An Evolution in Coatings

What began with drug-eluting stents has progressed to coatings with multiple actions and beyond. The following article, based on interviews with leading medical device coating companies, offers insight into the latest advancements.

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By Peter Cleaveland, West Coast Editor

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Many medical devices could not exist without today's advanced coating technology. Without lubricious coatings, catheters could not be threaded to where they are needed. Without drug-eluting coatings, arterial stents would rapidly succumb to restenosis. Without antibacterial coatings, the rate of nosocomial infection would skyrocket. Without the proper coatings for biocompatibility, any device contacting blood for more than a few minutes could lead to thrombi. Manufacturers are coming to believe that there are few medical devices that cannot benefit from the appropriate coating. This article will take a look at current trends in coating technology and give an idea of where things may go in the future.

Holding on to Your Heparin

Heparin has long been the choice for devices exposed to blood. Where the changes are taking place is in how the heparin is applied. A representative example is the MEDI-COAT system of Angiotech BioCoatings Corp. in Henrietta, NY, previously STS Biopolymers Inc., which consists of an inert, biocompatible polymer matrix used to entrap heparin complexes on the surface of medical devices. The heparin complex is released slowly over time when it is exposed to blood.
Yet, eventually, it is exhausted, points out Ih-Houng Loh, vice president of business development at AST Products Inc. in Billerica, MA, who suggests the process developed by Carmeda AB, which immobilizes the heparin with covalent bonding to the surface, shows some promise. "If you can immobilize heparin onto the surface, that's probably still the best approach," says Loh. "Because you are not going to deplete the heparin, it will stay on the surface all the time."

Margy Lydon, general manager, Angiotech BioCoatings, has a different opinion. “How long do you need it to be effective is the other question,” she says. “If you have a permanent implant, do you really need to have heparin on the surface for the lifetime of the device? I don’t know if anybody has an answer to that. I feel it warrants further investigation, and it really will depend on the specific device that you’re looking at.”

Biofilm Control

Any long-term penetration of the body, by a Foley catheter or an IV line, for example, creates a very real risk of morbidity or mortality due to the formation of biofilms, which can appear in just a few days and are difficult or impossible to eradicate once they become established. While antibiotics work well against free-floating (planktonic) bacteria, when those same bacteria colonize a surface, they produce a matrix of polysaccharides and proteins that protects them from antibiotics, antibacterial agents, and phagocytes.
This nasty little ecosystem can contain mixed populations of *Enterococcus faecalis, Staphylococcus spp, Streptococcus viridans, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Candida spp,* and others, depending on whether the surface involved is, for example, a central venous catheter or a urinary catheter.

Significant exchange of genetic material among different organisms can occur in such films, including those coding for antibiotic resistance. When bacteria are shed from the biofilm, they can move to other areas and lead to infections that can be treated with antibiotics but then recur because the biofilm that spawned them is unaffected. Biofilms can also lead to encrustations that can plug the lumen of a catheter.

The usual method for dealing with biofilms on catheters has been replacement. More recent approaches to combating biofilms center on rendering the surface toxic to colonizing bacteria or impeding their ability to adhere to the surface. Examples of the first approach include surface coatings containing silver compounds, antimicrobials such as benzalkonium (BAK) chloride, and such antibiotics as minocycline, rifampin, ciprofloxacin, and cephalosporin.

Another approach is to interfere with matrix formation by attacking the signaling mechanism by which bacteria coordinate their film-building activities and virulence, using so-called quorum sensing inhibitors (QSIs)[1]. Naomi Balaban at the University of California, Davis has done considerable work on the use of RNAIII inhibiting protein (RIP)[2,3], both alone and in combination with antibiotics and with the antimicrobial peptide dermaseptin b to inhibit production of biofilms and exotoxins by *S. aureus* and *S. epidermidis.*

Jeffrey B. Kaplan of the New Jersey Dental School in Newark has been investigating another approach: the use of an enzyme called dispersin B[4], which cleaves the polysaccharide molecules that hold a biofilm together. Research has shown that pre-

coating catheters with dispersin B prevented the formation of *S. epidermidis* biofilms, and, says Kaplan, it may also lead to a way to make the bacteria in existing biofilms more sensitive to conventional antibiotic therapy.

A number of companies have been formed to investigate and exploit various types of QSIs, although none seem to have products on the market, and one well-publicized firm essentially ceased operations in November. Bacterin International in Belgrade, MT, which did pioneering work with QSIs, has since abandoned this approach, according to President Guy Cook. “The earliest generation of QSIs were toxic,” says Cook, “so they couldn’t be used in medical devices.” Clinical testing revealed that these red sea algae-based materials were unsuitable for use in mammals. “There’s generations now that are non-toxic,” says Cook, “and there are companies ... that are working on QSIs, but the problem with QSIs is that it’s a new class of drug, and so you have a different regulatory hurdle to clear than you would with a relatively more simple antibiotic or antimicrobial.”

Cook points out another problem with QSIs: they’re expensive. “I think the number is 80 percent of medical devices are used for less than three days,” he says. “Everybody is thinking about implants, permanent implants, and things like that, but the reality is that the vast majority of medical devices are disposable &#151 IVs, Foley catheters, hemodialysis catheters &#151 and you need a low-dollar coating. And the QSIs are going to be expensive. If you put a $7 or $8 coating on a $10 catheter, you’ve got a very difficult problem in your marketing. If the standard of care is simply to pull that catheter and throw it away and put in a new one, can you really justify doubling or tripling or quadrupling the price of that catheter?”

Bacterin’s approach is to control drug delivery dynamics using more conventional antibiotics. “Our research has shown that if you can completely inhibit bacterial attachment for seven days or 14 days, essentially the bar has been set,” says Cook. “If you can attain essentially perfection, at least in our model for whatever period you’re looking at, why go to a new class of drug?” And, adds Angiotech BioCoatings Corp.’s Lydon, you can save money this way. “You would be able to extend the life of the catheter so it could be in place for a much longer period of time,” she says. “So, if you use one catheter vs. four catheters, you’re saving money. But where you’re really saving money is in preventing infections, because that’s where the costs really come into play. You have longer hospitalization stays, you have the cost of the treatment.”

Leaving When the Job Is Done

Restenosis has been a problem with metal stents from the beginning. The first approach to combating it was a durable coating that eluted drugs long enough for the vessel to heal and cover the stent with a layer of epithelial cells. “These coatings are getting more and more sophisticated,” says Charlie Olson, general manager of SurModics’ hydrophilic business unit in Eden Prairie, MN, “and medical device manufacturers are working with pharmaceutical partners to identify combinations of drugs that can be released from a single durable polymer system.”

The next step, he goes on, will be biodegradable coatings that will dissolve over time, and even more advances are on the horizon.
While drug-eluting coatings have reduced the rate of restenosis in most patients to single-digit levels, there are some classes of patients &#151 for example, diabetics &#151 in which a second procedure may be necessary. To address this, a new generation of stents is being developed. Actually made from drug-eluting biodegradable materials, these stents gradually dissolve, leaving nothing behind to interfere if a second procedure is ever required.

Physicians are also beginning to treat cases of vulnerable plaque &#151 “hot spots” in the vasculature that have the potential to close off an artery in the future and should be treated to prevent major problems down the road. Here again, it’s best if the stent disappears after it has done its job.

Thin Is In

As devices become smaller in profile and more intricate, the thinness of the coating becomes critical. “As devices are used in more challenging anatomy &#151 and they’re trying to access tighter, more distal lesions &#151 devices are constructed with thinner walled, more flexible materials and often have limited pushability, which is one of their issues,” says Olson. “They’re trying to make a small, low-profile device to get as far as they can, to navigate through that most tortuous anatomy, but to complement that, they absolutely need to have the most advanced hydrophilic coating.”
Says Lydon: “Some of the coronary stents have very intricate designs, so manufacturers are becoming more sophisticated in the ways in which they’re applying coatings to these.”

Mikki Larner, marketing director at 4th State Inc. in Belmont, CA, says: “I see surface modification via plasma processes as growing. The ability to modify the surface without affecting the bulk properties of the material being modified because of the ultra-thin layers, sometimes monomolecular layer, created in plasma processes is the primary driving force. Inherently, coatings deposited by plasma deposition processes are covalently bound, eliminating or greatly minimizing problems of the coating sloughing or flaking off. A dislodged particle a few angstroms thick is less likely to be a problem than particles microns thick from a conventional coating process. Plasma processes have the potential to covalently attach simple or complex molecules, possessing desirable biomedical interaction and properties, to medical devices without changing the bulk properties of these devices.”

What’s Ahead

Perhaps the biggest changes in coating technology will come from the combination of several activities in one coating: multi-functional coatings.
It’s possible, says Olson, “to provide both a hydrophilic surface for the delivery of that catheter and ultimately having a direct delivery function coming off the stent,

or possibly adding a two-step function, maybe a heparin coating over the top of the drug delivery if you want to make sure once it's been placed that the stent doesn't have a thrombus event. You can put a clot management program together and then ultimately have a long-term therapeutic event, and you want that drug to elute from 30 days out to as much as one to three years, which we're doing for ophthalmology."

Ih-Houng Loh suggests that another area to explore is the application of coatings in tissue, what he calls "a combination of a pharmaceutical with tissue engineering." He cites work at his own company in developing a new dry eye solution.

Bacterin, says Cook, is working on combination coatings as well. Some combine silver with antibiotics, although, says Cook, orthopedic surgeons are not well disposed toward silver. "Orthopedic surgeons don't like silver because it can discolor bone," he explains. "So, when they go in to repair bone after a year, it's turned black, and even though there's no real damage, black bone's not good." Bacterin is currently developing coatings that combine antimicrobials with pain management and osteoinductive materials, "so if we want to promote bone fusion into a hip or knee, we have that as well."

FDA Scrutiny

The question of FDA regulation inevitably arises as coatings increase in functionality, combination coatings become more common, and drug elution becomes a standard feature of more types. Will the agency look at the newer combination coatings as medical devices or as pharmaceuticals? And will it become more aggressive since the latest round of pharma-scandals?
4th State Inc.'s Larner thinks not but says it's still possible. "Nobody knows after this latest round how much more careful they will be. Right now everyone is waiting for the shoe to drop."

Angiotech BioCoatings Corp.'s Lydon feels that the agency's thought process is: "if you're trying to prevent something from happening, such as restenosis, the primary function of the device, say a stent, is still to keep the artery open, and the drug is there to help prevent restenosis from occurring, so the primary function of that device is still as a device." She adds, "I think that FDA is evolving in their thinking and their approach just as the technology is advancing. They're trying to figure out how to review these."

Olson at SurModics says, "the FDA has established a new OCP group (Office of Combination Products) to coordinate the review of hybrid drug-device products because depending on the primary mode of action, the combination product may be subject to both drug and device regulations."

Summary

Coatings for medical devices are becoming available with multiple therapeutic effects and are coming in thinner layers that hold more and more tightly to device surfaces. The future holds the promise of even greater functionality.

ONLINE

For additional information on the technologies discussed in this article, see *Medical Design Technology* online at www.mdtmag.com or the following websites.
&#149 www.angiotech.com
&#149 www.astp.com
&#149 www.bacterin.com
&#149 www.4thstate.com
&#149 www.surmodics.com/home.aspx

References

1. Cook, Gary, 2001. "Quorum Sensing Inhibitors in Medical Devices." SurFACTS in Biomaterials, 6 (2)

2. Balaban, Naomi et al, 2004. "A Chimeric Peptide Composed of a Dermaseptin Derivative and an RNA III-Inhibiting Peptide Prevents Graft-Associated Infections by Antibiotic-Resistant Staphylococci." Antimicrob Agents Chemother, 48 (7)

3. Balaban, et al, 2001. "Regulation of Staphylococcus aureus Pathogenesis via Target of RNAIII-activating Protein (TRAP)." J. Biol. Chem., 276 (4)

4. Kaplan, Jeffrey, 2004. "Genes Involved in the Synthesis and Degradation of Matrix Polysaccharide in Actinobacillus actinomycetemcomitans and Actinobacillus pleuropneumoniae Biofilms." Journal of Bacteriology, 186 (24).