

The commercial plant with a microjet reactor enables for the first time the mobile, continuous and large-scale GMP production of nanoparticles of active pharmaceutical ingredients.

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GMP-COMPLIANT MANUFACTURE OF NANOPARTICLES

Process skid for GMP-compliant manufacture of nanoparticles — A microjet reactor transforms pharmaceuticals into nanoparticles that are easily absorbed by the body. Now the patentee has scaled the process from the laboratory process to a GMP plant. The pharmaceutical company got support from a competent plant manufacturer.

ANN-KATHRIN HOFFMANN*

For some time now nanoparticles have been used in pharmaceutical medicine, and the benefits of doing so speak for themselves: Taken in this form, medicines are absorbed much more rapidly by the body and therefore reach full effect faster and at a lower dose. Using conventional techniques, nanoparticles for pharmaceutical use can only be produced slowly and laboriously

through a process of iterative grinding. However, a technology already established in inorganic chemistry now permits the faster, continuous production of nanoparticles using simple physical precipitation in a MicroJetReactor (MJR). Under laboratory conditions this process had been used successfully for the production of nanoparticles of active medical ingredients, but to produce them commercially

a full-scale technological facility was needed.

The patent for physical precipitation in MJRs is held by the pharmaceutical company leon-nanodrugs. Use of this key technology now permits the simple, faster, and

* The author is journalist in Sindelfingen. Kontakt to M+W Group, Stuttgart: Phone +49-711-8804-2624,

therefore more economical manufacture of nanoparticles. However, the laboratory equipment used to develop the technology was not designed for commercial production, and only has a maximum capacity of two to three liters. The idea was to build a commercial-scale facility with a capacity of 100 liters per batch, and for this purpose leon-nanodrugs needed a partner with expertise in plant construction.

GMP guidelines must be followed

For pharmaceutical production a wide array of certificates are needed to ensure that everything functions properly and that there is no risk to patients through defective production or contamination. Moreover, in a commercial installation for the manufacture of medicines for human use, different safety precautions are required from those applying for experimental production in a laboratory. GMP guidelines must be followed before the production platform can be used to make tablets or injection compositions for commercial use.

Accordingly, only companies with the necessary pharmaceutical industry knowledge, experience, and expertise came into question, and M+W Group GmbH could offer precisely this combination. Since 1912 M+W Group has been at the forefront when it comes to advanced engineering development and design solutions. "As chemists we needed a plant constructor who

could speak our language, was familiar with the industry and able to provide the necessary know-how," explains Dr. Elke Horstkotte, project manager at leon-nanodrugs. "The designer had to know what was involved in order to bring the project to a successful conclusion. This not only meant having a thorough understanding of industry requirements but also being able to independently come up with solutions to challenges and then design the periphery. In M+W we have found precisely that partner." In January 2016, leon-nanodrugs awarded the tender to M+W. Thereafter, M+W engineers, designers and software experts at the company's Stuttgart headquarter set about building in-house the first commercially viable large-scale MJR platform for pharmaceutical nanoparticle production.

From laboratory to commercial-scale facility

The first planning step was to define the technical configuration and requirements for the periphery. So far all that existed were laboratory-scale processes for the production of a few liters – the aim now was to scale these up to a platform capable of producing 100 liters at a time. A key feature of the MJR process is that the MicroJet-Reactor at the heart of the installation is no larger in the commercial production setup than in the laboratory device. The reactor possesses two tiny nozzles each a few 100 µm in diameter, which determine the liquid throughput rate and therefore the total capacity of the installation. After each production run, the installation and MicroJetReactor must be cleaned. To avoid having to dismantle the entire installation in order to do so, it

was important to ensure easy access to the reactor in order to clean it and if necessary replace it with a reactor fitted with smaller or larger nozzles.

One special feature of the production platform was the combination of high pressure in the liquid pipelines leading to the reactor with the use of organic solvents as a starter product. To produce the nanoparticles, the two liquids in the reactor are fired at each other under high pressure, while an inert gas is simultaneously introduced in order to ensure that the suspension of nanoparticles continuously descends into the collection receptacle. Key considerations when designing the installation were to maintain process controls and automatically monitor how fast the liquids are mixing and what pressure should be applied in the gas pipeline. The devices and measurement stations chosen were adjusted to the requisite volume flows, which were unknown at the time of order placement. If the continuously monitored process diverges from specifications, the suspension produced is immediately and automatically diverted from the product receptacle into the waste receptacle. A further issue is that using organic solvents means that the process involves a risk of explosion, in view of which the entire production platform had to be ATEX-compliant in design. To clean the installation an additional high-performance pump was installed to facilitate an automated cleaning-in-place process.

A further design challenge was posed by the structural requirements for the installation. The commercial-scale production platform comprises a total of five receptacles plus the associated periphery. Because leon-nanodrugs aims to use the pilot installation with various customers, a further requirement was that it had to be mobile. Therefore, in order to avoid complicated installation and dismantling processes the entire installation was fitted with rollers. The five receptacles are also fitted with rollers so that they can be filled and emptied away from the installation. For further processing of the nanoparticle suspension, the

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HEIKO SCHWARZ,
PROJECT MANAGER M+W



Source: M+W Group

mobile 100-liter product receptacle can be moved and connected to the next pharmaceutical facility without the need for wasteful refilling.

The software must ensure transparency

To comply with GMP requirements and leave the requisite audit trail, every working step performed by the installation must be precisely and transparently recorded down to the last detail, and the operating software must be able to perform these functions. "Every button that is pressed, every setting and every change must be apparent after the event," explains Heiko Schwarz, project manager at M+W. "Not all software is able to do that. For this purpose M+W therefore developed its own program, coordinated with the process skid, which met these requirements."

The program was based on modular TIA (total integrated automation) software by Siemens. The system is partly composed of prefabricated components for the installation-specific requirements, plus additional software developed in-house to control the valves and the frequency converter. Very specific process stages such as stirring, precipitation with or without nitrogen, emptying, and cleaning were also programmed.



Bild: M+W Group

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KARSTEN DEURINGER,
MANAGER SALES & BD

With Teamwork on course for success

As the entire process skid was produced in Stuttgart, both the designers and the software programmers were on site to test and deploy the system. As Manager of Sales & BD Karsten Deuringer points out, this is in line with M+W's corporate philosophy: "M+W's general rule is that every project is executed by a small team that is involved in the design process from start to finish. With pilot installations, the company takes particular care to ensure not only that teams work in close coordination with the customer but also that the engineers, mechanical engineers, and programmers involved in the project work closely together."

Leon-nanodrugs also considered that as an advantage. M+W thus provided the pharmaceutical company with everything it needed from a single source. The installa-

tion was produced to the customer's specific requirements, and progress was discussed at regular meetings.

Laboratory Experience and Practical Skills work together

Thanks to M+W's practical skills and Leon-nanodrugs' experience from the laboratory tests the joint project was a resounding success: "The GMP environment posed exacting requirements for the installation, and our internal process execution requirements have to be met. All of the resultant challenges were overcome thanks to our close collaboration with M+W, and to their skills and plant construction expertise," notes Elke Horstkotte with satisfaction. The fault-free functioning of the finished installation was verified in August 2016 through the Factory Acceptance Test, after which it was handed over to Leon-nanodrugs.

PROCESS-Tip

M+W exhibiting at **Achema**: Hall 9.1, Stand B3

Functioning of the MicroJetReactor (MJR)

HOW THE NANOPARTICLES ARE CREATED

Unlike previous processes for manufacturing nanoparticles for pharmaceutical use, the MJR produces them not by grinding but rather via physical precipitation. The active pharmaceutical ingredient is dissolved in a suitable organic solvent. If the active ingredient in question is not water-soluble, mixing the solution containing it with water leads to the spontaneous formation of tiny, solid particles of the ingredient. This simple physical process takes place continuously in the MJR under highly controlled conditions. In a chamber within the reactor, the two jets of liquid, namely the active ingredient solution and water, collide with each other under controlled reaction conditions, whereupon intensive mixing of the two takes place, leading to the formation of active ingredient particles a few hundred nanometers in diameter. Introducing nitrogen gas into the chamber then ensures that the liquid mixture is ex-

tracted from the reactor, along with the active ingredient nanoparticles. The suspension thereby produced is now ready for further pharmaceutical processing into tablets or injection compositions.



The microjet reactor allows a continuous process.

Source: M+W Group