Many vaccines, from those for measles to COVID-19, require a series of multiple shots before the recipient is considered fully vaccinated. Researchers at the Massachusetts Institute of Technology (MIT) have now developed core–shell microparticles that can be tuned to deliver their payload at different time points, which could be used to create “self-boosting” vaccines.

In a recent issue of *Science Advances* (https://www.sciencemag.org/doi/10.1126/sciadv.abn5315), the researchers described how these particles degrade over time, and how they can be tuned to release their contents at different time points.

“This is a platform that can be broadly applicable to all types of vaccines, including recombinant protein-based vaccines, DNA-based vaccines, even RNA-based vaccines,” says Ana Jaklenec, a research scientist at MIT’s Koch Institute for Integrative Cancer Research. “Understanding the process of how the vaccines are released, which is what we described in this paper, has allowed us to work on formulations that address some of the instability that could be induced over time.”

This approach could also be used to deliver a range of other therapeutics, including cancer drugs, hormone therapies, and biologic drugs, the researchers say.

The particles are made from poly(lactic-co-glycolic acid) (PLGA), a biocompatible polymer that has already been approved for use in medical devices such as implants, sutures, and prosthetic devices. To create cup-shaped particles, the researchers create arrays of silicon molds that are used to shape PLGA cups and lids. Once the array of polymer cups has been formed, the researchers employed a custom-built, automated dispensing system to fill each cup with a drug or vaccine. After the cups are filled, the lids are aligned and lowered onto each cup, and the system is heated slightly until the cup and lid fuse together, sealing the drug inside.

This technique, called SEAL (StampEd Assembly of polymer Layers), can be used to produce particles of any shape or size. The researchers wanted to learn more about how the particles degrade over time, what causes the particles to release their contents, and whether it might be possible to enhance the stability of the drugs or vaccines carried within the particles.

“We wanted to understand mechanistically what’s happening, and how that information can be used to help stabilize drugs and vaccines and optimize their kinetics,” Jaklenec says.

Their studies of the release mechanism revealed that the PLGA polymers that make up the particles are gradually cleaved by water, and when enough of these polymers have broken down, the lid becomes very porous. Very soon after these pores appear, the lid breaks apart, spilling out the contents.

“We realized that sudden pore formation prior to the release time point is the key that leads to this pulsatile release,” first author Morteza Sarmadi says. “We see no pores for a long period of time, and then all of a sudden we see a significant increase in the porosity of the system.”

The researchers set out to analyze how a variety of design parameters, including the size and shape of the particles and the composition of the polymers used to make them, affect the timing of drug release. They found that...
particle size and shape had little effect on drug release kinetics. This sets the particles apart from most other types of drug delivery particles, whose size plays a significant role in the timing of drug release. Instead, the PLGA particles release their payload at different times based on differences in the composition of the polymer and the chemical groups attached to the ends of the polymers.

“If you want the particle to release after six months for a certain application, we use the corresponding polymer, or if we want it to release after two days, we use another polymer,” Sarmadi says. “A broad range of applications can benefit from this observation.”

The researchers also investigated how changes in environmental pH affect the particles. When water breaks down the PLGA polymers, the byproducts include lactic acid and glycolic acid, which make the overall environment more acidic. This can damage the drugs carried within the particles, which are usually proteins or nucleic acids that are sensitive to pH. The researchers are now working on ways to counteract this increase in acidity, which they hope will improve the stability of the payload carried within the particles.

To help with future particle design, the researchers also developed a computational model that can take many different design parameters into account and predict how a particular particle will degrade in the body. This type of model could be used to guide the development of the type of PLGA particles that the researchers focused on in this study, or other types of microfabricated or three-dimensional printed particles or medical devices.

“We believe these core–shell particles have the potential to create a safe, single-injection, self-boosting vaccine in which a cocktail of particles with different release times can be created by changing the composition,” says Robert Langer, the David H. Koch Institute Professor at MIT and a member of the Koch Institute. “Such a single-injection approach has the potential to not only improve patient compliance but also increase cellular and humoral immune responses to the vaccine.”

Source: Massachusetts Institute of Technology