How to Develop Flow Processes

Flexible meso flow reactors for rapid process scale-up

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View of the complete KiloFlow system — a flow platform which contains glass meso-scale flow reactors enabling the user to perform synthetically demanding, and often forbidden, transformations at scale in a rapid and flexible manner. On the right: Integral XT 150 thermostat used to regulate the KiloFlow meso reactor temperature

The pharmaceutical industry in particular is still dominated by flexible batch processes and segmented unit operations. This article presents a portfolio of reactor equipment designed to facilitate the development flow processes in this sector. Using a unique scalable flow platform, the researcher can now rapidly evaluate and optimise synthetic processes on mg quantities of material and subsequently scale the process, in order to attain the target production volumes.

CHARLOTTE WILES, MICHAEL SEIPEL

It has long been discussed that micro reactors can be used for reaction screening, where low reactor volumes enable large quantities of data to be gathered rapidly using only milligrams of reagents. Once suitable reaction conditions are identified, the target volumes required for production can then, in principle, be attained using a combination of continuous operation and/or numbering-up [1].

Looking at this from a commercial standpoint however, it becomes clear that it is not economically feasible as to produce chemicals on a tonnes per annum scale would require hundreds to thousands of low volume micro channel reactors; therefore at a certain point, an increase in reactor volume is required. With the efficient thermal and mass transfer of micro reactors being key to their success, it is imperative when increasing reactor volume that the efficiency of these two processes is retained.

If this is not the case, re-optimisation is required in order to successfully translate a process from the laboratory to production and prevent the familiar 'failure to scale' observed for batch technology; in poorly designed systems this can be costly, both in terms of reagent consumption and time.

The 'Scale-up' Challenge

With these factors in mind, Chemtrix have developed a series of flow reactor platforms aimed at addressing the 'scale-up' challenge and affording researchers the rapid reaction screening that is needed in early process development using Labtrix (micro reactors) and the larger volume production using KiloFlow (meso reactors). Labtrix is a laboratory scale system designed for the evaluation of synthetic processes within micro reactors. Due to the small reactor volumes employed (1 to 20 µl), rapid and detailed process information can be generated using typically mg quantities of substrates, giving increased process insight into chemical transformations.

In addition, the large surface to volume ratio obtained within such reactors affords a safe processing environment for the study of previously forbidden chemistries. With an operating range of -15 to 195 °C, maintained using a Peltier device, at a constant backpressure of 20 bar, the system enables researchers to access reaction conditions that would not be conventionally explored due to the need for specialised high temperature and pressure equipment.

Once a series of reaction conditions have been identified on Labtrix, they can be trans-

C. Wiles is an employee of Chemtrix BV, Geleen/The Netherlands. M. Seipel works with Lauda Dr. Wobser GmbH & Co KG, Lauda Königshofen/Germany.
Contact Lauda: Phone +49 (0) 93 43 / 5 03 - 2 73

ferred to KiloFlow in order to produce the required volume of material.

KiloFlow is a flow platform which contains glass meso-scale flow reactors enabling the user to perform synthetically demanding, and often forbidden, transformations at scale in a rapid and flexible manner. KiloFlow is unique as it offers rapid mixing (ms range), excellent heat transfer and a wide (metal free) thermal operating range. With production volumes flexibly determined by the number of reactors housed within a tubeless holder, KiloFlow affords access to materials at throughputs ranging from $g \cdot h^{-1}$ to $tonne \cdot annum^{-1}$ in a modular platform capable of growing at the speed your development requires.

Scalable Flow Systems

Mixing is an important part of synthetic processes and is known to affect both the rate and selectivity of chemical transformations; consequently, it is essential that the mixing type and time is maintained when translating processes from micro- to meso-scale reactors. By employing staggered oriented ridge mixers (SOR) in both the micro- and meso-channel reactors, it has been shown, using the 'Fourth Bourne' reaction [2, 3] that the reactor volume can be scaled from 1 µl to 6.5 ml with no loss of mixing efficiency. This observation confirms that researchers can use Labtrix in early stage development, where materials and time are both limited and then scale successful processes to KiloFlow with confidence; without the need for re-optimisation, once more material is required.

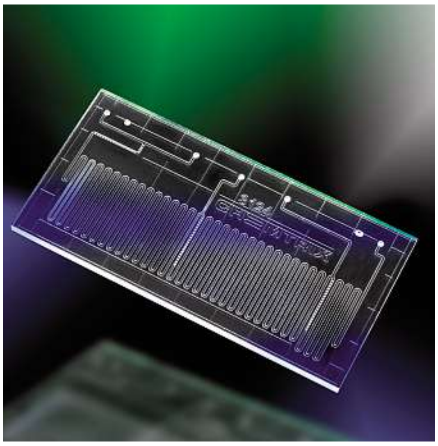
In addition to mixing, thermal management is important in maintaining product quality when performing reactions at an increased scale. Within KiloFlow, this is achieved in the production units by employing reagent pre-heating, via heat exchange modules, which ensure that reagents are at the reaction temperature ahead of mixing, with thermal regulation of the reactor contents achieved using integrated heat exchangers. Pre-heating and thermal control is provided by a process thermostat, Lauda Integral XT 150, which pumps regulated fluid through the glass heat exchangers over a reactor thermal range of -40 to 195 °C.

The small dimensions of the channels within the meso reactors have a significant influence on both the system pressure and the flow of the heat transfer liquid inside the heating/cooling layer. Regarding the correlation between flow resistance R and the radius (or diameter), the following equation has to be considered:

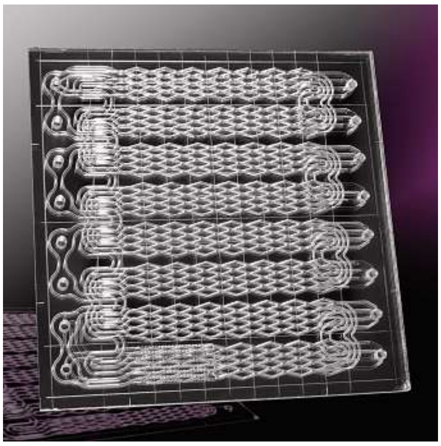
$$R = \frac{8 \cdot \eta \cdot l}{\pi \cdot r^4}$$

with R = flow resistance, η = kinematic viscosity, l = length of tube, r = radius.

A small reduction of the diameter means a significant increase of the resistance R because the radius r appears in the equation



Labtrix micro reactors



KiloFlow meso reactors

with the fourth power. Consequently, a powerful thermostat pump is required, such as the Integral XT 150; which can provide a maximum pressure of up to 2.9 bar and flow rates up to 45 $L\cdot min^{-1}$. The eight levels of the vario pump also enable application specific adaptation of the flow and pressure delivered to the reactor ensuring that the reactant and reactor temperature is maintained at ±1 °C; as measured within the KiloFlow reactors. Using integrated heat exchange the KiloFlow reactor design affords impressive volumetric heat exchange of 800 $W\cdot m^{2}\cdot K$ (Specific area = 4081 m^2/m^3 and U x S/V = 3265 $kW/m^3\cdot K$) affording efficient reactant pre-heating and thermal regulation of reaction mixer; ensuring excellent product quality over time.

Increased Production Capacity

In order to increase reactor volume further, additional reactor modules are required (6.5 ml reaction capacity per reactor). By integrating the heat exchange modules and reactors into a tubeless holder, gradient free thermal operation of multiple reactors is obtained. Owing to the fact that each reactor has a low pressure drop, typically 0.25 bar at 100 $ml\cdot min^{-1}$, the modules can be connected in order to increase the reactor volume. Connecting the modules in series, whereby the fluid output of one reactor becomes the fluid input of a second reactor etc., expands the reaction times accessible for a given flow rate or increases the production capacity for reaction times of several minutes. Conversely if the reactors are connected in parallel, fast reactions (1 s to 2 min) can be processed at higher throughputs whilst maintaining a low pressure drop across the system, as the reactant mixture is evenly distributed over multiple reactors and then combined into a single output stream.

The flexible reactor configuration also enables multiple reagent feeds (i.e. A + B —> Intermediate + C = P) to be employed, with the dosing position readily altered in the reactor holder; this means that only two reactor types are required with assembly affording multiple reaction options. The system is therefore flexible in number of reagent inputs (A, B, C and D), reactor configuration (serial or parallel), reactor number (up to 10 per holder) and holder number.

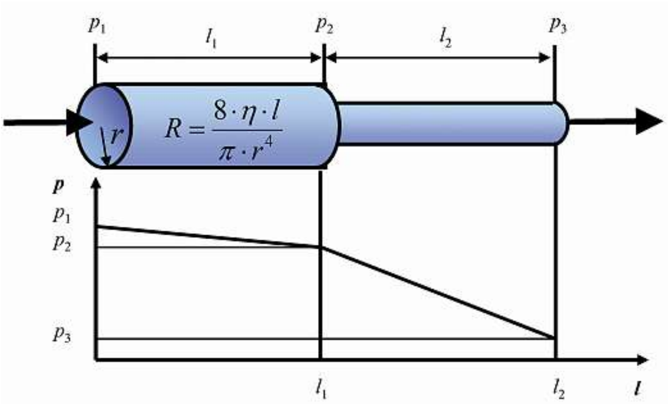
From a fine chemical perspective, the ability to alter the volume of a production process by increasing or decreasing a standard set of modules is of interest as this can reduce the associated operating costs, with 'batches' of compound prepared to order. The use of generic reactors also means that once a campaign is complete, the modules can be re-configured and employed for a different process; an important feature in an industry where product lifetimes can range from months to years.

With respect to the pharmaceutical industry, this high degree of flexibility is particularly attractive as it ensures that processes can be performed within a standard laboratory fume cupboard up to the $kg\cdot h^{-1}$ scale thus addressing the material requirements of Phase I and II without the need for dedicated equipment. It can then be decided for the handful of compounds that make it to production what the most cost effective and efficient synthetic route is and whether to use a dedicated flow reactor installation.

Conclusions

With a need to decrease costs across the chemical sector in order to increase profitability, continuous flow reactor technology is an emerging area that has the potential to bridge all aspects of a synthetic process. Through the development of a scalable flow technology platform, we can offer researchers at all stages of chemical R&D the opportunity to harness the proven advantages of flow reactor technology. Through close collaboration with the end user and suppliers, the engineering and chemical expertise of Chemtrix offers risk free entry into the rapidly growing field of continuous reactor technology and continued support at all stages of its implementation [4].

If there are extended requirements regarding temperature stability and temperature range, the Lauda Integral XT range offers further thermostats, with the Integral XT range covering a working temperature range of -90 up to 300 °C and a temperature stability up to 0.05 K.



Effect of tube diameter on flow rate

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[4] See www.chemtrix.com for additional information and publication details