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MICRO PROCESS ENGINEERING FOR FINE CHEMICALS

NOVEL PROCESS WINDOWS, SCALE OUT AND PRODUCTION-ORIENTED CASE STUDIES

Due to their unique features such as enhanced mass and heat transfer and inherent safety due to small reactor hold-up volumes microstructured reactors have found their way not only to lab-scale investigations but also in the meantime to numerous pilot- and production scale applications especially in the field of fine chemicals.

Microstructured reactors offer unique features such as enhanced mass and heat transfer and inherent safety due to small reactor hold-up volumes which can be exploited for continuous chemical processing [1-6]. A major trait of microreactor application derived therefrom is the attempt to adopt the reactor to the needs of the reaction and not to adopt the reaction/process conditions to limited performance capacities of conventional equipment. While this may lead to improvements using given chemical protocols, even more potential can be seen in allowing unusual process conditions not manageable with conventional equipment, allowing operating in “novel process windows” [7]. Furthermore, major topics in the area are currently validated approaches to come from lab- to pilot- and production scale and also solutions for continuous work-up systems.

In the following after general remarks, three production-oriented case studies from the scope of work of IMM will be given, allowing discussing and underpinning the above mentioned aspects of Chemical Micro Process Engineering.

Microreactor applications in the area of fine chemistry

Microreactors are in the meantime not only established in lab scale experimentation but have found their way to numerous pilot and production plants. So, in one of the latest reviews [8] concerning Chemical Micro Process Engineering, 27 industrial pilot and production cases are reported. Investigating these examples it is found that the focus of microreactor application is currently in the area of fine chemicals when applications in the area of energy are not taken into account. The same conclusion is reached when reviewing patents in the field of micro process engineering [9].

The work done by the Lonza AG, where 86 of their exclusive synthetic processes were examined with regard to a potential microreactor application, allows a deeper insight in the scope and in the motivation to apply microreactors in the fine chemical/pharmaceutical industry [10, 11]. Based solely on kinetic considerations, 50% of the reactions in question would benefit from a continuous processing and for most of them (44% of the total) a microreactor would be the preferred reaction device. Limits, however, do arise due to the presence of solids in the process, which currently excludes a large part (63%) of these reactions for microreactor application. Nevertheless, still 17% of all processes considered by the Lonza AG could benefit from the application of microreactors. For small scale and pilot productions, speed in process R&D, as well as the avoidance of scale-up issues were seen as the main drivers for microreactor application. In the case of large scale production, a gain in yield and safety are more decisive.

Novel process windows

The concept of “novel process windows” may include handling of instable intermediates, safe processing (including working in the explosive regime), setting reaction temperature and/or pressure at unusually high levels, and more. Illustrative examples for the “novel process windows” concept are the aqueous Kolbe-Schmitt synthesis using resorcinol in a microreactor under high pressure and high temperature conditions [12] and the room temperature continuous operation mode for the synthesis of phenyl boronic acid [13]. In the first case, the batch process was transferred on the lab-scale from a batch process under reflux condition (water as solvent) to a continuous processing in a mixer-tube set-up at higher temperatures (up to 220 °C) and higher pressure (up to 40-70 bar) at IMM. The higher temperature naturally accelerates reaction speed. The higher pressure is necessary to keep the reaction media in single phase state. The realisation of high temperature and pressure is quite easily feasible in the mixer-tube set-up. Compared to the batch process, a reduction of reaction time by a factor of about 2,000 and an increase of space-time yield by a factor of 440 were reached. In the case of the phenyl boronic acid synthesis from phenyl magnesium bromide and boronic acid trimethyl ester performed by Clariant GmbH in Frankfurt, Germany on a pilot-scale level, the improved mixing and heat transfer properties of a continuous micromixer-tube set-up allowed to operate the process at room temperature with no loss in selectivity compared to the batch process which requires cryogenic process conditions.

Cost analysis of microreactor applications

The increase of space-time yield is often decisive to make microreactor processing profitable when compared to batch or semi-batch operation as a benchmark. Regarding the above mentioned Kolbe-Schmitt synthesis, cost analysis revealed - not unexpectedly - that it makes no sense to change the batch process to a continuous (microreactor)process without changing the process parameters. Only the achieved increase in space-time yield by operating under novel process conditions rendered the continuous process cost competitive [14]. Corresponding considerations can also be made for large-scale processes in the range of 10,000 t/a [14]. Furthermore, cost analysis in the case of the synthesis of precious fine chemicals revealed that the microreactor cost itself contributes only marginally to the complete cost allocation [15].

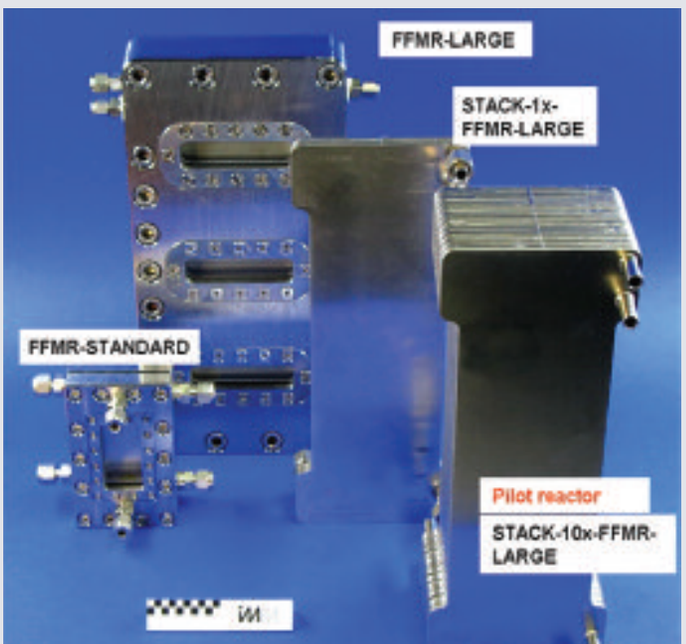

Fig. 1 - Falling Film Microreactors of IMM illustrating the approach followed to come from lab- to pilot-scale throughput

Three case studies and considerations to reach production scale

Although the number of pilot and production scale microreactor applications is already impressive, there is still the need for more documented and validated approaches to reach production scale. In the following, three examples are given out of the scope of IMM's work within publicly funded projects.

1st Case study: continuous gas/liquid-contacting

The standard Falling Film Microreactor (FFMR-STANDARD) for gas/liquid-reactions developed by IMM in which liquid films of a few tens of micrometer thickness and interfacial areas up to 20,000 m^2/m^3 combined with an effective heat exchange can be obtained represents a broadly used microstructured lab tool in the area of gas/liquid contacting (see e.g. [16-19]). In the context of the German publicly funded project µ.Pro.Chem (Förderkennzeichen 16SV1991) with the partners Basf AG, Evonik Degussa GmbH, and IMM one topic was to transfer this lab-scale device which is successfully applied for the Evonik Degussa GmbH process of an ozonolysis towards pilot scale and production scale [20]. Targeted pilot throughput is thereby for the liquid in the order of about 10 l/h which represents a one-hundred fold increase compared to the lab-scale device FFMR-STANDARD. To reach production scale, a further increase of throughput by a factor of 10-100 is required.

The followed approach by IMM to reach pilot scale was first to design a larger base unit with an about tenfold increase of structured surface area and then in a next step to design a pilot reactor based on (tenfold) internal numbering-up. The direct route by a parallelization (either internal or external numbering-up) by a factor of 100 starting from the lab scale device FFMR-STANDARD was regarded as too challenging with respect to an equal gas/liquid flow distribution. Therefore, in the first step a falling film microreactor with a larger reactor plate has been developed and realized. The microchannel width and depth has been kept constant compared to FFMR-STANDARD while both the number of channels and the length of the channels have been increased by a factor of $10^{0.5}$ keeping the principal design in this new falling film microreactor (FFMR-LARGE) similar to the one of the FFMR-STANDARD. The next step then was to come to a pure plate design for this larger base unit as basis (called STACK-1x-FFMR-LARGE) for the later internal numbering-up resulting in the pilot reactor (called STACK-10x-FFMR-LARGE). Corresponding prototypes have been successfully realized (see Fig. 1).

An essential issue for the desired performance of the reactors is to ensure equal distribution of the gas and the liquid in the reactor. This refers both to the distribution concerning the single reaction channels on a reactor plate but also to the distribution of the fluids over the stack of plates in the pilot reactor. The reactor development work has therefore been accompanied and supplemented by experimental work dealing with the characterization of the reactor performance and also with studying equal distribution of gas and liquid in the reactor for all developed reactor types mainly using the CO_2 absorption in an aqueous sodium hydroxide solution as test system. These investigations have confirmed that the larger base unit FFMR-LARGE can be operated at a tenfold throughput as compared to FFMR-STANDARD while keeping similar reactor performance. For the case of the CO_2 absorption this was not unexpected. However, it has to be kept in mind that for other chemistries this is not necessarily true since the operation conditions between FFMR-STANDARD and FFMR-LARGE differ: liquid throughput per channel is larger as well as the residence time of the liquid in the case of FFMR-LARGE compared to FFMR-STANDARD. Also it was shown that the step from FFMR-LARGE to STACK-1x-FFMR-LARGE has not changed reactor performance. In this case, number and dimension (including length) of the channels has been kept constant; thereby confirming that in the new pure plate design equal distribution is ensured by the design as in FFMR-LARGE. The experimentation with the first prototype of the pilot-scale reactor STACK-10x-FFMR-LARGE revealed some underperformance. In the following the pilot reactor was modified in order to measure liquid flow rate per plate at the outlet of each plate. In the following investigations focused on improving liquid distribution over the plate stack by inserting adjusted flow distributer inserts into the central feed tube. With this modification

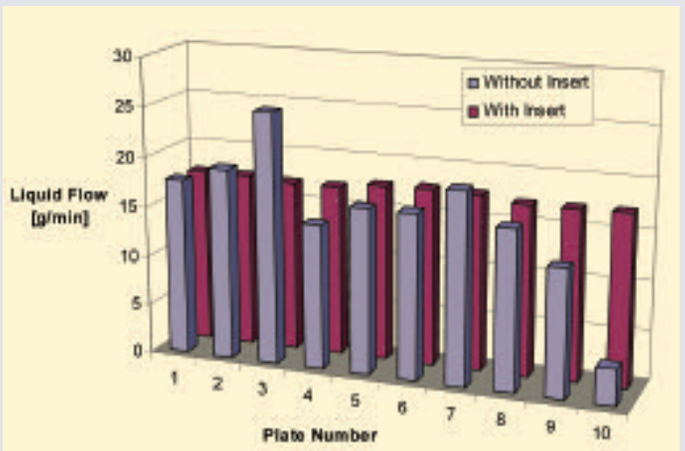

Fig. 2 - Flow distribution in first prototype of a pilot-scale falling film microreactor consisting of a stack of ten functional elements without feed insert (front) and with feed insert (back)

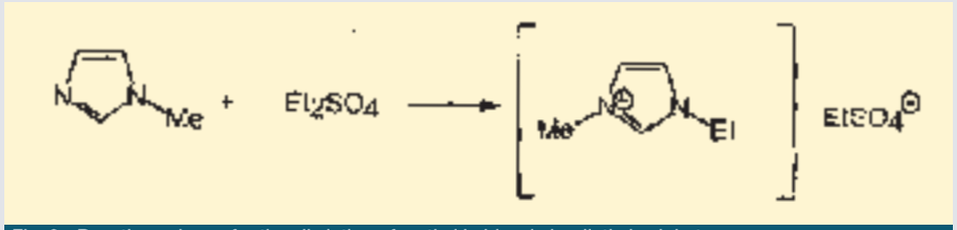

Fig. 3 - Reaction scheme for the alkylation of methyl imidazole by diethyl sulphate

it was possible to attain liquid equal distribution (see Fig. 2). Finally, the second prototype of the pilot-scale reactor STACK-10x-FFMR-LARGE-V2 has been successfully implemented in the pilot plant of Evonik and operated for the ozonolysis reaction.

This example makes tangible that ensuring equal distribution is one of the most important issues during reactor development.

As mentioned previously, production scale requires a further increase of throughput by a factor of 10-100. Taking the realized pilot reactor as starting point, production scale could in principle be reachable by putting the corresponding amount of reactors in parallel, i.e. by pure external numbering-up. Alternatively, it is conceivable to follow a combined internal and external numbering-up. The decision depends on several factors e.g. costs for periphery to control a large number of reactors operated in parallel, feasible internal numbering-up factor with ensured equal distribution of the fluids, and fabrication issues (e.g. the size of a welded reactor may be limited to the size of the oven required during the fabrication). Albeit in the specific case a concrete answer was not derived, it illustrates which additional topics could come up to reach large production throughputs.

Besides the concepts of numbering-up discussed so far (also called scale-out as opposed to scale-up), further general approaches for reaching production scale are under consideration. Smart dimensioning of the production reactor is one of them whereby it is tried to work with the largest structures feasible while keeping the process benefits of reactor structuring. Furthermore, production scale may also be reached by representing only the decisive step by a microreactor while keeping the rest of the plant untouched (plant upgrading, retrofit) or using a multi-scale design.

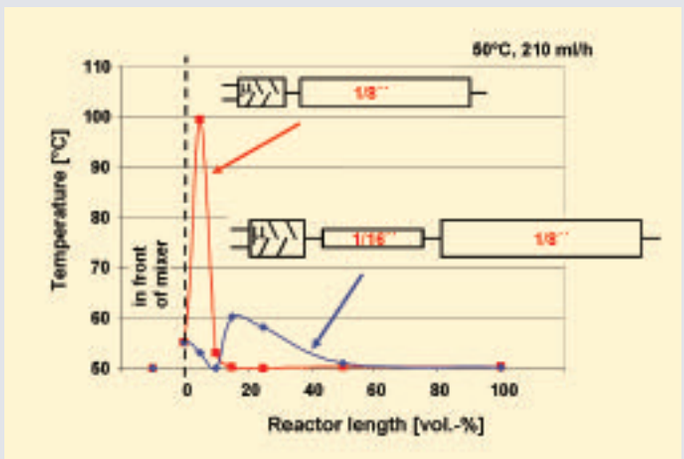

Fig. 4 - Temperature profile in the micromixer-tube set-up for two different tube diameter dimensions

2nd Case study: ionic liquid synthesis

In the framework of the EU project IMPULSE [21], the limitations of conventional batch processing and the potential of continuous microreactor based operation for the highly exothermic alkylation of methyl imidazole by diethyl sulphate leading to an ionic liquid has been investigated in detail (Fig. 3). The industrial partner involved thereby is Solvent Innovation GmbH, Köln, Germany in the meantime having become a part of Merck KGaA, Darmstadt, Germany.

State-of-the-art production for this ionic liquid is done via a batch operation where one major quality control factor is product colour. The formation of some ionic liquids is a very fast highly exothermic reaction with the danger of hot spot formation negatively impacting product quality. Therefore, in conventional batch operation slow dosing below the kinetic limits is performed leading to long reaction times (in the range of hours) and reduced plant capacity. Here, due to advantages in heat and mass transfer the employment of microreactors offers a way of circumventing this problem.

In a first step, a quite simple set-up consisting of a micromixer to contact the undiluted reactants followed by a Teflon tube with an outer diameter of 1/8" and a total inner volume of 7.5 ml as residence time section both embedded in a thermostat bath allowed the transfer of the process into a continuous one with required residence times in the range of only a few minutes for almost complete conversion. The obtained ionic liquid was already only slightly yellow in colour. The tube section was equipped with thermocouples distributed over the length of the tube to monitor the temperature profile over the whole length of the tube. Fig. 4 shows the obtained profile for a total flow rate of 210 mL/h.

The temperature profile clearly shows the formation of a hot spot at the beginning of the tube section. Albeit this, product quality was already improved compared to lab-scale batch processing because coloring already was significantly reduced. In a next set of experiments the first part of the 1/8" tube section (10% of the original total inner volume) was exchanged by a 1/16" tube section

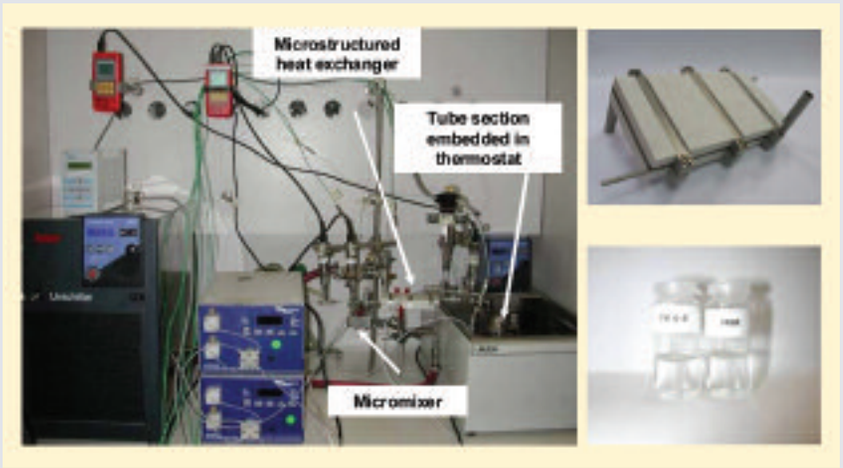

Fig. 5 - Second generation microreactor-based experimental set-up for ionic liquid synthesis

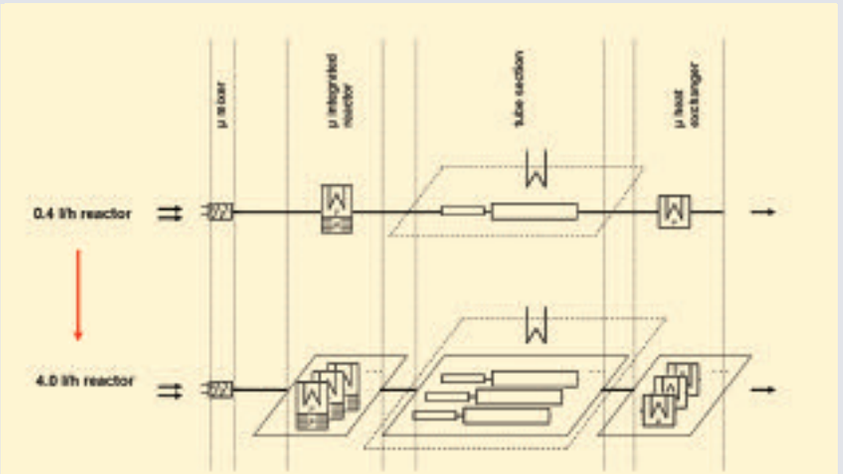

Fig. 6 - Illustration of approach followed to come from lab- to pilot-scale in the case of the microreactor based ionic liquid synthesis

with the same total inner volume. The smaller dimension leads to an improvement in the heat removal capacity. Repetition of the experiments now led to a reduction of the hot spot from 50 °C to 10 °C (see Fig. 4). In the following tube section, temperature decreases steadily to finally bath temperature. Here, the reaction heat removal capacity of the 1/8" section is sufficient. This first lab-scale experiments and the used set-up nicely illustrates the idea to adapt the reactor to the need of the reaction requirements.

Based on the results obtained, an adapted reactor set-up already envisioning higher production throughput (about 4-8 L/h) has been developed. In this concept, a microstructured heat exchanger forms the reactor part which has to handle the largest heat release, i.e. replacing the 1/16" tube part by an even more efficient heat exchanger structure, followed again by a tube section for the residence time required to complete the reaction [22]. For a total flow rate of 0.4 l/h, a first prototype of this micro reactor has been realized and was successfully tested (see Fig. 5).

As mentioned above, the realized reactor concept already envisioned higher throughputs. The approach thereby (see Fig. 6) will be to increase throughput of the microstructured heat exchanger by adding more identical reactor plates to the reactor stack (internal numbering-up [23]). The following tube section will be replaced by a multi-tubular reactor. In the case of the micromixer, the micromixer used can be kept. The experiments have shown that the reaction is not mixing sensitive and therewith the only function of the micromixer is to ensure complete mixing before the mixture is entering the microstructured heat exchanger while keeping the therefore required volume small. A corresponding demonstrator unit will be realized in 2008.

3rd Case study: continuous two-phase liquid/liquid-contacting

In the framework of the German publicly funded BMBF project POKOMI (Förderkennzeichen 16SV1984), the synthesis of OLED materials via Suzuki-polycondensation employing microreactor technology is investigated. The corresponding industrial partner involved therein is Merck KGaA, Darmstadt, Germany. The focus of the work performed by IMM was the development, realization, characterization, and application of suited microstructured reactors for biphasic liquid/liquid contacting as well as the establishment of a continuous work-up system allowing pilot scale throughput [24].

Generally, the Suzuki coupling is a homogeneously palladium catalysed C-C cross coupling reaction with industrial applications in the synthesis of flavours, fine chemicals, and active pharmaceutical ingredients (API). Here, Suzuki-polycondensation is targeted for the synthesis of polymer light emitting diodes (PLED). State-of-the-art Suzuki reactions are carried out in a liquid-liquid biphasic solvent system in a batch process. However, a limiting factor is the interfacial area provided for the reaction to proceed which has to be sufficiently large to ensure no mass transfer limitation.

The two phase solvent system used in the project, a ternary mixture of dioxane/toluene/water in a ratio of 1:1:1, does not form a stable emulsion and therefore coalescence occurs, dramatically decreasing the interfacial area. In order to overcome this problem of coalescence, two different reactor concepts were developed, one being based on the repeated destruction of formed solvent droplets by redispersion units along the reaction pathway of a (micro)structured reactor (called redispersion microreactor), the second using a high porosity metal foam to ensure continuous mixing throughout the reactor.

In the redispersion microreactor concept, redispersion can be accomplished either by an array of fine microstructured channels set in the reactant flow from time to time or in the same manner by a metallic foam insert. The proof-of-principle, i.e. that the structured inserts refresh the dispersion and break-up coalesced droplets, has been done with a lab-scale reactor with exchangeable inserts and an inspection window to follow the two-phase flow pattern within the reactor [25]. This reactor concept has not been followed further because in the project the preference was given to the second reactor concept. Nevertheless, the reactor concept is used successfully in other lab-scale investigations of IMM.

The second reactor concept investigated employed a metal foam filled tube reactor whereby the metal foam should function as a form of a static continuous mixer-reactor. Again, it was first aimed to establish a proof-of-concept using a lab-scale reactor which consists as major reactor part of a 1/2" tube filled with the metal foam of 95% porosity and 400 μm pore size (see Fig. 7).

A great advantage of the foam filled reactor concept is the low pressure drop over the foam structures. The pressure drop over the reactor was measured for different velocities and ranged from almost no pressure drop for sufficiently small velocities up to 2.2 mm/s to 1.2 bar at the highest investigated velocity of 4.1 mm/s.

In order to test the reactor performance in a real Suzuki coupling reaction, the cross coupling of phenylboronic acid and 4-bromotoluene in the presence of a palladium-tri-(o-tolyl)-phosphine catalyst was carried out. As expected, an increase in reaction temperature leads to an increase in conversion as shown in the graph of Fig. 8. At best so far, a conversion of about 90% at 140 °C was reached. Here it has to be noted that the reaction

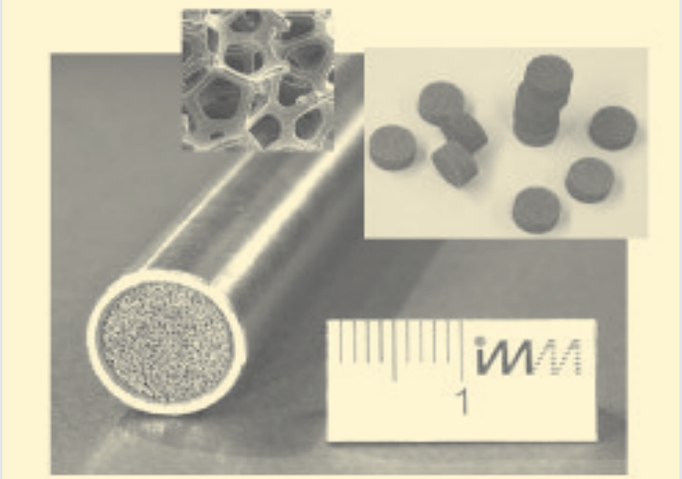

Fig. 7 - Metal foam filled tube reactor. Metal foam contains 95% porosity and 400 μm pore size

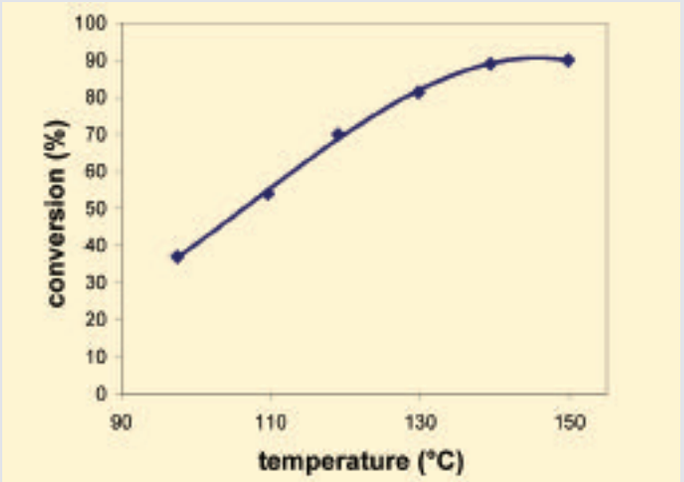

Fig. 8 - Conversion versus temperature for the Suzuki coupling of phenylboronic acid and 4 bromotoluene

temperature lies well above the boiling point of the employed solvent mixture which is due to the use of an overpressure in the reactor of 7-14 bars following the concept of "Novel Process Windows" to enable chemistry in microreactors [26].

Since only a very small amount of homocoupling product of the boronic acid derivate is observed, selectivity is about equivalent to conversion. Given a conversion of about 90% and the used flow rate, the space-time-yield amounts to 125 kg/m^3 h.

After this successful pre-testing, currently a reactor is manufactured using this concept of metal foam inserts as static mixers to be employed in the Suzuki-polycondensation at larger throughputs. The pilot reactor will differ from the lab-scale reactor with regard to flow velocity in the foam. It has to be investigated if the underlying assumptions regarding reactor performance can be shown on pilot scale.

This application example also allows to address an additional aspect not often openly covered in literature. As mentioned above, besides developing microreactor concepts to enable the performance of Suzuki-polycondensation, a continuous work-up process was to be established allowing pilot scale throughput. IMM therefore developed a set-up consisting of three settlers including two water washing steps (see Fig. 9). The set-up includes IMM micromixers for contacting of the polymer solution with the washing water.

The developed washing unit is suited for total flow rates between 1.8 and 6 l/h. It could be in particular proven that a stable and time-independent filling and discharging of the settler occurs without any flooding or draining effects. Additionally, the dynamic operation during system start-up has been investigated, especially concerning the filling of the siphons.

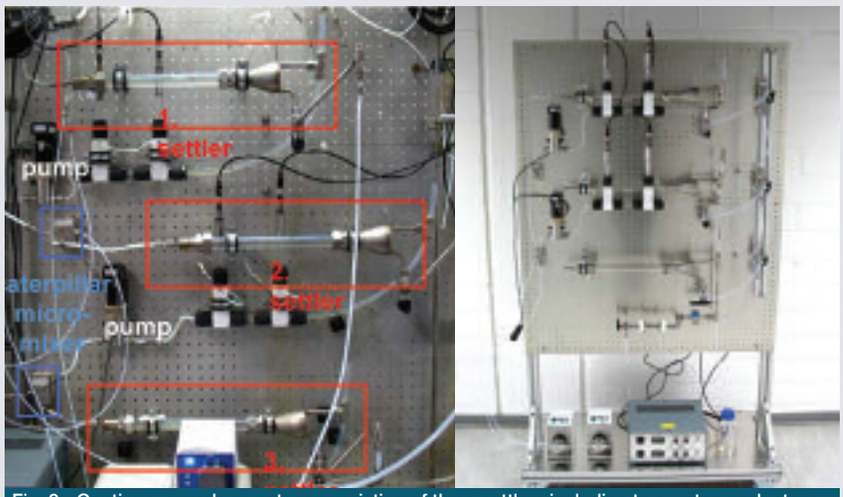

Fig. 9 - Continuous work-up set-up consisting of three settlers including two water wash steps

Conclusions

Microstructured reactors are established as lab tools in numerous application areas. Furthermore, there is an already impressive and steadily growing list of pilot and production examples, especially in the area of fine chemicals. Work on the topic of scale-up is still considered as one major focus in current activities in the field. Furthermore, there is a request for continuous separation technologies.

Acknowledgements: The work described has been enabled especially by the public funded EU-project IMPULSE and the BMBF-projects POKOMI & µ.Pro.Chem funded by the German Governement. Further thanks go to all people involved in the cited projects, at IMM but also from the project partners.

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ABSTRACT

Ingegneria di processo con microreattori per la produzione di fine chemicals. Alcuni esempi di applicazioni

Reattori micro strutturati hanno già trovato numerose applicazioni non solo al livello di laboratorio ma anche per produzioni su scala pilota o industriale, specialmente nel settore dei prodotti di chimica fine, grazie alle loro caratteristiche peculiari di più efficiente trasferimento di massa e di calore e per la loro migliore sicurezza operativa.

Vengono qui descritti in dettaglio tre esempi di ricerca applicata effettuati da IMM (Institut für Mikrotechnik Mainz GmbH) in stretta collaborazione con industrie tedesche.