



# VESTA™: Nanoscale Thermal Analysis

Application Note #12

Nanoscale Thermal Analysis of Medical Devices Using the VESTA

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## Introduction

Materials property characterization is central to nearly all facets of medical device design, production, and pre or post-use testing. Material properties are routinely evaluated to meet needs in R&D & quality assurance, and to obtain regulatory approval for sale. Devices that have been used clinically or experimentally are also routinely analyzed to better understand mechanisms of degradation, wear and tear, and/or failure.

Polymers are widely used either solely or in combination with other materials in applications that include catheters, electrode lead insulations (e.g. cardiac pacing or nerve stimulating), orthopaedic bearings, sutures, drug release coatings (e.g. cardiovascular stents) and many more. Polymers are heterogeneous materials that can have substantial variations in physical properties over micron to millimeter length scales due to changes in molecular weight, crystallinity, mixing uniformity of drugs in pharmacologically active coatings, and the degree and morphology of phase separation in blends, co-polymers, and composites. Morphological characterization of polymers is typically done with different types of microscopy, while functional and intrinsic properties such as molecular weight (MW) and mechanical strength are typically evaluated on bulk specimens without providing spatial information. Bulk thermal analysis techniques including differential scanning calorimetry (DSC), thermal mechanical analysis (TMA) and others are also widely used to elicit information on polymer properties such as phase and component mixing. However, these thermal analysis methods are limited to the assessment of the average or aggregate properties of samples that are hoped to be “representative” of manufactured devices, since such samples are necessarily removed from or created separately from manufactured devices. Since “representative” analytical specimens are required, *in situ* variations in material properties on manufactured devices may be missed. In addition to limitations on the analysis of manufactured devices and regions of devices, existing thermal analyses are also nearly impossible to perform on thin polymer coatings.

The Vesta (Ansys Instruments) is a new analytical instrument that enables manufactured medical devices to be analyzed for functional thermal transition properties via Transition Temperature Microscopy (TTM). With TTM, the assessment of thermal properties may be made in any identified specific region of a device or specimen, thus uniquely integrating spatial information with thermal properties. This thermal property measurement provides information on MW, crystallinity, component mixing, and phase segregation that can be used to guide R&D, enable production methods development, and provide production quality control. Additionally, these thermo mechanical measurements also provide insight into mechanisms of localized degradation, wear and/or failure of devices after testing or following clinical use.

This application note illustrates the assessment of thermal transition properties of several different types of polymeric medical devices and discusses the information that can be gleaned from such analyses.

## Instrumentation

The Vesta Instrument incorporates a micro-machined inverted pyramidal thermal probe that is fabricated on an AFM-like (atomic force microscope) cantilever. An optical microscope enables users to position the thermal probe onto sample regions of interest. When directed, the Vesta system will then bring the <30 nm radius thermal probe tip into mechanical contact with the specimen. The probe can also be programmed for automatic positioning in order to perform a series of measurements or to generate a Transition Temperature Map (TTM). Once in contact with the region of interest the probe tip is resistively heated while the cantilever provides sensitive force control and measurement between the tip and sample. This provides localized thermo mechanical analyses that are displayed in the form of a plot of the physical deflection of the thermal probe on the specimen versus the probe temperature. With most specimens (e.g. Figure 1.1), as the probe is heated the specimen first expands and thus moves the probe tip up. At a transition temperature, the specimen will begin to soften and the tip thus begins to move down into the specimen. This temperature versus deflection curve is a local thermal analysis (LTA) plot. The probe can be heated up to 450°C at ramp rates up to 600,000°C/min, thereby enabling high throughput measurements at temperatures appropriate for essentially any polymeric or organic material. Material softening, melting and even remelting can be monitored to provide information on MW, phase and blend mixing and other physicochemical properties. The spatial resolution of the measurement is dependent on the thermal probe radius of 30 nm, and on the local thermal properties of the material. With most polymeric systems, this enables local thermal analysis at a sub 100-nm scale.

## Experimental Results and Discussion

### Example 1: UHMWPE orthopaedic bearings and materials

Ultra high molecular weight polyethylene (UHMWPE or PE) is an extremely successful bearing material for orthopaedic hip and knee bearings, with millions of devices in use and about a hundred thousand new PE-bearing hip and knee arthroplasty devices implanted per year. Nonetheless, it has been long established that wear of the PE impairs device function and that wear particulates released from these bearings generate chronic inflammatory responses. Consequently, there

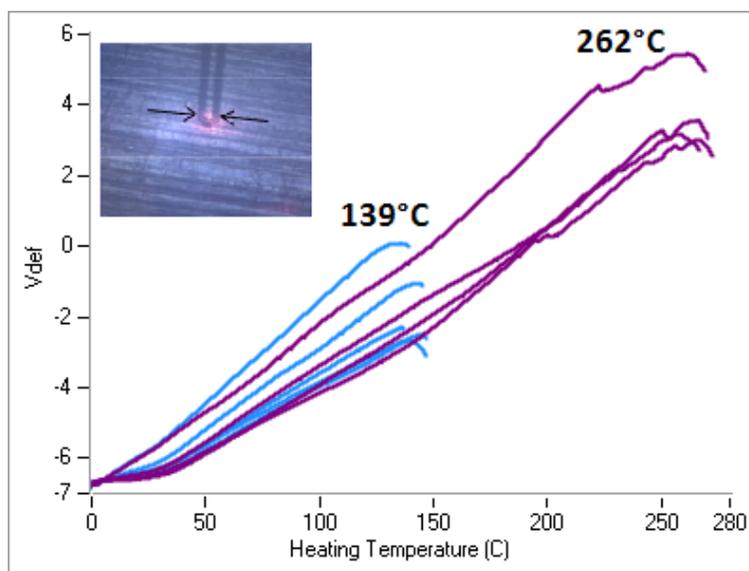


Figure 1.1: Local thermal analysis (LTA) plots show mechanical deformation of un-crosslinked UHMWPE (smooth blue curves peaking at ~139 C) and 100 kGy radiation cross-linked UHMWPE (red, less smooth, curves peaking at ~262 C). Inset photo shows thermal probe cantilever overlying the un-crosslinked specimen, with the arrows indicating the location of the thermal probe tip that is under the cantilever.

has been extensive research to improve device durability that has revealed mechanisms that include mechanical wear and oxidation that are correlated with changes in PE molecular weight, crystallinity, and cross-link density. Although it is not entirely clear what material properties are important for long term biocompatibility in total hip and knee arthroplasty prosthetics, physical cross-link density and crystalline morphology are two properties that are well known to affect PE bearing function. [1] The evaluation of PE crystalline structure is difficult and laborious, requiring tedious sample preparation for transmission electron microscopy in a process that requires several days with specimens that are removed from bulk samples or devices. Until now, there have been no rapid analysis methods for crystallinity (and cross-link density), and no methods to enable the direct evaluation of these critical properties in manufactured devices. The Anasys Vesta, as an instrument that evaluates thermal transition properties that are directly dependent on MW, crystallinity and cross-link density, uniquely enables rapid measures in both experimental materials and in production devices.

In the present study, several UHMWPE's were analyzed including conventional UHMWPE's as in wide use, radiation cross-linked UHMWPE's since these appear tougher and less prone to wear [2] and UHMWPE's infused with alpha-tocopherol (vitamin E) provided as an antioxidant. [3] In addition, a retrieved explanted knee bearing was examined demonstrating molecular degradation in identified regions.

Figure 1.1 shows several representative local thermal analysis (LTA) plots for virgin UHMWPE (GUR 1050 resin) with a viscosity average MW of approximately  $5 \times 10^6$ . This figure also shows LTA plots for the same PE after cross-linking with 100 kGy radiation. The un-crosslinked PE shows a smooth curve that is characteristic of MW and compositional uniformity, with a  $T_m$  onset at 139°C. In contrast, the LTA plots of the radiation cross-linked PE exhibited substantial irregularities indicative of molecular heterogeneity. The  $T_m$  of this material occurred at 262°C, along with a shoulder at 139°C that is consistent with DSC analysis of this material. [4] Additionally, the probe penetrated less than half as deep into the radiation cross-linked PE than the un-crosslinked PE. These thermal mechanical properties are consistent with known and expected properties of radiation cross-linked PE. [5]

Figure 1.2 shows three LTA plots for an alpha-tocopherol (vitamin E) impregnated sample of the radiation crosslinked PE. The sample has a gradient of alpha-tocopherol content that is clearly visible (not shown). The LTA curves taken at different points across the gradient show a substantial effect on the thermal transition curves, with higher levels of alpha-tocopherol correlating to a softer material at 120°C, which is below the  $T_m$ . Thus, alpha-tocopherol induces a concentration-dependant plasticization effect.

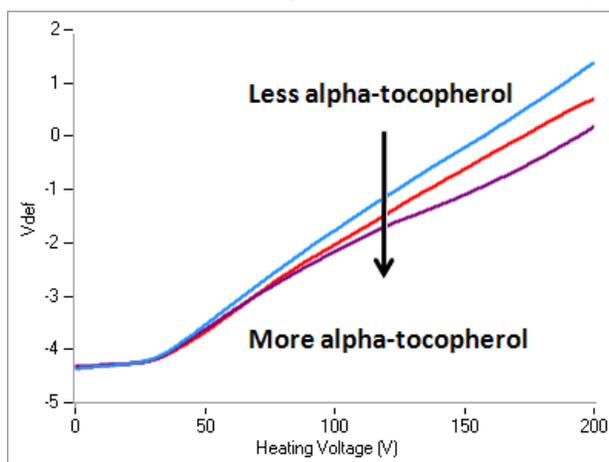


Figure 1.2: Local thermal analysis plots of alpha-tocopherol impregnated radiation crosslinked UHMPE. Softening of the material is observed to correlate with alpha-tocopherol content.

An explanted UHMWPE knee bearing was examined that showed substantial material breakdown, especially on the left side of the photo (1.3a). The detailed history of this clinical implant is not known, but this implant was produced about two decades ago. To evaluate the capability of the Vesta to assess material properties in less obviously damaged materials, LTA was performed on two regions on the much less damaged right side of the implant. These regions were 3-4 mm apart as shown in Figure 1.3. One region near the edge of the device appeared pristine (1.3b) while the second region was in a circa 3 x 1 mm pit that otherwise showed no obvious damage such as discoloration (1.3c). Thermal analysis in the undamaged region showed smooth and consistent LTA curves characteristic of native UHMWPE (similar to Figure 1) but with a  $T_m$  transition at 108°C. This lower  $T_m$  transition, compared to the higher  $T_m$  in Figure 1, is most likely due to lower MW polymers that were used at the time this implant was made. In contrast to the undamaged region, the LTA curves taken in the middle of the pit varied substantially, with one LTA curve showing multiple transitions indicative of MW breakdown, and a second appearing more like native PE. This variation shows that damaged regions exhibit more varied thermal properties, likely indicative of MW, crystallinity, oxidation, or other changes in the polymer. As noted, except for the pit, this region otherwise appears undamaged and un-discolored by visual inspection. Thus, thermal-mechanical analysis with the Vesta is able to detect non-obvious changes in polymer properties.

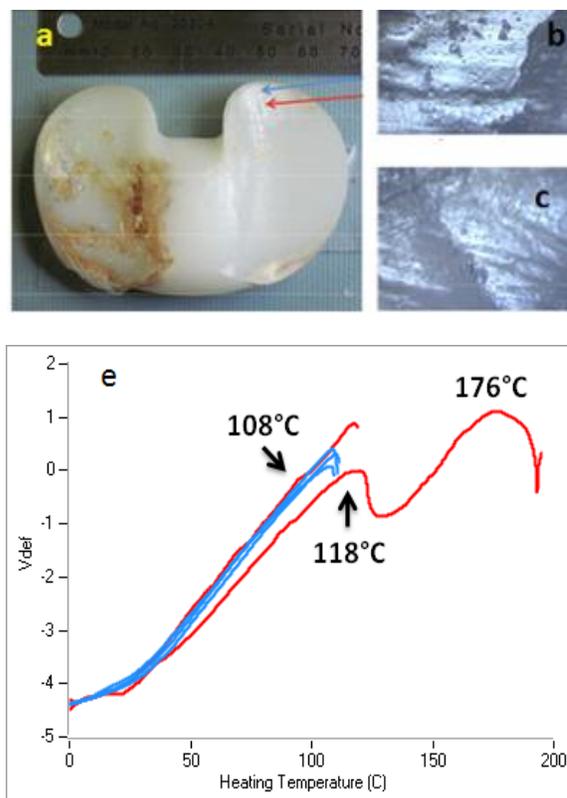


Figure 1.3: Photograph of an explanted UHMWPE knee bearing (a) and two regions of LTA analysis as indicated with the arrows. Region shown in b and indicated with upper blue arrow shows no visible damage. Region c indicated with lower red arrow is in the small pit. Local thermal analysis curves (e) are shown for the two regions: Region b (blue curves with 108°C peak) and region c (red curves with 118°C peaks, one of which has a second 176°C peak).

**Summary:** LTA is able to discern changes in thermal properties indicative of MW, crystallinity and/or cross-link density in conventional, radiation cross-linked, and alpha-tocopherol impregnated UHMWPE. Additionally, LTA can detect local changes in PE properties due to wear or other damage that are not obvious on visual inspection, as shown with a previously implanted whole knee bearing.

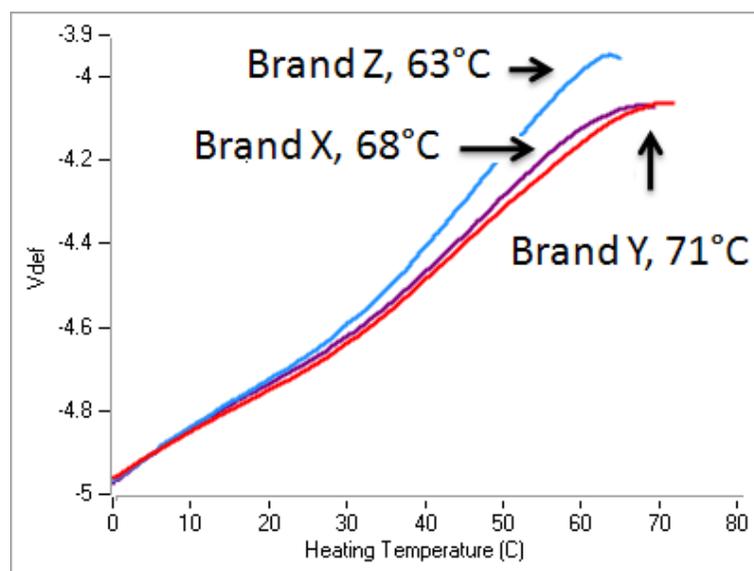
### **Example 2: Drug coated cardiovascular stents**

Drug coated stents are widely used in interventional cardiology with several hundred thousand placed in patients in the United States every year.[6] The distribution of the drug in the matrix polymer, the crystallinity of the drug, and the MW and crystallinity of the polymer matrix have substantial effects on the release kinetics, which in turn can greatly alter biological responses. While spectroscopic microscopies such as IR and Raman can image drug distribution within coatings at the micron scale, such methods are limited in their capabilities in providing sub-micron resolution. Secondly, until now, no known method could directly measure crystallinity or

phase mixing of drugs and matrix polymers coated onto stents. With the submicron LTA enabled with the Vesta, this is now possible. In the following study, several drug-coated stents were analyzed. These coatings were all based on poly-DL-lactic acid (PDLLA) polymer matrixes, but otherwise varied in formulation. For reasons of confidentiality the sources of the stents and their compositions are not provided in the following table:

Stent Type	Formulation	Solvent
Brand X	PDLLA + Drug A + excipients	Solvent 1
Brand Y	PDLLA + Drug B + excipients	Solvent 2
Brand Z	PDLLA + Drug C + excipients	Solvent 3

An LTA curve is shown for each stent in Figure 2.1, along with a photomicrograph of the region of analysis of each stent obtained with the Vesta. The plots show that the  $T_g$  transitions were slightly different for the three stents, ranging from 63 to 71°C. These transitions are somewhat higher than the typical 50-60°C  $T_g$  of pure PDLLA. This may be due to the higher heating rate used in the LTA or due to the inclusion of the drug.



The Vesta was then used to provide Transition Temperature Maps (TTM) of  $T_g$  measurements in an array. For each map, 36 separate LTA measurements were automatically performed at 10  $\mu$ m spatial intervals in a 50 x 50  $\mu$ m region (Figure 2.2). Note the substantial differences in the uniformity and pattern of the  $T_g$  onset for the three stents. Since the drugs have substantially higher transition temperatures than the PDLLA matrix, this indicates that there were substantial differences in the local content of the drug in each of the  $\sim$ 30 nm regions that were thermally analyzed. For example, the Brand Y stent showed a single region of very high drug content (as measured with  $T_g$ ) surrounded by relatively uniform composition ( $T_g$ ). In contrast, there was a very small range of drug content in Brand Z, and an intermediate range in Brand X.

Figure 2.1: A typical LTA curve is shown for each stent with the average peak thermal transition labeled (arrows). Micrographs of the analyzed region are shown for each stent “brand.”

**Summary:** It was clearly observed that the three different stents varied considerably in their average thermal properties, and in the morphological character of the distribution of these thermal properties. The dominant thermal transition observed was the  $T_g$  of the PDLLA. Overall, it has been shown that thermal analysis performed with the Vesta can detect significant compositional and morphological structure within drug coated stents.

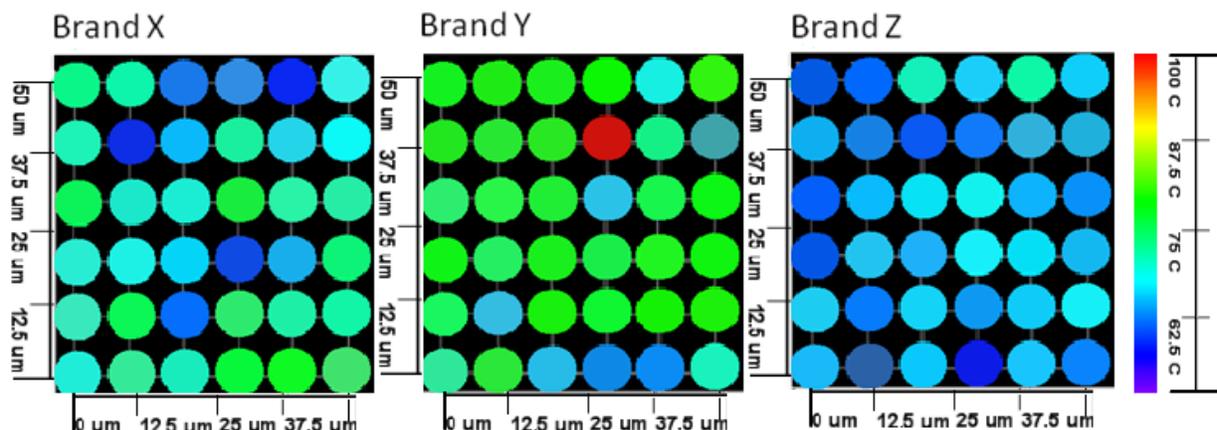


Figure 2.2: Transition temperature maps are shown for the 3 stents. For each map 36 separate measurements were obtained at 10  $\mu\text{m}$  spatial intervals in an x-y grid. Each colored circle represents a single measurement, with the onset of the  $T_g$  ( $^{\circ}\text{C}$ ) depicted by the color scale.

### Example 3: Vestamid and Pebax Catheters

Two commercially available catheters were obtained and then examined as shown in Figure 3.1. These were a catheter made from Vestamid catheter (a nylon) and from Pebax (a block copolyamide). Compositional details of these specific catheter samples are otherwise unknown. The Vestamid catheter showed a very consistent  $T_m$  of  $120 \pm 3^{\circ}\text{C}$ , while the Pebax catheter showed a very consistent  $T_m$  of  $160 \pm 3^{\circ}\text{C}$ . These  $T_m$  transitions appear consistent with the known properties of these commercially available materials.

**Summary:** Vesta analysis of these catheters showed highly uniform  $T_m$  measurements thus indicating uniform properties.

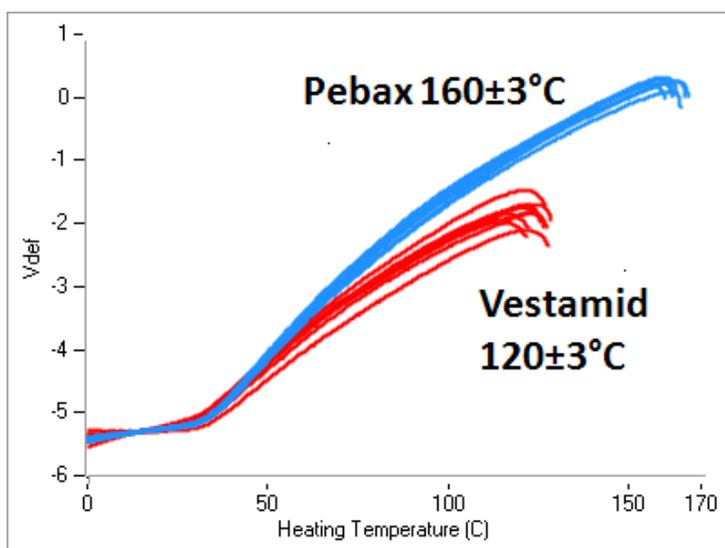


Figure 3.1: LTA curves and range of melting temperature for the Vestamid catheter (red) and the Pebax catheter (blue curves).

### Example 4: Contact lenses

Two unused off-the-shelf contact lenses were examined with LTA. Both lenses were the same size, brand and composition, but varied in power (-3.50 and -3.00), and were produced about one year apart. These lenses were composed of a hydrogel, but for reasons of confidentiality the source and composition are not disclosed here. The lenses were removed from their original consumer packaging, rinsed for over 4 hours in three 20 ml changes of distilled water to remove any packaging salts and/or preservatives, and then air-dried overnight.

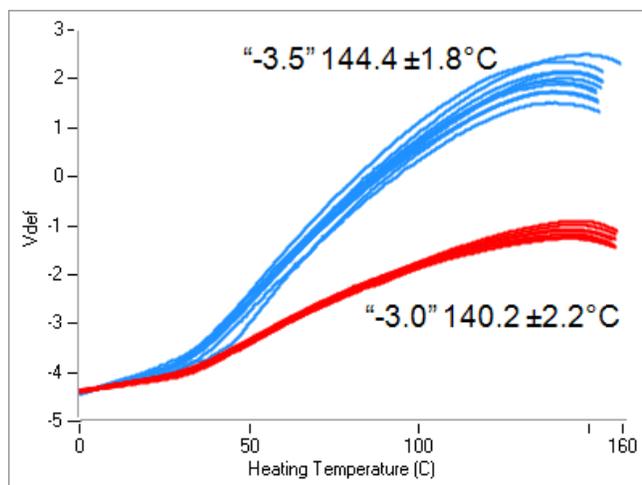


Figure 4.1: LTA measurement curves and the average melting temperature (mean  $\pm$  sd) of two unused off-the-shelf hydrogel contact lenses. The -3.00 lens curves are shown in red (lower set) and -3.5 lens curves are shown in blue (upper set).

Figure 4.1 shows that the  $T_m$  varied slightly between the two lenses. The 3.0 and the 3.5 power lenses had respectively, mean  $\pm$  standard deviation  $T_m$  of  $140.2 \pm 2.2^\circ\text{C}$  and  $144.4 \pm 1.8^\circ\text{C}$  from 10 separate LTA measures of each lens in various locations. Each lens was quite consistent in its own thermal properties, yet the two lenses did not have the same  $T_m$ . The circa  $4^\circ\text{C}$  difference in  $T_m$  between the lenses suggests that there was a small difference in the MW of the polymers, other chemical components, and/or slight differences in the fabrication protocols for these two similar lenses.

batches had slightly different melting temperatures indicating differences in polymer structure or chemistry.

**Summary:** Vesta analysis revealed uniformity of the  $T_m$  of each contact lens in 10 different measurement locations. However, Vesta also revealed that the two different lenses manufactured in different batches had slightly different melting temperatures indicating differences in polymer structure or chemistry.

## Conclusions

The Anasys Vesta enables powerful analyses of thermal transition properties of experimental and fully functional medical derive polymers. Vesta enabled local thermal analyses (LTA) and transition temperature mapping (TTM) reveal underlying structural and compositional details that are not apparent from visual inspection or from conventional or spectroscopic microscopy. The Vesta analyses provide insight into drug coating structure and function, polymeric molecular degradation, and product uniformity. Since Vesta enables such measurements on functional fully manufactured devices, and on explanted devices, such information can be readily applied to R&D, Quality Control, Quality Assurance, and Failure Analysis.

## Acknowledgements

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2. Dr. Stephen Spiegelberg, Cambridge Polymer Group, Inc. Boston, MA.
3. Individuals and firms that prefer to remain anonymous.

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