8 Record the volume of 0.01 N sodium thiosulfate used to the nearest 0.05 mL.

A1.8.1 Use a 25 mL burette for titrating when the anticipated BPO assay is less than 1.0 %.

A1.8.2 Use a 50 mL burette for titrating when the anticipated BPO assay is greater than 1.0 %.

A1.8.3 Process a blank sample through steps A1.2 to A1.7.

A1.9 Calculate the results as follows:

A1.9.1 Calculate the percent of dibenzoyl peroxide present in sample using the equation:

$$\% \; BPO = \frac{(V - B) \times N \times 12.11}{W} \qquad (A1.1)$$

where:

V = mL $Na_2S_2O_3$ used for sample titration,
N = normality of $Na_2S_2O_3$,
W = weight of sample (g), and
B = average mL of $Na_2S_2O_3$ used for the blank titrations.

A2. LEACHABLE MONOMER ANALYSIS

A2.1 Monitoring Leachable Monomer from Cured Bone Cement

A2.1.1 *Sample Preparation*:

A2.1.1.1 For each lot of material to be tested, prepare four rectangular cement plaques from each of three different packages of cement 3 ± 0.1 mm thick, 5 ± 0.1 mm wide and 15 ± 0.1 mm long.

A2.1.1.2 Machined polyethylene molds may be to conveniently used for preparing the test plaques.

A2.1.1.3 Mix the cement according to the manufacturer's recommendations and then place it in the molds and allowed it to cure for 30 ± 1 min at 23 ± 1°C.

A2.1.1.4 After the curing period, remove the plaques from the molds and weigh each to an accuracy of ±0.1 mg.

A2.1.1.5 Within 5 min from removal of the cured plaques from the molds, place each plaque into a separate sealed 20 mL vial containing 5 ± 0.1 mL of water (Specification D1193, Type II) held at 37 ± 1°C in a temperature controlled oven or bath.

A2.1.1.6 At time intervals of 1, 24, 72 and 168 h (±0.25 h) after being submerged in the water, the plaques are removed from the water extract solutions and the resulting solution analyzed by gas chromatography for dissolved monomer.

A2.1.2 *Analysis:*

A2.1.2.1 A gas chromatography system may be used to quantify the concentration of monomer in the aqueous extract solutions. The following analytical parameters have been found to be suitable for quantifying methylmethacrylate (MMA) monomer. Other parameters may be used if they can be shown to give equivalent results.

A2.1.2.2 *Detector*—Flame Ionization.

A2.1.2.3 *Column*—SUPELCOWAX 30 m length × 0.53 mm ID × 0.5 µm film.

A2.1.2.4 *Detector Temperature*—260ºC, FID.

A2.1.2.5 *Injector Temperature*—200ºC.

A2.1.2.6 *Injection Volume*—0.5 µl.

A2.1.2.7 *Temperature Program*—isothermal at 45ºC for 2.75 min, ramp to 250ºC at 20ºC/min, isothermal at 250ºC for 4 min.

A2.1.2.8 *Head Pressure*—5 psi.

A2.1.2.9 *Splitless Hold Time*—0.1 min.

A2.1.2.10 The gas chromatograph shall be calibrated using at least four solutions of known monomer concentration in water. The calibration samples are prepared by measuring, by weight, the MMA monomer in 20 mL headspace vials, and mixing with distilled water. After equilibrating for 2 h, an aliquot of each solution is transferred to a 2 mL gas chromatography (GC) autosampling vial.

A2.1.2.11 The range of the concentrations used to calibrate the chromatograph shall bracket the experimental concentrations. In one example, the gas chromatography-flame ionization detector (GC-FID) system was calibrated with six working standards of methylmethacrylate monomer in water at concentrations of 10, 30, 70, 150, 300, and 450 µg/g.

A2.1.2.12 The area from the GC peaks corresponding to the MMA were determined as a function of concentration and plotted as MMA peak area versus MMA concentration.

A2.1.2.13 The least squares correlation constant (R^2) shall be at least 0.99.

A2.1.2.14 The amount of eluted monomer in the unknown samples are determined by measuring the area under the MMA peak in the sample, determining the concentration of MMA from the calibration curve, and multiplying this concentration by the mass of solution in each vial. The mass of eluted monomer is reported in units of [milligrams MMA/gram bone cement].

A2.2 Monitoring Leachable Monomer from Curing Bone Cement

A2.2.1 Prepare an appropriate number of pre-weighed glass extraction vials and caps (16 mL) using a microbalance with 0.01 mg resolution.

A2.2.2 One minute after the bone cement is mixed, transfer about 1 g samples of the mixed cement into each of the empty weighed extraction vials and immediately replace the caps. Reweigh each vial and sample and calculate the exact weight of each cement sample. All transferring shall be completed within 2 min of mixing.

A2.2.3 At the specified time periods from the start of mixing shown in Table A2.1, pipette 5 mL (5 g) of distilled water into each vial.

A2.2.4 The bi-phasic system is allowed to equilibrate for 30 s, at which point 4 mL (4 g) the water is transferred to an empty labeled vial.

A2.2.5 These water extracts are then subsequently diluted 1:10 with additional water prior to analysis. The weight of this final analyte solution is then recorded. A schematic of the protocol is shown in Fig. A2.1.

A2.3 Analysis

A2.3.1 The extracts may be analyzed as described in A2.1.2.

TABLE A2.1 MMA Elution Sampling Times

	Time after starting of mixing to sample eluant exposure (minutes)		
Sample	3	7	11

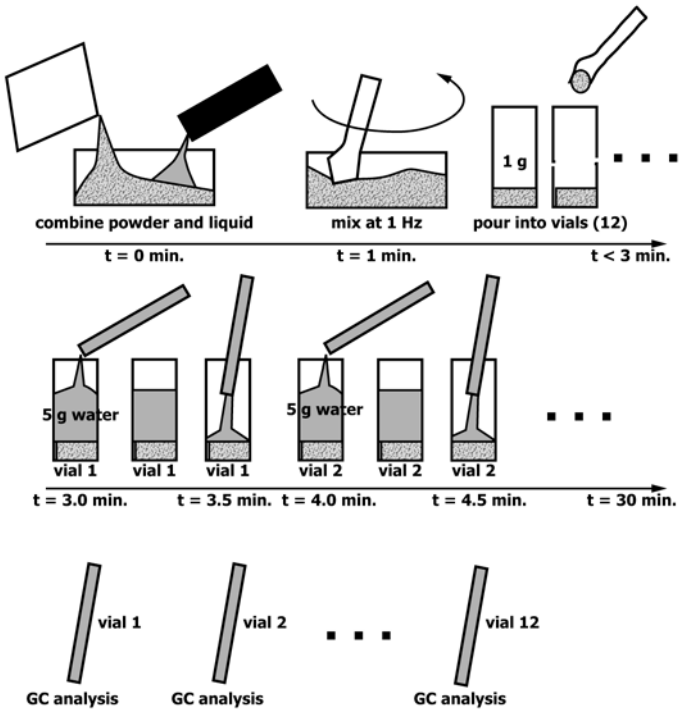


FIG. A2.1 Schematic Diagram of Extraction and Analysis Protocol

APPENDIX

(Nonmandatory Information)

X1. RATIONALE

X1.1 Bone cement is a powder-liquid system that is currently sold worldwide for the fixation of internal orthopedic appliances. Because it plays a key role in highly synchronized surgical procedures such as total joint replacement, its setting characteristics must be known and consistent each time. The material must also have adequate physical properties for placement and function. To these ends, the standard is addressed.

X1.2 Many of the tests are obvious forms of good manufacturing practice; others may be more subtle and require some elaboration.

X1.2.1 The stability test measures the viscosity after storing the liquid at 60°C. This procedure is an accelerated aging test to ensure that the monomeric component of the bone cement does not readily polymerize prematurely while stored before use.

X1.2.2 The dough and set times check that the material will be ready for placement at the proper time in the surgical procedure *and that it will set* neither prematurely nor in a delayed fashion.

X1.2.3 The maximum temperature test makes sure that the mass will not *release excessive heat* during setting. This heat release could be damaging to the patient's tissue if not properly controlled.

X1.2.4 The dough and setting times and maximum temperature test also evaluate other important parameters. These tests will only yield results consistently in the required time and temperature ranges if the powder particle size distribution, the liquid to powder ratio, the complex chemical compositions of both the powder and liquid, and the catalyst amount and distribution have been properly formulated and meted out, and strict quality control during all stages of manufacturing is carefully monitored.

X1.2.5 The viscosity tests of the predough material and intrusion evaluations demonstrate that the material will flow into the bony interstices and around prostheses to produce adequate mechanical interlocking upon setting of the material.

X1.2.6 The compressive strength test indicates if the set material will be strong enough for clinical applications.

X1.3 Further topics presently under consideration for eventual addition to the specification are as follows:

X1.3.1 Other mechanical tests, such as tension, flexion, and fracture toughness, which may be more sensitive to internal porosity and surface defects than the current compression test.

X1.3.2 Statement of biocompatibility of the cement.

X1.3.3 Shortening the time spans of the indentation tests.

X1.3.4 Requiring doughing and setting time data to be furnished with product information.

X1.3.5 Investigating changes in physical properties when leachable additives, such as antibiotics, are purposefully added.

X1.3.6 To define the optimum conditions of the viscosity test methodology so that the performance standards can be established.

X1.4 It should be noted that this document contains both test methodology and performance standards. Currently, in the case of viscosity measurement, only the test methodology has been described. This methodology will serve as a basis for future performance standards.

X1.5 The amount of residual peroxide in acrylic bone cement formulations has significant influence on the material's handling characteristics. The method described in Annex A1 is suitable and convenient for quantifying residual peroxides used in most current formulations however other techniques (HPLC, FTIR, and so forth) may be used if sufficient sensitivity and specificity can be demonstrated.

X1.6 Excessive amounts and rate of methylmethacrylate released by curing and cured acrylic bone cements during clinical use can have significant detrimental affects on the patient. The method described in Annex A2 is suitable for evaluating these characteristics for methylmethacrylate however other experimental parameters may be needed for different monomer formulations. Other techniques (HPLC, LC/MS, GC/MS, and so forth) may also be used if sufficient sensitivity and specificity can be demonstrated.

REFERENCES

(1) Williams, D. F., and Roaf, R., *Implants in Surgery*, W. B. Saunders Co., Ltd., London, 1973, pp 216–218.

(2) Linder, L., *Biocompatibility of Orthopedic Implants*, Vol II, Boca Raton: CRC Series in Biocompatibility, Williams, D. F. (ed.), CRC Press, 1982, pp. 1 to 23.

(3) *U.S. Pharmacopoeia*, Revision 20, Mack Publishing Co., Easton, PA, 1980, p 880.

(4) Tordella, J. P., ed., *Transactions of the Society of Rheology*, Vol 1, 1957, p 203.

(5) Philippoff, W., and Gaskins, F. H., eds., *Transactions of the Society of Rheology*, Vol 2, 1958, p 263.

(6) Bagley, E. B., and Birk, A. M., eds., *Journal of Applied Physics*, Vol 31, 1960, p 556.

(7) Rabinowitsch, R., *Zeitschrift Fuer Physikalische Chemie*, Vol A145, 1929, p 1.

(8) Macosko, C., *Rheology: Principles, Measurements, and Applications*, Wiley-VCH, Inc., 1994.