RESEARCH NEWS

Next-generation encapsulation technology

FDmiX: Fast, robust series production of nanoparticles

Nucleic acid-based medications such as mRNA vaccines offer tremendous potential for medicine and are opening up new therapeutic approaches. These active ingredients must be enclosed inside nanoparticles to ensure that they get to where they are needed inside the body's cells. The Fraunhofer Institute for Production Systems and Design Technology IPK and FDX Fluid Dynamix GmbH have worked together to develop a technology platform for the production of nanoparticles that can achieve particle quality and stability at levels previously out of reach: FDmiX, short for Fraunhofer Dynamic Mixing Technologies. Swiss chemical and pharmaceutical company Lonza has now licensed the technology for its own good manufacturing practice (GMP) production activities.

RNA and DNA, both nucleic acids, are not only found in cells; they can also be components of medications. One common example widely known from the coronavirus pandemic is mRNA vaccines. Medical professionals the world over are very hopeful about nucleic acid-based active ingredients, which offer potential as therapies for diseases that were previously difficult to treat, including some forms of cancer. However, safely and effectively transporting these sensitive nucleic acids to the cells, where the messages they carry can be translated into proteins, has proven to be a significant challenge thus far. A protective envelope is needed to get the sensitive active ingredient into the cells. These nanoparticles are produced using fluid mixing processes. Very thorough, rapid mixing is necessary to produce particles of the requisite quality. Impinging jet mixers (also known as T-mixers or Y-mixers) are available for industrial-scale applications. They enable high throughput, but at the expense of mixing quality.

Better, faster mixing

In the Fraunhofer Dynamic Mixing Technologies (FDmiX) platform, Fraunhofer IPK and FDX Fluid Dynamix GmbH have managed to bridge the gap between mixing quality and throughput. The FDmiX platform allows for consistently high mixing quality at any scale, from the lab right up to mass production. It has already successfully passed tests aimed at production of lipid and polymer nanoparticles and of nanoemulsions. As extensive testing has shown, the mixing quality of the FDmiX technology platform is superior to the systems that have been available to date, enabling production of particles at previously unattainable levels of quality. The system is also impressive in terms of its scaling capability, as encapsulation can take place with volume streams ranging from

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5 ml/min to 1.5 l/min without affecting the particle properties. Lonza, a global development and production partner to the pharmaceutical, biotech, and neutraceuticals markets, has licensed the patented FDmiX technology and is already using it.

"Human cells defend themselves against foreign genetic material. That's why the mRNA active ingredients have to be enclosed inside nanoparticles. So the particles act as a protective envelope, encapsulating the substance until it has entered the cell inside the body," says Christoph Hein, head of the Ultra- and High-precision Technology division at Fraunhofer IPK in Berlin. To be able to produce the nanoparticles, the active ingredient dissolved in a buffer has to be mixed with another solution, such as a lipid solution. Once the two liquids have been combined, lipid nanoparticles are formed which in turn form a lipid envelope around the active ingredient. "With the FDmiX platform, we can produce significantly smaller and more homogeneous particles and even adjust their size. FDmiX lets us produce mixtures of a previously unattainable level of homogeneity with very short mixing times. That's relevant because the mixing quality not only determines the quality of the nanoparticles, but ultimately also how effective they are."

Clever nozzle design leads to homogeneously mixed nanoparticles

But how can a high and consistent mixing quality be combined with throughput? The centerpiece of the FDmiX platform is an OsciJet nozzle from FDX Fluid Dynamix GmbH. Inside the nozzle, a jet of liquid is positioned on one of the sides of the main chamber. Before leaving the nozzle, a small part of the jet is deflected into a side channel. At the end of the side channel, it meets the main jet again and pushes it to the other side. This causes the main jet to oscillate continuously from one side to the other at a high frequency. In this way, the jet of lipid solution oscillating through the nozzle meets the stream of the mRNA active ingredient at a perpendicular angle, creating a homogeneous mixture with nanoparticles of uniform size. In tests of conventional impinging mixers (also known as T-mixers or Y-mixers), by contrast, the lipid solution and mRNA active ingredient collide before flowing together through the same channel. This creates a dynamic vortex, resulting in inhomogeneous particles of lower quality. "In encapsulation tests on mRNA in lipid nanoparticles using different mixers and flow rates, FDmiX generated smaller particles with significantly lower size distribution compared to a T-mixer at the same flow rate," Hein explains. In tests, the project partners produced nanoparticles about ten to 20 percent smaller than those produced using a T-mixer. They also had significantly smaller size distribution and high encapsulation efficiency and particle integrity.

Large quantities of nanoparticles are needed during the clinical phase and the subsequent production stage. Here as well, the technology from Fraunhofer IPK and FDX Fluid Dynamix GmbH is impressive: The two project partners developed and tested mixers for various pressure and flow rates. The smallest mixers (FDmiX XS) can work at flow rates under 5 milliliters per minute, while the largest (FDmiX XL) can work at more than 1.5 liters per minute.

Broad range of applications for FDmiX nanoparticles

The nanoparticles produced in this way can be used for a wide range of applications, well beyond encapsulation of mRNA and stabilization of vaccines. For example, this technology can also be used in cardiology for cardiac catheter coatings. When a balloon catheter is expanded during an examination, nanoparticles are absorbed into the arterial wall, preventing new deposits from forming there. This can help to prevent stenosis, or narrowing of the blood vessels. Nanoparticles are also used in tumor therapy, and the molecules may also be helpful in treating neurodegenerative diseases such as Alzheimer's and other forms of dementia.

Fig. 1 FDmiX M mixer for producing nanoparticles

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