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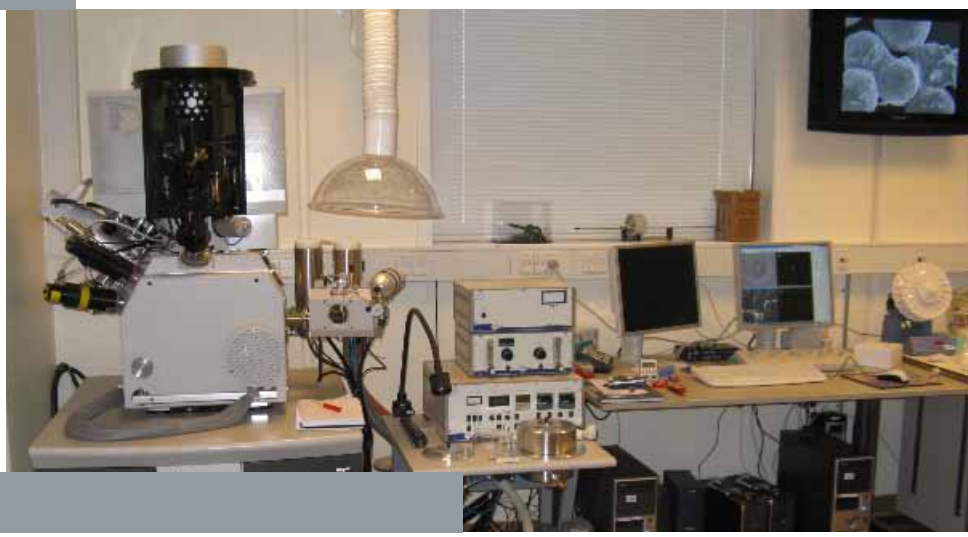

FeF Chemicals, a subsidiary of Norvo Nordisk

Research Team at FeF Chemicals Seeks Ways to Lower Cost of Insulin to Treat Diabetes

Using an FEI Helios NanoLab™ aids development of silica gel for insulin purification

"We can proceed with research in a way that we couldn't before. Using Helios we are able to cut the particles and look inside the pore structure. We hadn't been able to do that before."

—Soren Johnsen
Head research scientist for the microscopy department at the FeF Silicon Center of Excellence

FeF Chemicals A/S is the preferred supplier of quaternary ammonium compunds to the leading pharmaceutical, cosmetic, and chemical companies worldwide.

Headquarters: Koge, Denmark.

www.fef-chemicals.com

FeF Chemicals, a wholly owned subsidiary of Novo Nordisk in Koge, Denmark, produces quaternary ammonium compounds (quats) for a wide range of applications. The company's synthesis process makes FeF a leading supplier of both crystalline and solutions of quats by ensuring a very high level of purity. Using raw materials of high purity and following a stringent quality system, FeF products are ideal for pharmaceutical applications.

FeF also produces silica gel used by Novo Nordisk for purification of insulin and insulin analogs. In collaboration with Novo Nordisk, FeF Chemicals A/S has a Silica Center of Excellence near Copenhagen. The mission of the Novo Nordisk/FeF Silica Center of Excellence is to make a significant contribution to the company's position as a world leader in diabetes treatment. Today diabetes affects more than 230 million people worldwide—six percent of the world's adult population. For the Silica Center of Excellence lab, it is vitally important to study silica gel to make continuous product improvements. Silica gel (SiO_2) is a powder used for preparative chromatography purification of insulin and insulin analogs. The powder consists of spherical particles with a particle size of 10-20 microns. The lab's goals are to:

- **Improve purification methods**
- **Lower production costs of insulin**

Challenge

"Our challenge is to develop the material used for the purification of insulin and insulin analogs for diabetes treatment. To do this, we study the pore structure inside a silicon particle," says Soren Johnsen, research scientist in charge of the microscopy department at the FeF Silicon Center of Excellence. Through research and development, FeF seeks to increase their understanding of tiny silica gel pores that are roughly 10 nm in diameter.

Using a contract lab for FIB (focused ion beam) and SEM (scanning electron microscope) sample preparation and examination, FeF quickly discovered that they could not obtain adequate results to further their research.

After using a contract lab for a long period of time, FeF came to a conclusion. “Using an outside lab slowed the pace of our research. We were not able to get the detail we needed to fulfill our mission,” says Johnsen. “Because of the time spent on sending samples back and forth it could take some time before we got the results. After we received the results, we sometimes weren’t sure it was the right structure we were looking at,” says Johnsen. “This gave us doubt about the structure. The quality of the work conducted by the contract lab was quite good but it is very difficult and time consuming to do research through a contract lab. You need to be there and see the sample in the microscope in order to get the best information.”

A second significant challenge is the difficult task of preparing a sample of a porous compound’s structure. “We have to make certain the pore structure doesn’t fill with material as we mill it away,” says Johnsen.

Why FEI

When FeF Chemicals investigated microscopy equipment to enable in-house sample preparation and imaging of delicate silica gel, they sought demonstrations by industry leaders. At the FEI Nanoport in Europe, near Amsterdam, FeF was impressed by the demonstration of the DualBeam™ Helios Nanolab™.

“The demonstration was a success. We brought our own sample and the highly-skilled application specialist at FEI demonstrated some of the possibilities,” says Johnsen.

The Solution

What puts the Helios NanoLab in a class of its own is its ability to offer the highest imaging, contrast, stability, and speed. It ensures the best resolution, reproducible metrology, and the best control of the beam for writing purposes. The outstanding imaging capabilities of the Helios NanoLab include its novel FESEM technology, featuring sub-nanometer resolution at 15 kV, and better than 1.5 nm at 1 kV without beam deceleration.

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“We can proceed with research in a way that we couldn’t before. Using Helios we are able to cut the particles and look inside the pore structure. We hadn’t been able to do that before. Helios combines a FIB and a SEM, now we have both in one instrument. We also installed a cryostage for looking at materials such as soft gels made of cross-bound sugars. These materials are very fragile when you dry them. Using the cryostage, we are able to look inside by making samples in cryogenic conditions,” says Johnsen.

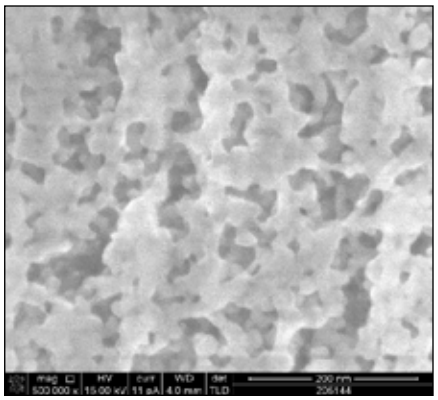

Fig. 1: Pore structure of a FIB- sliced silica bead

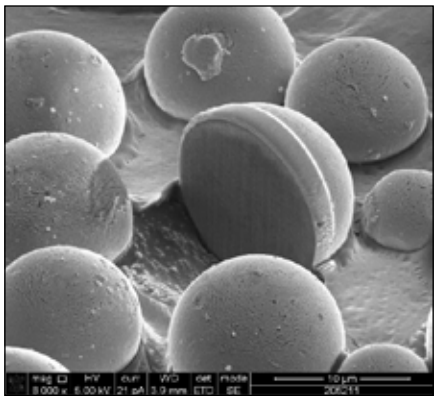

Fig. 2: Silica beads on a carbon tape one are sliced in half by using FIB

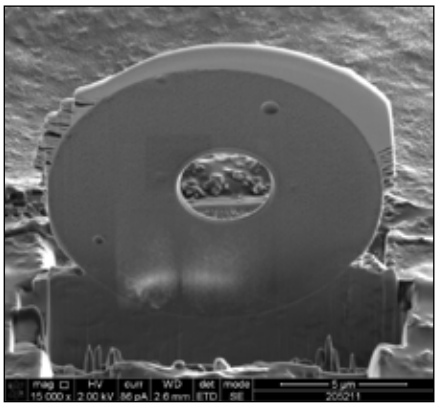

Fig. 3: FIB Lamella made of a silica bead containing a cavity in the center of the bead

The Result

“The equipment we got from FEI was tailor-made for looking at the pore structure in silica gel,” says Johnsen. “We chose FEI because they showed the highest resolution on our application. At that time we didn’t have any techniques for making certain we didn’t fill the pores during milling. We have that now,” explains Johnsen.

No longer limited by an outside lab’s capability, Helios is spurring innovation at FeF while expanding their research boundaries. “We have the possibility to look at soft gels, something we couldn’t do before. With Helios, now we think about what we can do. Now we can look at other porous and, if needed, frozen materials,” says Johnsen. “FEI was the best choice.”

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