

DSM Background information

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'Micro Reactor'

Pharmaceutical manufacturing at a scale smaller than the human hair – with “micro reactor” technology

Traditional Manufacturing

In order to produce pharmaceuticals, a large number of complex chemical steps need to take place. In the traditional production method starting materials, solvents and catalysts are added to large vessels in a specified order and kept there for a certain time to convert the starting materials into intermediate products.

These are in turn purified and tested for quality. Then they enter the following reaction step in the next set of reactors. Complex syntheses of pharmaceutical products can consist of more than 20 of these steps.

Using large vessels to produce pharmaceuticals has a number of disadvantages. Most importantly, large-scale chemical reactions in these large vessels deliver large quantities of unwanted – sometimes dangerous – by-products. These by-products have to be disposed of, resulting in a negative environmental impact.

The traditional production method – which also requires heavy use of energy resources and can generate a lot of heat that needs to be cooled – is not very efficient, more solvents, catalysts and other starting materials are needed than desirable.

Micro Reactor Manufacturing

To address all these issues, a new technology is emerging to produce pharmaceuticals: **micro reactors**. This technology has left the drawing table and is for example used for the production by DSM Fine Chemicals in Linz (Austria) of naproxcinod, an arthritis drug in development, for the French pharmaceutical company NicOx.



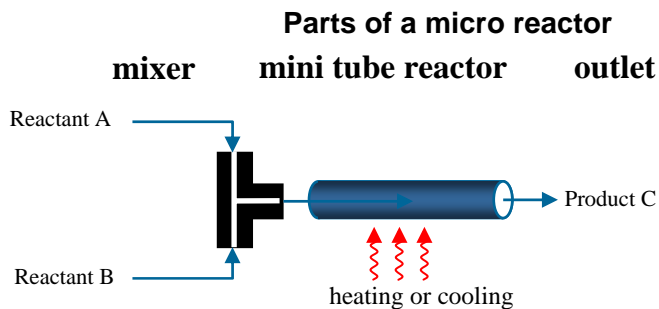
A micro reactor is a continuous tube reactor with a small channel diameter. To reach the desired throughput of such a reactor, it contains thousands of small channels in parallel, each of them surrounded by coolant. In this way, the average micro reactor can be as small as a small cupboard and can handle 1000-2000 kilograms of product per hour, with yields more than 20% higher than in the traditional large vessels and a much lower CO₂ footprint and at

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lower costs. Measured per cubic meter ($\text{kg}/\text{m}^3\text{h}$) the productivity increase is by a factor of 10^3 - 10^4 .

A micro reactor has a volume of around 3 liters, compared to 10,000 liters for a large vessel. The size difference can be seen in the picture (left). The reaction rate is, due to the smaller scale, much quicker and also easier to control, resulting in a higher yield and a lower rate of unwanted by-products. It is also more cost-efficient, as micro reactors consume less energy and are scalable as well.

The key lies in the small and short tubes used in micro reactors. Conventional large vessels use tubes with a diameter of up to 4 meters; micro reactors can have tubes with a diameter as small as 10 microns (which is equal to one-tenth of a human hair) up to 5 millimeters. As reactions in these narrow spaces can be very fast, the tubes can be short, which allows a typical micro reactor to be small enough to be carried by one person.



Commercial Success

At its Linz facility DSM – as one of the frontrunners in applying this technology on a larger scale to pharmaceutical production – has already produced nearly 1 million kilograms of pharmaceutical products using micro reactors.

Micro reactors show superior processing performance in chemical processes, allowing process conditions that otherwise would not be possible.

And there is more: micro reactors can handle sequences of operations on hazardous reaction mixtures such as mixing, dilution, extraction, neutralization in a safe, well controlled way. This allows keeping all dangerous operations and reaction mixtures within the boundaries of the reactor. The mixture that leaves the reactor is harmless again.

For instance, in the production of



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naproxinod for NicOx, large quantities of a nitrated intermediate are needed. Nitration reactions must be handled carefully because they generate products that can violently decompose. Strict control of reaction conditions is needed to make the nitration selective and to allow extraction and neutralization of the desired nitrated product. In the traditional production process this would call for specialized safety equipment but also a much lower yield.

Working with glass specialist Corning, Inc. DSM designed a micro reactor system that combines three key process steps—the nitration reaction, neutralization, and workup. Due to the small scale of the system, it took only 18 months from feasibility studies to large-scale production.

DSM has been working on the development of micro reactors for more than a decade. The system developed with Corning for naproxinod will be the first industrial-scale use of micro reactors for producing a pharmaceutical product under current Good Manufacturing Practices (cGMP).

The Future for Cost-Effective, Environmentally Friendly Micro Reactor Technology

Also, large pharmaceutical companies are increasingly looking at micro reactor technology as an alternative production method, as it provides a cost-effective and more environmentally friendly way to produce active pharmaceutical ingredients.

Researchers believe that as much as 30% of fine chemicals and pharmaceuticals currently in production could be made more efficiently using micro reactors.

For DSM, the potential of micro reactor technology is not limited to the production of pharmaceutical products or fine chemicals. Its applications are not restricted to this and research currently focuses on the production of other specialty chemicals.

About DSM Pharma Chemicals

DSM Pharma Chemicals, a business unit of DSM Pharmaceutical Products, is a global provider of custom manufacturing services to the pharmaceutical industry. Services include the production of advanced intermediates such as unnatural amino acids and derivatives, registered materials and active pharmaceutical ingredients. The menu of technologies includes biocatalysis, homogeneous catalysis, fermentation and chiral technologies.

Under the direction of account management teams, DSM Pharma Chemicals is able to deliver comprehensive custom manufacturing services to the spectrum of pharmaceutical companies including emerging pharmaceutical companies and large pharmaceutical companies.

From clinical to commercial services, DSM focuses the right resources on providing the highest level of service and quality while applying innovative solutions to satisfy customers' unique manufacturing needs.

DSM Pharmaceutical Products realized EUR 419 million in net sales in 2008 and consists next to DSM Pharma Chemicals of DSM Biologics, DSM Pharmaceuticals,

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Inc. and DSM Exclusive Synthesis. DSM Pharmaceutical Products is part of the Pharma cluster of Royal DSM N.V.

DSM – the Life Sciences and Materials Sciences Company

Royal DSM N.V. creates solutions that nourish, protect and improve performance. Its end markets include human and animal nutrition and health, personal care, pharmaceuticals, automotive, coatings and paint, electrical and electronics, life protection and housing. DSM manages its business with a focus on the triple bottom line of economic prosperity, environmental quality and social equity, which it pursues simultaneously and in parallel. DSM has annual net sales of about €8 billion and employs some 22,700 people worldwide. The company is headquartered in the Netherlands, with locations on five continents. DSM is listed on Euronext Amsterdam. More information: www.dsm.com