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Article

Microreactortechnology: Real-Time Flow Measurements in Organic Synthesis

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Abstract: With the commercial availability of integrated microreactor systems, the numbers of chemical processes that are performed nowadays in a continuous flow is growing rapidly. The control over mixing efficiency and homogeneous heating in these reactors allows industrial scale production that was often hampered by the use of large amounts of hazardous chemicals. Accurate actuation and in line measurements of the flows, to have a better control over the chemical reaction, is of added value for increasing reproducibility and a safe production.

Keywords: microreactor; mass flow meter; flow control; flow chemistry; thermal flow sensor

1. Introduction

With the commercial availability of microfluidic devices such as microreactor systems, integrated dispensing units and in-line analysis, the numbers of lab scale chemical processes that are performed in a continuous flow, is currently growing rapidly and several examples of industrial processes are known [1–3]. Where initial developments in microreactor technology mainly focused on the design of the microreactor chips (silicon, glass, polymers like polydimethylsiloxane) for a controlled addition of small quantities of reagent in reaction channels up to microliter volumes, a clear shift is observed from the design of microreactors to the development of chemical processes in a microreactor for a precise control of reaction parameters [4–6].

Microreactor technology enables increased process control due to inherently excellent heat dissipation, especially in scale up, and often shows beneficial effect when batchwise syntheses turn out to be low yielded [7,8]. There are three main types of reactions described in literature that show enhanced efficiency when performed in a continuous flow: (i) "instantaneous" reactions (t_r < 1 s) which are controlled by mixing efficiency; (ii) "fast" reactions (1 s < t_r < 10 min) which are predominantly kinetically controlled and ii) slow reactions (t_r > 10 min) [9]. Although reaction times longer than 10 min in general do not benefit from flow chemistry, reactions can be significantly intensified, thereby decreasing reaction time by effective heating and mixing at increased pressure in a microreactor.

The ability for engineering already in the early stage of new product development, allows chemists to perform exothermic reactions and the ability to work with highly toxic chemicals at industrial scale [10–12]. The capability for accurate flow actuation and in line measurements of these flows, to have a better control over the chemical reaction, shows additional value in increased reproducibility at lab scale, and is of major importance for a safe production in scale up.

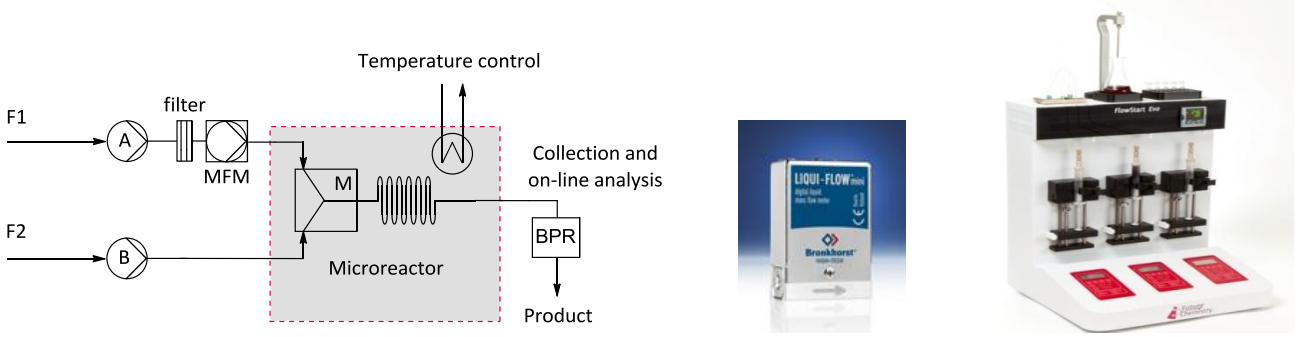
In this article we describe the opportunities of flow metering in flow chemistry on microliter scale measured with a mass flow meter (MFM). Initially, the accuracy of the pumps was measured with the MFM using water as solvent. Next, the robustness of the MFM was investigated with a diversity of organic solvents frequently used in organic processes. To conclude, three different chemical processes were screened in flow, using the MFM as an external feedback on actual flow rate.

2. Results and Discussion

2.1. Apparatus

FutureChemistry's FlowStart *Evo* (See Figure 1) [13] was used in the flow chemistry experiments. The glass microreactor used had an internal volume of 100 µL, a channel width of 600 µm, a channel depth of 500 µm and an effective channel length of 360 mm. The channel layout contained an additional mixing unit (M), being of the folding flow type [14]. Flowcontrol measurements were performed using the Liquiflow mini mass flow meter (MFM) from Bronkhorst High Tech [15].

Figure 1. Schematic drawing of the microfluidic setup (**a**) including (**b**) the Liquiflow mini and (**c**) the FlowStart *Evo*.



(**a**) (**b**) (**c**)

2.2. Fluidic Activation: Accuracy of Pumping Devices

Development and scale up of a chemical reaction is a time consuming process. Flow chemistry significantly decreases this time for development because this technique enables a fast optimization of process parameters with controlled reaction times in a microreactor by accurate flow rates. Liquids ranging from test samples to various reagents and wash fluids must be dispensed in these reactors, depending on its application. Dispensing of liquids is generally controlled by positive displacement metering pumps with a high resolution stepper motor. Its high resolution allows fluid actuation of solvents at very low flow rates down to 0.21 µL/min using a 1 mL syringe. FutureChemistry's FlowStart *Evo* has three integrated syringe pumps for accurate fluid handling. With desired residence times varying from 10 seconds up to 20 minutes in the microreactor, flow rates ranging from 1.5 µL/min up to 850 µL/min are required.

In microreactor technology, dispensing of liquids becomes a critical parameter in the submicroliter range. To investigate the accuracy of the pumps in the Flowstart *Evo*, they were tested in a range from 0.0625 up to 10.0 µL/min. Without back pressure applied, an excellent linear response of average flow rate was obtained with a flow rate >0.5 µL/min and with only 1–2% deviation from the set flow rate (See Figure 2). With a flow rate <0.5 µL/min however, a significant deviation was measured resulting in a high offset in the calibration curve. Despite the excellent accuracy of the pumps, a large fluctuation in actual flow was obtained (See Figure 3, green line). This fluctuation is caused by a small pressure gradient set over the flow path caused by the small inner diameter of the tubing (0,01"). In order to suppress these fluctuations, a back pressure (40 PSI) was connected end-of-line to moderate the pressure, and thus the flow, and the flow rate was measured with a fixed flow rate (see Figure 3, blue line). Whilst the fluctuation in flow decreased significantly, the average flow rate was left unchanged. With a microreactor placed in between the pump and the back pressure regulator similar flow rates were obtained (BPR, See Figure 1).

Figure 2. Average flow rates in a range from (**left**) 0–1.0 µL/min and (**right**): 0–10 µL/min.

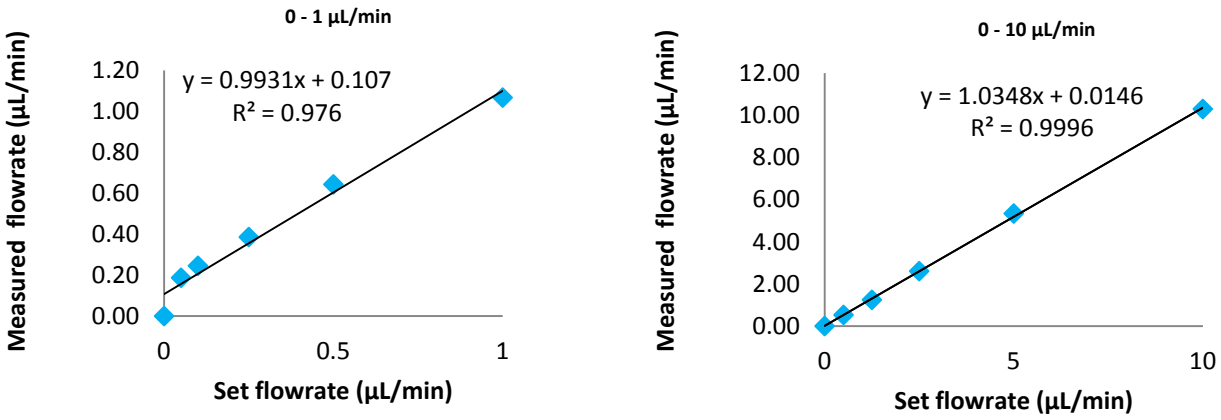
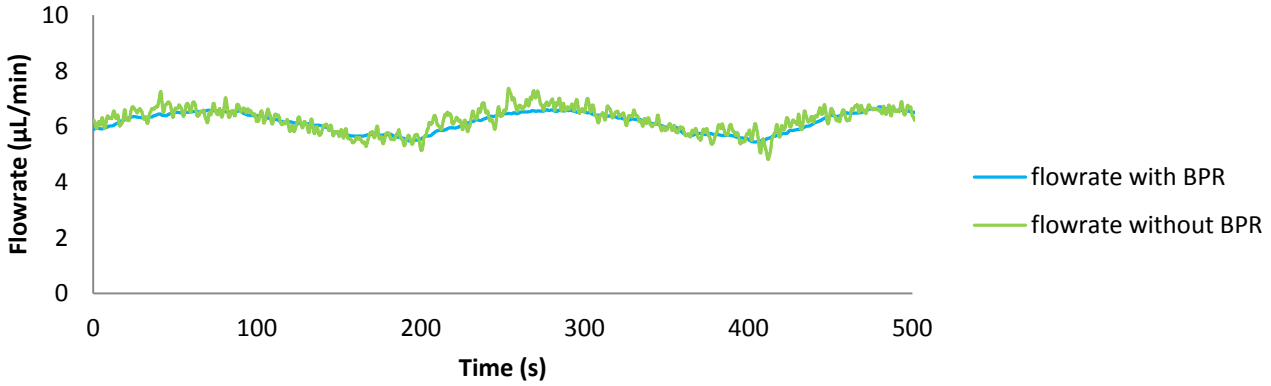


Figure 3. Influence of back pressure to actual flow rate, with set flow rate at 6.0 µL/min.



The fluctuation of the flow is mainly caused by the step resolution of the pump (volume dispensed per step); the higher the step resolution, the lower the fluctuation in flow. The 1 mL volume syringe used in the previous experiments has an internal diameter of 4.61 mm. To investigate the influence of the internal diameter to the fluctuation, syringes with different internal diameter were tested (See Equation (1)). A 100 µL volume syringe (d = 1.01 mm) with a four-folded decrease in internal diameter was therefore ought to further decrease fluctuation of the flow. Although the deviation of the actual average flow rate was only 2% from the set value, the fluctuation appeared to be unchanged. Moreover, a repetitive refill of the syringe makes it impractical to use. An increase in internal diameter on the other hand, using a 5 mL syringe with an internal diameter of 10.3 mm, resulted in only a slight increase in deviation of the average flow rate.

$$V = \frac{\mathrm{A} \times 10^{-3} \times \pi \times \mathrm{d}^2}{4} \quad (1)$$

where V = Volume dispensed per step (µL/step)
A = minimum pusher advance (=0.02261161 µm/step)
d = internal diameter of the syringe (mm)

The inherent oscillation of the flow is caused by a slight curvature of the thread and its thread pitch gauge correlates to the period of oscillation; the smaller the thread pitch gauge, the smaller the period at fixed flow rate (See Equation (2)). The thread pitch gauge of 1.20 mm (F = 0.1, T = 200, See Figure 3), calculated from the experimental results using a 1 mL syringe (d = 4.61 mm), nicely corresponds with the pitch gauge as measured (1.195 mm).

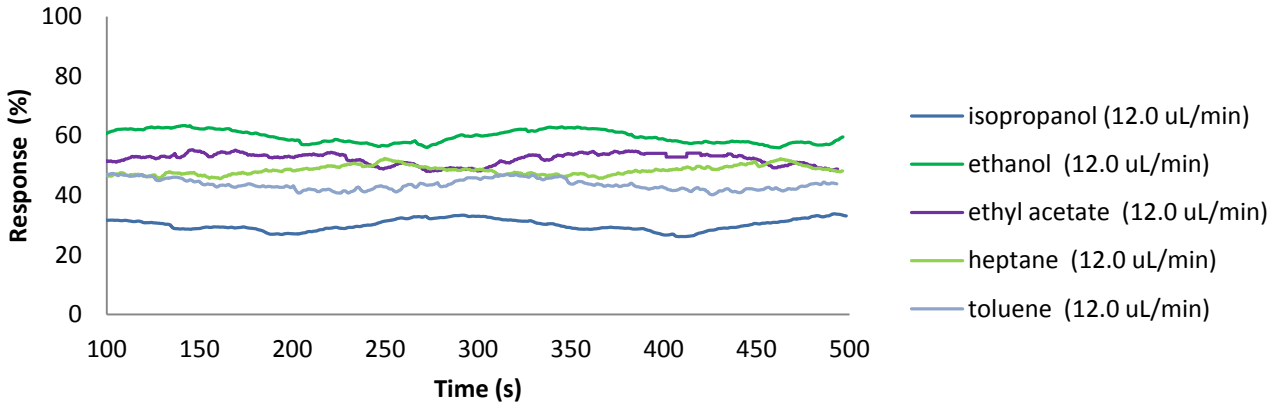
$$\mathrm{P} = \frac{\mathrm{F} \times \mathrm{T} \times 4}{\pi \times \mathrm{d}^2} \quad (2)$$

where P = Thread pitch gauge (mm)
F = Flow rate (µL/s)
T = Period (s)
d = Internal diameter of the syringe (mm)

With a reproducible flow measured in a range of 0.5–10.0 µL/min, using demiwater as the solvent, the possibilities of real-time flow measurements of organic solvents with the MFM were investigated. The flow meter operates on a thermal, thru-flow measuring principle based on the heat capacity (Cp)

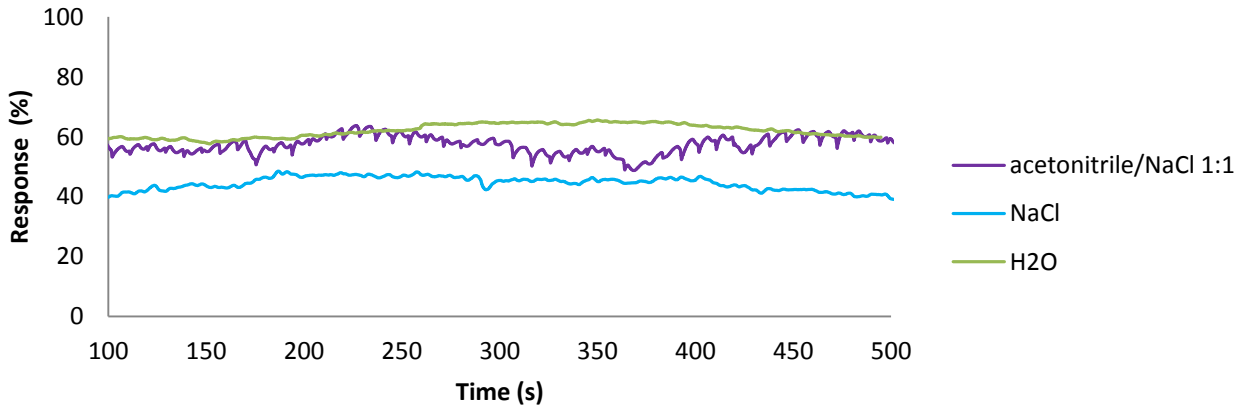
of the solvent. Differences in response are therefore mainly explained by the differences in heat capacity of the solvents of choice. With a fixed flow, a variety of organic solvent that is extensively used in organic synthesis was screened (See Figure 4). The results show similar oscillating effect and standard deviation for most organic solvents compared to water. Volatile solvent like diethylether (bp = 35 ℃) and dichloromethane (bp = 40 ℃) however, show large deviations in flow, ranging from 0 to 100% relative flow rate. Based on the thermal measuring principle of the MFM, it is most likely that these fluctuations result from vapor formation of the solvent inside the MFM.

Figure 4. Response on flow rate of different organic solvents.



With the non-volatile organic solvents successfully measured with the MFM, the viability of the flow meter using (heterogeneous) mixtures and salt solutions was investigated (See Figure 5). When a saturated solution of sodium chloride (NaCl) was pumped through the flow meter during one hour, a consistent flow of solvent was collected without precipitation of salts in the MFM. A similar result, albeit with increased fluctuation, was obtained when a homogeneous mixture of acetonitrile and an aqueous solution of sodium chloride (NaCl) (1:1) was pumped through the MFM. A two phase liquid flow of toluene and an aqueous solution of sodium chloride (NaCl) (1:1) showed a drastic increase of fluctuation and were therefore unable to be measured accurately with the MFM.

Figure 5. Response on flow rate with Demiwater (H_2O); A homogeneous mixture of acetonitrile and aqueous NaCl (1:1); A saturated sodium chloride solution.



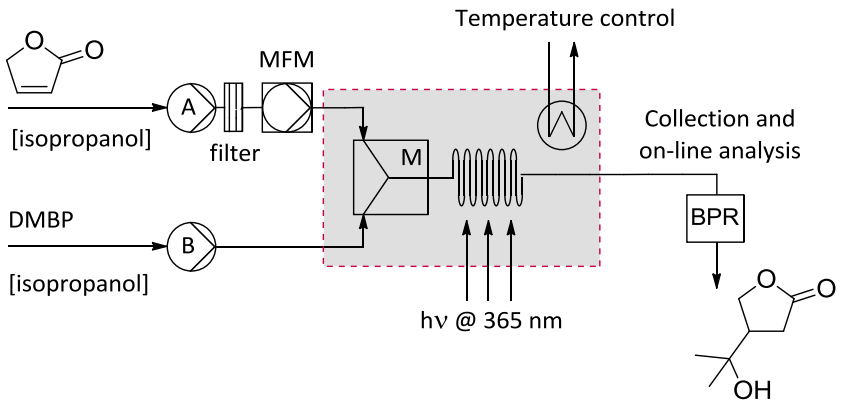
2.4. Application of Flow Meters in Chemical Processes

External feedback on flow rate provides additional information in flow chemistry for increased safety when working at large scale, e.g., when outflow of reactive intermediates is observed due to high offset or when highly toxic reagents are used. To demonstrate the use of the MFM already in the early stage of development, thereby recording the actual flow rate during the reaction, the inlet of the substrate in different chemical reactions has been screened using the MFM for flow metering.

2.4.1. Photochemical Oxidation of Furanone

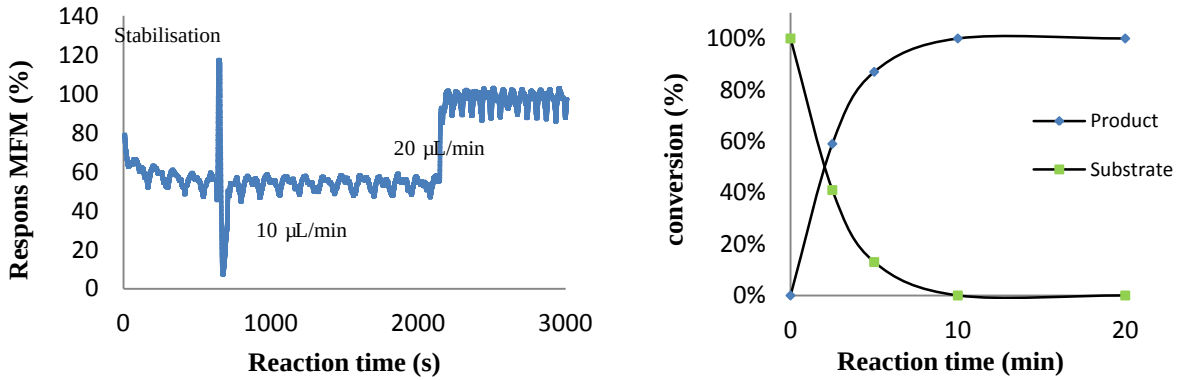
Photochemistry is an organic chemistry tool often neglected. This is mostly due to batch limitations, where light penetration into the vessel is minimal, reaction reproducibility is hampered by differences in set-up and the reaction mixture is significantly heated by the lamp. In continuous flow, reaction volumes are small most of the time, and relatively low optical power is required to efficiently penetrate the microreactor channel. Therefore, LEDs can be used as light source, which can be described in most cases as (almost) monochromatic photon sources with well-defined power. The temperature of the small microreactor volume is also easily controlled. A photochemical oxidation of furanone was performed using the setup as depicted in Figure 6 [16]. A back pressure (BPR) of 40 PSI was applied for a consistent flow, as measured by the mass flow meter.

Figure 6. Schematic setup for the photochemical oxidation of furanone.



The Syringe A was loaded with the furanone (0.05 M solution in isopropanol) and syringe B with a photosensitizer (10% v/v DMBP solution in isopropanol). Upon UV-radiation, a reaction is then performed. The results from the flow analysis with the MFM indicate a stable system within 15 min, with a set flow rate of 10.0 µL/min (t_r = 10 min). Samples were collected every 5 min ($t_{collect}$ = 1.0 min) and analyzed at-line. After 20 min the flow rate was set at 20.0 µL/min (t_r = 5.0 min). Again, samples were collected every 5 min (See Figure 7). The samples collected were analyzed using HPLC and the results plotted, as depicted in the graph. The flows were measured using the MFM. Small fluctuations in flow are compensated by extended reaction times to obtain full conversion, as found in the screening of reaction time. The results show 86% conversion within 5 min and a full conversion with a reaction time of 10 min.

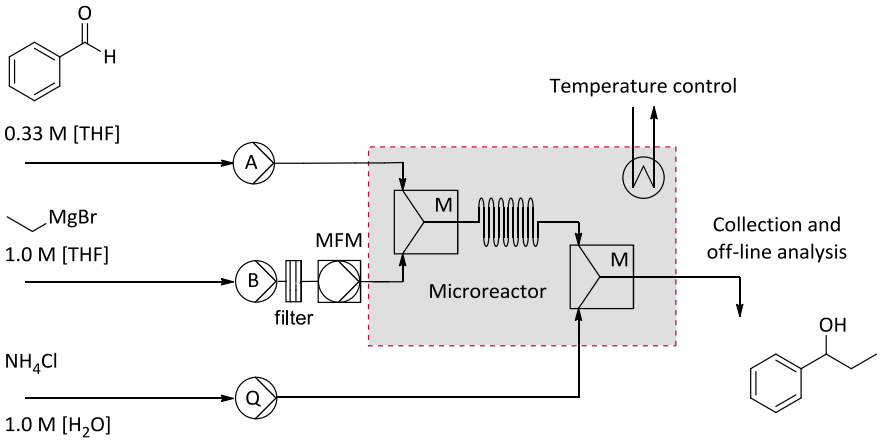
Figure 7. Flow metering of the photochemical reaction.



2.4.2. Grignard Reactions of Benzaldehyde

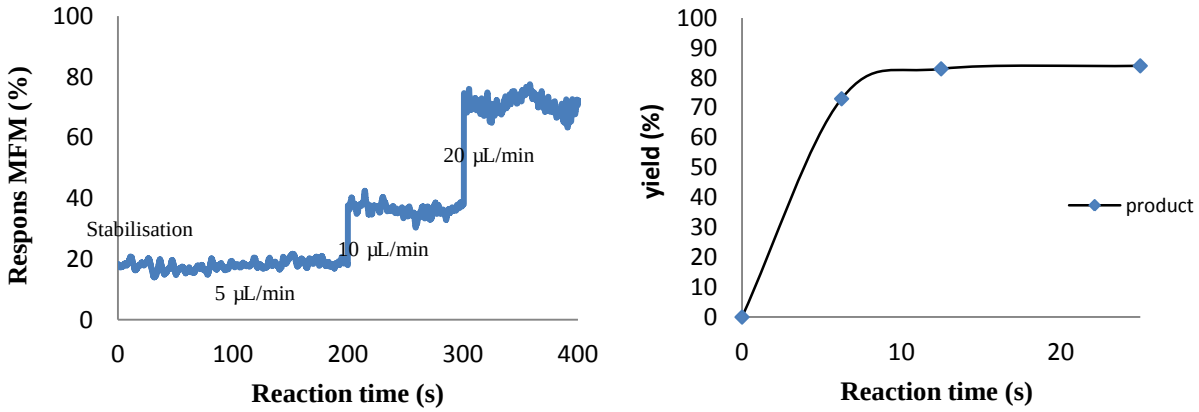
The Grignard reaction is a very useful organic transformation, as it effectively provides a carbanion by treatment of the corresponding halide with magnesium metal [17]. Alternatively, a variety of Grignard reagents is available as commercial solutions. In batch, Grignard reactions have to be conducted at strict anhydrous conditions under an inert atmosphere, as the reagent is very sensitive to atmospheric moisture. Continuous flow solves this issue, as the total system is inherently free of air. A Grignard reaction with benzaldehyde was performed using the setup as depicted in Figure 8. A back pressure (BPR) of 40 PSI was applied for a consistent flow, as measured by the mass flow meter.

Figure 8. Schematic setup for the Grignard reaction with benzaldehyde.



The syringe A was loaded with the substrate (benzaldehyde, 0.33 M) and Syringe B was loaded with ethyl magnesium bromide (1.0 M solution in THF). The reaction was quenched with ammonium chloride (Q). The samples collected were analyzed using GC and the results plotted, as depicted in Figure 9. The results showed a consistent conversion of 84% within 10 s with a benzaldehyde to ethylmagnesium bromide ratio of 1.25 at 30 ℃, with the flow of the Grignard reagent measured with the mass flow meter. In general, Grignard reactions might be sensitive to clogging the microreactor due to precipitation of magnesium salts formed in the reaction, depending on its concentration. In this case, flow control can provide additional value in a continuous production related to robustness and reproducibility of the process.

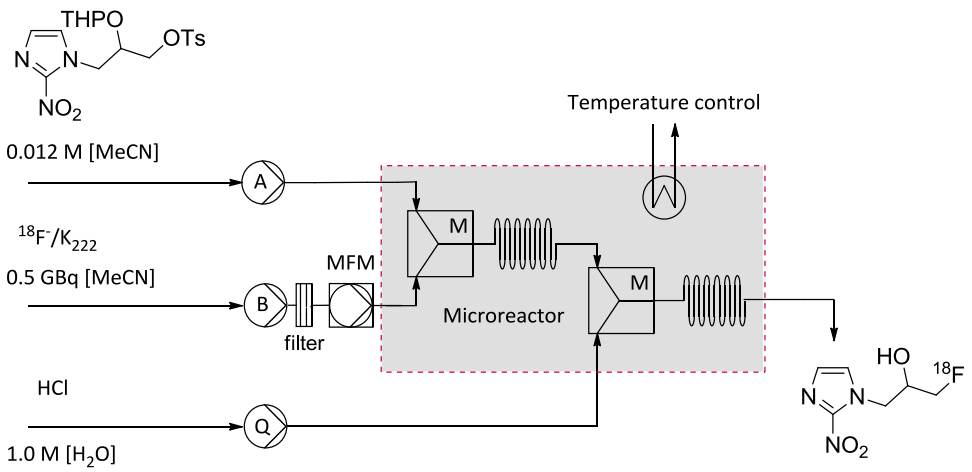
Figure 9. Flow metering of the Grignard reaction.



2.4.3. ^{18}F-Radiolabeling

Positron emission tomography (PET) is a nuclear medicine imaging technique which produces a three-dimensional scan of functional processes in the body by injecting a radiolabeled, biologically active molecule (tracer) into a patient. PET is often used in clinical oncology (medical imaging of tumors), and for clinical diagnosis of certain diffuse brain diseases such as those causing various types of dementias. PET is also an important research tool to map normal human brain and heart function. The batch synthesis of these PET tracers in hospitals is limited due to the necessity of specialized laboratories equipped with large hot-cells, required for shielding of the radiation during synthesis.

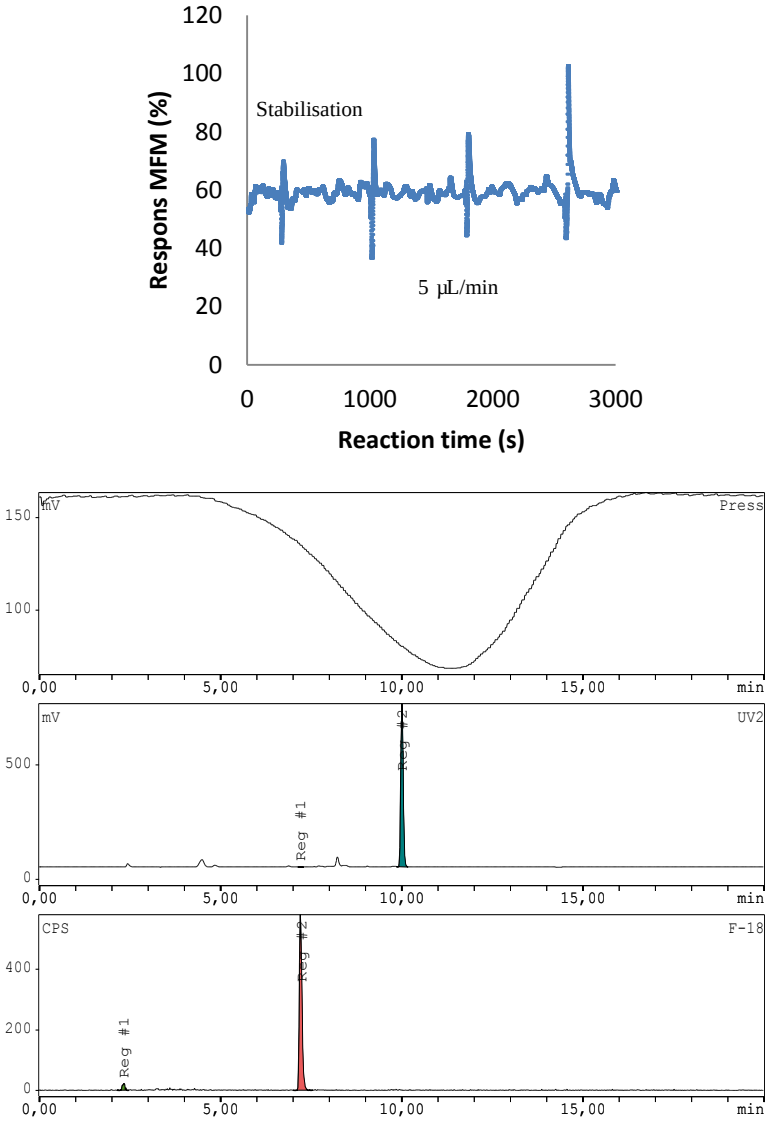
Figure 10. Schematic setup for the synthesis of a PET-tracer (FMISO).



Because the preparation of the PET tracers is not trivial, microreactor technology has become of interest in the synthesis of PET-tracers due to their enhanced reproducibility. Flowcontrol is of great additional value now to avoid unwanted radiation exposure. As an example, a generally used PET-tracer called FMISO, is prepared in a two-step procedure using the setup as depicted in Figure 10. A back pressure (BPR) of 40 PSI was applied for a consistent flow, as measured by the mass flow meter. Leakage of the radionuclide (^{18}F) can result in extended radiation exposure to the user. In this case, flow control provides additional value for a continuous production in a safe manner.

The syringe A was loaded with the substrate (NITTP, 0.012 M) and Syringe B was loaded with the radionuclide-complex (^{18}F/K222). In the second step, the unstable intermediate was hydrolyzed to FMISO with 1.0 M hydrogen chloride. A fixed reaction time of 10 min for the fluorination reaction and an additional 1 min for hydrolysis was set. The product collected was analyzed using C-18 HPLC and the result plotted, as depicted in Figure 11. The result showed a conversion of 98%, with the flow of the radionuclide (^{18}F) measured with the mass flow meter.

Figure 11. Flow metering of the synthesis of FMISO.



3. Conclusion

In microreactor technology, accurate flow rate at low throughput (1–20 µL/min) is required for a high reproducibility and safety, especially when highly reactive (radioactive) and/or toxic chemicals are used. Positive displacement metering pumps with a high resolution stepper motor provide for excellent flow rates within the submicroliter dispensing of solvents and the MFM provides a very useful tool to accurately measure these flow rates and therefore provide for an external feedback. Small fluctuations in flow are caused by the stepper resolution of the pump, but can be minimized by

back pressure regulation end-of-line. Oscillation of the flow rates on the other hand is caused by a slight curvature of the thread. Mixtures of solvents and reaction solutions show significant deviations from set values, as calibrated for water. Therefore, either the differences in heat capacity of the solvents of choice have to be taken into account, or the MFM has to be calibrated for the specific solvents/mixtures.

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