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Where the Rubber Hits the Road: Molecularly Tailored Films Bring Surface Enhancements for Biomedical Devices

When living cells confront a solid surface, they will interact with it in a variety of ways. This interaction is dynamic and complex, and is of profound significance in the design of biomedical devices that interface with tissues or microorganisms. To control and manipulate this process, high-tech coating of surfaces offers a range of benefits in the industrial, medical, and diagnostic realms. A number of companies are exploring various designs for coating materials in order to improve their performance and generate new biomedical products.

Pulsed plasma deposition technology

Coating technology is long established, with many established players (see Table 1). One company has adopted an unusual strategy in approaching this challenge. The Texas biotechnology firm **AeonClad Coatings, LLC**, a portfolio company of **Emergent Technologies, Inc.**, a life sciences commercialization firm, applies molecularly tailored films in the form of a plasma (that is, as an ionized gas) to produce

biological, electrical, chemical, and physical surface enhancements. The proprietary methods employ electrical currents in a vacuum to force the ionization process, followed by plasma polymerization. This allows creation of highly uniform and controlled surfaces, and has the advantages of a mild, solvent-free treatment protocol, highly controllable and applicable to virtually any solid surface. The thickness of the coating can be tightly adjusted and a wide range of surface groups employed, including carboxy groups, amines, epoxides, and alcohols.

In the tailoring process, the groups are polymerized to the surface, and then can be reacted with a number of different molecules, including biomolecules. This protocol is known as the variable duty cycle pulsed radiofrequency plasma technique.

Hydrogels produced by pulsed plasma polymerization

Hydrogels are materials composed of hydrophilic cross-linked molecules with a high water content, noted for their good bio-

Table 1 Coatings for medical devices

Company	Product	Comments
AeonClad Coatings (Austin, TX), www.aeonclad.com/	Surface coating technology	Plasma deposition
AST Products Inc. (Billerica, MA), www.astp.com/surface_plasma.html	BioLAST	Water-based coating technology
Carmeda AB (Upplands Vasby, Sweden), www.goremedical.com/	Carmeda [®] BioActive Surface (CBAS [®])	Bioactive coating mimics nonthrombogenic properties of endothelial lining of blood vessels
4th State Inc. (Belmont, CA), www.4thstate.com/index.htm	Develops plasma technologies for clients	Contractual agreements
Hydromer (Branchburg, NJ), www.hydromer.com/stent_coatings.htm	Stent coating process	Hydrophilic or hydrophobic coatings for drug delivery technology or stent coating
Medivas (San Diego, CA), www.medivas.com/Technology.html	Biodegradable polymers	Drug delivery, imaging by loading polymers with caged paramagnetic metal ions
Microfab (Plano, TX),www.microfab.com/ technology/biomedical/Stents.html	Coating systems	Ink based
Specialty Coating Systems (Indianapolis, IN), www.scscoatings.com/parylene_applications/ medical.aspx	SCS parylene medical coatings	Thin-film parylene conformal coatings
SurModics (Eden Prairie, MN), www.surmodics.com/technologies-delivery.html	Polymeric coating	Various medical applications

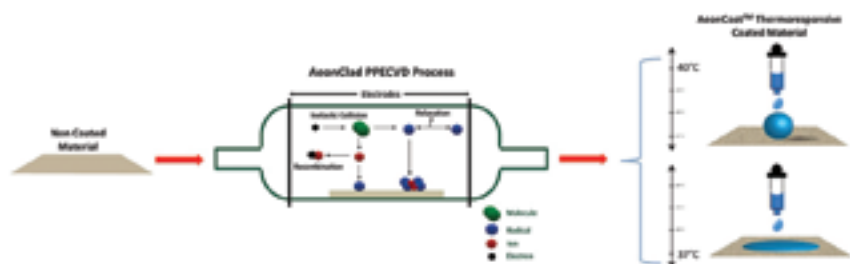


Figure 1 Hydrophobicity phase change demonstrated by **AeonClad's** thermoresponsive plasma polymerized films (hydrogel) over 3° temperature change. The **AeonClad** pulsed plasma enhanced chemical vapor deposition (PPECVD) process is commonly used to modify a wide variety of surfaces among the medical, biological, and industrial markets. This process is highly controllable and reproducible, demonstrating good control of film thickness and density of surface functional groups. Shown is a sample material treated with the PPECVD process. A new class of monomers was used to polymerize the surface, generating a thermoresponsive film on the material. The nature of the new surface (right panel) can transition from hydrophilic (bottom) to hydrophobic or less hydrophilic (top) when heat is applied, as shown with the addition of water onto the surface. This hydrophobicity transition can occur over as small as three degrees. The thermoresponsive films can be tuned for transition over a wide range of temperatures.

compatibility, satisfactory strength, and mass transfer rate. These qualities make them good candidates for a variety of biological applications.¹ One potential application of the technology is in the production of hydrogel films, generated through polymerization of select monomers such as acrylamides. By designing appropriate monomer mixtures, hydrogels can be adapted for use in drug delivery and tissue engineering, and as humidity sensors. **AeonClad** has employed pulsed plasma polymerization to develop hydrogels that behave thermoresponsively, for such tasks as controlled release rates in drug delivery systems.

Finding needles in the mass spectrometry haystack

Another promising application of the pulsed plasma deposition technology is the on-probe affinity capture (OPAC) matrix-assisted laser desorption/ionization (MALDI)-MS technique.² This procedure was developed to facilitate the analysis of low concentrations of biomolecules contained in complex biological samples. The technology is designed as a soft ionization technique used in mass spectrometry, permitting rapid capture on a probe surface of protein molecules from a cluttered biological soup. The first step is the formation on the probe of a plasma polymer with an amine functional group to which biotin is then immobilized, as shown in *Figure 1*. Then, a bioaffinity ligand coupled to avidin can be complexed to the biotin on the probe and reacted with a complex protein mixture containing the target protein. After washing away the unbound material, the probe with the target bound to it is then inserted in the mass spectrometer. It is especially convenient for analyzing serum samples, in which the most interesting proteins are difficult to isolate and present in picomolar concentrations. The on-probe attachment is efficient and saves steps and material that would otherwise be lost in the isolation and transfer process. The versatility of the pulsed plasma deposition technology means that many different molecules could be adapted to the system for rapid and extremely sensitive macromolecular analysis.

Protecting indwelling medical devices

Yet another significant application of the technology is the development of coated surfaces for indwelling medical devices.³ This is an active field of endeavor, with a number of companies offering different solutions to the complex medical issue of biofilm formation (see Table 1). Ordinarily, plastic lines, catheters, and other implanted materials have a tendency to become coated with bacteria, forming a matrix known as a biofilm. A component of this process is the aggregation of platelets on the surface of this matrix. **AeonClad** has carried out a series of in vivo experiments in which mice were implanted with stents with and without an EO₂V coating applied through the plasma surface modification technology. Platelet adhesion was measured using ¹¹¹In-labeled platelets, with the result that the uncoated stents bound 10 times as many platelets as the treated items.

Improved cell adhesion drives tissue engineering

Engineering of cells in vitro to build artificial organs is a burgeoning field. There has been a wealth of studies focused on designing scaffolds that will support the proliferation of natural structures that can replicate the function of the authentic organ. Materials developed for these applications range from synthetic materials such as poly(ethylene glycol) to natural polymers, including hyaluronic acid. These candidates are modified with photoreactive groups in order to form appropriate cross-links that constitute the scaffold.⁴ In general, hepatocytes demonstrate retention of liver function more readily when they are grown on matrices that mimic a more natural environment. Wang et al.⁵ investigated a well-defined synthetic peptide that can self-assemble into three-dimensional interweaving nanofiber scaffolds to form a hydrogel, PuraMatrix (3DM Inc., Cambridge, MA), as a substrate for hepatocyte culture with good retention of liver function.

Carlisle et al.⁶ employed the pulsed plasma deposition technique in order to fashion an adhesion construct consisting of an adhesion peptide linked to polyethylene glycol linked in turn to allyl-amine.

Several groups have investigated the adhesive properties of different biomaterials. Cai et al.⁷ have evaluated poly(lactic acid) (PLA) as a means of promoting effective attachment of esophageal cells on biomaterials. They subjected PLA to surface modification by coupling extracellular matrix (ECM) proteins on its surface to promote cell adhesion. All the results demonstrate the effects of surface functionalization on the biophysical responses of primary embryonic fibroblasts (PEFs) in cell adhesion. Fibronectin-immobilized PLA demonstrates promising potential for application as an engineered esophagus substitute. Two typical ECM proteins, collagen type I (COL) and fibronectin (FN), were immobilized on the PLA surface with the aid of glutaraldehyde as a cross-linker between aminolyzed PLA and ECM proteins.

Conclusion

Plasma-applied films are an unusual approach to resolving a wide range of problems in medical device manufacture. Many of these

questions have hampered development in the technology of coating surfaces since its inception. Because of their versatility, uniform performance, and ease of applicability, pulsed plasma deposition offers significant advantages over traditional medical coating technologies.

There are certain issues yet to be resolved, including inflammatory responses from hosts implanted with devices coated with the plasma applied films; this may require designing a range of compounds and evaluating their inflammatory potential when used to coat stents or other medical devices. While clinical trials are always demanding, the road to approval for medical devices is substantially easier than for drugs, suggesting that **AeonClad** will move its product development into the clinic within a fairly brief time frame.

References

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