



Convergent Medical Devices for Treating Disease: Solid State Chemistry Analytical Challenges for Drug-Device Combinations



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Speaker: Cynthia A. Maryanoff, Ph.D.

Cordis, a Johnson and Johnson Company

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As a newcomer to the AWIS meetings, I really had no idea what to expect. I tried to keep my speculations about what the night would hold to a minimum, and I found that the women, with whom I was fortunate to speak, blew me away. My group of colleagues from the University of Pennsylvania arrived early, and we sat down with the speaker. We talked about a wide range of topics: from small molecules and new types of biological methods for drug design to what it's like to be a woman in chemistry. As the conversation progressed, all of my original nerves were eased, and I began to really look forward to Dr. Cynthia Maryanoff's presentation and her perspective as a distinguished scientist from Johnson & Johnson.

Alice Marcy introduced the speaker, and I could barely scribble down all of the various awards and honors achieved by Dr. Maryanoff. What was even more impressive to me was the breadth of positions of authority she held at various corporations within the pharmaceutical industry. After getting her Bachelor's degree from Drexel University in 1972, Dr. Maryanoff pursued a Ph.D. in Organic Chemistry from Princeton University. After a short post-doctoral position, she joined Smith-Kline and eventually settled in with McNeil, the first Johnson & Johnson (J&J) subsidiary. At McNeil she served as the global head of Chemical and Pharmaceutical Development. In 2004 she moved to Cordis, a medical device unit of J&J, where she remains today as a Distinguished Research Fellow and the head of Solid State Chemistry.

Dr. Maryanoff began her talk with a few words of advice for which I was grateful to hear as a young graduate student just beginning my career. She discussed her life as a chemist, how times have changed, and the ups and downs of the job market. Mixed with witty humor were some valuable pieces of information for graduate students and others entering the job market: you must network, you must start now, and the importance of being a well-rounded scientist. She painted an elegant picture of new technologies conceived and executed by J&J. In addition, she described the chemical evaluation used to develop Cypher and NEVO, two unique cardiac stents used in the treatment of blocked arteries. The concept behind the stent is simple: send a deflated tube through the femoral artery, place it directly within

the area of blockage, and inflate to allow blood flow; add some protective polymer coatings to bind the metal, and an immiscible dual polymer and drug layer to aid in the healing process and you are done. Another thing I learned that night from Dr. Maryanoff: it is never that easy, especially when dealing with the FDA and clinical trials. In order for the stents to be used in humans one of the most important regulations is consistency; can you make the same immiscible coating every time? Even if you figure out a way to make it uniformly and consistently, how do you prove that your stent is worthy to be on the market?

In thinking about this problem, the J&J team of brilliant scientists decided to develop their own technology to assess the problem using analytical chemistry methods. Using confocal raman to determine the spatial resolution as well as depth, the release profiles were obtained for the drug from the exterior of the stent (the part that will lie on the internal wall of the artery). The drug is released from the polymer and drug layer into the artery to promote healing. It was shown that after 60 hours, the areas that had drug (based on confocal raman imaging) had dissipated over time. Using Atomic Force Microscopy (AFM), the depth of the remaining pores could be assessed using very high microscopic resolution. The last aspect of this project that I found astounding was the use of previously obtained data to speculate on how the drug from the bottom of the polymer and drug coating was rising to the top. It was determined experimentally that the drug on the surface elutes first leaving behind a pore; the drug pockets close to the surface rise up and release the drug creating new pores; and the drug pockets that were deep inside the coating use these newly formed internal cavernous pores to their advantage. The drug is released into the pore and travels through the empty space to the artery. This exemplifies the thoughtful science that went into the development of Cypher. The use of two immiscible polymers allows the pushing and movement of the drug pockets to the surface.

After the technology had been developed for Cypher, the next project for J&J was NEVO. The main difference between the two stents is the use of a biodegradable polymer. The idea behind coating the stent with the drug sirolimus is not to treat the original plaque build up but rather to use the drug's antiproliferative properties to prevent restenosis. Once the healing process has occurred, the drug and the polymer are no longer necessary. NEVO makes use of a biodegradable polymer that is no longer present after 75 days. Unlike Cypher, the polymer and drug amalgam is inside small circular holes within the metal framework. Despite the structural differences, the analytical evaluation of NEVO was similar to Cypher; the drug elution curves were obtained using HPLC and correlated to a decrease in molecular weight, to show that the stent was decreasing in mass in direct proportion to the quantity of drug being released.

J&J designed a test that was unique to NEVO to assess the degradation of the polymer coating during the insertion process. A hard plastic catheter course was invented by J&J, which is now considered a scientific standard, to mimic the worst-case scenario path traveled by the stent. After many cycles, the polymer coating was checked for integrity, and any damage seen in NEVO was attributed to the original insertion and not to the movement in the catheter. Lastly, Dr. Maryanoff discussed the final hurdle for NEVO: the possibility for the polymer to plump up or fall out. A series of novel testing machines were developed with the help of the Princeton Chemical Engineering department, and the NEVO stent was shown to be consistent and nonintrusive to other biological functions once inside the artery.

Overall, the novel chemical testing that had to be designed and executed for the stents to be marketable drugs amazed me. Dr. Maryanoff and her team developed elegant analytical methods that enabled many companies to quickly follow suit and ride on the coat tails of J&J. As a new member of AWIS-PHL, I thoroughly enjoyed the scientific presentation, but even more, the conversation I had with Dr. Maryanoff after the talk. As a second year graduate student, I was encouraged by her advice to take action now and begin networking and developing myself as a well-rounded chemist. Originally, I was nervous about attending, but now I am anxiously awaiting the next chance to talk to another woman as unique and insightful as Dr. Cynthia Maryanoff.