



Rapid Evaluation of Surface Properties of Medical Tubing for Process Development and Quality Assurance

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Abstract

Important surface properties of medical tubing, such as wettability, adhesion, antithrombogenicity, and biocompatibility depend on the chemical composition and structure of the uppermost 2-3 nanometers of the material. This region corresponds to only a few molecular layers. Control of the properties and consistency of this layer is a critical part of medical device manufacture. Surface chemical composition and structure is typically evaluated using surface sensitive analysis techniques such as attenuated total reflectance infrared spectroscopy (ATR-FTIR) and X-ray photoelectron spectroscopy (XPS). Evaluating biologic properties such as antithrombogenicity may require even more unwieldy tests such as uptake of radiolabeled reagents. While these tests can provide excellent and detailed information for process development and process trouble shooting, they are impractical to deploy as routine quality assurance techniques.

Surface free energy is another material property that is very sensitive to subtle changes in surface composition and structure as well as properties. It is a potential quality assurance tool for medical device manufacture, but its use has been hampered by a lack of techniques suitable for rapid and convenient deployment in a manufacturing environment. This presentation discusses the rapid measurement of surface energy of small diameter medical tubing via ballistic deposition of sub-microliter drops of water. Contact angles determined using this method were correlated to surface chemical composition and thrombogenicity for treated and untreated surfaces, and represent a potentially fast and easily deployed quality assurance assay that is practical for medical device manufacture.

Introduction

Understanding and controlling surface properties is vital for creating high-performance medical devices. Materials interact with their environment through their surfaces, and surfaces have properties that are quite distinct from the bulk. A critical characteristic of a material's surface is its excess reactivity: molecules present in a surface are not in chemical equilibrium due to the fact that they have unsatisfied reactive sites presented to the free surface. This excess reactivity represents chemical potential, literally the potential to enter into a chemical reaction (primary or secondary) with another substance.

This chemical potential is referred to as *surface energy*. This excess energy associated with a surface results in the properties that we associate with surfaces, such as functionalization, adhesion, and contamination.

As a result of this excess energy, surfaces evolve with time at a rate that depends on the amount of available surface energy, the molecular mobility of the surface molecules, and the characteristics of the environment. Figure 1 shows a schematic of the evolution of surface energy with time. A freshly created surface has a high concentration of active sites, meaning that the rate of decay is most rapid immediately after creation. As reactive sites are consumed through reaction with the environment and/or decay due to reorientation, the decay rate decreases logarithmically and the residual energy approaches an asymptotic value characteristic of the material and the contaminants present in the environment.

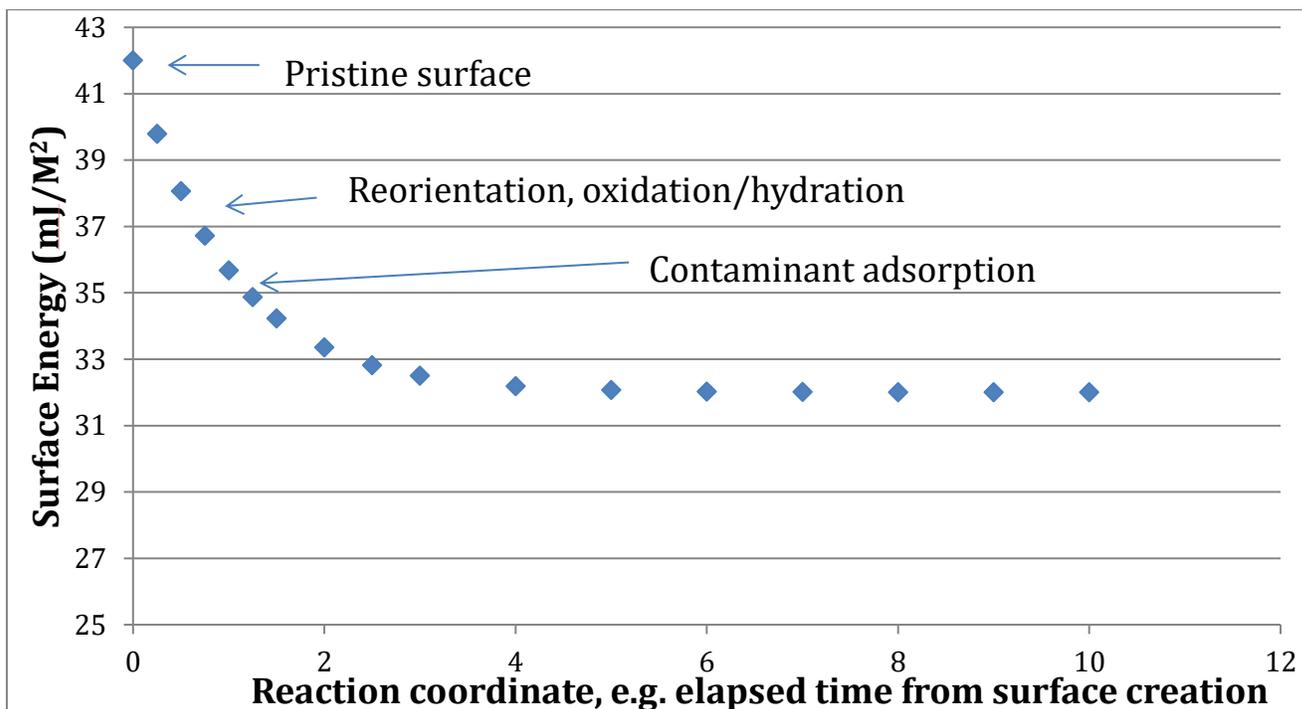


Figure 1. Evolution of surface free energy with elapsed time from surface creation. The ordinate (energy per unit area) and abscissa (elapsed time) in this figure are arbitrarily scaled; actual values depend on material, initial surface composition, and environment.

If we want to create a surface with specific properties through adhesion of a substance or through chemical grafting, this process has to be carried out while the surface to be modified has enough surface free energy to allow the reaction to occur. For example, we may plasma treat a polymer to promote adhesion of a coating. A plasma treated surface will decay in reactivity after plasma treatment in a manner similar to that shown in Figure 1. The coating must be brought into contact with the surface soon enough after plasma treatment so as to ensure that there remains enough residual reactivity to promote adhesion.

Surface energy is an important surface characteristic, and measurement of surface energy is a critical part of surface treatment and coating processes. Surface energies of liquids (termed *surface tension*) can be measured directly by measuring the force required to remove a platinum ring from a liquid (Tensiometry). Surface tension of solids has to be measured indirectly, either through measuring the heat evolved when gases or liquids are adsorbed onto a surface (e.g. inverse gas calorimetry), or much more commonly by measuring the physical interactions of a liquid with a surface (contact angle measurements). The basic principle of a contact angle measurement is shown in Figure 2.

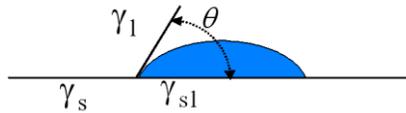


Figure 2. Liquid drop in physical equilibrium with a solid surface. γ_s = surface free energy, γ_l = liquid surface free energy (surface tension), γ_{sl} = residual surface free energy remaining at the interface after the liquid and solid have interacted.

When a liquid drop is brought into contact with a surface, the equilibrium shape that is assumed depends on the balance of forces existing at the solid-gas, liquid-gas, and solid-liquid interfaces. The balance of forces in the plane of the surface is expressed by the Young equation:

$$\gamma_s = \gamma_{sl} + \gamma_l \cos\theta$$

Which shows that the cosine of the liquid contact angle is directly proportional to the solid surface free energy. Figure 3 shows an example of the validity of this relationship demonstrated for a series of plasma treated polyethylenes [1].

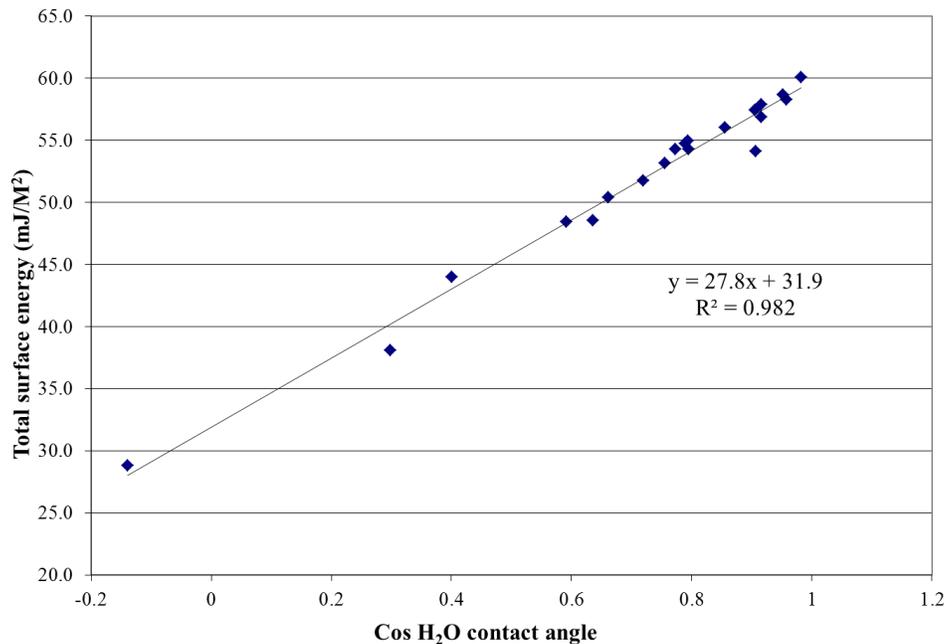


Figure 3. Relationship between total surface energy for a series of plasma treated polyethylenes and cosine of the water contact angle. From [1].

Figure 3 shows that for a homologous series of materials, a single contact angle measurement can be correlated to the total surface energy. Note that this relationship would not necessarily hold true for a comparison of dissimilar materials; however, for the purposes of process development or process control, precise measurement of surface energy can reduce to a relatively straightforward and simple contact angle measurement.

This paper discusses the use of a novel contact angle measurement process to evaluate the surface properties of small diameter medical tubing to confirm the presence of a functional coating. In this process, a very thin, flexible, super-hydrophilic coating (Sustain™) is chemically bonded onto the catheter surface. Sorption of water by this coating forms a fully hydrated surface with some properties approaching that of liquid water. This creates a surface which effectively inhibits thrombosis and biological fouling. Figure 4 shows electron micrographs of coated tubing cross sections.

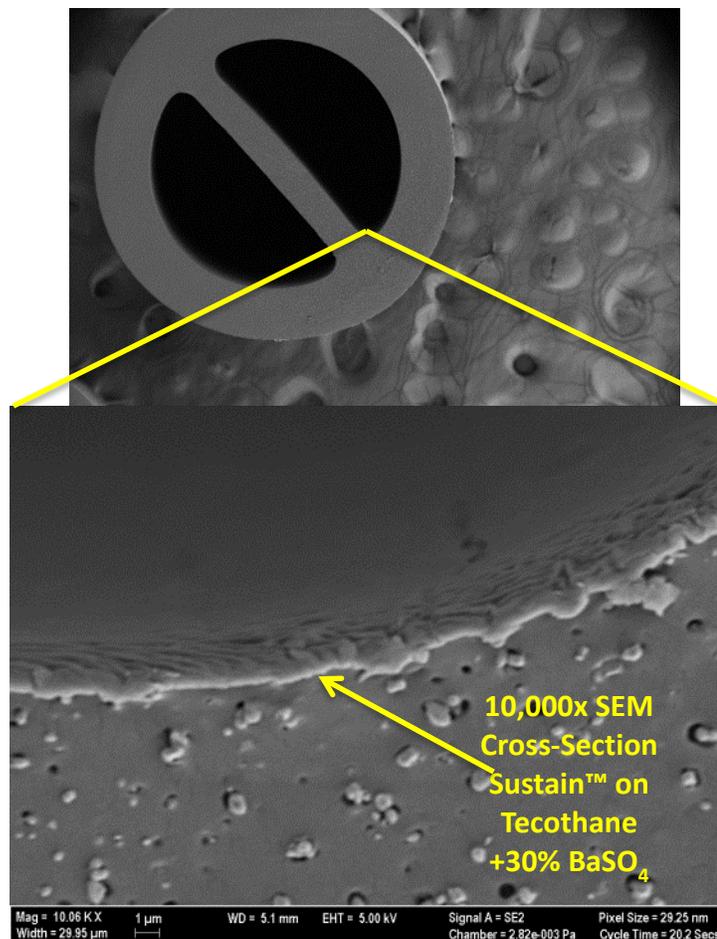


Figure 4. Cross section images of Tecothane tubing coated with Sustain™ hydrophilic coating.

The presence and performance of this coating needs to be verifiable in manufacture, yet is too thin to be visible to the eye. Its presence can be readily quantified via Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR) due to the characteristic infrared absorption bands of the Sustain™ coating, or Energy Dispersive X-ray Analysis (EDS) due to unique elemental content of the Sustain™ coating. However, simply determining its presence is independent of and not predictive of its performance as a super-hydrophilic surface modification. Qualification for vascular performance can be performed by human clinical trials, animal *in-vivo* studies, blood flow loops, and protein binding assays, but all of these techniques are time and resource intensive. It was postulated that because the performance of this coating is closely related to its wetting properties, a rapid interrogation of wetting properties could potentially not only identify the presence of the coating but replace the current protein binding assay as an indicator that the wetting properties were consistent with those of a super-hydrophilic coating.

In this work, coated samples produced in a series of coating trials were analyzed by a standard ¹²⁵I-fibrinogen Protein Binding Assay. In this assay, catheters are exposed to a solution of radiolabeled human fibrinogen under defined conditions; the amount of adsorbed fibrinogen is directly proportional to the count rate and is predictive of *in-vivo* performance. This data was correlated to contact angle measurements to establish the efficacy of a contact angle measurement as a quality assurance tool.

Experimental

The substrates used in this work were 6Fr “Double-D” 2- lumen extrusions used for vascular catheters (see Figure 4). The polymer was Lubrizol® Tecothane® 90A filled with 30% BiOCl microcrystals for medical device *in-situ* radioopacity (i.e. determination of proper vascular catheter placement in a patient by X-ray). Figure 5 shows images of this material at various magnifications.

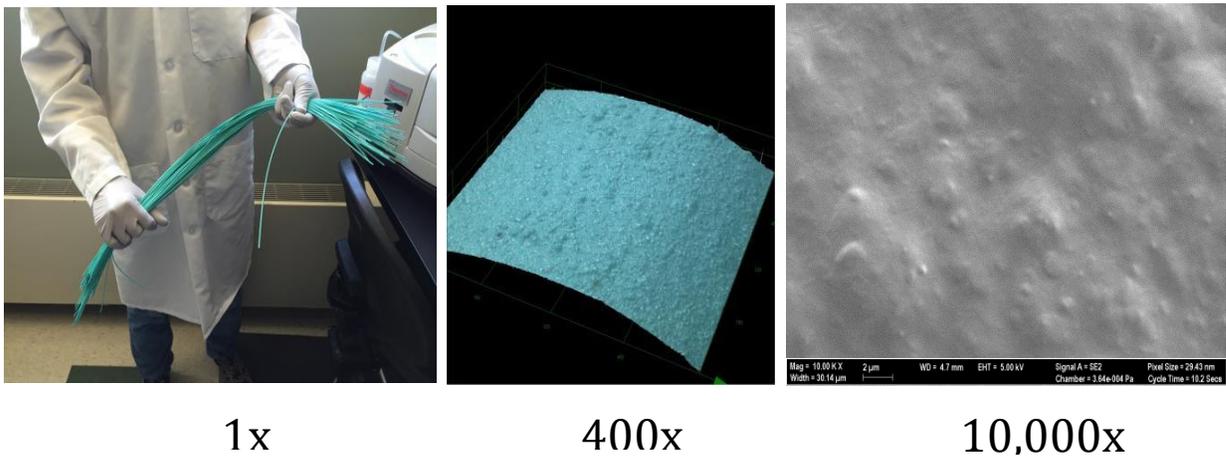


Figure 5. Lubrizol® Tecothane® 90A filled with 30% BiOCl microcrystals.

The experiment consisted of evaluation of 48 individual Sustain™ reaction batches on the Tecothane® tubing. These batches were part of a larger series of experiments consisting of small variations in proprietary chemistry for the purpose of process optimization.

Also included were 48 unmodified control samples. Samples were first analyzed for water contact angle using a Surface Analyst™ SA3001 handheld contact angle instrument (BTG Labs, Inc.). Figure 6 shows an example of a measurement. This instrument deposits a 0.6µl drop of liquid (in this case HPLC-grade water) via Ballistic Deposition: multiple 0.01 µl droplets are ejected onto the surface from a valve, coalesce on the surface to form a single drop, and then the contact angle is calculated from the volume and the average diameter of the resulting drop. This measurement requires about 2-3 seconds to obtain and is sensitive to subtle details of the molecular composition of the surface [2]. 10 contact angle measurements were obtained from each sample. ¹²⁵I-Fg assays were performed on the same (or similar) samples; the measured radioactivity was converted to amount of fibrinogen adhered in ng/cm². For radio assay measurements, n = 3 replicate measurements (3x 2cm extrusion per 1µCi/mL-Fg 37°C 1hr 60rpm). Contact angle results were correlated to fibrinogen assay results. It is important to note that the time and resources required to collect a ¹²⁵I-Fg assay datum are several orders of magnitude larger than that for the Surface Analyst™ SA3001.



Figure 6. Left: Surface Analyst SA3001 contact angle instrument. 6Fr tubing sample can be seen in the black fixture. Right: example of automated drop shape analysis on Ballistically Deposited 0.6µl water drop.

Results and discussion

Figure 7 shows the correlation of radio assay results with contact angle measurements. Non-fouling performance, defined as 500-100 ng/cm² adhered fibrinogen, correlated to water contact angles that were $\leq 88^\circ$.

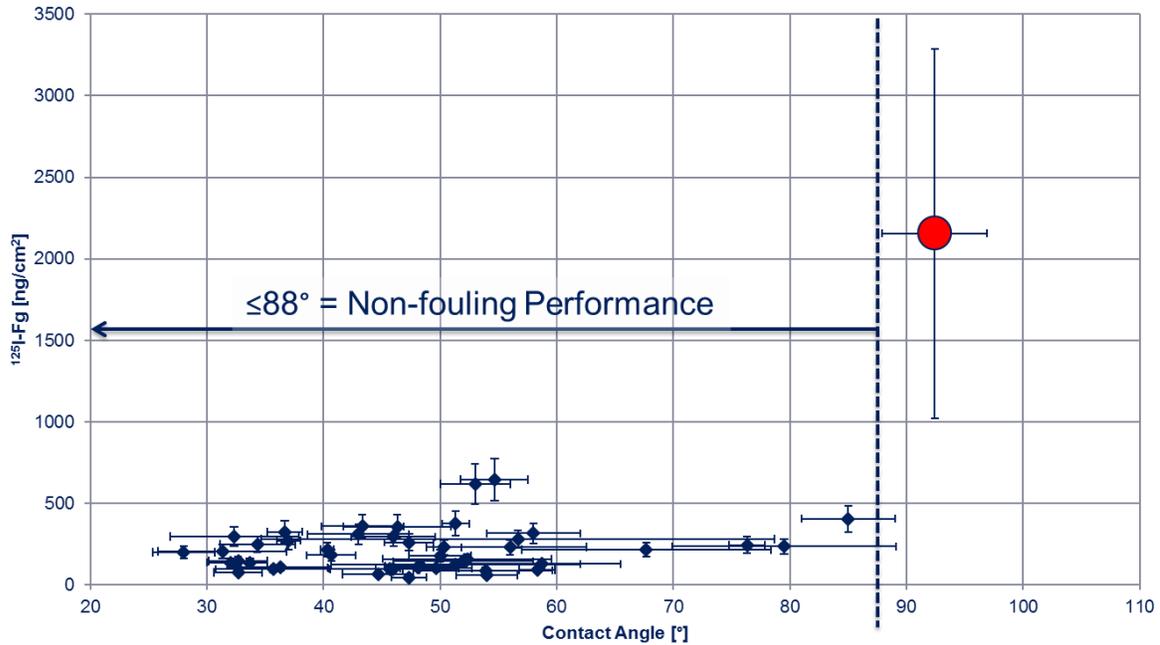


Figure 7. Correlation of radio assay for fibrinogen adhesion (ordinate) with water contact angle (abscissa).

The samples that demonstrated non-fouling performance showed a wide range of contact angles ($20^\circ \leq \theta \leq 85^\circ$), indicating a range of surface properties, but no significant difference in non-fouling performance. There are differences in the surfaces of these samples that were not reflected in radio assay performance. The origin of these differences is not yet clear but indicate a possible subtle change in the coating not related to thrombogenicity.

Conclusions

This data demonstrated a clear contact angle cutoff that defined acceptable vascular performance. Furthermore, it provided a clear go/no-go check that could be useful for manufacturing. The Surface Analyst™ SA3001 can perform a rapid, non-destructive, inexpensive binary evaluation of the presence/absence of the Sustain™ coating. There is currently too much inherent variation on the product test samples and the ¹²⁵I-Fg assay results to determine if the contact angle measurements can be used to predict “high resolution” *in-vivo* performance. However, the BTG SA3001 shows promise to replace the expensive and time consuming radio assay for qualification of Sustain™ performance.

References

1. R.G. Dillingham, B.R. Oakley, A.D. Gilpin, J. Adhesion Science and Technology 29 **9** 890-895 (2015).
2. M. Strobel, S.M. Kirk, L. Heinzen, E. Mischke, C.S. Lyons, J. Endle, D. Poirier, G. Dillingham, J. Adhesion