CARBOGEN AMCIS
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FROM BATCH TO FLOW

Scaling matteson homologation with flow chemistry

How CARBOGEN AMCIS transformed a challenging reaction into a robust GMP-compliant process

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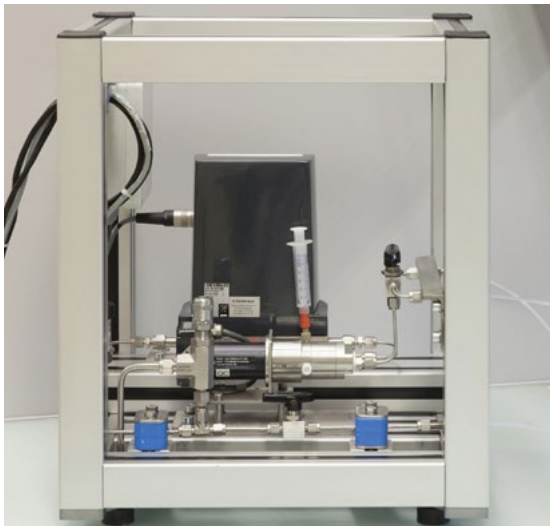
MATTESON HOMOLOGATION IN FLOW

A case study by Franz Amann
Senior Scientist Development at CARBOGEN AMCIS



Scaling chemical processes from the lab to production is never straightforward. Traditional batch methods often reveal hidden challenges—poor mixing, heat management, or unexpected impurities—that can jeopardize efficiency and product quality.

In this ebook, you'll discover how CARBOGEN AMCIS tackled these exact challenges during the scale-up of a Matteson homologation. You'll learn:

- **Why batch scale-up failed** and the root cause of unexpected impurities
- **How flow chemistry provided a solution**, ensuring fast mixing, controlled heat transfer, and reliable conversion
- **The main technical hurdles**, from clogging to pressure management, and how they were overcome
- **How a modular and non-ATEX system design** enabled cost efficiency, flexibility, and GMP compliance
- **What successful process validation looks like** in a real-world pharmaceutical context

By the end of this ebook, you'll gain not only practical insights into applying flow chemistry for complex transformations but also a roadmap of considerations when moving from lab to industrial scale.

FROM BATCH TO FLOW: SCALING MATTESON HOMOLOGATION WITH FLOW CHEMISTRY

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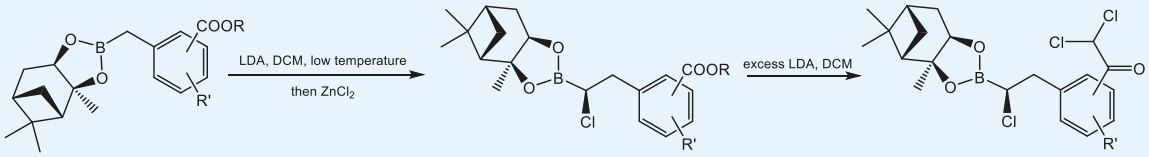
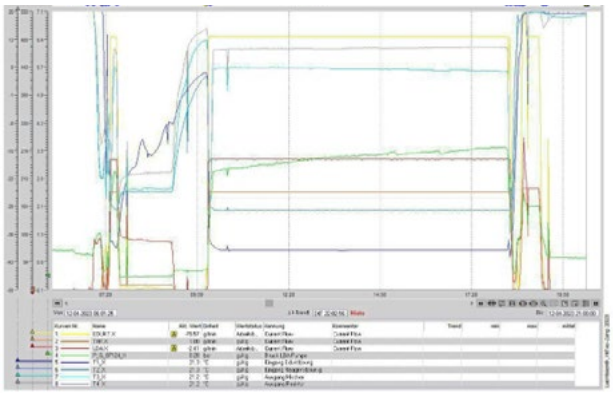
After a successful lab development, the first 5 kg scale-up of a Matteson prolongation gave inferior results. More reagent was needed to achieve conversion > 90 % and a specific side product was found in amounts never seen before.

Structure elucidation made clear that the impurity is a result of bad mixing. Sub-surface reagent addition, lower temperature or full stirrer speed gave only minor improvements and further scale-up required technical modifications.



A new approach to improve the process

- Based on these observations, a continuous process became attractive. A first test in a system as simple as a syringe pump, some PTFE tubing and a dry-ice bath revealed that the chemistry works in flow as well. The initial conversion – deprotonation of DCM and addition to the boronic ester – is extremely fast and takes only slightly longer than the mixing of the reagents. Slower mixing, triggered by batch scale-up, results in zones of a high reagent excess where the second addition to the impurity becomes likely. For all flow systems, from the very first test in the lab up to the final production set-up the mixing zone stayed always in the range of microliters - during lab development an 1/8" static mixer, an 1/8" T-piece on scale. These small volumes provide sufficient mixing even at moderate flow rates.
- Fortunately, it could be shown that the warm-up of the reaction mixture during the fast conversion has no detrimental effect on the result. In the final version of the intensified process, the virtual mixing temperature of -35°C at the entrance rises to ca. +10°C within less than a second. It would have been a challenge to manage this heat rise even in a small flow system.
- The major problem during scale-up was clogging in the tube system based on 1/4" (ca. 6 mm OD) parts. Traces of moisture form lithium hydroxide from LDA sticking to the walls. Additionally, the lithium dichloromethylide that is not consumed in the desired reaction decomposes to form polymeric impurities also leading to a slow pressure increase in the system (pressure profile: green line in scheme to the right). The clogging could be mitigated by a precise dosage of LDA to minimize the excess of lithium dichloromethylide and accepting a trace of starting material to be left. Inorganic deposits were controlled by a rinsing routine and low limits for moisture especially in the solvents.

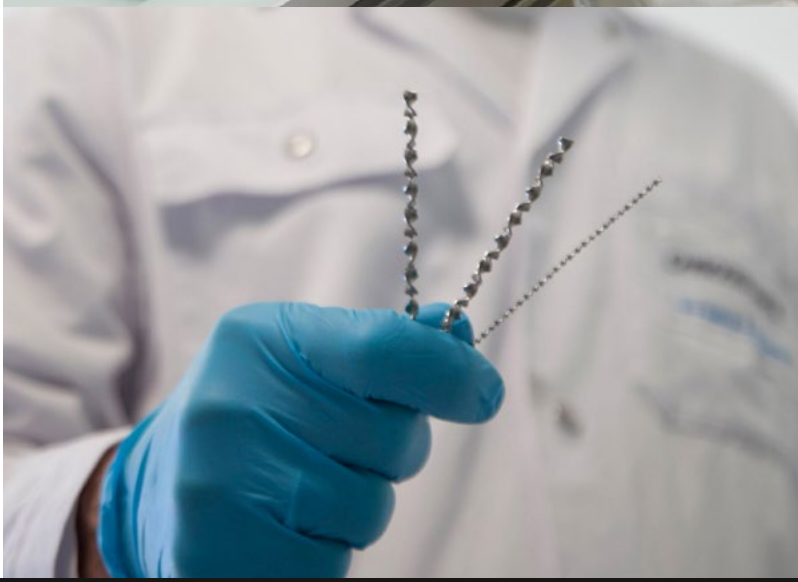


FROM SMALL LABORATORY SCALE TO A ROBUST FLOW CHEMISTRY AT LARGE SCALE

The positive initial results in the lab had to be translated into a production protocol.

Additionally, unlike for batch chemistry, the equipment had to be designed, too. The set-up for production was based on three principles.

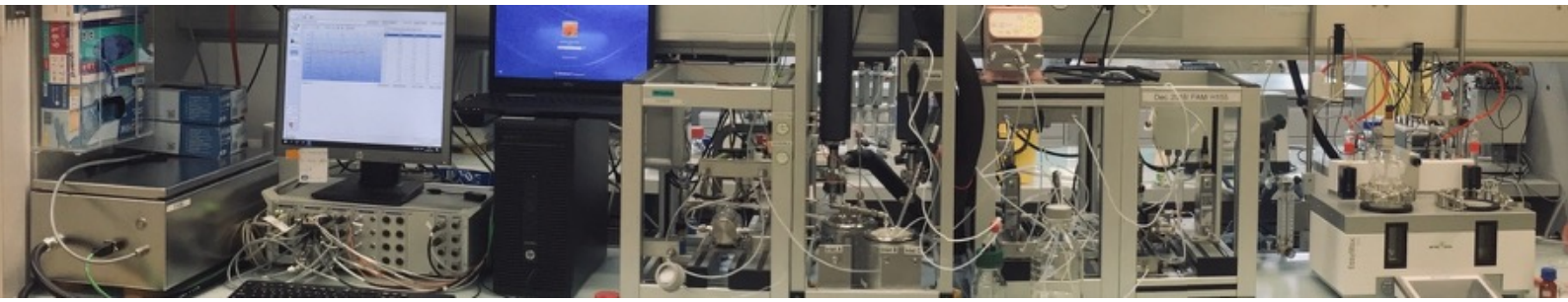
- **Modular design:** The set-up consists of several individually qualified components that can be combined to fulfill the requirements of through-put, cooling power and system pressure. Modifications as needed for larger batches can be done simpler as the qualification only requires demonstration of the suitability for the intended reaction. We take trained musicians to form an orchestra.
- **Non-ATEX:** The flow reactor, due to its small dimension, can be located in a regular fume hood. All large volumes are stored behind walls in the ATEX production area. This helps to keep equipment cost low and allows for a wider range of system components. Nevertheless, measures for a controlled shut-down in case of a leakage have to be in place. The system delivers ca. 800 ml of chemicals per minute.
- **Simplicity:** All components are commercially available and have not been built for a specific, flow chemistry purpose facilitating replacement in case of failure and ensuring long-term availability. The modules were assembled, tested and qualified on site. The development of the hardware from the very beginning created valuable knowledge supporting safe operation.



SUCCESSFUL PROCESS AND COMPUTER SYSTEM VALIDATION

The intended use for a commercial pharmaceutical product required a validation of the process. This could be completed successfully.

One of the first steps in the validation process was to prove that the set-up for the different laboratory test runs is actually a suited model of the production device. Performing the PAR-study in the full scale device would have required enormous amounts of reagents. Nevertheless, the "skyline" of the lab 1/8" set-up (below) is still impressive. The final validation production campaign could be finished successfully while gaining more experience with the novel system.



- A computer system validation (CSV) for this bespoke system was done in parallel due to GMP requirements. The system now has a certain degree of automation mainly to handle critical situations such as leakages or the running out of solutions. A next step could be the use of valve drives that allow for full automized start-up and shut-down schedules.
- Now, the system is running for 8 h for each batch of 60 kg of the intermediate. The batch size is mainly limited by the size of the receiving vessel for work-up. For even higher amounts, a continuous work-up would have to be added to the existing protocol.

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