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Standard Specification for Implantable Epoxy Electronic Encapsulants[1]

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1. Scope

1.1 This specification covers thermoset plastics based on diglycidyl ethers of bisphenol A and amino functional curing agents or amine catalysts.

1.2 The epoxy encapsulants covered by this specification are intended to provide a tissue-compatible protective covering for implantable medical devices such as pulse generators, telemetry devices and RF receivers. The biocompatibility of epoxy plastics has not been established. Epoxy plastic is a generic term relating to the class of polymers formed from epoxy resins, certain curing agents or catalysts and various additives. Since many compositions and formulations fall under this category, it is essential that the fabricator assure safety of implantability of the specific composition or formulation for the intended use by current state-of-the-art test methods. This specification can be used as a basis for standardized evaluation of biocompatibility for such implantable encapsulants.

1.3 The encapsulants covered by this specification are for use in devices intended as long-term implants.

1.4 *Limitations*—This specification covers only the initial qualification of epoxy encapsulants for implantable electronic circuitry. Some of the requirements are not applicable to routine lot to lot quality control.

1.5 *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:*

D 149 Test Method for Dielectric Breakdown Voltage and Dielectric Strength of Solid Electrical Insulating Materials at Commercial Power Frequencies[2]

D 150 Test Methods for A-C Loss Characteristics and Permittivity (Dielectric Constant) of Solid Electrical Insulating Materials[2]

D 257 Test Methods for D-C Resistance or Conductance of Insulating Materials[2]

D 570 Test Method for Water Absorption of Plastics[3]

D 638 Test Method for Tensile Properties of Plastics[3]

D 790 Test Methods for Flexural Properties of Unreinforced and Reinforced Plastics and Electrical Insulating Materials[3]

D 883 Terminology Relating to Plastics[3]

D 1042 Test Method for Linear Dimensional Changes of Plastics Under Accelerated Service Conditions[3]

D 1239 Test Method for Resistance of Plastic Films to Extraction by Chemicals[3]

D 1434 Test Method for Determining Gas Permeability Characteristics of Plastic Film and Sheeting[4]

D 1763 Specification for Epoxy Resins[3]

D 1898 Practice for Sampling of Plastics[3]

D 2240 Test Method for Rubber Property—Durometer Hardness[5]

D 2471 Test Method for Gel Time and Peak Exothermic Temperature of Reacting Thermosetting Resins[6]

D 2562 Practice for Classifying Visual Defects in Parts Molded from Reinforced Thermosetting Plastics[6]

D 2566 Test Method for Linear Shrinkage of Cured Thermosetting Casting Resins During Cure[6]

D 2734 Test Method for Void Content of Reinforced Plastics[6]

D 3137 Test Method for Rubber Property—Hydrolytic Stability[5]

F 74 Practice for Determining Hydrolytic Stability of Plastic Encapsulants for Electronic Devices[7]

F 135 Test Method for Embedment Stress Caused by Casting Compounds on Glass-Encased Electronic Components[7]

F 602 Criteria for Implantable Thermoset Epoxy Plastics[8]

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[2] *Annual Book of ASTM Standards*, Vol 10.01.

[3] *Annual Book of ASTM Standards*, Vol 08.01.

[4] *Annual Book of ASTM Standards*, Vol 15.09.

[5] *Annual Book of ASTM Standards*, Vol 09.01.

[6] *Annual Book of ASTM Standards*, Vol 08.02.

[7] *Annual Book of ASTM Standards*, Vol 10.04.

[8] *Annual Book of ASTM Standards*, Vol 13.01.

F 748 Practice For Selecting Generic Biological Test Methods for Materials and Devices[8]
F 895 Test Method for Agar Diffusion Cell Culture Screening for Cytotoxicity[8]
F 981 Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Bone[8]
2.2 *AAMI Standard:*
EOS-D E-O Sterilization Standard[9]

3. Classification

3.1 Encapsulants shall be classified as follows:
3.1.1 *Type I*—Those encapsulants which contact the tissue directly or indirectly.
3.1.2 *Type II*—Those encapsulants used only within hermetically sealed containers. The epoxy encapsulant has no contact with tissues or physiological fluids.

4. Chemical Composition

4.1 *Additives* (Type I Encapsulants Only):
4.1.1 *Reactive Diluents*—The following compounds when used as reactive diluents shall not be used in concentrations greater than 12 parts per hundred resin (phr).
4.1.1.1 Butyl glycidyl ether (BGE).
4.1.1.2 Phenyl glycidyl ether (PGE).
4.1.2 *Other Additives* (see Note 1)—Other additives shall be shown to be nonextractable in 37°C physiological saline for the device design life in concentrations sufficient to significantly affect the properties of the encapsulant or to produce a significant biological reaction.

NOTE 1—Other additives, as indicated in Criteria F 602, include compounds such as nonreactive diluents, fillers, release agents, and the like.

4.1.3 *Phthalate Esters*—Phthalate esters such as dibutyl phthalate shall not be used in concentrations ≥10 phr.
4.2 *Mix Ratios* (Type I and Type II Encapsulants):
4.2.1 *Amines*—The mix ratio shall be maintained at ±5 equivalent % of stoichiometry.
4.2.2 *Catalysts*—The mix ratio shall be maintained within the ranges recommended by the formulator.
4.3 *Carbonates* (Type I and Type II Encapsulants)—The encapsulant shall be poured under conditions such that the formation of amine carbonates is minimized. The device manufacturer may specify maximum limits of carbon dioxide or water vapor, or both, in the atmosphere in which the encapsulant is being mixed or poured.

5. Physical Properties

5.1 *Type I Encapsulants*:
5.1.1 *Peak Exotherm Temperature* (Test Method D 2471)—The peak exotherm temperature during cure shall be kept below the maximum acceptable value for the lowest temperature rated component of the device.
5.1.2 *Fully Cured Specimens*—The required properties measured on fully cured specimens conditioned as in 6.1 are as follows:
5.1.2.1 *Transparency*—In cases where no fillers or reinforcements are used, the encapsulant shall have sufficient transparency so that the circuitry may be visually inspected after encapsulation.
5.1.2.2 *Foreign Particles*—No foreign particles, particulate matter and gross contamination shall be observed when checked under 2× wide field magnification.
5.1.2.3 *USP Biological Tests Plastic Containers, Class IV*[10]—Pass.
5.1.2.4 USP Pyrogen Test[11] or other Pyrogen methods which have been demonstrated to be of equal or greater sensitivity—Pass.
5.1.2.5 *Sterilant Residues* (AAMI EOS-D)—Where applicable, the concentration of ethylene oxide, ethylene chlorohydrin, ethylene glycol, and dichlorodifluoromethane (or the equivalents) at the time of implant shall be shown to be within safe limits prescribed by the device manufacturer.
5.1.2.6 The cure shrinkage (Test Method D 2566) or embedment stress (Test Method F 135) shall be ≤2%. The stress shall not exceed the limits of the most pressure-sensitive components.
5.1.2.7 Tissue Culture Test (Agar Overlay)[12] or Test Method F 895—Pass.
5.1.2.8 While cell culture methods as described in Test Method F 895 may be appropriated for the batch-to-batch screening of fully cured specimens, the basic recipe used should have been qualified for its overall tissue response by methods such as those suggested in Practice F 748 for "Implanted Devices Principally Contacting Tissue and Tissue Fluid" including testing according to Practice F 981.
5.1.3 *Required Cured Properties Measured in Long-Term Immersion Tests for Type I Encapsulants*—The property values prescribed in Table 1 shall be obtained at 22 ± 3°C and 50 ± 10 % relative humidity on specimens conditioned as in 6.3. Samples shall be wiped dry prior to test with a lint-free tissue, as appropriate.
5.1.4 Optional cured properties measured after accelerated immersion for Type I encapsulants may be determined for screening purposes after conditioning as in 6.2.
5.2 *Type II Encapsulants*:
5.2.1 *Peak Exotherm Temperature* (Test Method D 2471)—The peak exotherm temperature during cure shall be kept below the maximum acceptable value for the lowest temperature rated component of the device.
5.2.2 The property values prescribed in Table 2 shall be determined at 22 ± 3°C (71.6 ± 5.7°F) and 50± 10 % relative humidity on fully cured samples conditioned as in 6.1.

6. Specimen Preparation

6.1 *Preparation*—Prepare specimens used for evaluation of properties of the cured material in the same manner as the

[9] Available from Association for Advancement of Medical Instrumentation, 1500 Wilson Blvd., Suite 417, Arlington, VA 22209.

[10] *U.S. Pharmacopeia*, XXIII, 1995, pp. 1783-1787.
[11] *Ibid.*, pp. 1696-1697.
[12] Guess, W. L., et al., *Journal of Pharmaceutical Sciences*, Vol 54, 1965, pp. 1545–1547.

TABLE 1 Cure Requirements for Long-Term Immersion Tests for Type I Encapsulants

Property	Requirement	ASTM Method
Extraction	<1 % in water	D 1239
Water absorption	≤4 %	D 570
Dielectric strength	>11.8 kV/mm	D 149
Dielectric constant	>2.0	D 150
Dissipation factor	<0.05	D 150
Elongation	>1.5 %	D 638
Flexural strength	≥1380 MPa	D 790
Gas permeation	[A]	D 1434
Hardness	≥60 Shore D	D 2240
Dimensional stability	<0.5 % change	D 1042
Tangent modulus	≥1380 MPa	D 638
Tensile strength (with outgassing power sources)	≥55 MPa	D 638
Tensile strength (without outgassing power sources)	≥7 MPa	D 638
Visual defects	none that adversely affect the safety, efficacy, or reliability of the device	D 2562
Voids	none that adversely affect the safety, efficacy, or reliability of the device	D 2734
Volume resistivity	$10^{10}\Omega\cdot$ cm	D 257

[A] For those devices containing gas-evolving power sources, the hydrogen permeation coefficient shall be 1.18×10^{-3}[(STP)(cm^3)(mm)/(atm)(day)(cm^2)]; or the encapsulant shall allow the escape of 0.06 cm^3 of hydrogen per cell day; or provision shall be made to ensure that gaseous material evolving from the power sources will be adequately disposed of in such a manner that the encapsulant is not comprised.

TABLE 2 Cure Requirements for Long-Term Immersion Tests for Type II Encapsulants

Property	Requirement	ASTM Method
Foreign particles	none visible	...
Cure shrinkage or embedment stress	≤2 %	D 2566 or F135, respectively
Dielectric constant	>2.0	D 150
Dielectric strength	>11.8 kV/mm	D 149
Dissipation factor	<0.05	D 150
Dimensional stability	<0.5 % change	D 1042
Visual defects	none that adversely affect the safety, efficacy, or reliability of the device	D 2562
Voids	none that adversely affect the safety, efficacy, or reliability of the device	D 2734
Volume resistivity	$10^{10}\Omega\cdot$cm	D 257

intended product. Such conditioning shall include all specified relevant variables for the product prior to implant including specimen size or shape, cure time, cure temperature, post-cure, cleaning, packaging, sterilization, and aeration.

6.2 *Accelerated Immersion*:

6.2.1 For screening purposes, immerse specimens prepared as in 6.1 in refluxing physiological saline of pH 7.4 ± 0.2 for 7 days.

6.2.2 Prior to evaluation, allow the specimens to equilibrate to the test temperature of 22 ± 3°C (71 ± 5°F) in physiological saline of pH 7.4 ± 0.2.

6.2.3 Condition one set of controls at 100 ± 3°C (212 ± 5°F) and another set at 22 ± 3°C (71.6 ± 5°F) for 7 days at 50 ± 10 % relative humidity.

6.2.4 Since two variables, heat and moisture, are inherent in this test, data from specimens refluxed 7 days in saline may be compared to controls conditioned dry at 100°C and at 22°C. Thus, one may estimate the long-term effects of moisture as opposed to the effects of moisture and heat or heat alone.

6.3 *Long-Term Immersion* (Test Method D 3137 or Practice F 74):

6.3.1 Prepare the specimens in accordance with 6.1.

6.3.2 During initial qualification of the formulation, immerse specimens in 37 ± 3°C (73 ± 5°F) aerated physiological saline of pH 7.4 ± 0.2 with periodic sampling for evaluation as is appropriate for a period of time consistent with projected service life. It is required that immersion continue for the projected service life of the device. For devices intended for long-term implant, however, it may not be practical to complete tank tests over the device's projected service life before one can claim compliance with the specification. One shall be considered in compliance with this section of the specification, therefore, if specimens meet the requirements of 5.4 after 1 year's immersion.

6.3.3 Store controls at 22 ± 3°C (71 ± 5°F) and 50 ± 10 % relative humidity.

7. Inspection

7.1 As a minimum, the following methods shall be used to characterize the formulation prior to mixing:

7.1.1 Infrared spectroscopy on each component.

7.1.2 Amine number on curing agent.

7.1.3 Epoxide equivalent weight on resin.

7.2 As a minimum, the following methods shall be used to characterize the "mixed" or "hardened" polymer:

7.2.1 Infrared spectroscopy.

7.2.2 Spectrographic analysis.

7.2.3 Total nitrogen.

8. Packaging and Package Marking

8.1 Packaging shall bear appropriate lot numbers that directly relate to the identification of the homogeneous batches which are the source of the encapsulant.

8.2 Packaging shall provide appropriate protection for the epoxy components of the device.

9. Keywords

9.1 encapsulants; evaluation of biocompatibility; implantable medical devices

APPENDIXES

(Nonmandatory Information)

X1. RATIONALE

X1.1 Epoxies as a general class of thermoset polymers may exhibit a wide range of properties depending upon the formulation. This specification is intended to describe minimum requirements for materials for use as encapsulants in implantable electronic components. It remains the responsibility of the device manufacturer to determine whether the particular formulation utilizes meets other specific requirements of the particular end use application.

X1.2 Epoxy encapsulants have been used in the manufacture of implantable electronic components for many years and have been found to exhibit acceptable tissue response. Whenever changes are made in the formulation of an encapsulant, the possibility exists that there may be changes in the tissue response. This specification therefore calls for requalification of different formulations to assure no adverse effects on the tissue response while allowing for cell culture screening batch-to-batch. This specification does not attempt to address the amount of change in formulation which would necessitate re-testing. The material and device manufactures will need to make that determination based upon their own experience, published data, and consultations with experts experienced in this area.

X2. BIOCOMPATIBILITY

X2.1 The suitability of these materials from a human implant perspective is dependent on the specific application. The biologic tests appropriate for the specific site, such as recommended in Practice F 748 should be used as a guideline.

X2.2 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 use of specific compositions and formulations of this material class referred to in this standard has shown that an acceptable level of biological response can be expected, if the material is used in appropriate applications.