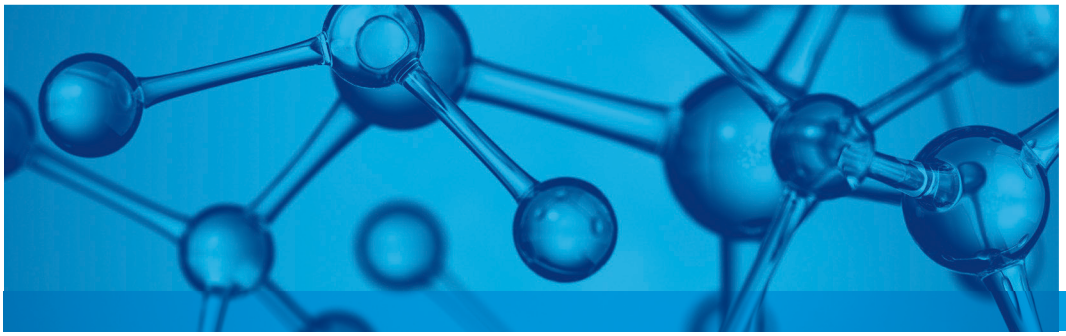

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Shelf Life and Sterilization Study

Radel® R-5000 NT

Radel® polyphenylsulfone (PPSU) is part of Solvay's family of Healthcare grade polymers, a line of high-performance polymers offered for use in medical devices and instruments, specifically those that are in contact with bodily tissue or fluids for less than 24 hours. Radel® PPSU is available in a range of viscosities, as well as transparent and opaque colors.

This document presents test results showing that Radel® R-5000 NT is highly resistant to changes in mechanical, thermal, and chemical properties after being exposed to gamma, steam, and ethylene oxide (ETO) sterilization procedures. In addition, thermally accelerated aging studies spanning five years show that the calculated shelf-life of Radel® R-5000 NT to be in excess of 100 years in closed ambient conditions.

Accelerated Aging Procedures

Test samples were prepared by injection molding Radel® R-5000 NT from production lot M07497T. Standard published injection molding parameters for Radel® PPSU resin were used to prepare ASTM Type I tensile bars and ASTM flexural bars. Samples had a nominal 3.12 mm thickness and were not annealed prior to testing.

For both non-sterilized and gamma-sterilized testing, the standard aging test samples were stored in a climate controlled area kept at 23 °C and 50 % relative humidity. The accelerated aging test samples were placed inside a calibrated oven set to 100 °C with a constant air flow rate. Samples pulled at 12, 24, 36, 48 and 60 month intervals were tested in Solvay's Alpharetta, GA, laboratories which have ISO 9001 and A2LA certifications and are ISO 17025 compliant. Test method details are provided in the Equipment References section at the end of this document.

Gamma Sterilization

Samples for gamma sterilization were submitted to the Sterigenics Facility in Charlotte, NC. Sterilization was conducted using Sterigenic's procedures per requirements of the submitted packaging and material load. Actual radiation dosage conditions for all mechanical and physical test specimens are documented in Sterigenic Dose Map 6944 run on Aug. 6, 2010. Test samples submitted for biocompatibility testing were gamma sterilized and radiation levels were documented in Sterigenic Dose Map 6956 on Sept. 12, 2010.

Samples radiated on Aug. 6, 2010 were exposed to 4 cycles with a nominal dosage level of 30 kGy per pass for a total minimum exposure of 116.3 kGy and maximum exposure of 143.0 kGy. Samples radiated on Sept. 12, 2010 were exposed to 3 cycles with a nominal dosage level of 37 kGy per pass for a total minimum exposure of 107.5 kGy and maximum exposure of 117.8 kGy. After exposure, samples were returned to Solvay for property evaluation and inclusion in the standard and accelerated aging study.

Shelf Life and Gamma Sterilization Results

Standard and accelerated aging results with and without Gamma exposure are presented in the following tables. Tables 1 and 2 show results without Gamma sterilization and tables 3 and 4 show results with Gamma exposure.

Test results indicate that Radel® R-5000 NT is highly resistant to significant changes in its mechanical, thermal, and chemical properties when exposed to both standard and accelerated aging conditions. Samples maintained at 100 °C for five years experienced a slight increase in strength and modulus, along with a slight decrease in elongation.

This is believed to be caused by an annealing effect resulting from the samples being kept at elevated temperatures. Samples irradiated with gamma radiation displayed an initial color shift, which is typical for these types of polymers; combined with long term heat aging, this color shift became significant. However, minimal changes in other tested properties were seen while no change in biocompatibility was observed even with this extreme conditioning. Please refer to the Explanation of Color Change section for a description of ΔE values.

Table 1: Radel® R-5000 NT shelf life without gamma sterilization (aged at 23 °C, 50 % RH)

Property	Unit	As Molded	1 Year	2 Years	3 Years	4 Years	5 Years	Test Method
Color – CIE L*a*b								
Color change	ΔE	0.0	0.3	–	1.1	1.0	6.5	
Characteristic temperatures								ASTM D3418
Glass transition (T_g)	°C	220.8	223.1	222.3	221.3	222.7	223.3	
Tensile properties								ASTM D638
Strength at yield	MPa	73.1	73.1	73.1	73.1	73.8	73.1	
Elongation at yield	%	8.0	7.3	8.2	8.0	8.0	8.0	
Strength at break	MPa	60.1	65.4	61.8	68.1	60.1	60.7	
Elongation at break	%	37.4	62.2	46.0	68.0	29.0	43.0	
Modulus	MPa	2,386	2,365	2,399	2,441	2,441	2,455	
Biocompatibility								
Cytotoxicity		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:5
Physiochemical		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:18

Table 2: Radel® R-5000 NT shelf life without gamma sterilization (aged at 100 °C, 50 % RH)

Property	Unit	As Molded	1 Year	2 Years	3 Years	4 Years	5 Years	Test Method
Color – CIE L*a*b								
Color change	ΔE	0.0	1.6	–	5.9	3.3	12.9	
Characteristic temperatures								ASTM D3418
Glass transition (T_g)	°C	220.8	222.2	221.5	219.1	223.1	222.8	
Tensile properties								ASTM D638
Strength at yield	MPa	73.1	76.5	76.5	76.5	75.8	76.5	
Elongation at yield	%	8.0	7.5	7.4	7.4	7.4	7.1	
Strength at break	MPa	60.1	65.8	63.4	67.0	65.2	62.1	
Elongation at break	%	37.4	59.0	42.0	59.0	59.0	35.0	
Modulus	MPa	2,386	2,303	2,372	2,399	2,379	2,455	
Biocompatibility								
Cytotoxicity		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:5
Physiochemical		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:18

Table 3: Radel® R-5000 NT shelf life with gamma sterilization (aged at 23 °C, ambient RH)

Property	Unit	As Molded	1 Year	2 Years	3 Years	4 Years	5 Years	Test Method
Color – CIE L*a*b								
Color change	ΔE	12.0	13.0	–	15.4	12.7	25.3	
Characteristic temperatures								ASTM D3418
Glass transition (T_g)	°C	223.9	222.4	222.3	221.0	223.0	221.2	
Tensile properties								ASTM D638
Strength at yield	MPa	73.1	73.1	73.1	73.8	73.8	73.1	
Elongation at yield	%	8.0	7.8	8.1	8.0	8.1	8.0	
Strength at break	MPa	59.9	66.5	61.3	62.1	60.3	60.7	
Elongation at break	%	27.2	64.1	42.0	46.0	33.0	43.0	
Modulus	MPa	2,365	2,386	2,434	2,489	2,461	2,455	
Biocompatibility								
Cytotoxicity		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:5
Physiochemical		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:18

Table 4: Radel® R-5000 NT shelf life with gamma sterilization (aged at 100 °C, ambient RH)

Property	Unit	As Molded	1 Year	2 Years	3 Years	4 Years	5 Years	Test Method
Color – CIE L*a*b								
Color change	ΔE	12.0	23.1	–	25.3	24.6	42.6	
Characteristic temperatures								ASTM D3418
Glass transition (T_g)	°C	223.9	222.1	222.3	222.3	222.7	223.7	
Tensile properties								ASTM D638
Strength at yield	MPa	73.1	76.5	77.2	76.5	76.5	76.5	
Elongation at yield	%	8.0	7.4	7.4	7.3	7.3	7.3	
Strength at break	MPa	59.9	67.5	62.3	64.8	64.7	63.2	
Elongation at break	%	27.2	63.6	40.0	52.0	55.0	46.0	
Modulus	MPa	2,365	2,330	2,386	2,427	2,406	2,386	
Biocompatibility								
Cytotoxicity		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:5
Physiochemical		Pass	Pass	Pass	Pass	Pass	Pass	ISO 10993:18

Explanation of Biocompatibility Testing

Samples submitted for biocompatibility testing were tested by NAMSA laboratories using appropriate protocols for ISO 10993:5 and 10993:18. The ISO10993:18 testing was conducted with two extracts: sodium chloride (NaCl) and hexane. Cytotoxicity and physiochemical testing results are summarized in Table 5.

Table 5: Radel® R-5000 NT biocompatibility testing acceptance criteria

Property	Unit
Cytotoxicity	
Cell reactivity	Grade 0 – no cell lysis
Physiochemical testing – aqueous NaCl	
Non-volatile residue	≤ 1 mg
Residue on ignition	≤ 1 mg
Heavy metals	≤ 1 ppm
Buffering capacity	≤ 1.0 ml
Physiochemical testing – Hexane	
Non-volatile residue	≤ 1 mg
Residue on ignition	< 1 mg
Turbidity	≤ 0.3 NTU

Thermal Aging

Thermal aging was used to accelerate the shelf-life aging study of Radel® R-5000 NT. There are multiple approaches commonly used with plastics to estimate the equivalency of accelerated thermal aging.

Method 1: Every 10 °C doubles the rate

A standard rule in the plastics industry, outlined by Hukins et al. (2008), is that increasing the temperature by 10 °C doubles the rate of aging, as illustrated by Equation 1, where f is the accelerated aging factor.

Equation 1: $$f = 2^{\frac{\Delta T}{10}}$$

Radel® R-5000 NT underwent a five-year aging study at 23 °C and 100 °C. At the five-year mark, all test results indicate that there is no measurable thermal decomposition. Plugging ΔT = 100 – 23 = 77 °C into Equation 1 estimates that Radel® R-5000 NT aging at 100 °C for five years is equivalent to 23 °C for 1,040 years.

Method 2: Arrhenius' Equation

The Arrhenius' equation (Equation 2) is commonly used to estimate the acceleration factor caused by thermal-oxidative accelerated aging, where k is the chemical reaction rate, A is the pre-factor, E_a is the activation energy, R is the universal gas constant, and T is the absolute temperature.

Equation 2: $$k = Ae^{-\frac{E_a}{RT}}$$

A modification of Arrhenius' equation (Equation 3) can be used to estimate the increase in reaction rate brought about by an increase in temperature, where k_2/k_1 is the acceleration factor brought about by the increase in temperature from T_1 to T_2.

Equation 3: $$\frac{k_2}{k_1} = \frac{Ae^{-\frac{E_a}{RT_2}}}{Ae^{-\frac{E_a}{RT_1}}} = e^{-\frac{E_a}{R} \times \left(\frac{1}{T_2} - \frac{1}{T_1}\right)}$$

This simplification assumes that the pre-exponential factors for each temperature are approximately equivalent when both temperatures fall within the same phase. In order to solve for k_2/k_1, an activation energy must be determined for thermal-oxidative decomposition observed as a result of the accelerated aging.

However, this poses a problem with Radel® R-5000 NT because no significant thermal decomposition occurred at 23 °C or 100 °C at the five-year test mark. Theoretically, no thermal decomposition corresponds to infinite activation energy. When assuming an activation energy that approaches infinite, the shelf life of Radel® R-5000 NT would be limitless, according to Equation 3. An alternative conclusion is that the rate of decomposition is too slow to be measurable. Since PPSU is considered a thermally stable polymer, it is reasonable to assume that high activation energy is required to decompose the material; therefore, it is believed that a safe estimation for aging can be obtained by using an activation energy of

a less thermally stable polymer. Assuming a very small activation energy, such as the E_a = 85 kJ/mol at 100 °C of low density polyethylene (LDPE) estimated by Ding et al. (1999), equation 3 estimates that 100 °C for 5 years is equivalent to 23 °C for 6,245 years.

In conclusion, Radel® PPSU is very thermally stable, showing no to minimum signs of degradation at 23 °C and 100 °C over five years. Conservative use of the standard plastic industry rules for accelerated aging or Arrhenius' equation estimates that five years of 100 °C accelerated thermal aging performed on Radel® R-5000 NT is equivalent to at 1,000+ years at 23 °C.

Steam Sterilization

Radel® R-5000 NT samples were exposed continuously in a Pre-Vac sterilizer for 500 cycles using the following conditions:

- Unit: Amsco Century Sterilizer SV-136H
- Cycle: Pre-Vac
- Temperature: 134 to 136 °C
- Pressure: 35 to 37 psig
- Vacuum: 27 in. Hg
- Sterilization times: 18 minutes sterilization, 10 min drying, 36 minutes total cycle

The unit uses a dedicated steam generator supplied by filtered, deionized water, which is chemically balanced per the sterilizer unit manufacturer's recommendations. Testing method details are provided in the equipment references section of this document. Relative results of the effects of 500 cycles of steam sterilization on Radel® R-5000 NT are presented in Table 6.

Extensive testing indicates that Radel® R-5000 NT can resist significant changes in mechanical, thermal, and chemical properties after 500 cycles of steam sterilization. A slight increase in strength and modulus along with a slight decrease in elongation was observed due to an annealing effect of the elevated temperatures used during steam sterilization. Please refer to the Explanation of Color Change section in this document for a description of ΔE values. While slight changes were observed in testing conditions, they were all within the confines of expected testing error. With no significant changes resulting from aging or steam sterilization, it is believed that samples can be stored for an indefinite time after exposure to steam sterilization without any adverse effects on properties.

Table 6: Radel® R-5000 NT steam sterilization results

Property	Unit	As Molded	500 Cycles	Test Method
Color – CIE L*a*b				
Color change	ΔE	0.0	3.0	
Characteristic temperatures				ASTM D3418
Glass transition (T_g)	°C	220.8	222.6	
Tensile properties				ASTM D638
Strength at yield	MPa	73.1	80.0	
Elongation at yield	%	8.0	7.0	
Strength at break	MPa	60.1	62.3	
Elongation at break	%	37.4	37.4	
Modulus of elasticity	MPa	2,386	2,372	
Biocompatibility				
Cytotoxicity		Pass	Pass	ISO 10993:5
Physiochemical testing		Pass	Pass	ISO 10993:18

Ethylene Oxide (ETO) Sterilization

Radel® R-5000 NT samples were submitted to the Sterigenics Facility in Smyrna, GA, for ethylene oxide (ETO) sterilization, which was conducted using Sterigenics procedures per requirements of the submitted packaging and material load. Actual conditions are documented in Sterigenic work orders 542504, 544611, 547965, 552296, and 556340 from Nov. 14, 2010 to Dec. 9, 2010.

The average gas exposure time for 5 ETO cycles was 12.3 hours. Samples and supporting Certificates of Processing were returned to Solvay for property evaluations and documentation. Details of testing methods are provided in the Equipment References section of this document. Relative results of Radel® R-5000 NT exposed to 5 cycles of ETO sterilization are presented in Table 7.

Test results indicate that Radel® R-5000 NT is resistant to mechanical, thermal, and chemical changes after ETO sterilization. While slight changes were observed in some testing conditions all were within the confines of expected testing error. With no significant changes resulting from aging or ETO sterilization, it is believed that samples can be stored for an indefinite time after exposure to ETO sterilization without any adverse effects on properties.

Table 7: Radel® R-5000 NT ETO sterilization results

Property	Unit	As Molded	500 Cycles	Test Method
Color – CIE L*a*b				
Color change	ΔE	0.0	0.6	
Characteristic temperatures				ASTM D3418
Glass transition (T_g)	°C	220.8	223.3	
Tensile properties				ASTM D638
Strength at yield	MPa	73.1	73.8	
Elongation at yield	%	8.0	8.1	
Strength at break	MPa	60.1	64.5	
Elongation at break	%	37.4	56.1	
Modulus of elasticity	MPa	2,386	2,378	
Biocompatibility				
Cytotoxicity		Pass	Pass	ISO 10993:5
Physiochemical testing		Pass	Pass	ISO 10993:18

Explanation of Color Change

LAB color space was used for evaluation of color change. Color space is tracked using three values: L (brightness), a (red/green), and b (blue/yellow), representing a three-dimensional color space. A single numerical value, ΔE, can be used to estimate the degree of overall color change using Equation 4. Color changes as seen by the naked eye are summarized in Table 8.

Equation 4: $$\Delta E = \sqrt{(L_2-L_1)^2 + (a_2-a_1)^2 + (b_2-b_1)^2}$$

Table 8: Typical ΔE significance to the naked eye

ΔE Value	Color change as seen by the naked eye
$\Delta E < 1$	Unable to distinguish
$1 \leq \Delta E < 2$	Noticeable by some upon a close inspection
$2 \leq \Delta E < 3$	Noticeable upon inspection
$\Delta E \geq 3$	Obvious change in color

Equipment References

Tensile testing was conducted on an Instron® 5569 Load Frame at 2 in/min test speed per the ASTM D638 standard.

Thermal properties were tested using a TA Instruments® Q20 Differential Scanning Calorimeter per ASTM D3418 standard. Analysis used 1st and 2nd heat with a 20 °C/min ramp rate.

Color Change was measured on the wide end of a Type I tensile bar using a BYK Gardner® Colorsphere Instrument; Reflectance mode, CIE L*a*b* scale with a D65 – 10° illuminant and observer.

Cytotoxicity (ISO 10993-5) and Physio-Chemical analysis (ISO 10993-18) were conducted by the NAMSA laboratories in Northwood, OH.

Literature References

D. W. L. Hukins, et al., "Accelerated Aging for Testing Polymeric Biomaterials and Medical Devices," Med. Eng. & Phy., Vol. 30, pp. 1270–1274, 2008.

S. Ding, et al., "Polymer Durability Estimates Based on Apparent Activation Energies for Thermal Oxidative Degradation," Therm. Acta, 367–368, pp. 107–112, Apr. 2000.

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