Designation: F2579 – 18

Standard Specification for Amorphous Poly(lactide) and Poly(lactide-co-glycolide) Resins for Surgical Implants[1]

This standard is issued under the fixed designation F2579; 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 virgin amorphous poly(lactide) homopolymer and poly(lactide-co-glycolide) copolymer resins intended for use in surgical implants. The poly(DL-lactide) homopolymers covered by this specification are considered to be amorphous (that is, void of crystallinity) and are polymerized either from *meso*-lactide or from equimolar (racemic) combinations of D-lactide and L-lactide. The poly(DL-lactide-co-glycolide) copolymers covered by this specification are also considered to be amorphous and are co-polymerized from a combination of glycolide and either meso-lactide or racemic quantities of D-lactide and L-lactide, and typically possess nominal mole fractions that equal or exceed 50 % lactide.

1.2 Since poly(glycolide) is commonly abbreviated as PGA for poly(glycolic acid) and poly(lactide) is commonly abbreviated as PLA for poly(lactic acid), these polymers are commonly referred to as PGA, PLA, and PLA:PGA resins for the hydrolytic byproducts to which they respectively degrade. PLA is a term that carries no stereoisomeric specificity and therefore encompasses both the amorphous atactic/syndiotactic DL-lactide-based polymers and copolymers as well as the isotactic D-PLA and L-PLA moieties, each of which carries potential for crystallization. Therefore, specific reference to DL-PLA is essential to appropriately differentiate the amorphous atactic/syndiotactic DL-lactide-based polymers and copolymers covered by this specification. Thus, inclusion of stereoisomeric specificity within the lactic acid-based acronyms results in the following: poly(L-lactide) as PLLA for poly(L-lactic acid), poly(D-lactide) as PDLA for poly(D-lactic acid), and poly(DL-lactide) as PDLLA for poly(DL-lactic acid).

1.3 This specification covers virgin amorphous poly(lactide)-based resins able to be fully solvated at 30°C by either methylene chloride (dichloromethane) or chloroform (trichloromethane). This specification is not applicable to lactide-based polymers or copolymers that possess isotactic polymeric segments sufficient in size to carry potential for lactide-based crystallization, which are covered by Specification F1925 and typically possess nominal mole fractions that equal or exceed 50 % L-lactide. This specification is not applicable to lactide-co-glycolide copolymers that possess glycolide segments sufficient in size to deliver potential for glycolide-based crystallization, thereby requiring fluorinated solvents for complete dissolution under room temperature conditions. This specification is specifically not applicable to lactide-co-glycolide copolymers with glycolide mole fractions greater than or equal to 70 % (65.3 % in mass fraction), which are covered by Specification F2313. This specification is not applicable to block copolymers or to polymers or copolymers synthesized from combinations of D-lactide and L-lactide that differ by more than 1.5 total mole percent (1.5 % of total moles).

1.4 This specification addresses material characteristics of both poly(DL-lactide) and poly(DL-lactide-co-glycolide) resins intended for use in surgical implants and does not apply to packaged and sterilized finished implants fabricated from these materials.

1.5 As with any material, some characteristics may be altered by processing techniques (such as molding, extrusion, machining, assembly, sterilization, and so forth) required for the production of a specific part or device. Therefore, properties of fabricated forms of this resin should be evaluated independently using appropriate test methods to assure safety and efficacy.

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

1.7 *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*

[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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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:*[2]

D1505 Test Method for Density of Plastics by the Density-Gradient Technique

D2857 Practice for Dilute Solution Viscosity of Polymers

D4603 Test Method for Determining Inherent Viscosity of Poly(Ethylene Terephthalate) (PET) by Glass Capillary Viscometer

D5296 Test Method for Molecular Weight Averages and Molecular Weight Distribution of Polystyrene by High Performance Size-Exclusion Chromatography

E1252 Practice for General Techniques for Obtaining Infrared Spectra for Qualitative Analysis

E1994 Practice for Use of Process Oriented AOQL and LTPD Sampling Plans

E2977 Practice for Measuring and Reporting Performance of Fourier-Transform Nuclear Magnetic Resonance (FT-NMR) Spectrometers for Liquid Samples

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

F1925 Specification for Semi-Crystalline Poly(lactide) Polymer and Copolymer Resins for Surgical Implants

F2313 Specification for Poly(glycolide) and Poly(glycolide-co-lactide) Resins for Surgical Implants with Mole Fractions Greater Than or Equal to 70 % Glycolide

F2902 Guide for Assessment of Absorbable Polymeric Implants

2.2 *ANSI Standards:*[3]

ANSI/ISO/ASQ 13485 Medical devices -- Quality management systems -- Requirements for regulatory purposes

ANSI/ISO/ASQ Q9000 Quality Management Systems, Fundamentals and Vocabulary

ANSI/ISO/ASQ Q9001 Quality Management Systems, Requirements

2.3 *ISO Standards:*[3]

ISO 10993 Biological Evaluation of Medical Devices

ISO 80000-9 Quantities and units -- Part 9: Physical chemistry and molecular physics

2.4 *U. S. Pharmacopeia (USP) Standards:*[4]

USP 231 United States Pharmacopeia: Chemical Analysis – Heavy Metals

USP 232 United States Pharmacopeia: Elemental Impurities – Limits

USP 233 United States Pharmacopeia: Elemental Impurities – Procedures

USP 781 United States Pharmacopeia: Physical Tests – Optical Rotation

USP 788 United States Pharmacopeia: Particulate Matter in Injections

2.5 *Other Documents/Websites:*

ICH Q3C International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Quality Guideline: Impurities: Residual Solvents[5]

ICH Q3D International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guideline for Elemental Impurities[5]

21 CFR 820 Code of Federal Regulations, Title 21, Part 820, Quality System Regulation[6]

NIST Special Publication SP811 Guide for the Use of the International System of Units (SI)[7]

FDA Guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process' – Guidance for Industry and Food and Drug Administration Staff.

3. Terminology

3.1 *Definitions:*

3.1.1 *virgin polymer*—the initially delivered form of a polymer as synthesized from its monomers and prior to any processing or fabrication into a medical device.

4. Materials and Manufacture

4.1 All raw monomer components and other materials contacting either the raw monomer(s) or resin product shall be of a quality suitable to allow for use of such resin in the manufacture of an implantable medical product. Such quality includes adequate control of particles and other potential contaminants that may affect either the toxicity of or the cell response to the as-implanted or degrading final product.

4.2 All polymer manufacturing (including monomer handling, synthesis, pelletization/grinding and all subsequent steps) shall be undertaken under conditions suitable to allow for use of such resin in the manufacture of an implantable medical product.

5. Chemical Composition

5.1 The amorphous poly(DL-lactide) polymers covered by this specification shall be composed either of *meso* -lactide or a racemic combination of D-lactide and L-lactide. The amorphous poly(DL-lactide-co-glycolide) copolymers covered by this specification can be of variable copolymer ratios and shall

[2] 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.

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

[4] Available from U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.

[5] Available from ICH Secretariat, c/o IFPMA, 30 rue de St-Jean, P.O. Box 758, 1211 Geneva 13, Switzerland. Available online at http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html.

[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 Institute of Standards and Technology (NIST), 100 Bureau Dr., Stop 1070, Gaithersburg, MD 20899-1070, at http://physics.nist.gov/cuu/Units/bibliography.html.

be composed of a combination of glycolide and either *meso*-lactide or a racemic combination of D-lactide and L-lactide where the glycolide mole fraction is less than 70 % (65.3 % in mass fraction). To assure such composition and the attainment of the desired properties, the following tests are to be conducted.

5.2 *Chemical Identification:*

5.2.1 The identity of the virgin polymer shall be confirmed either by infrared, ^{1}H-NMR, or ^{13}C-NMR spectroscopy.

5.2.2 *Infrared Identification:*

5.2.2.1 Identity of either poly(lactide) homopolymer or poly(lactide-co-glycolide) copolymer may be confirmed through an infrared spectrum exhibiting major absorption bands only at the wavelengths that appear in a suitable reference spectrum. Analysis shall be conducted using infrared spectroscopy methods similar to those described in Practice E1252. A typical infrared transmission reference spectrum and a typical infrared absorption reference spectrum for DL-PLA homopolymer are shown in Fig. 1, with example spectra for copolymers presented in Fig. 2. While poly(lactide-co-glycolide) copolymers will each have their own respective spectrum that will vary in response to copolymer ratio, this analytic method typically lacks sensitivity sufficient for quantification of copolymer ratio as specified in 7.1.2.

5.2.2.2 Additional or variable spectral bands may be indicative of sample crystallinity or either known or unknown impurities, including residual monomer, solvents, and catalysts (refer to limits specified in Table 1).

5.2.2.3 Since an infrared spectrum cannot distinguish between the different lactide stereoisomers, it is utilized here only as a means of identifying the non-stereospecific poly(lactide) component of a poly(lactide)-based polymer or copolymer.

5.2.3 *Proton Nuclear Magnetic Resonance (^{1}H-NMR) Identification:*

5.2.3.1 Identity of either poly(lactide) homopolymer or poly(lactide-co-glycolide) copolymer may be confirmed through sample dissolution, ^{1}H-NMR spectroscopy, and the use of a suitable reference spectrum. Sample dissolution is in either deuterated chloroform, deuterated dichloromethane (methylene chloride) or other substantially proton-free solvent able to fully solvate the specimen without inducing competing spectral bands. Analysis shall be conducted using methods similar to those described in Practice E2977. Typical proton NMR reference spectra for 100 % DL-PLA homopolymer and 85 % DL -PLA:15 % PGA copolymer are shown in Fig. 3 and Fig. 4, respectively.

5.2.3.2 Additional spectral bands may be indicative of known or unknown impurities, including residual monomer, solvents, and catalysts (refer to limits specified in Table 1).

5.2.4 *Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR) Identification:*

5.2.4.1 Identity of either poly(lactide) homopolymer or poly(lactide-co-glycolide) copolymer may be confirmed in a solid state through ^{13}C-NMR spectroscopy and the use of a suitable reference spectrum. Analysis shall be conducted using methods similar to those described in Practice E2977.

5.2.4.2 Additional spectral bands may be indicative of known or unknown impurities, including residual solvents and catalysts. Refer to the limits specified in Table 1.

5.3 *Specific Rotation:*

5.3.1 The virgin homopolymer or copolymer shall have a specific rotation of –2.5 to +2.5 degrees when measured in either chloroform, methylene chloride, or tetrahydrofuran at 20°C using a polarimetry method equal to or equivalent to the Optical Rotation procedure described in USP <781>.

5.4 *Molar Mass:*

NOTE 1—The term molecular weight (abbreviated MW) is obsolete and should be replaced by the SI (Système Internationale) equivalent of either relative molecular mass (M_r), which reflects the dimensionless ratio of the mass of a single molecule to an atomic mass unit [see ISO 80000-9], or molar mass (M), which refers to the mass of a mole of a substance and is typically expressed as grams/mole. For polymers and other macromolecules, use of the symbols M_w, M_n, and M_z continue, referring to mass-average molar mass, number-average molar mass, and z-average molar mass, respectively. For more information regarding proper utilization of SI units, see NIST Special Publication SP811.

5.4.1 The molar mass of the virgin polymer shall be indicated by inherent viscosity (IV) in dilute solution. In addition to inherent viscosity (but not in place of), mass average molar mass and molar mass distributions maybe determined by gel permeation chromatography (GPC) according to the general procedure described in Test Method D5296, but using either chloroform or dichloromethane and appropriate calibration standards.

NOTE 2—Molar mass calibration standards (for example, polystyrene or polymethylmethacrylate) provide relative values only, and are not to be confused with an absolute determination of a lactide-based polymer's molar mass.

5.4.2 Determine the inherent viscosity of the polymer preferentially in chloroform at 30°C using procedures similar to those described in Practice D2857 and Test Method D4603. Determination at a lower temperature of 25°C is allowable, provided the utilized equipment delivers the required thermal control and, if requested by the purchaser, an experimentally supported 30°C equivalent concentration-appropriate extrapolated result is also reported within the supplied certification. If the required sample of the subject copolymer ratio does not fully dissolve in chloroform, alternatively utilize dichloromethane (methylene chloride) as the dissolution solvent. Note that any incomplete sample dissolution, precipitation from solution, or the formation of gels will produce inconsistency and variation in observed drop times.

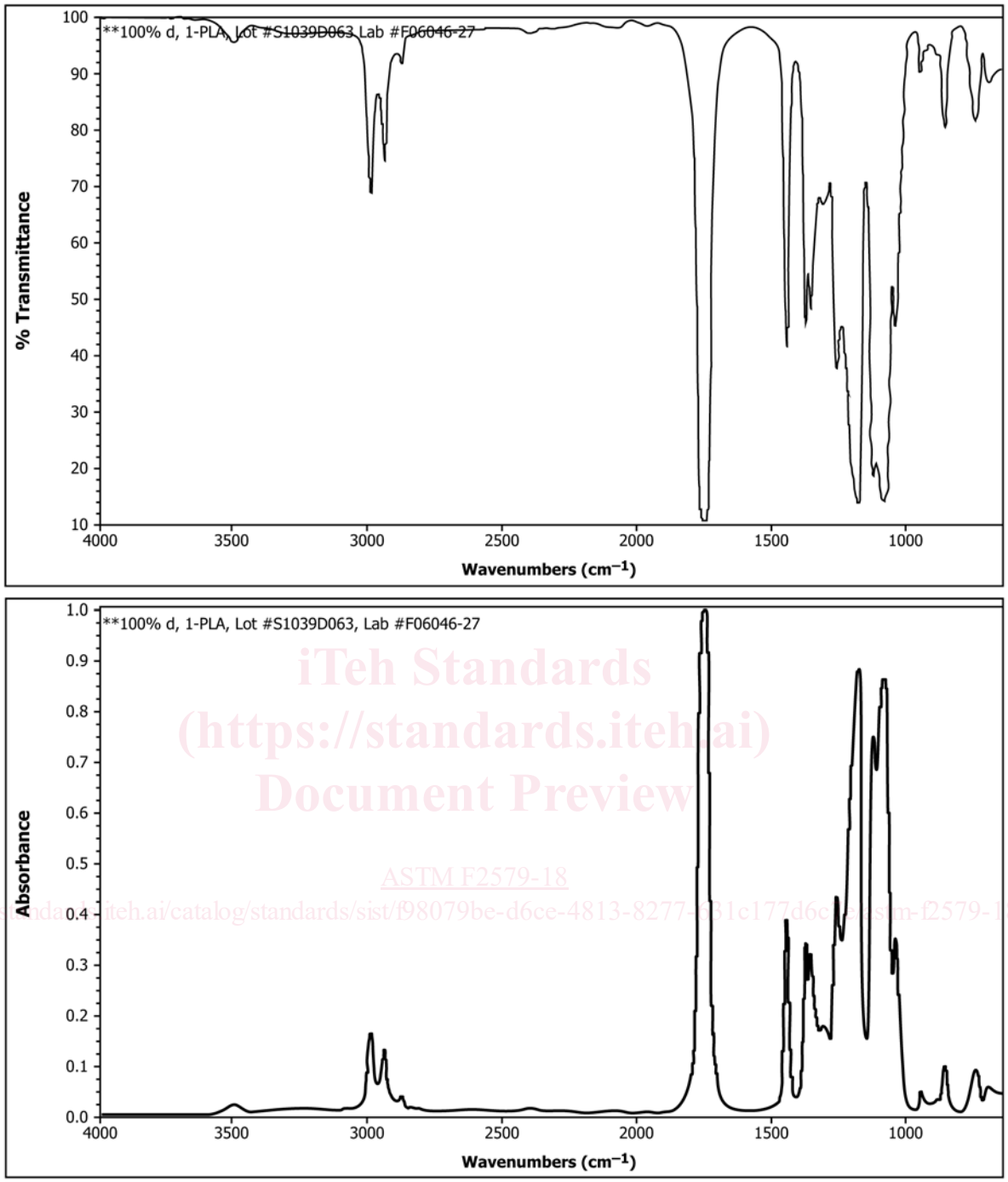
NOTE 3—The IV test duration for each sample should be minimized to reduce risk of resin concentration changes due to evaporative loss of solvent.

5.4.3 Inherent viscosity is determined utilizing the following:

$$IV = \frac{\ln(t/t_o)v}{w} \quad (1)$$

or

$$\mathrm{IV} = \frac{\ln(t/t_o)}{C} \quad (2)$$



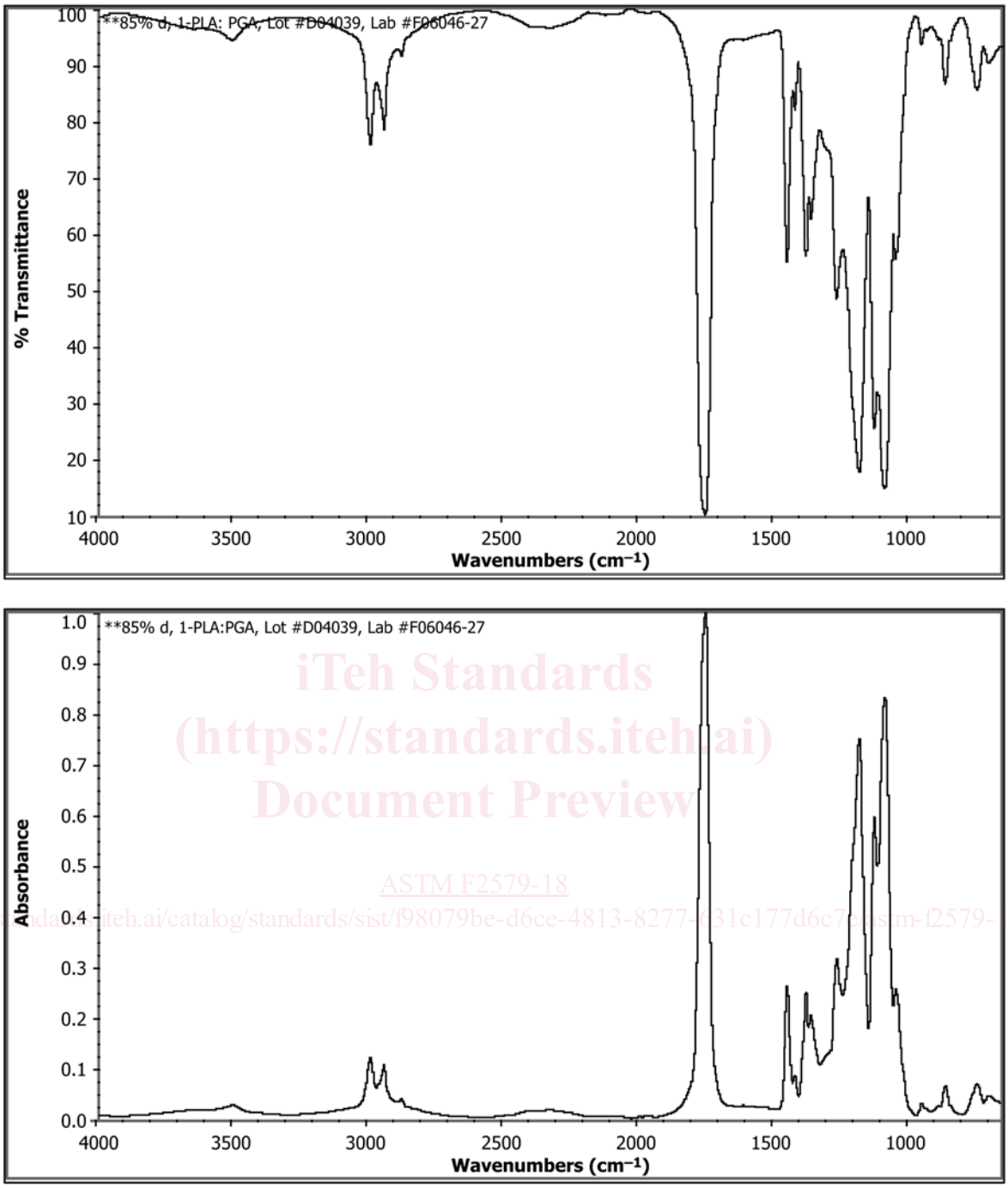
Example infrared spectra are alternative presentations of an amorphous 100 % DL-PLA homopolymer. (Spectra are courtesy of W. L. Gore & Associates, Inc., Flagstaff, AZ 86001, USA.)

FIG. 1 Poly(DL-lactide) Resin Infrared Spectra

where:

IV = inherent viscosity (at 30°C in dL/g),
t = efflux time in seconds for diluted solution,
t_o = efflux time in seconds for source solvent,
w = mass of polymer being diluted (in grams),
v = dilution volume in deciliters (Note: 1 dL = 100 mL), and
C = concentration of dilute solution (*w/v*).

5.4.4 Resin concentration shall be 0.5 % *w/v* or less. When reporting results identify the solvent utilized, analyte concentration, and analysis temperature.



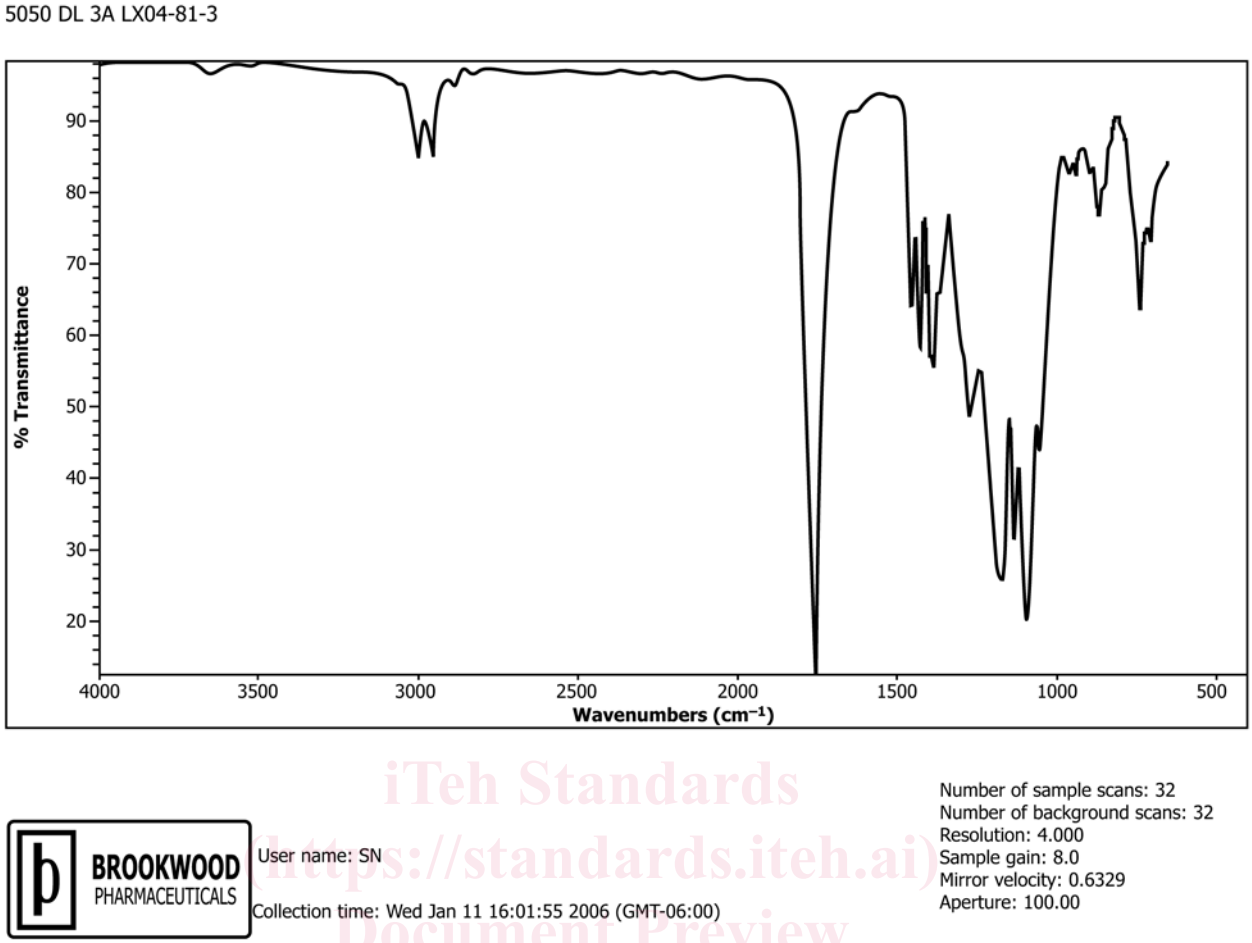
Example infrared spectra are alternative presentations of an amorphous 85% DL-PLA:15% PGA (mole ratio) copolymer. (Spectra are courtesy of W. L. Gore & Associates, Inc., Flagstaff, AZ 86001, USA.)

FIG. 2 Poly(lactide-co-glycolide) Resin Infrared Spectra

5.5 *Residual Monomer:*

5.5.1 The virgin polymer shall have a combined total residual monomer content less than or equal to 2.0 % in mass fraction. Residual monomer levels up to 3 % are acceptable if deemed by the purchaser to be suitable for the intended end-use application. Alternatively, a purchaser may require monomer content significantly less than 2 % to address processing or intended end-use requirements, or both (see Section S1—Biocompatibility).

5.5.2 Determine the mass fraction of residual monomer by gas chromatography, HPLC, ^{1}H-NMR spectroscopy (using deuterated chloroform, deuterated dichoromethane or other



Supplied example infrared spectrum of an amorphous 50 % DL-PLA:50 % PGA (mole ratio) copolymer is courtesy of Lakeshore Biomaterials, 756 Tom Martin Dr., Birmingham, AL 35211, USA.

FIG. 2 Poly(lactide-co-glycolide) Resin Infrared Spectra *(continued)*

substantially proton-free solvent able to fully solvate the specimen), or other suitably sensitive analytic method as agreed upon by the supplier and purchaser.

5.6 *Residual Solvents:*

5.6.1 If any solvent is utilized in any resin manufacturing or purification step, determine the residual levels of any utilized solvent(s) by gas chromatography or other suitable method as agreed upon by the supplier and purchaser. Acceptable residual levels of a particular solvent shall be reflective of toxicity, with a maximum acceptable limit consistent with ICH Q3C. The detection limit for the chosen analytic method shall be adequate to assure compliance with the applicable ICH guideline and the determined residual(s) and applied concentration limit(s) shall be reported. If no ICH concentration guideline has been established for a utilized solvent, an entry of "no ICH guidance available" shall be reported in instead of a limit.

5.6.2 To minimize potential for toxic interaction of solvent combinations, cumulative Total Solvent Combination Residuals shall be limited to 1000 ppm (refer to the limit specified in Table 1). This limit has the effect of allowing ICH Q3C Quality Guidelines when a single solvent system is utilized and less than 1000 ppm when combinations of more than one solvent are utilized (regardless of individual solvent toxicity).

5.7 *Elemental Impurities:*

5.7.1 The significance of Elemental Impurities within an absorbable polymer is ultimately dependent on the dimensional characteristics of the final product and the rate of release of those initially interstitial elements into the surrounding tissue and extracelluar fluid. Thus, any risk assessment of such impurities will be dependent on the final product design and intended application. Consequently, this raw material (not final device) standard provides for appropriate reporting of Elemental Impurities values, but does not mandate any specific performance requirements. More detailed and pharmaceutical oriented guidance regarding the appropriate means for both monitoring and assessing relevant Elemental Impurities within a final product can be found in USP Chapters <232> and <233> and in the ICH HARMONISED GUIDELINE FOR ELEMENTAL IMPURITIES - Q3D.