ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Subscriber access provided by Universiteit Utrecht

Full Paper

Coupling Continuous Flow Microreactors to MicroNIR Spectroscopy: Ultra-Compact Device for the Facile In-line Reaction Monitoring.

Renan Galaverna, Rafael Luis Ribessi, Jarbas José Rodrigues Rohwedder, and Julio Cezar Pastre

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.8b00060 • Publication Date (Web): 12 Jun 2018

Downloaded from http://pubs.acs.org on June 13, 2018

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Coupling Continuous Flow Microreactors to MicroNIR Spectroscopy: Ultra-Compact Device for the Facile In-line Reaction Monitoring

Renan Galaverna,[#] Rafael L. Ribessi,[#] Jarbas J. R. Rohwedder and Julio C. Pastre**

Institute of Chemistry, University of Campinas - UNICAMP, PO Box 6154 - Zip Code 13083-970, Campinas, SP, Brazil.[#] These authors contributed equaly to this work.

Correspondence to Julio Cezar Pastre, Institute of Chemistry, University of Campinas - UNICAMP, PO Box 6154 - Zip Code 13083-970, Campinas, SP, Brazil. E-mail: juliopastre@iqm.unicamp.br. Phone: +55 (19) 3521 31 43.

KEYWORDS. Coupling, MicroNIR, Flow Chemistry, 5-HMF, In-line monitoring

ABSTRACT. In this study, we applied a portable near-infrared spectrophotometer (microNIR) for the in-line monitoring of the 5-hydroxymethylfurfural (5-HMF) synthesis in a continuous flow microreactor. Under the best reaction condition using isopropyl alcohol/DMSO as reaction solvent and a fixed-bed reactor packed with solid acid catalyst, total conversion of D-fructose was observed and 5-HMF was obtained in 95% yield in just 11.2 minutes of residence time. Principal Component Analyses (PCA) and multivariate control chart based on Hotelling's T^2 and

Q-residual were also performed and proved the excellent response of the compact microNIR device for the in-line monitoring of 5-HMF production, without variation in the yield over 8 hours per day, during 5 days. Our results demonstrate the great potential for the application of this compact device in the monitoring of laboratory scale reactions, which can be extended to industrial scales.

INTRODUCTION

The synthesis of bio-based chemicals under continuous flow conditions has increased over the last years.[1] This growing motivation follows the recent development of continuous flow chemistry as an enabling technology, which brings several advantages compared to the traditional synthesis in batch for both organic and inorganic syntheses.[2] Regarding the synthesis of bio-based materials, an impressive number of valuable compounds have been successfully obtained from lignocellulosic biomass.[3] In particular, molecules such as 5-hydroxymethylfurfural (5-HMF) has been extensively investigated in view of its broad applications as building block to achieve feedstocks for bulk chemicals, polymers, solvents, and fuels.[4] 5-HMF is usually synthesized under acidic conditions from C6 carbohydrates, including fructose, glucose, chitosan, cellulose, sucrose, starch, agarose, inulin, and raw biomass.[4] Among the sugars cited, fructose has been the main choice since it provides better conversions and yields through a rapid and direct dehydration reaction.[5]

Continuous processing is widely used for the manufacturing of petrochemicals and bulky chemicals. In the last decade, the use of continuous flow microreactors in the lab scale has significantly increased and numerous reviews have been reported, highlighting the benefits of this technology.[2] Reactions in continuous flow regime allow rapid and easy optimization of some key reaction parameters by simply changing the flow rate to introduce different stoichiometric

amounts of reagents along with a precise control of the temperature/pressure and residence time. Bearing this in mind, the coupling of continuous flow microreactors to analytical tools is highly desirable since this would allow a constant monitoring and instantaneous detection of the reaction species which consist in reactants, transient intermediates and final products.[6] This approach also allows automation by software control as well as self-regulation of the reaction process.[7] Indeed, several analytical techniques such as FTIR,[8] Raman,[9] UV-Vis,[10] HPLC,[11] GC,[12] MS,[13] and NMR[14] have been successfully employed for a series of continuous flow reactions for in-, on- and off-line monitoring.

FTIR spectroscopy coupled to flow microreactors is one the most used technique for in-line reaction monitoring.[8a,b] This can be rationalized in view of some commercially available ATR-based probes, which offer easy coupling to flow microreactors and easy operation. For instance, Nigel and co-workers demonstrated several examples of reaction monitoring using FTIR, such as fluorination, oxazole formation, hydrogenation, Curtius rearrangement, and azide formation.[8a] Other recent studies include oxidation of allylic alcohols and trifluoromethylation of heteroarenes,[8c] thermolysis,[8d] aminocarbonylation[8e] and amine-redox reaction under flow regime.[8f]

A widely used and complementary alternative to FTIR is Raman spectroscopy. Although FTIR provides highly specific and instantaneous information about reaction partners (reagents, intermediates and products), Raman spectroscopy presents some advantages over FTIR. For example, water cause strong interference and reduces the sensitivity of FTIR for reactions performed in aqueous media. Intense overtones and combination bands also contribute to a difficult spectrum interpretation. In contrast, water interference, intense overtones and combination bands are factors that do not impose complications in the Raman analysis.[15] Thus,

the benefits of Raman spectroscopy coupled to flow microreactors for in-line monitoring have been successfully demonstrated recently. Some examples comprise oxidations catalyzed by tetra-*N*-propylammonium perruthenate,[9a] Michael additions,[9b] kinetic studies,[9c] and other relevant applications.[9d-h]

Regarding the synthesis of inorganic materials using microreactors in continuous flow regime, UV-Vis spectroscopy offers an excellent and accessible tool for the in-line monitoring since many types of inorganic materials (complexes, clusters, nanoparticles, etc) show absorption that involves transitions between filled and unfilled d-orbitals of the metal ion in the UV-Vis region. This attractive coupling has been demonstrated for several inorganic synthesis such as fluorescent nanoparticles,[10a] gold nanoparticles,[10b] and transition metal clusters such as Periodic Mesoporous Organosilicas (POMs).[10c] Photochemical reactions were also investigated by the use of UV-Vis devices coupled to flow microreactors.[10d]

A more precise approach for in-line monitoring can be offered by the coupling of high sensitive techniques to continuous flow microreactors. For example, HPLC, GC, and MS provide an ideal ambient for in-line quantitative monitoring. Unlike the FTIR, UV-Vis, and Raman techniques, some crucial care must be taken for these approaches. For instance, HPLC, GC, and MS require indispensable split to introduce only a small amount of the reaction crude for in-line monitoring to avoid saturation of the detector. Bearing this in mind, accurate quantitative and qualitative approach for in-line monitoring has been demonstrated in the literature using HPLC,[11] GC,[12] and MS techniques.[13]

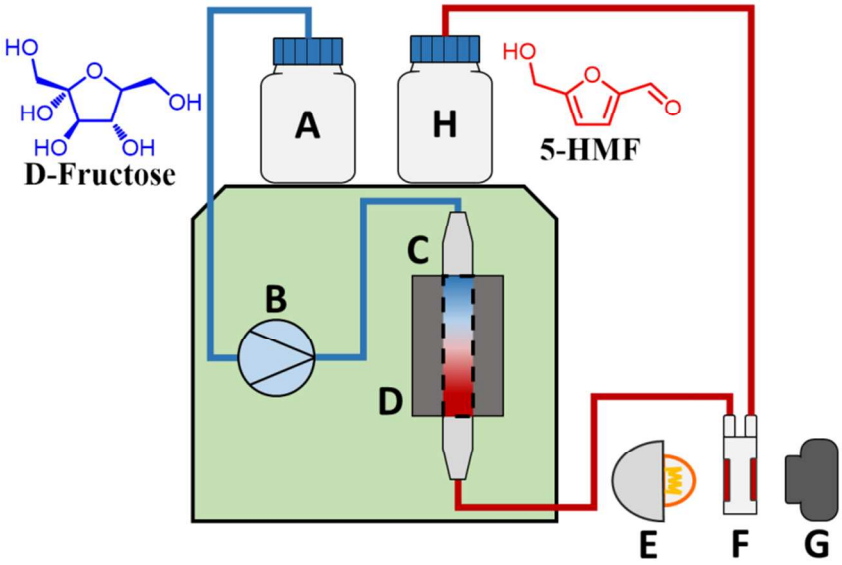
NMR is another attractive technique explored for in-line monitoring coupled to flow microreactors for several organic reactions once it is a powerful and useful tool for structural elucidation.[14a-j] For example, Cronin and co-workers using a benchtop NMR spectrometer (43

MHz) performed ^{19}F NMR, COSY, and HSQC experiments to follow electrophilic fluorinations in continuous flow regime.[14a]

It is worth mentioning that combining flow chemistry and analytical tools is also important for the development of process analytical technology (PAT). PAT consists in the use of different analytical techniques, usually associated with multivariate statistical data analysis, in order to obtain a greater understanding, continuous monitoring, and improvement of the process.[16] Some high performance analytical techniques, such as MS and NMR, are suitable for PAT, but the high cost for acquisition, implementation, and maintenance are some drawbacks for their routine use. Thus, techniques that deliver high analytical performance (precision, accuracy, and robustness) at lower costs are more attractive for PAT.[16] In this context, near-infrared spectroscopy (NIRS) shows ideal features for the in-line monitoring of different processes when associated to chemometric tools.[17] NIRS analysis requires little or no sample preparation, it has short response time and great response, and it is a non-destructive method. In addition, the instrumentation used in NIR spectrophotometers is robust, suffering less damage from environmental conditions, thus being particularly suitable for industrial environments.[17]

Recently, fast technological developments have provided great improvements in analytical instrumentation. A trend that is observed in the market is the miniaturization of various analytical tools,[18] including NIRS.[19] NIR ultra-compact devices, also known as microNIR, unlike traditional benchtop devices (FT-NIR) have no moving parts due to the monochromator used as a thin film Fabry-Perot cavity or wedge interference filter type. Taking into account their low weight (< 100 g), they can be classified as hand-held devices and recent studies have reported their potential application for the quantification of drugs,[20a] monitoring the quality of fruits,[20b] and quantification of gases.[20c]

Based on the techniques described herein, there is a lack of studies showing the coupling of continuous flow microreactors to microNIR spectroscopy for in-line reaction monitoring. In that way, we demonstrate herein the application of a hand-held NIR spectrophotometer coupled to a continuous flow microreactor for the in-line monitoring of a bio-based process previously investigated by our group.[21] For this purpose, the dehydration reaction of D-fructose into 5-HMF was evaluated and, considering the fundamentals of green chemistry, a heterogeneous catalytic system was chosen along with an alcohol-mediated reaction. To this end, fructose dehydration reaction was performed using solid acid-catalyst Amberlyst-15 and isopropanol/DMSO (15% v/v) as solvent system. Chemometric methods were also applied and demonstrated process robustness, reproducibility and signal stability, confirming that microNIR devices are a promising tool for in-line monitoring of the reactions performed in continuous flow regime (**Scheme 1**).



Scheme 1. Schematic assembly of microNIR coupled to flow for in-line monitoring of the dehydration reaction of D-Fructose into 5-HMF: **A**) bottle with reagent, D-Fructose solution; **B**) piston pump; **C**) glass column filled with Amberlyst-15; **D**) temperature controller; **E**) tungsten lamp; **F**) flow cuvette; **G**) microNIR Spectrophotometer and; **H**) collection flask for 5-HMF.

EXPERIMENTAL SECTION

Materials and Methods: Starting materials and reagents were obtained from commercial sources and used as received unless otherwise specified. Organic solutions were concentrated under reduced pressure on an IKA rotary evaporator RV-10 Control. ^{1}H NMR experiment was recorded on Bruker 250 MHz. The flow reactions were performed in an integrated continuous flow reactor FlowSyn system (UNIQSIS). NIR spectra were recorded on microNIR (Viavi, USA) spectrophotometer.

General procedure for continuous flow reactions: The continuous flow reactions were performed in a FlowSyn system (from UNIQSIS) using the following conditions: In a round-bottomed flask of 1.5 L containing a magnetic stirrer were added 45 g of D-fructose in 1 L of a *i*-PrOH/DMSO solution (15 % v/v) and heated at 60 °C to completely dissolve the D-fructose. An OmniFit® glass column (10 mm i.d. × 50.0 mm length) was packed with Amberlyst-15 (2.0 g, void volume of 2.8 mL). A 5 bar back-pressure regulator was placed after the reactor to maintain the system pressurized. The flow rate was varied from 4.0 to 0.25 mL.min^{-1} at 110 °C. Before the direct pumping of the D-fructose solution through the system, the packed column was heated up and flushed with *i*-PrOH/DMSO solution (15 % v/v) for 30 min. Before collecting the NIR spectra and/or taking samples for off-line analysis, a residence time of three times was run for each flow rate to ensure steady-state operation. After achieving steady-state, samples of 10 mL were collected and analyzed by quantitative ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard to determine the chemical yield for 5-HMF product.

Continuous flow microreactor coupled to the microNIR spectrophotometer for in-line monitoring: In-line monitoring reaction of D-fructose into 5-HMF by microNIR was performed according with the assembly shown in **Figure 1**. A tungsten lamp (50 W, Spectral Products,

USA) controlled by a power supply was used as radiation source (**Figure 1E**). The lamp was turned on at least 30 minutes before the start of the experiments. Two flow cuvettes (Hellma, Germany) were used to monitor the reaction and both have 3 mm of optical path and 40 mm^2 of window (**Figure 1F**). One of them was connected to the outlet of the glass column, while the other was kept empty for obtaining the backgrounds spectra. Lastly, a microNIR spectrophotometer (Viavi, USA), operating in the spectral range of 1150 to 2150 nm, 15 ms integration time and average of 50 scans by spectrum was used to monitor the reaction in which each spectrum counted 127 variables (**Figure 1G)**. A mean spectrum of three scans was obtained for each sample.

Data processing: All chemometric treatments and models were performed using the Unscrambler X software version 10.3 (Camo, Norway). For the construction of all chemometric models (PLS and PCA's), NIR spectra were preprocessed with the Savitzky-Golay first derivative (7-point window and 2nd order polynomial) and mean centered.

The Partial Least Squares regression (PLS) model was constructed with NIR spectra from the different reaction yields and the reference data obtained by qHNMR (reference method). Two sets of data were used, each obtained on different days. For the calibration set, 27 spectra were used and for the prediction set, 9 spectra were used.

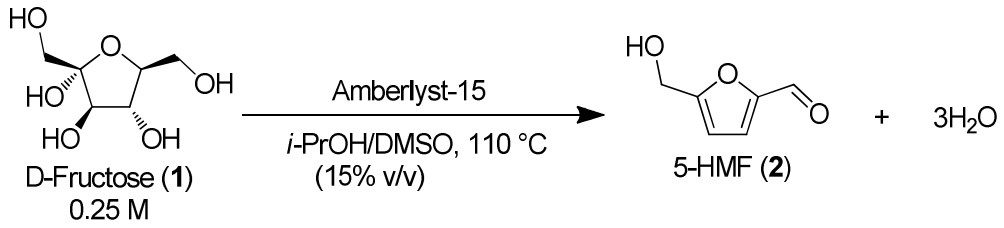
Principal Components Analyzes (PCA) was used as tool for the exploratory analyses and to monitor the conversion of D-fructose into 5-HMF under continuous flow conditions. Firstly, it was constructed a PCA model to evaluate all the date set. For this purpose, spectra from both maximum reaction yield (95%, 0.25 $mL.min^{-1}$) as well as those from different reaction yields (4 up to 0.5 mL min^{-1}) were used and resulted in 74 spectra. Next, a second PCA model was constructed to obtain the limit values of the multivariate control charts: Q-residual and Hotlling's

T^2, both with 95% confidence using two principal components. In order to calculate the limits of control charts, ten spectra were used from the samples with maximum yield (95%, 0.25 mL. min^{-1}), which was previously confirmed with the reference method (qHNMR). Finally, to monitor the reaction, a new PCA model was constructed using 54 spectra obtained from the reaction monitoring at 0.25 $mL.min^{-1}$ by 8 hours per day during 5 days. Note that the measures were performed every 45 min.

RESULTS AND DISCUSSION

To date, there are few studies on the use of analytical tools for on- or in-line monitoring of the dehydration reaction of C6-sugars into 5-HMF. It is worth mentioning that this approach would be crucial for the scale up of this process towards industrial applications, which is still pending. Toward this end, we recently evaluated the use of FTIR spectroscopy for the in-line monitoring of the 5-HMF production[21] and Dai and co-workers investigated the influence of sulfonated resins on the stability of 5-HMF by recording the *in-situ* ATR-IR spectra.[22]

In view of our interest in the preparation of 5-HMF, and considering the potential of reaction monitoring techniques for continuous flow process development, we decided to investigate the use of a hand-held microNIR device to monitor the dehydration reaction of D-fructose into 5-HMF using the conditions developed previously by our group (**Scheme 2**).[21]



Scheme 2. Schematic representation of the dehydration of D-fructose (**1**) to afford 5-HMF (**2**).

Firstly, some preliminary experiments were performed to find out which range of wavelengths would be suitable for subsequent in-line monitoring for the dehydration reaction of D-fructose into 5-HMF using the microNIR device. For this purpose, some off-line measures were performed with the starting D-fructose solution (0.25 mol L^{-1}) and with the reaction mixtures that represent 50% and 95% yield for 5-HMF, based on our previous work.[21,23] It is important to mention that the use of samples obtained from the reaction stream (and not a solution of standard 5-HMF obtained from commercial sources) was detrimental, since water is obtained in this process as a co-product (3 molecules of water per molecule of fructose) and also accounts for the variation in the NIR spectrum. The spectra obtained for each solution was overlapped and shown in **Figure 1**.

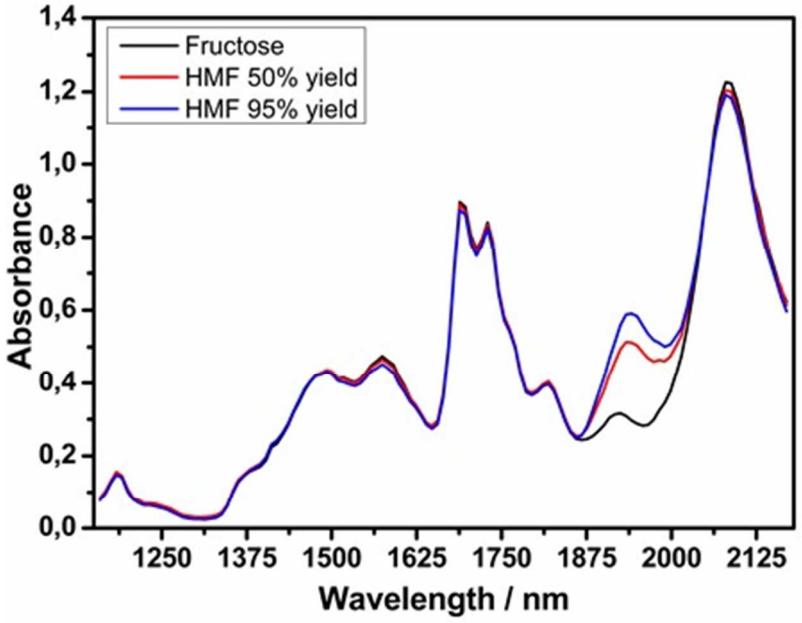


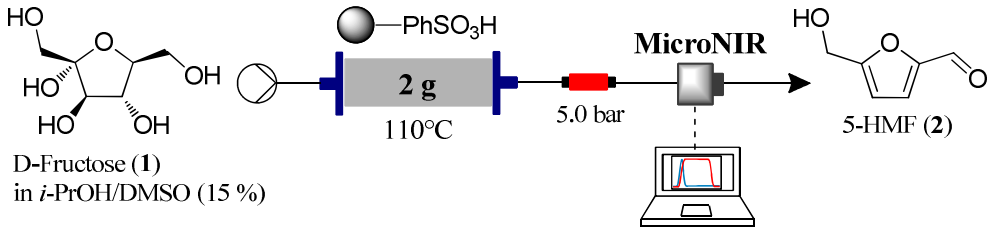
Figure 1. Spectra obtained for the off-line analysis using the microNIR device for D-fructose solution (black line), 5-HMF solution for 50% yield (red line), and 5-HMF solution for 95% yield (blue line).

As can be seen in **Figure 1**, there is a significant spectral variation in the range from 1870 to 2010 nm within the region of NIR spectrum shown here, which could be associated with the

conversion of D-fructose into 5-HMF. The greater and lower absorption intensity were correlated to the HMF solution with higher yield (95%) and D-fructose solution (black line), respectively. The variation in the spectrum can be attributed to the overlapping of absorption bands of the species formed in the reaction medium, which are three molecules of water and one molecule of 5-HMF for each D-fructose molecule. For instance, water shows strong absorption in the range 1850-2000 nm, which corresponds to its combination band.[24] In addition, another important contribution comes from the aldehyde functional group in the 5-HMF product, which displays second overtone of the carbonyl stretching in the same region.[24] From these observations, we concluded that the band centered in 1925 nm was formed by contributions of the both product and co-product. Note that the water also has a band with maximum in 1400 nm, which corresponds to the first overtone of the OH bond, however, due to the hydrogen bonds with the solvents, this band are less intense and not as visible as the band in the 1870-2010 nm range.[25]

After these initial off-line measures, we confirmed that microNIR was suitable for the proposed study. In that way, we performed an in-line experiment to assess the response of the microNIR device to different reaction conditions (*i.e.* different flow rates). Thus, the microNIR spectrometer was placed after the fixed-bed reactor filled with Amberlyst-15 and the reaction stream was passed through the flow cell for in-line monitoring (**Figures S1-S5**). The flow rate ranged from 4.0 to 0.25 mL.min^{-1} and the results are presented in **Table 1**.

Table 1. Dehydration of D-fructose into 5-HMF under different flow rates.[a]



Entry	Flow rate (mL.min^{-1})	Residence time (min)	5-HMF Yield (%)[b]

1	4.00	0.70	17.95
2	3.50	0.80	22.45
3	3.00	0.93	26.10
4	2.50	1.12	35.40
5	2.00	1.40	48.70
6	1.50	1.90	61.35
7	1.00	2.80	72.50
8	0.75	3.73	84.23
9	0.50	5.60	86.60
10[c]	0.25	11.2	95.10

[a]Flow Conditions: 45 g of D-fructose in 1 L of a *i*-PrOH/DMSO solution (15 % v/v) using a column packed with Amberlyst-15 at 110 °C and a BPR of 5 bar. [b]The yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [c] Complete conversion for D-fructose was observed by ^{1}H NMR analysis of the reaction mixture using D_2O.

From the **Table 1**, it is clear that higher flow rates decrease the yield for 5-HMF (entries 1, 2 and 3). In sharp contrast, lower flow rates led to the opposite reaction outcome, affording superior 5-HMF yields due to the higher contact time between D-fructose and the catalyst (entries 8, 9 and 10). As expected according to our previous study,[21] in the optimum reaction condition, 5-HMF was obtained in 95% yield in just 11.2 minutes of residence time at a flow rate of 0.25 mL.min^{-1} with total conversion of D-fructose (entry 10). The amount of DMSO in *i*-PrOH, catalyst loading, flow rate and temperature were not further refined to improve the HMF yield/selectivity once these attempts were already evaluated previously, showing that this result cannot be improved beyond 95%.[21] For example, a longer residence time could increase the formation of the main byproduct (*i*-propoxymethylfurfural) and the resin Amberlyst-15 is not stable above 120 °C, as well as higher amounts of DMSO are not attractive for a sustainable process.[27]

For each flow rate presented in the **Table 1**, NIR spectra were also in-line recorded and aliquots of the output stream were collected and analyzed by quantitative ^{1}H NMR analysis

(qHNMR). **Figure 2** shows the overlapped spectra and the excellent response of microNIR to the 10 different flow rates. The ^{1}H NMR spectra obtained for each flow rate (4 to 0.25 mL.min^{-1}) is also provided on the ESI (**Figure S6**). The advantage of using qHNMR as reference method is that there is no requirement to construct an analytical curve for the development of the analytical method, which makes the developed method simpler compared to chromatographic techniques, for example. In addition, the quantification of the chemical yield could also be done by an indirect method, for example, by the quantification of water by Karl Fisher titration. (remover?)

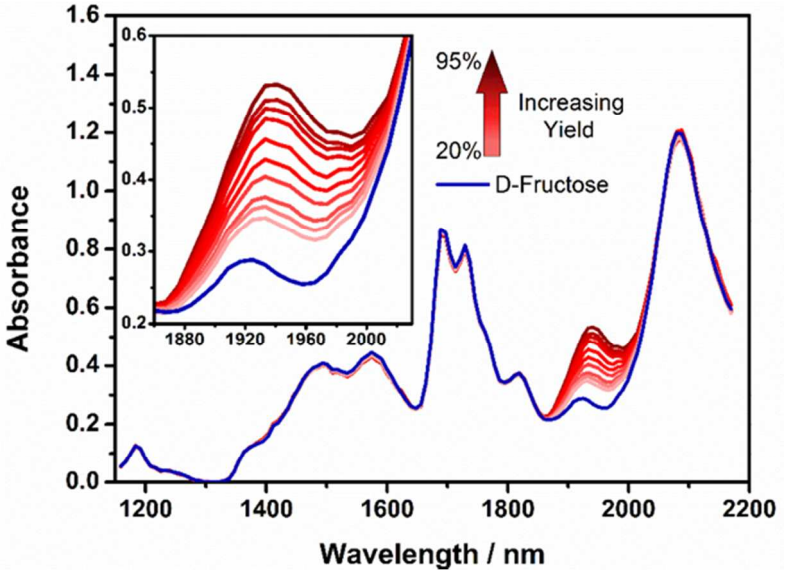


Figure 2. Raw microNIR spectra obtained for the dehydration reaction of D-fructose into 5-HMF under 10 different flow rates.

From these results, it was possible to construct a multivariate calibration model (PLS model), in which yield values obtained with the NMR analyses were used as reference values for the NIR spectra calibration (**Table 2).** PLS model plot, which relates the reference values obtained by qHNMR analyses with the predicted values provided by NIR spectroscopy analyses, is also provided on the ESI (**Figure S7**).

Table 2. Root mean square errors and determination of coefficients for PLS model.

PLS Model	Calibration	Validation	Prevision
RMSE	1.71[a]	1.94[a]	2.14[a]
R^2	0.9958	0.9950	0.9938

[a] RMSEs in % of yields.

As can be seen in **Table 2**, the model presented values for the determination of coefficients (R^2) higher than 0.99 and the values obtained for root mean squared errors (RMSEs) were close to 2% yield, which is in agreement with the accuracy usually obtained by the reference method (qHNMR).[28] Both values show a high adjustment between the reference method and the secondary method (microNIR). Therefore, we show that there is a correlation between these methods and the yields of the reaction, consequently, can be monitored by NIR spectroscopy. Thus, the PLS model could be used to verify when the reaction process achieves the optimum condition as well as when a process deviation occurs in the continuous flow regime. However, in the present study, we chose to use PCA model by the construction of control charts to perform the in-line reaction monitoring, since this approach is easier to be implemented in reaction systems, with a minor necessity of constant recalibrations.

Although the microNIR device showed excellent response by the application of different flow rates and offering opportunities to construct the PLS model, all these experiments were performed during a short period (same day) and the evaluation of reproducibility of the device cannot be drawn under these circumstances. In this context, to demonstrate the reproducibility of the microNIR device, the catalyst stability/recyclability, and also the process robustness, a long-term experiment was conducted over a period of 5 days (8 hours per day) using the same column filled with Amberlyst-15. At this part, the optimum reaction condition (0.25 $mL.min^{-1}$) for 5-

HMF synthesis was used and continuously monitored in an experiment of 40 hours. The NIR spectra were collected every 45 minutes (**Figure 3**).

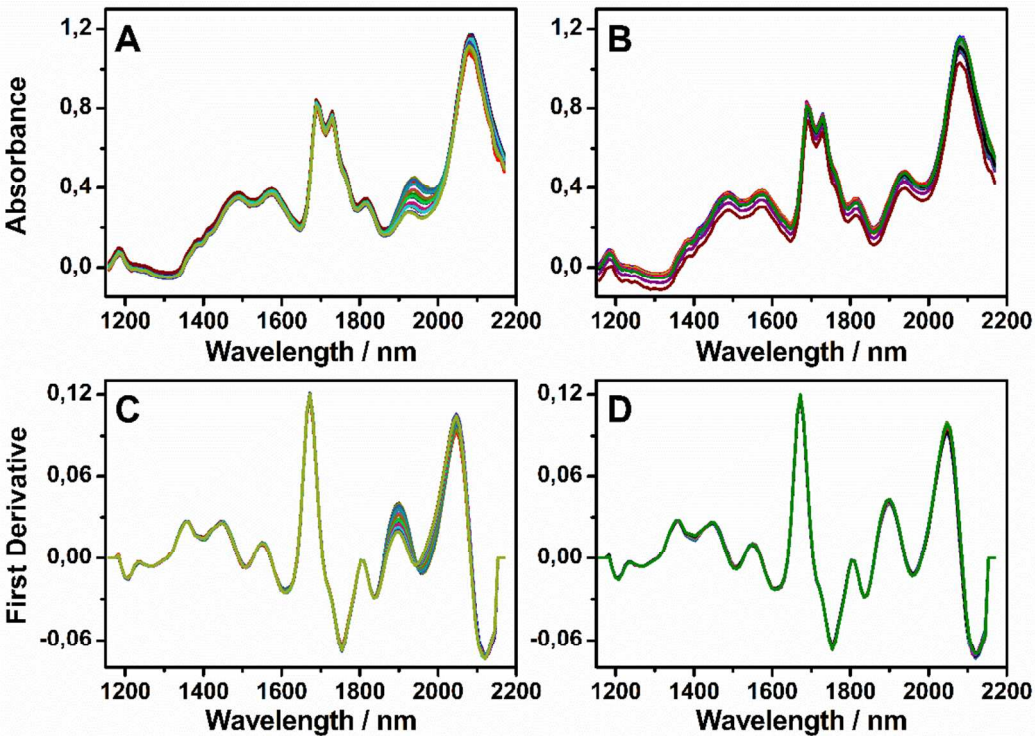


Figure 3. **A)** raw microNIR spectra obtained for the variation of the flow rate (4.0 to 0.25 mL.min^{-1}); **B**) raw microNIR spectra obtained during the process monitoring over 40 hours (at 0.25 mL.min^{-1} flow rate); **C**) first derivative of the spectra obtained for the variation of the flow rate; **D**) first derivative of the spectra obtained during the process monitoring over 40 hours.

Raw microNIR spectra are presented in the **Figure 3A** and **3B**. In **Figure 3A** is shown the overlapping of raw spectra obtained in different days of measurements varying the flow rate from 4.0 to 0.25 mL.min^{-1}. In **Figure 3B** is shown the overlapping of all raw spectra obtained during the 40 hours of in-line monitoring at flow rate of 0.25 mL.min^{-1}. Note that the both raw spectra present an offset in its baseline and this behavior is typical for single beam equipment, due to variations in the temperature of the radiation source and the detector.[17] Thus, the spectral

baseline offset was corrected with the application of the first derivative and the corrected spectra can be seen in the **Figure 3C** and **3D**. **Figure 3C** confirms the good reproducibility of the microNIR device since there is only a variation in the spectral range of 1875-2010 nm, which corresponds to different chemical yields due to the different residence times at which the D-fructose solution was exposed to the catalyst. **Figure 3D** shows the spectra of the reaction monitoring after correction of the baseline offset and no significant variation in the region from 1870 to 2010 nm was observed, which indicates that the reaction system remained stable during this period (40 h).

Next, Principal Component Analysis (PCA)[29,30] was used as a tool for exploratory analysis. The PCA reduces the information contained in all wavelengths for only a few principal components (PC). The correlated information from different wavelengths is clustered into the same PC. Furthermore, the first PC contains correlated information of the wavelength with the greatest spectral variance, and this variance explained by each PC decreases with the increase in the amounts of PCs until all variance is explained. The original information from the dataset is then projected onto the space of the principal components.[29,30] The **Figure 4A** and **4B** show the scores and loadings for the PCA model constructed using both date set as explained in the experimental section. **Figure 4C** and **4D** show the scores and loadings for the PCA model constructed using only the date from the in-line reaction monitoring at 0.25 $mL.min^{-1}$ by 40 hours.

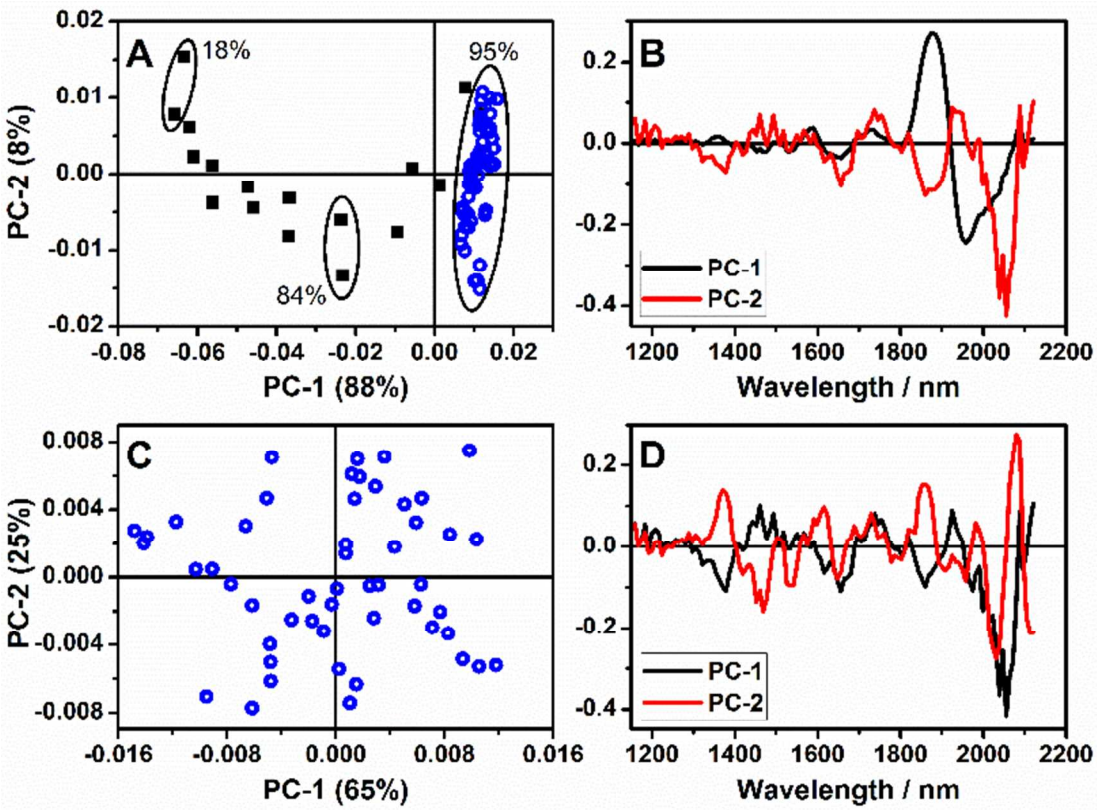


Figure 4. A) scores and; **B**) loadings obtained for the PCA of all sets of samples (flow rates from 4.0 to 0.25 mL.min^{-1}); **C**) scores and; (**D**) loadings obtained for the PCA of samples from the reaction monitoring at 0.25 mL.min^{-1} over 40 hours).

The **Figure 4A** shows that the scores are distributed along PC-1 according to the concentration of 5-HMF (or its chemical yield) obtained from different flow rates. In addition, looking at the loadings of PC-1 in the **Figure 4B** it becomes clear that the wavelengths which have greater relevance for this component are precisely those with greater variation in the 1870-2010 nm range. Furthermore, PC-2 present small random variations of the spectrum, *i.e.* it carries part of the noise information. These two PCs in combination explain 96% of the variance of the dataset. The **Figure 4C** shows the scores for measures of the reaction monitoring, which exhibit a random distribution of the samples in PC-1 and PC-2, each one have 65% and 25% and explain 90% of the variance of the dataset. The loadings shown in **Figure 4D** also display only

information relating to the spectral fluctuations, without having a large spectral variance. The results presented for this PCA model are expected, because the spectral variations in this dataset are caused from the instrumental noises, having little influence from reaction yields fluctuation.[17]

Although the PCA model developed describes well our data, only a visual evaluation of scores and loadings cannot be considered to assess the stability of the reaction system. One of the methods used to address the presence of abnormal variations in a reaction process is based in the control chart construction. Bearing this in mind, and after the reduction of the variables using PCA, we constructed a multivariate control chart using the Hotelling's T^2 and Q-residual to verify catalyst stability over the 40 hours of in-line reaction monitoring.[31-33] To this end, a PCA model was constructed to obtain the limit values of the Hotelling's T^2 and Q-residual with 10 samples, which were analyzed by the qHNMR method. The limit values obtained and the measures taken during the in-line monitoring are shown in **Figure 5A** e **5B**. This was done to ensure that the limits obtained to each control chart were calculated with spectra of samples that present the maximum reaction yield.

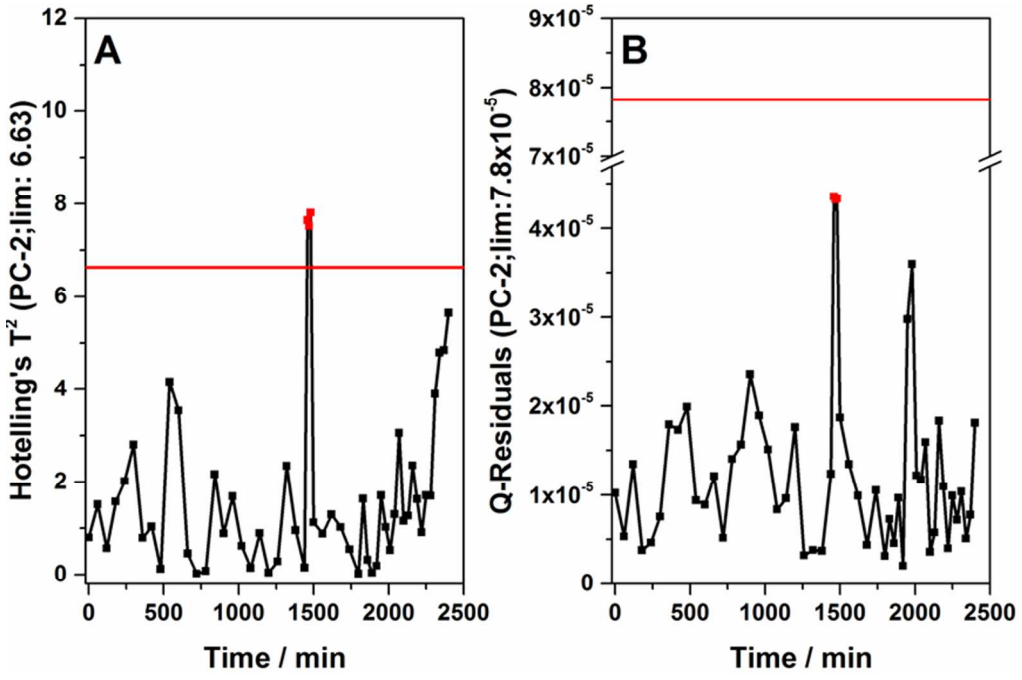


Figure 5. Multivariate control chart building with two principal components based on **A)** Hotelling's T^2; and **B)** Q-residual for monitoring of the reaction over 40 hours (2400 min). The red dots in both charts show the intentional deviation in the process.

Hotelling's T^2 and Q-residual values are applied to detect anomalous samples when PCA is used for exploratory data analysis.[31-33] In the monitoring of a process, these parameters inform when a sample is outside of the control limits. Hotelling's T^2 values are calculated with the information from the first PCs and represent how far a sample is from the center of the PCA model. In this context, the control chart is sensitive to samples that have different absorbance intensities in the same wavelengths, with greater variance, used in the construction of the PCA model.[31-33] Q-residual values are a complementary tool since they are calculated from information not included in the PCA model. Hence, its control chart is useful to detect samples that have different spectral profiles from those which were used in the PCA model construction. Therefore, these values can inform when the reaction progress is out of control.[31-33] For example, if at any given time a measure has a value greater than the limit for Hotelling's T^2 (red line in **Figure 5A**), this indicates that there was a change in the reaction yield and, possibly, there was a variation in the flow rate or temperature. On the other hand, when a measure presents a value greater than the limit for Q-residual, this indicates that there was some type of contamination in the system or the formation of a by-product occurred. In that way, when the measure has both values greater than the limits, a combination of these effects may be occurring, which indicates that there has a process deviation in the reaction system.

Therefore, to verify the reliability of the control chart presented herein, we simulated a process deviation by changing the reaction yield from 95% (0.25 $mL.min^{-1}$) to 84% (0.75

mL.min^{-1}). Note in the **Figure 5** (highlighted in the red dots) that after 1500 min of monitoring at 0.25 mL.min^{-1}, we disturbed the system by changing the flow rate to 0.75 mL.min^{-1} and the control chart using Hotelling's T^2 alerted us about the process deviation. As described before, a deviation on the yield only can be detected by the Hotelling's T^2 chart. Indeed, disregarding the simulation, all measurements are below the limit value in both control charts. This indicates that the system remained stable during the 40 hours of in-line monitoring by the compact microNIR device using the same column filled with Amberlyst-15 at flow rate of 0.25 mL.min^{-1}. Over this time, 27 g of D-Fructose were processed and produced 19 g of 5-HMF in 95% yield, which correspond to a D-fructose/catalyst ratio of 6 mol%.

Conclusions

In conclusion, microNIR spectroscopy was successfully applied for the in-line monitoring of the conversion of D-fructose into 5-HMF in a continuous flow fixed-bed microreactor. Our work also demonstrates that portable NIR spectrophotometers can be used as an alternative analytical tool to benchtop equipment with high-cost and normally used for in-line reaction monitoring studies.[7-14] MicroNIR device give us valuable insights on the events occurring within the process by the construction of Hotelling's T^2 and Q-residual control charts, such as the high stability of the Amberlyst-15, which was used by 8 hours a day, 5 days a week for 5-HMF synthesis. These results also demonstrate the feasibility of applying a continuous flow system to produce 5-HMF at the laboratory scale, which could be expanded for future industrial application. Finally, our findings confirm this low-cost and portable device as a promising tool for in-line reaction monitoring in continuous flow regime, which can be extended to other types of reaction process.

Acknowledgments

The authors gratefully acknowledge financial support from the São Paulo Research Foundation – FAPESP (J.C.P., awards No. 2014/26378-2 and 2014/25770-6), CNPq (J.C.P., award No. 453862/2014-4), and Instituto Nacional de Ciências e Tecnologias Analíticas Avançadas (INCTAA – FAPESP award No. 2008/57808-1 and CNPq award No. 573894/2008-6). We also thank CAPES (R.G.) for fellowship. We are also thankful to the Obesity and Comorbidities Research Center – OCRC (FAPESP, award No. 2013/07607-8) for providing us with the UNIQSIS flow system used in this work.

Supporting Information Available. ^{1}H NMR spectra for different flow rates, PLS plot and pictures of the set-up showing the microNIR coupled to the flow system are presented.

Notes and References

1. (a) T. M. Kohl, B. Bizet, P. Kevan, C. Sellwood, J. Tsanaktsidisa and C. H. Hornunga. Efficient synthesis of 5-(chloromethyl)furfural (CMF) from high fructose corn syrup (HFCS) using continuous flow processing. *React. Chem. Eng*., 2017, **2**, 541. (b) C. Schotten, D. Plaza, S. Manzini, S. P. Nolan, S. V. Ley, D. L. Browne and A. Lapkin. Continuous Flow Metathesis for Direct Valorization of Food Waste: An Example of Cocoa Butter Triglyceride. *ACS Sustain Chem Eng*., 2015, **7**, 1453. (c) J. M. Tukacs, R. V. Jones, F. Darvas, G. Dibó, G, Lezsák and L. T. Mika. Synthesis of γ-valerolactone using a continuous-flow reactor. *RSC Adv*., 2013, **3**, 16283. (d) F. Ferlin, S. Santoro, L. Ackermann and L. Vaccaro. Heterogeneous C–H

alkenylations in continuous-flow: oxidative palladium-catalysis in a biomass-derived reaction medium. *Green Chem*., 2017, **19**, 2510. (e) T. M. Kohl, B. Bizet, P. Kevan, C. Sellwood, J. Tsanaktsidis and C. H. Hornung. Efficient synthesis of 5-(chloromethyl)furfural (CMF) from high fructose corn syrup (HFCS) using continuous flow processing. *React. Chem. Eng*., 2017, **2**, 541. (f) G-Y. Jeong, A. K. Singh, S. Sharma, K. W. Gyak, R. A. Maurya and D-P. Kim. One-flow syntheses of diverse heterocyclic furan chemicals directly from fructose via tandem transformation platform. *NPG Asia Materials.*, 2015, **7**, e173. (g) J. M. Bermudez, J. A. Menéndez, A. A. Romero, E. Serrano, J. Garcia-Martinez and R. Luque. Continuous flow nanocatalysis: reaction pathways in the conversion of levulinic acid to valuable chemicals. *Green Chem*., 2013, **15**, 2786. (h) M. H. Tucker, A. J. Crisci, B. N. Wigington, N. Phadke, R. Alamillo, J. Zhang, S. L. Scott and J. A. Dumesic. Acid-Functionalized SBA-15-Type Periodic Mesoporous Organosilicas and Their Use in the Continuous Production of 5-Hydroxymethylfurfural. *ACS Catal*., 2012, **9**, 1865.

2. (a) S. G. Newman and K. F. Jensen. The role of flow in green chemistry and engineering. *Green Chem*., 2013, **15**, 1456. (b) K. S. Elvira, X. C. Solvas, R. C. R. Wootton and A. J. deMello. The past, present and potential for microfluidic reactor technology in chemical synthesis. *Nat Chem*., 2013, **5**, 905. (c) D. E. Fitzpatrick, C. Battilocchio and S. V. Ley. Enabling Technologies for the Future of Chemical Synthesis. *ACS Central Science.*, 2016, **2**, 131. (d) T. D. McQuade and P. H. Seeberger. Applying Flow Chemistry: Methods, Materials, and Multistep Synthesis. *J. Org. Chem.* 2013., **78**, 6384.
3. (a) H. I. Furkan and B. C. Remzi. Lignocellulosic biomass: a sustainable platform for the production of bio-based chemicals and polymers. *Polym. Chem*., 2015, **6**, 4497. (b) R. A. Sheldon. Green and sustainable manufacture of chemicals from biomass: state of the art.

Green Chem., 2014, **16**, 950. (c) J. Becker, A. Lange, J. Fabarius and C. Wittmann. Top value platform chemicals: bio-based production of organic acids. *Curr Opin Biotechnol.*, 2015, **36**, 168. (d) J. Haveren, E. L. Scott and J. Sanders. Bulk chemicals from biomass. *Biofuel Bioprod Bior.*, 2008, **2**, 41.

4. (a) S. Basudeb, M. and A-O Mahdi. Advances in 5-hydroxymethylfurfural production from biomass in biphasic solvents. *Green Chem*., 2014, **16**, 24. (b) P. T. Siew, Y. Guangshun and Z. Yugen. Hydroxymethylfurfural production from bioresources: past, present and future. *Green Chem*., 2014, **16**, 2015. (c) R. C. Benjamin, E. T. Rodrigo, G. K. Kurtis and T. R. Ronald. Biomass to Furanics: Renewable Routes to Chemicals and Fuels. *ACS Sustainable Chem. Eng.,* 2015, **3**, 2591. (d) W. Tianfu, W. N. Michael and H. S. Brent. Catalytic dehydration of C6 carbohydrates for the production of hydroxymethylfurfural (HMF) as a versatile platform chemical. *Green Chem.,* 2014, **16**, 548.
5. R. Noma, K. Nakajima, K. Kamata, M. Kitan, S. Hayashi and M. Hara. Formation of 5-(Hydroxymethyl)furfural by Stepwise Dehydration over TiO_2 with Water-Tolerant Lewis Acid Sites. *J. Phys. Chem. C.*, 2015, **119**, 17117.
6. (a) V. Sans and L. Cronin. Towards dial-a-molecule by integrating continuous flow, analytics and self-optimisation. *Chem. Soc. Rev*., 2016, **45**, 2032. (b) D. C. Fabry, E. Sugiono and M. Rueping. Online monitoring and analysis for autonomous continuous flow self-optimizing reactor systems. *React. Chem. Eng*., 2016, **1**, 129.
7. (a) A. Lapkin and D. J. C. Constable. Green Chemistry Metrics: Measuring and Monitoring Sustainable Processes*,* Wiley-Blackwell, Chichester, 2008, 344 pages. (b) D. E. Fitzpatrick, C. Battilocchio, S. V. Ley. *Org. Process. Res. Dev.,* 2016, **20**, 386. (c) J. S. Moore and K. F. Jensen. *Angew Chem Int Ed Engl.,* 2014, **53**, 470. (d) J. S. Moore and K. F. Jensen. *Org.*

Process Res. Dev., 2012, **16**, 1409. (e) D. Helmdach, P. Yaseneva, P. K. Heer, A. M. Schweidtmann and A. A. Lapkin. *ChemSusChem.,* 2017, **10**, 3632.

8. (a) C. F. Carter, H. Lange, I. R. Baxendale, S. V. Ley, J. Goode, N. Gaunt and B. Wittkamp. ReactIR Flow Cell: A New Analytical Tool for Continuous Flow Chemical Processing. *Org. Process Res. Dev*. 2010., **14**, 393. (b) A. Perro, G. Lebourdon, S. Henry, S. Lecomte, L. Servanta and S. Marre. Combining microfluidics and FT-IR spectroscopy: towards spatially resolved information on chemical processes. *React. Chem. Eng*., 2016, **1**, 577. (c) A. G. O'Brien, O. R. Luca, P. S. Baran and D. G. Blackmond. In Situ FTIR Spectroscopic Monitoring of Electrochemically Controlled Organic Reactions in a Recycle Reactor. *React. Chem. Eng*., 2016, **1**, 90. (d) T. Durand, C. Henry, D. Bolien, D. C. Harrowven, S. Bloodworth, X. Franck and R. J. Whitby. Thermolysis of 1,3-dioxin-4-ones: fast generation of kinetic data using in-line analysis under flow. *React. Chem. Eng*., 2016, **1**, 82. (e) J. S. Moore, C. D. Smithac and K. F. Jensen. Kinetics analysis and automated online screening of aminocarbonylation of aryl halides in flow. *React. Chem. Eng*., 2016, **1**, 272. (f) J-S Poh, D. L. Browne and S. V. Ley. A Multistep Continuous Flow Synthesis Machine for the Preparation of Pyrazoles via a Metal-Free Amine-Redox Process. *React. Chem. Eng*., 2016, **1**, 101.

9. (a) S. A. Leung, R. F. Winkle, R. C. Wootton and A. J. deMello. A method for rapid reaction optimisation in continuous-flow microfluidic reactors using online Raman spectroscopic detection. *Analyst.,* 2005, **130**, 46. (b) S. Schwolow, F. Braun, M. Radle, N. Kockmann and T. Roder. Fast and Efficient Acquisition of Kinetic Data in Microreactors Using In-Line Raman Analysis. *Org. Process Res. Dev*., 2015, **19**, 1286. (c) S. Mozharov, A. Nordon, D. Littlejohn, C. Wiles, P. Watts, P. Dallin and J. M. Girkin. Improved Method for Kinetic

Studies in Microreactors Using Flow Manipulation and Noninvasive Raman Spectrometry. *J. Am. Chem. Soc.,* 2011, **133**, 3601. (d) T. A. Hamlin and N. E Leadbeater. Raman spectroscopy as a tool for monitoring mesoscale continuous-flow organic synthesis: Equipment interface and assessment in four medicinally-relevant reactions. *Beilstein J. Org. Chem*., 2013, **9**, 1843. (e) E. Cao, M. Sankar, S. Firth, K. F. Lam, D. Bethell, D. K. Knight, G. J. Hutchings, P. F. McMillan and A. Gavriilidis. Reaction and Raman spectroscopic studies of alcohol oxidation on gold–palladium catalysts in microstructured reactors. *Chem. Eng. J*., 2011, **167**, 734. (f) M. Lee, J-P. Lee, H. Rhee, J. Choo, C. G. Yong and E. K. Lee. Applicability of laser-induced Raman microscopy for in situ monitoring of imine formation in a glass microfluidic chip. *J Raman Spectrosc*., 2003, **34**, 737. (g) L. Guerrini and D. Graham. Molecularly-mediated assemblies of plasmonic nanoparticles for Surface-Enhanced Raman Spectroscopy applications. *Chem. Soc. Rev*., 2012, **41**, 7085. (h) M. P. Cecchini, J. Hong, C. Lim, J. Choo, T. Albrecht, A. J. deMello and J. B. Edel. Ultrafast Surface Enhanced Resonance Raman Scattering Detection in Droplet-Based Microfluidic Systems. *Anal. Chem*., 2011, **83**, 3076. (i) Pinho B. and Hartman. R. L. Microfluidics with in situ Raman spectroscopy for the characterization of non-polar/aqueous interfaces. *React. Chem. Eng*., 2017, **2**, 189.

10. (a) S. Krishnadasan, R. J. C. Brown, A. J. deMello and J. C. Mello. Intelligent routes to the controlled synthesis of nanoparticles. *Lab Chip.,* 2007, **7**, 1434. (b) V. Sans, S. Glatzel, F. J. Douglas, D. A. Maclaren, A. Lapkin and L. Cronin. Non-equilibrium dynamic control of gold nanoparticle and hyper-branched nanogold assemblies. *Chem. Sci*., 2014, **5**, 1153. (c) P. J. Kitson, M. H. Rosnes, V. Sans, V. Dragone and L. Cronin. Configurable 3D-Printed millifluidic and microfluidic 'lab on a chip' reactionware devices. *Lab Chip.*, 2012, **12**, 3267.

(d) H. Lu, M. A. Schmidt and K. F. Jensen. Photochemical reactions and on-line UV detection in microfabricated reactors. *Lab Chip.*, 2001, **1**, 22.

11. (a) J. P. McMullen and K. F. Jensen. An Automated Microfluidic System for Online Optimization in Chemical Synthesis. *Org. Process Res. Dev*., 2010, **14**, 1169. (b) J. P. McMullen, M.T. Stone, S. L. Buchwald and K. F. Jensen. An Integrated Microreactor System for Self-Optimization of a Heck Reaction: From Micro- to Mesoscale Flow Systems. *Angew. Chem., Int. Ed*., 2010, **49**, 7076. (c) B. J. Reizman and K. F. Jensen. An Automated Continuous-Flow Platform for the Estimation of Multistep Reaction Kinetics. *Org. Process Res. Dev*., 2012, **16**, 1770. (d) B. J. Reizman, Y-M. Wang, S. L. Buchwald and K. F. Jensen. Suzuki–Miyaura cross-coupling optimization enabled by automated feedback. *React. Chem. Eng*., 2016, **1**, 658. (e) T. C. Malig, J. D. B. Koenig, H. Situ, N. K. Chehal, P. G. Hultin and J. E. Hein. Real-time HPLC-MS reaction progress monitoring using an automated analytical platform. *React. Chem. Eng*., 2017, **2**, 309. (f) N. Holmes, G. R. Akien, A. J. Blacker, R. L. Woodward, R. E. Meadows and R. A. Bourne. Self-optimisation of the final stage in the synthesis of EGFR kinase inhibitor AZD9291 using an automated flow reactor. *React. Chem. Eng*., 2016, **1**, 366.

12. (a) A. J. Parrott, R. A. Bourne, G. R. Akien, D. J. Irvine and M. Poliakoff. Self-Optimizing Continuous Reactions in Supercritical Carbon Dioxide. *Angew. Chem. Int. Ed*., 2011, **50**, 3788. (b) R. A. Bourne, R. A. Skilton, A. J. Parrott, D. J. Irvine and M. Poliakoff, P. Adaptive Process Optimization for Continuous Methylation of Alcohols in Supercritical Carbon Dioxide. *Org. Process Res. Dev*., 2011, **15**, 932. (c) A. McNally, C. K. Prier, D. W. C. MacMillan. Discovery of an α-amino C-H arylation reaction using the strategy of accelerated serendipity. *Science.*, 2011, **334**, 1114.

13. (a) J. J. Haven, J. Vandenbergh and T. Junkers. Watching polymers grow: real time monitoring of polymerizations via an on-line ESI-MS/microreactor coupling. *Chem. Commun*., 2015, **51**, 4611. (b) N. Holmes, G. R. Akien, R. J. D. Savage, C. Stanetty, I. R. Baxendale, A. J. Blacker, B. A. Taylor, R. L. Woodward, R. E. Meadowse and R. A. Bourne. Online quantitative mass spectrometry for the rapid adaptive optimisation of automated flow reactors. *React. Chem. Eng*., 2016, **1**, 96. (c) T. W. T. Bristow, A. D. Ray, A. O'Kearney-McMullan, L. Lim, B. McCullough, A. Zammataro. Utility of Ion Mobility Mass Spectrometry for Drug-to-Antibody Ratio Measurements in Antibody-Drug Conjugates. *J. Am. Soc. Mass Spectrom*., 2014, **25**, 1794. (d) D. L. Browne, S. Wright, B.J. Deadman, S. Dunnage, I. R. Baxendale, R. M. Turner and S. V. Ley. Continuous flow reaction monitoring using an on-line miniature mass spectrometer. *Rapid Commun. Mass Spectrom.,* 2012, **26**, 1999. (e) J. S. Mathieson, M. H. Rosnes, V. Sans, P. J. Kitson and L. Cronin. Continuous parallel ESI-MS analysis of reactions carried out in a bespoke 3D printed device. *Beilstein J. Nanotechnol*., 2013, **4**, 285. (f) M. R. Kristyn, Z. Xing, X. L. Shelly, H. G. Gilles, C. Guilong, Z. Zhongli, F. S. William and H. H. Herbert. Real Time Pharmaceutical Reaction Monitoring by Electrospray Ion Mobility-Mass Spectrometry. *Int. J. Mass Spectrom.,* 2013, **336**, 27.

14. (a) V. Sans, L. Porwol, V. Dragone and L. Cronin. A self optimizing synthetic organic reactor system using real-time in-line NMR spectroscopy. *Chem. Sci*., 2015, **6**, 1258. (b) E. Danieli, J. Perlo, A. L. L. Duchateau, G. K. M. Verzijl, V. M. Litvinov, B. Blumich, F. Casanova. On-Line Monitoring of Chemical Reactions by using Bench-Top Nuclear Magnetic Resonance Spectroscopy. *ChemPhysChem.,* 2014, **15**, 3060. (c) T. H. Rehm, C. Hofmann, D. Reinhard, H-J. Kost, P. Löb, M. Besold, K. Welzel, J. Barten, A. Didenko, D.

V. Sevenard, B. Lix, A. R. Hillson and S. D. Riegel. Continuous-flow synthesis of fluorine-containing fine chemicals with integrated benchtop NMR analysis. *React. Chem. Eng.,* 2017, **2**, 315. (d) M. V. Gomez, H. H. J. Verputten, A. Diaz-Ortiz, A. Moreno, A. de la Hoz and A. H. Velders. On-line monitoring of a microwave-assisted chemical reaction by nanolitre NMR-spectroscopy. *Chem. Commun*., 2010, **46**, 4514. (e) J. Bart, A. J. Kolkman, A. J O-de. Vries, K. Koch, P. J. Nieuwland, H. Janssen, J. van Bentum, K. A. M. Ampt, F. P. J. T. Rutjes, S. S. Wijmenga, H. Gardeniers and A. P. M. Kentgens. A Microfluidic High-Resolution NMR Flow Probe. *J. Am. Chem. Soc*., 2009, **131**, 5014. (f) F. Dalitz, M. Cudaj, M. Maiwald and G. Guthausen. Process and reaction monitoring by low-field NMR spectroscopy. *Prog. Nucl. Magn. Reson. Spectrosc*., 2012, **60**, 52. (g) A. Nordon, A. Diez-Lazaro, C. W. L. Wong, C. A. McGill, D. Littlejohn, M. Weerasinghe, D. A. Mamman, M. L. Hitchman and J. Wilkie. Consideration of some sampling problems in the on-line analysis of batch processes by low-field NMR spectrometry. *Analyst.*, 2008, **133**, 339. (h) E. Danieli, J. Perlo, B. Blumich and F. Casanova. Small magnets for portable NMR spectrometers. *Angew. Chem., Int. Ed*., 2010, **49**, 4133. (i) J. Y. Buser and A. D. McFarland. Reaction characterization by flow NMR: quantitation and monitoring of dissolved H_2 via flow NMR at high pressure. *Chem. Commun*., 2014, **50**, 4234. (j) M. V. Gomez, A. M. Rodriguez, A. de la Hoz, F. JimenezMarquez, R. M. Fratila, P. A. Barneveld and A. H. Velders. Determination of Kinetic Parameters within a Single Nonisothermal On-Flow Experiment by Nanoliter NMR Spectroscopy. *Anal. Chem*., 2015, **87**, 10547. (k) S. S. Zalesskiy, E. Danieli, B. Blümich and V. P. Ananikov. Miniaturization of NMR Systems: Desktop Spectrometers, Microcoil Spectroscopy, and "NMR on a Chip" for Chemistry, Biochemistry, and Industry. *Chem. Rev*., 2014, **114**, 5641.

15. I. Lewis, H. Edwards. Handbook of Raman Spectroscopy. 1st Ed, Boca Raton: CRC Press, 2001, 1072 pages.

16. (a) A. Chanda, A. M. Daly, D. A. Foley, M. A. LaPack, S. Mukherjee, J. D. Orr, G. L. Reid, D. R. Thompson and H. W. Ward. Industry Perspectives on Process Analytical Technology: Tools and Applications in API Development. *Org. Process Res. Dev.*, 2015, **19**, 63. (b) N. N. Misra, Carl Sullivan and P. J. Cullen. Process Analytical Technology (PAT) and Multivariate Methods for Downstream Processes. *Current Biochemical Engineering,* 2015*,* **2***,* 4. (c) S. Challa and R. Potumarthi. Chemometrics-based process analytical technology (PAT) tools: applications and adaptation in pharmaceutical and biopharmaceutical industries. *Appl Biochem Biotechnol*., 2013, **169**, 66.

17. C. Pasquini. Near Infrared Spectroscopy: fundamentals, practical aspects and analytical applications. *Braz. Chem. Soc*., 2003, **14**, 198.

18. A. Gałuszka, Z. M. Migaszewski, J. Namieśnik. Moving your laboratories to the field--Advantages and limitations of the use of field portable instruments in environmental sample analysis. *Environ. Res*., 2015, **140**, 593.

19. L. Sun, C. Hsiung, C. G. Pederson, P. Zou, V. Smith, M. Gunten and N. A. O'Brien. Qualitative and Quantitative Pharmaceutical Analysis with a Novel Handheld Miniature near-Infrared Spectrometer. *J. Near Infrared Spectrosc.*, 2013, **21**, 445.

20. (a) O. Kolomiets, U. Hoffmann, P. Geladi and H. W. Siesler. Quantitative determination of pharmaceutical drug formulations by near-infrared spectroscopic imaging. *Appl Spectrosc.,* 2008, **62**, 1200. (b) C. A. dos Santos, M. Lopo, R. N. Páscoa and J. A. Lopes. A review on the applications of portable near-infrared spectrometers in the agro-food industry*Appl Spectrosc*., 2013, **67**, 1215. (c) R. L. Ribessi, T. A. Neves, J. J. R. Rohwedder, C. Pasquini,

I. M. Raimundo, A. Wilk, V. Kokoric and B. Mizaikoff. iHEART: a miniaturized near-infrared in-line gas sensor using heart-shaped substrate-integrated hollow waveguides. *Analyst.*, 2016, **141**, 5298.

21. R. Galaverna, M. C. Breitkreitz and J. C. Pastre. Conversion of d-Fructose to 5-(Hydroxymethyl)furfural: Evaluating Batch and Continuous Flow Conditions by Design of Experiments and In-Line FTIR Monitoring. *ACS Sustainable Chem. Eng*., 2018, **6**, 4220.
22. J. Dai, L. Zhu, D. Tang, X. Fu, J. Tang, X. Guo and C. Hu. Sulfonated polyaniline as a solid organocatalyst for dehydration of fructose into 5-hydroxymethylfurfural. *Green Chem*., 2017, **19**, 1932.
23. Flow Conditions: 2.25 g of D-Fructose was dissolved in 50 mL of *i*-PrOH/DMSO (15%) and a glass column (OmniFit® 10 mm i.d. × 50.0 mm length) was packed with Amberlyst-15 (2.0 g, void volume of 2.8 mL) operating at 110 °C along with a 5 bar back-pressure regulator. Flow rate of 2 and 0.25 $mL.min^{-1}$ gave us yields of 50 and 95% for 5-HMF, respectively.
24. E. W. Ciurczak and Donald A. Burns. Handbook of Near-Infrared Analysis, 3rd Edition. Boca Raton: CRC Press, 2007, 834 pages.
25. Y. Chen, Y. Ozakib and M. A. Czarnecki. Molecular structure and hydrogen bonding in pure liquid ethylene glycol and ethylene glycol–water mixtures studied using NIR spectroscopy. *Phys. Chem. Chem. Phys*., 2013, **15**, 18694.
26. (a) C. Jinzhu, L. Kegui, C. Limin, L. Ruliang, H. Xing and Y. Daiqi. Conversion of fructose into 5-hydroxymethylfurfural catalyzed by recyclable sulfonic acid-functionalized metal–organic frameworks. *Green Chem*., 2014, **16**, 2490. (b) L. Yuan, L. Hui, S. Changhua, G. Xiaomin, L. Huaming, Z. Wenshuai, Y. Sheng and H. Changri. The dehydration of fructose

to 5-hydroxymethylfurfural efficiently catalyzed by acidic ion-exchange resin in ionic liquid. *Bioresource Technol.*, 2013, **133**, 347.

27. D. Prat, O. Pardigon, H-W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani and P. Hosek. Sanofi's Solvent Selection Guide: A Step Toward More Sustainable Processes. *Org. Process Res. Dev.*, **2013**, *17*, 1517.
28. G. F. Pauli, T. Gödecke, U. B. Jaki and D. C. Lankin. Quantitative 1H NMR. Development and Potential of an Analytical Method: An Update. *J Nat Prod.,* 2012, **4**, 834.
29. S. Wold. Principal component analysis. *Chemometr. Intell. Lab.,* 1987, **2**, 37-52.
30. R. Bro and A. K. Smilde, Principal component analysis. *Anal. Methods.*, 2014, **6**, 2812.
31. P. Phaladiganon, S. B. Kim, V. C. P. Chen and W. Jiang. Principal component analysis-based control charts for multivariate nonnormal distributions. *Expert Syst Appl.*, 2013, **40**, 3044.
32. K. Laursen, M. A. Rasmussen and R. Bro. Comprehensive control charting applied to chromatography. *Chemometrics Intell Lab Syst.,* 2011, **107,** 215.
33. A. Nijhuis, S. de Jong and B. G. M. Vandeginste. Multivariate statistical process control in chromatography. *Chemometrics Intell Lab Syst.,* 1997, **38**, 51.

Table of Contents Graphic