Continuous manufacturing as a tool for early- and late-stage fluorination of pharma & agro actives

Dr Dirk Kuschneck of **Microinnova** shares some case studies of using flow in fluorination

Incorporating process intensification strategies and continuous modes of operation in fluorination processes has been of great interest in recent years, especially in the pharmaceutical and agrochemical sectors. This can be attributed to highly reactive and toxic species hold-up minimisation, excellent mixing and/or heat-exchange capabilities, as well as the implementation of production plant encapsulation techniques to mitigate potential process-related issues.

In the pharmaceutical industry, approximately 30% of newly developed small molecule APIs contain at least one fluorine molecule, primarily due to the favourable solubility properties of fluorinated compounds in blood. In the agrochemical sector, approximately 50% of newly developed AIs incorporate at least one fluorine molecule.

By incorporating fluorine into the molecular structure of the active, properties such as uptake into the plant or providing a long-term effect are enhanced. Recently, more and more fluorine has been added to actives in the pharmaceutical and agrochemical industries, but at the cost of their ultimate biodegradability.

Project leader Franz Strauss and other members of the Microinnova team

PFAS issues

Currently, per- and polyfluoroalkyl substances (PFAS) – sometimes referred to as 'forever chemicals' - are a hot topic. They have been detected basically everywhere on our planet, from deep in the sea to human brains. The long-term effect of exposure to PFAS is unknown and governments worldwide are discussing possible bans.

PFAS are all substances with very high fluorine content. The principal definition of PFAS is that at least one carbon atom needs to be fully fluorinated. An example for this might be a R-CF_3 or R-CF_2-R moiety within the molecule.

With its technology, Microinnova provides selective fluorination only to specific positions in the molecule, by which the good properties of the fluorine can be provided to the active, while maintaining degradability. While we are of course aware of the issues arising from the use of PFAS, we are confident that certain applications benefit greatly from the presence of fluorine. Especially in critical applications, such as cancer treatment, fluorinated APIs are state-of-the-art and have been proven to save lives.

Fluorination strategies

Two distinct strategies employed for the synthesis of fluorinated APIs are early-stage and late-stage fluorination. The distinction between these routes lies in how they use fluorine.

Early-stage fluorination involves the incorporation of fluorinated building blocks, obtained from inexpensive reagents, during the initial phases of synthesis. In contrast, late-stage fluorination requires the use of highly selective reagents to introduce fluorine into the final API structure.

The selection of an appropriate synthesis route requires theoretical and practical evaluation of each molecule involved in the process. However, general trends can be identified based on the structural characteristics of the molecules. Case studies on flucytosine synthesis are presented at the end of this article.

When assessing late-stage fluorination strategies, it is essential to consider the economic perspective on both a laboratory and a manufacturing scale. At laboratory scale, specialised agents such as diethylaminosulfur trifluoride (DAST) are often preferred, due to their easy handling and reduced reactivity. On the other hand, their high cost makes them impractical for large-scale manufacturing processes.

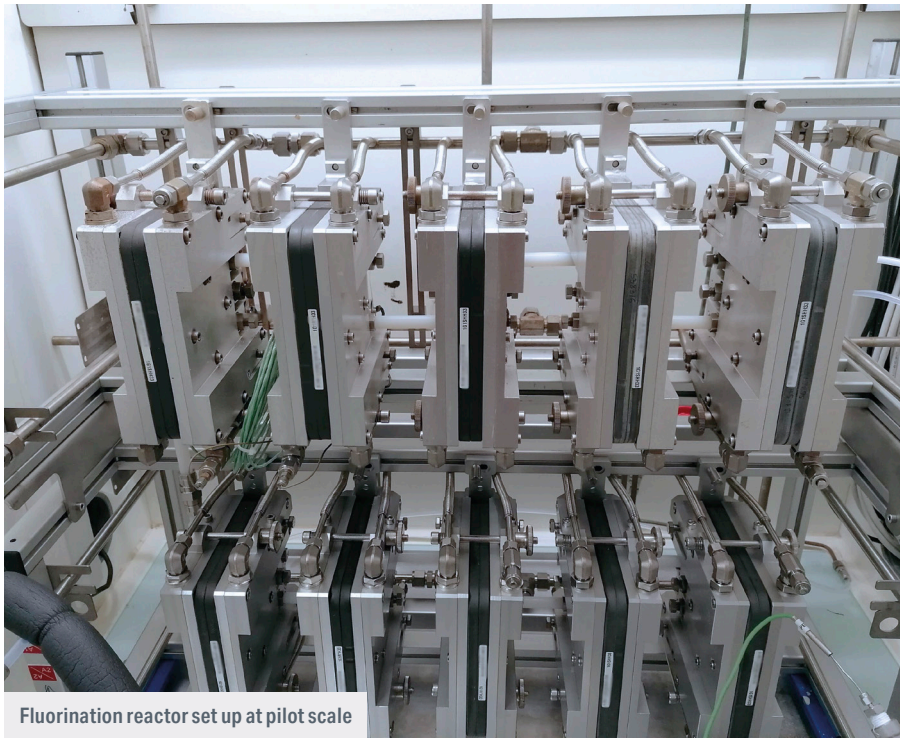
Therefore, when considering larger-scale production, selective strategies utilising flow chemistry techniques become more interesting. Flow chemistry enables precise control over reaction conditions, efficient reagent utilisation and enhanced scalability, thereby offering potential cost advantages for the implementation of early-stage and late-stage fluorination in manufacturing processes.

Phases of the process

The development of a continuous fluorination process from initial research to full-scale production involves several distinct phases. In the first phase, known as process research, a comprehensive literature survey is conducted, and initial basic (batch) tests are performed to gather fundamental knowledge.

Subsequently, in the process design phase, the process concept is formulated, encompassing the first idea about production or pilot plant design, considering crucial economic factors, such as the estimated costs for the whole development, engineering and equipment. Development then progresses to the chemical feasibility phase, wherein the main process development and relevant parameters are determined, ensuring the feasibility of the proposed approach.

During the technical feasibility phase, trials are carried out using already scalable equipment, demonstrating the process viability on a larger scale. At this point, the concept of the pilot plant, if required, is finalised. Through engineering phases (basic and detailed), the plant is designed, and all essential components and process parameters are determined. At the end of the detailed engineering phase, the pilot or production plant can be fully constructed and automated.



Fluorination reactor set up at pilot scale

Case studies

During our first case study, we took a process from the literature for the synthesis of flucytosine, utilising elemental fluorine, for which the development work-up to chemical feasibility had already been performed and we went further in the realisation pathway. During the technical feasibility, we transitioned to process on scalable equipment.

Due to the larger size of this equipment, a scale-up of one order of magnitude had already been made. Within the larger system, we started facing new effects that were never faced in the small-scale system, such as blocking of the inlets because of back-flow. By slight adaptations of the process, we were able to overcome the issues, transfer the literature process to a scalable system and produce some kilograms of flucytosine.

In a second case study, we started at the very beginning of the development pathway in which we selected potential candidates for fluorination with elemental fluorine on a theoretical basis. The most promising were tested in principle lab trials, and a first optimisation of processing conditions was performed.

We were able to obtain results within our lab system similar to those described in literature. Conditions in this lab system are already similar to those in the scalable system; hence a direct transfer to the technical feasibility is planned as the next step. ●

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