SIMULATING THE RELEASE MECHANISM IN DRUG-ELUTING STENTS

Engineers at Boston Scientific are revolutionizing medical device designs. Their recent simulations of drug-eluting stents provide an understanding of the drug release mechanism by tying experimental findings to a computational model.

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Treating arteries in the heart that have been blocked by plaque is a common challenge for medical professionals. Known as stenosis, this condition restricts blood flow to the heart, resulting in symptoms such as shortness of breath and chest pain. It is sometimes resolved using stents, which are small, mesh-like tubular structures designed to treat blocked arteries. They are usually placed in the coronary artery and expanded with a balloon catheter to keep the artery open, as depicted in Figure 1.

While stents are successful at holding arteries open, an artery can re-narrow because of excessive tissue growth over the stent. This is called restenosis and is the body's natural healing response, but it can actually impede recovery. Thus, drug-eluting stents were developed to deliver medicine — which acts to reduce cell proliferation and prevent the unwanted growth — into the artery tissue. These contain a coating composed of medicine and a polymer matrix designed to provide a controlled delivery; each strand of the stent mesh is surrounded by this coating (see Figure 1C). Stent designs have improved dramatically in recent years in an effort to reduce restenosis rates, but much remains unknown regarding the release process.

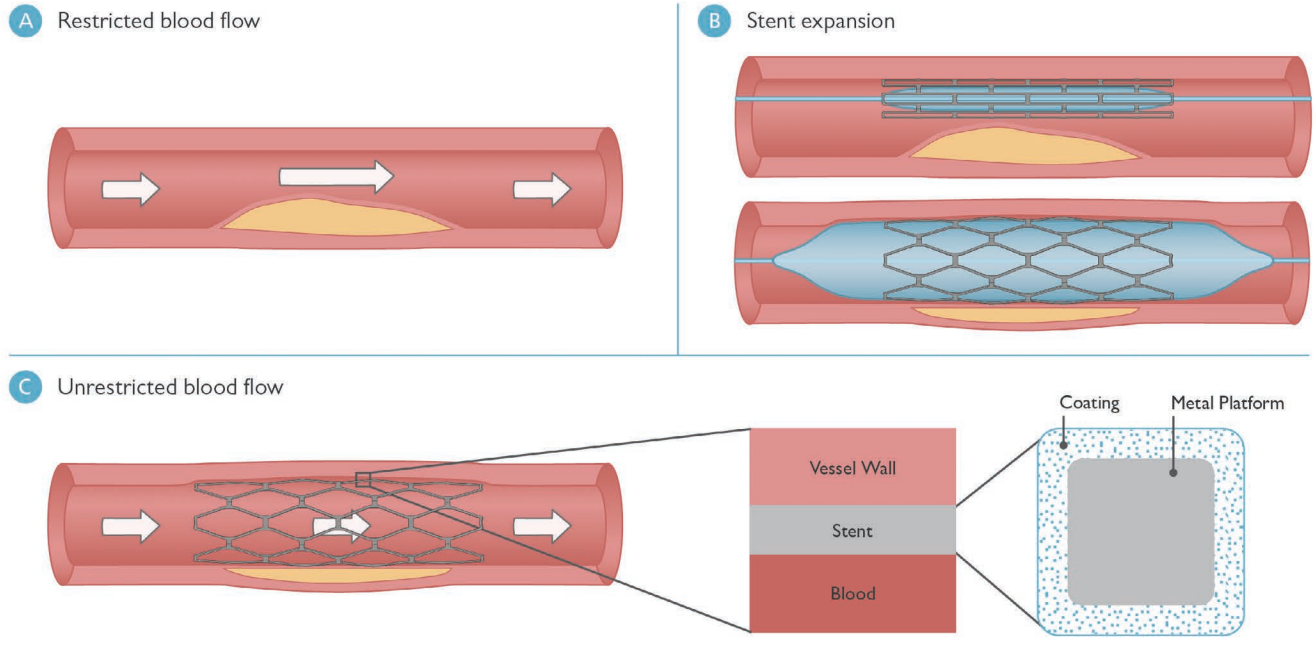

FIGURE 1. A. Restricted blood flow in a vessel; B. Stent insertion and expansion; C. Normalized blood flow (left), arrangement inside a blood vessel (center), and cross-section of a stent strut (right).

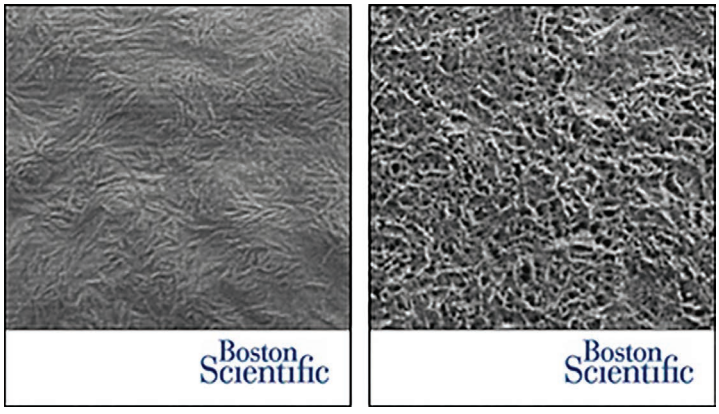

FIGURE 2. The coating microstructure prior to release (left) and the interconnected empty pores surrounded by the polymer matrix following the release from the coating (right).

DRUG RELEASE BEHAVIOR

Travis Schauer, Ismail Guler, and a team of other engineers at Boston Scientific, a company that develops devices and technologies to diagnose and treat a wide range of medical conditions, have sought to better understand the mechanism of medicine release with computer simulation. Using COMSOL Multiphysics®, they have modeled a stent coating to investigate the release profile (the rate at which the medicine diffuses out of the coating and into the vessel tissue) and the influencing factors. They used the Optimization Module in COMSOL to fit their simulation as closely as possible to experimental data curves. Schauer explained, "By gaining knowledge of the underlying mechanisms and microstructure of the coating, we are able to understand the release process and tailor it to achieve a desired profile." Ultimately, this may lead to a level of control over the release that has until now been impossible.

The stent coating that Schauer and Guler modeled is a microstructure with two phases: a medicine-rich, surface-connected phase and a phase with drug molecules encapsulated by a polymer. The development of this microstructure is affected by the solubility of the drug, the drug-to-polymer ratio, and the processing conditions during manufacturing. When the stent is inserted into an artery, the medicine-rich phase quickly dissolves and diffuses into the tissue, leaving behind interconnected cavities (pores) in the polymer coating, as depicted in Figure 2. Meanwhile, the molecules encapsulated by the polymer diffuse more slowly.

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MODELING MEDICINE DELIVERY

Schauer and Guler idealized the complex geometry of the coating microstructure: in their model, the coating consists of a pattern of cylindrical pores filled with solid medicine surrounded by a polymer shell containing both the dissolved drug and solid drug encapsulated by the polymer. The molecules diffuse radially and axially, and the microstructure geometry only changes radially — at the boundary between shell and pore. Therefore, a two-dimensional axisymmetric model (see Figure 3) was sufficient.

Using COMSOL has allowed Schauer and Guler to easily customize their model. "We focused on understanding the transport phenomena at hand instead of spending time on cumbersome programming," Schauer remarked. "We customized the underlying equations according to our needs directly through the user interface." They performed simulations for two release profiles, in vitro and in vivo cases, seeking a description of the cumulative release of the medicine. "We wanted to understand why certain release profiles were observed," said Guler and Schauer. "We compared experimental data to the release profiles generated in our simulations to confirm our findings."

Schauer and Guler tracked both the dissolution of solid drug and the diffusion of dissolved drug. As it dissolves within the pores, the pores fill with liquid media from the surrounding tissue. The medicine has a different solubility limit in the liquid

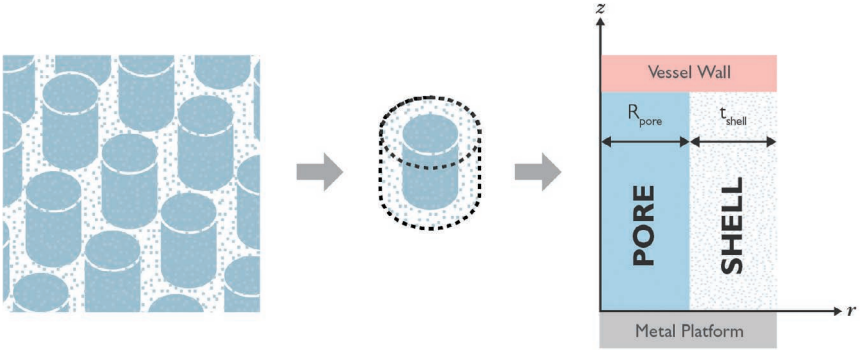

FIGURE 3. Idealized microstructure of the stent coating. A single pore-shell was modeled (center). The labels R_{pore} and t_{shell} (right) refer to the pore radius and the shell thickness.

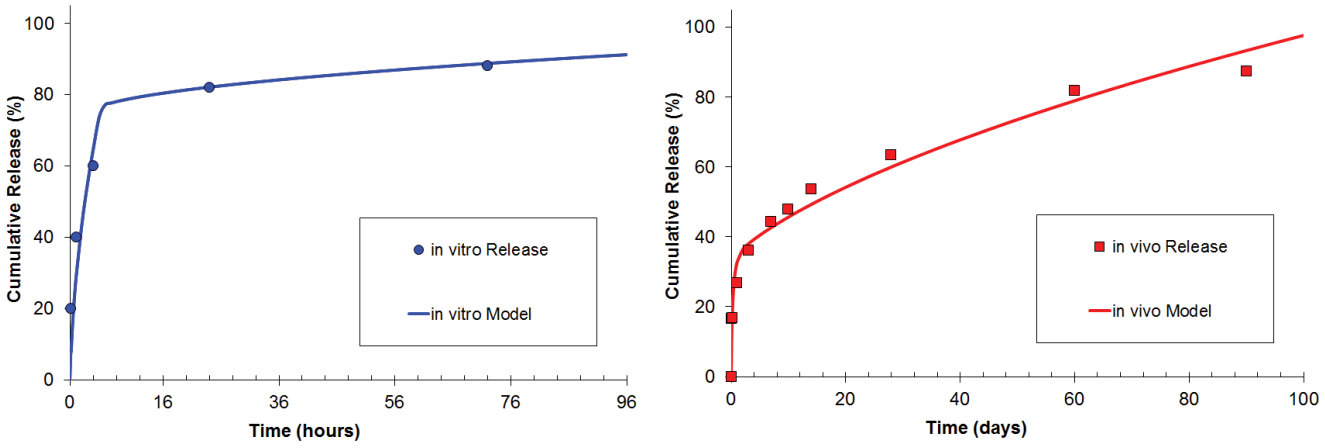

FIGURE 4. Simulation results alongside experimental results showing release curves for the in vitro and in vivo cases.

media than it does in the polymer, which results in a discontinuity in the dissolved medicine concentration at the interface between pore and shell. As Guler explained, "The appropriate interface conditions were easily implemented in COMSOL using a stiff-spring method, which ensured the continuity of the diffusive flux." The customizable boundary conditions available in COMSOL Multiphysics allowed Schauer and Guler to easily add the necessary terms.

Certain model parameters had to be estimated because they were 'effective' values that could not be measured directly, such as the polymer shell thickness. Another was the retardation coefficient that accounts for the twisted shape and constriction of the pores, steric effects, and other potential influences on the diffusion through the pores. These parameters were refined using the Optimization Module. Schauer and Guler made an initial guess for the shell thickness and retardation coefficient, based on experimental kinetic drug release (KDR) data. They compared the model's predicted release profile to the KDR curves. Based on the results, the Optimization Module modified the shell thickness and retardation coefficient to obtain the best fit between the model results and the experimental data. The release curves (see Figure 4) confirm that the medicine in the pores releases quickly, while the dispersed molecules in the shell diffuse slowly through the encapsulating polymer. The results in Figure 5 depict the faster dissolution and diffusion in the pore, compared to the shell.

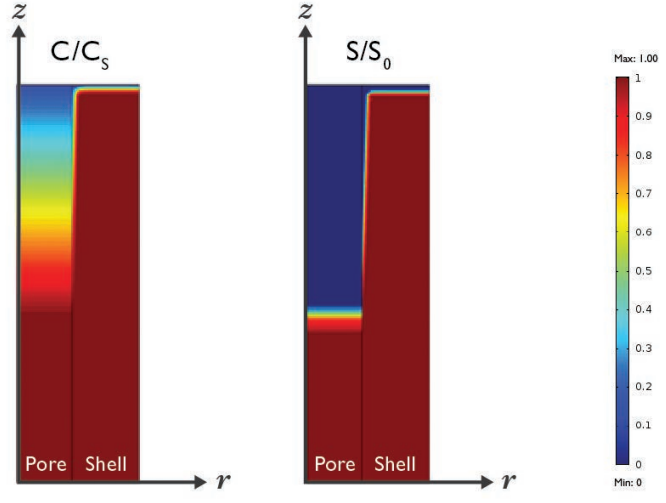

FIGURE 5. Predicted medicine concentration for the in vitro case at time = 2 hours; C/C_s = dissolved drug concentration/solubility limit (left), S/S_0 = solid drug concentration/initial solid drug concentration (right).

FUTURE STENT STUDIES

Reducing restenosis rates is an ongoing goal for doctors and medical professionals that is greatly aided by drug-eluting stents. The modeling approach employed by Schauer and Guler offers valuable insight into one type of release mechanism. Although the simplified micro-structure model does not capture all the details of the release curves, the pore-shell simulation showed good agreement, lending confidence to the appropriateness of their idealized model.

Researchers at the U.S. Food and Drug Administration (FDA) are developing even more comprehensive simulations, based on diffuse-interface theory, to examine the microstructure formation. These models aim to explain the relationship between processing, microstructure, and release behavior in controlled systems. Ultimately, simulation has the potential to give medical device designers more control over the delivery process, and improve treatment for patients with cardiovascular disease. ■