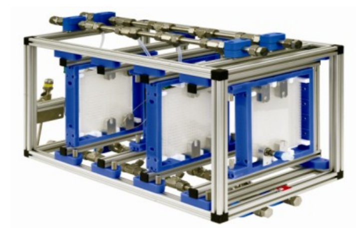
THE COUNCIL FOR CHEMICAL RESEARCH
Advancing the Chemical Enterprise through Collaboration

Proceedings from CCR's

14th New Industrial Chemistry and Engineering (NIChE) Conference

on
Micro-Reactor Technologies:
A Critical Tool for Process Optimization and Intensification



The Council for Chemical Research sponsored its 14th NIChE conference on Micro-Reactor Technologies on September 21-23, 2009, at the National Institute of Standards and Technology in Gaithersburg MD.

The conference goal was to inform the chemical science and technology research community of the state-of-the-art of micro-reactor technology and related enabling technologies. The sessions were designed to give a rationale for the use of micro-reactors for R&D as well as production; describe technological advances and applications of micro-reactors; and feature a variety of case studies as well as other enabling technologies such as sensors, separations etc.

Micro-reactors can provide the tools for enhancing sustainability of many processes by:

- Reducing solvent use
- Increasing yield while minimizing waste
- Increasing productivity via continuous processing
- Increasing reaction rates via reduced volumes

The meeting provided a venue for world-leading experts to describe transformational technology and lead animated discussions that included topics from green and novel chemistries to innovative process and product design.

Conference support was provided by the US EPA, Corning, 4Rivers and CPAC; and the meeting was hosted by NIST.

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Opening Remarks

The conference was opened by **Mel Koch**. Dr Koch is the Executive Director of the Center for Process Analytical Chemistry (CPAC) at the University of Washington. CPAC, established in 1984, is a consortium of Industrial, National Laboratory and Government Agency Sponsors addressing multidisciplinary challenges in Process Analytical Technology (PAT) and Process Control through fundamental and directed academic research.

Dr Koch provided a short description of the history of ***Micro-Reactors*** that led to this timely CCR sponsored workshop on micro-reactors. The workshop focused on the technical aspects of micro-reactors and the technologies that enable them, and attracted interest from a variety of industrial organizations.

In the late 1990's there was a presentation at a technical gathering called *Total Micro-Analytical Systems,* where a plenary lecture was delivered by Professor Ehrfeld of the IMM (Institute for Micro-technology at Mainz). Ehrfeld described micro-reactor developments at IMM and predicted that any chemical that had a production need of up to 50 tons per year was a candidate for using micro-reactors in a number-up configuration. This was an intriguing concept that generated much discussion, as it challenged many disciplines to think about chemical production in a different way.

Early work (in the 1980's) on the concept of using micro-reactors for 'just-in-time' manufacture of hazardous materials was also pursued by organizations in the US, including PNNL, DuPont, MIT, etc. but it did not achieve a demonstration status. However, it is noteworthy that in the past 15 years there have been a number of successful technical developments in the world of micro-unit operations and several commercial offerings of these developments. Successful production operations are being publicized, including an impressive example from Hans Wurziger of Merck in Germany where 20 tons of production with significant gains in yield, along with impressive reductions in energy, waste, solvent use, and footprint of operations were demonstrated. Ehrfeld's prediction was being realized.

This NICHE workshop on Micro-reactors brought together a variety of key technical people to present research and commercialization results in the micro-reactor field. Also, a number of experts were invited to describe technical advances in the areas of measurement science, separations, and sampling. These advances are considered enabling technologies that allow the use of micro-reactors to monitor the unit operations, and separate the products of the reaction. These technologies are critical to effective use of the micro-reactors in industrial processes.

Session 1

Why Micro-Reactors for Research, Development and Production?

The first plenary session was comprised of speakers from industry, academia, and government. Their charge was to make the case for the use of micro-reactors in both R&D and in scaled-up production.

Sergio Pissovini of Corning-France made the first technical presentation entitled *Advanced Flow Reactors: Teaming up with Chemistry and Chemical Engineering for "Greener" Processes and Improved Economics.* His presentation on flow reaction technology focused on the advantage of having one tool for process development on up to pilot and industrial production. The "cascaded" advantages of solvent reduction and lower energy consumption prove that the technology is providing significant operating and investment cost reduction jointly with a "greener" overall process.

Martin O'Connell from the Institut für Mikrotechnik Mainz GmbH (IMM), Germany and Co-Authors from that Institut and the Eindhoven University of Technology (TU/e), The Netherlands, provided a presentation entitled *Micro Process Engineering for Fine Chemistry and Fuel Processing – From Lab to Pilot Production towards Sustainability.* The presentation illustrated how milli- and micro- process technologies contribute to (a) green processing, (b) process intensification and (c) sustainability in the chemical industry. The role that novel process windows play was demonstrated using examples from the field of fine chemistry (often non-catalytic). Catalytic applications in micro process technology in the field of heterogeneous catalysis, particularly for fuel processing to generate hydrogen for fuel cells was discussed.

The Status and opportunities of Micro-reactors in Discovery and Development was addressed by Klavs Jensen of MIT in the US. He affirmed that continuous micro-reactors are a transformational new technology since they provide integrated systems capable of providing new understanding of fundamental chemical processes as well as rapid, continuous discovery and development of new products with less use of resources and waste generation. He cited examples where Microsystems were used to perform processes that are difficult to accomplish by conventional techniques. The potential for scaling micro-reactor results to production was also discussed.

Michael Gonzalez from the US Environmental Protection Agency, Office of Research and Development presented a paper entitled Merging Green Chemistry, Process Intensification, Process Analytics, and Metrics for Optimizing Sustainability in Chemical Synthesis. The US EPA is particularly interested in the pursuit of this technology to reduce the environmental footprint of chemical processing. He emphasized the growing awareness of the necessity to merge disciplines and knowledge when tackling a new chemical synthesis or making improvements to an existing process.

Session 1 Discussion Period

In order to frame the discussion, participants, particularly those from industry, were asked to identify barriers to the more widespread use of micro-reactors. Ray Chrisman facilitated the discussion.

Barriers identified included:

- Issues with solids
- Existing infrastructure is not compatible
- Varying degree of understanding/education of the capabilities of micro-reactors

Experts generally agreed that:

- Not all reactions are applicable to micro-reactor technology (perhaps approximately 10-20%).
- Understanding of which type of reactions are applicable is not clear throughout the community.
- Niche markets are perhaps the more applicable areas – pharma, foods, fragrance, specialty chemicals.
- The importance of multi-disciplinary teams - chem and chem. E - working together at the outset was emphasized.
- For current commodities, the key issue is risk of changing what is working.
- Enabling new products or markets is a key driver for the use of micro-reactors.
- Micro-reactors often offer an advantage over traditional technologies by reducing time to market.

Session 2

Technological Advances and Applications of Micro-Reactors

The second session focused on applications of state-of-the-art micro-reactor technology. Doug Galloway of UOP opened with a presentation entitled *Application of Micro-Reactors in Scale-up Operations.* He stated that pace of process development, and the search for novel catalysts or adsorbant materials, also requires the development and application of advanced characterization tools. The talk therefore focused on the use of micro-reactors and related technologies in characterization tools that are used at UOP during process development.

Paul Watts of the University of Hull, UK and Chemtrix BV in the Netherlands followed with a presentation titled *Enhanced Chemical Synthesis in Micro-Reactors.* He asserted that micro-reactor technology is an emerging technique that enables those working in research and development to rapidly screen reactions utilising continuous flow, leading to the identification of reaction conditions that are suitable for use at a production level. He said that these technologies offer advantages over conventional R&D methodologies that include improved safety, efficiency, and shorter development cycles.

A presentation titled *Modular Microreaction Systems – From Lab to Production* was made by Samrat Mukherjee of Bayer Technology Services Americas. He focused on the important role of this new technology in the chemical pharmaceutical industry, in the areas of research, development and production. Individual modules – such as micro-mixers, micro-heat-exchangers, microreactors, sensors and actuators - can be quickly assembled into unique “chemical plants” providing unprecedented flexibility, quicker development resulting in faster time to market.

James Cuff of Merck and Co. Inc further emphasized the value of microreactors in pharmaceutical research in his talk titled *Online Analysis of Flowing Streams using Micro-flow HPLC.* The work he described the application of a commercial microfluidic high pressure liquid chromatographic system that allowed in line monitoring and optimization of flow streams.

The *Uses of Microreactors for the Large Scale Manufacture of Life Science Compounds* was the subject of the presentation by David Ager of DSM Pharmaceutical Products. He presented two case studies: the first was for a very exothermic reaction used in the manufacture (including scale up) of an agrochemical intermediate; and the second involved a continuous separation process in the cGMP manufacture of a drug candidate for which formation of a nitrate ester is the key step.

Session 2 Discussion Period

The second discussion period focused on the applications of microreactors, and technological advances, and was facilitated by Michael Gonzalez of the US EPA. The speakers from Session 2 served as the panel members.

General observations were:

- Microreactors provide a good change for many reactions that are currently batch style.
- The timing is good for implementation in pharma since the FDA is open to accepting flow techniques – *Quality by Design.*
- Solids can be a potential problem. Reactions that produce precipitates are mostly avoided at this time, but perhaps could be handled with modular systems.
- Separation processes have to be made more efficient, and built into the microanalytical system.
- It is necessary to look at the entire life cycle of a process when evaluating the use of microreactors in a process.
- Some companies do a complete cost analysis of the switch to microreactors – if it doesn't save money there is no implementation.
- When infrastructural changes are required to "entrenched" processes, decisions to implement the new technology are often based on initial capital investment and other risks.

Microreactors could provide the greatest impact in the following areas

- Safety
- Reduction of production of waste
- Reduction in amount and use of reactants, such as solvents
- New chemistries that optimize reactions and eliminate hazards
- Potentially more sustainable and "greener"
- Reduced time to market
- Energy savings

Session 3
Making the Case for Micro-Reactors; Case Studies

This session delved further into the application of microreactors and the resulting advantages over conventional techniques. Ray Chrisman, Dow Chemical (retired) opened the session with a talk titled *Utilization of Microreactor Technology for Reaction Characterization.* He described that the characteristics of microreactors enable most reactions to be studied independent of equipment limitations and gave examples of their use for a wide breadth of chemistries from high molecular weight polymerizations to complex specialty materials. The importance of data treatment and approaches to improve data quality were also discussed.

A case study titled *Production of Fuels and Petrochemicals* was presented by Laura Silva of Velocys. She described a very successful pilot scale demonstration using microchannel Fisher-Tropsch reactors. A field demonstration based on the results obtained from this pilot plant is planned for early 2010 and will utilize biomass derived from synthetic gas. Other applications for microreactor technology planned at Velocys include steam methane reforming distillation, vinyl acetate monomer synthesis, and hydroprocessing.

Mel Koch of the Center for Process Analytical Chemistry at the University of Washington closed this session with a presentation entitled *Benefits of Online Sensors for Advanced Flow Reactor Analysis, Optimization and Control.* He described experiments that demonstrated the value of the advanced flow reactor platform in conjunction with micro-analytical tools and modular sampling systems components to improve process understanding and control.

Session 3a
Enabling Technologies

The workshop continued with a session entitled *Enabling Technologies*. It was planned that the discussion of topics presented in Session 3 would be combined with those of Session 3a. This session opened with a presentation by Paul Scholl of Mettler Toledo AutoChem, Inc. titled *in situ Reaction Analysis for Understanding and Providing Control Feedback in Continuous Flow Reactors Using Mid-IR Spectroscopy.* Fourier Transform Infrared Spectroscopies are becoming more widely used in industry because they provide information both in realtime and *in situ*. This paper focused the development and application of mid IR spectroscopy for realtime analysis of corrosive chemistry, condensation reactions, polymerizations, catalysis, Grignard reactions, low temperature organo-metallic chemistry and a variety of other chemical systems in continuously flow reactor systems.

Ian Lewis of Kaiser Optical Systems presented a paper titled *The Applicability of Raman Analyzers for In Situ Studies in Small-Volume Reactors.* Raman spectroscopy has emerged as a viable *in situ* analytical and process control tool. Developments in sampling and sampling interfaces have allowed Raman analyzers to be integrated into reactors from the macro to the micro scale. This paper focused on the use of Raman analyzers for the study of small reactor systems including sealed microwave systems, continuous flow reactors, NeSSI platform devices, and small volume thermal reactors.

Sessions 3 and 3a Discussion Period

Session 3 focused on the making the case for microreactors; and Session 3a described some enabling technologies. The speakers from both sessions served on the panel, while Michael Gonzalez of the EPA facilitated the discussion. The following concepts emerged.

Analytical Needs for inline, realtime sensing include:

- Multi-component, solution–phase separations
- Wireless- based imbedded sensors to detect in-line failures
- Quality control in real time
- Analytics for condition-based (rather than time-based) maintenance
- Ability to predict reliability of instrumentation after in is in storage
- Common, open-source, standardized software to analyze data

Emphasis was placed on the importance of software to enable advances. Examples given were:

- Analysis of data from multidimensional chromatography for metabolomic studies (bio-oil)
- Analysis of Raman data for syngas measurements

Session 4
Enabling Technologies

Session 4 continued with presentations of enabling technologies that facilitate the implementation of microreactors in commercial settings. The session opened with a presentation by Joseph Stetter of KWJ Engineering Inc; and Illinois Institute of Technology titled the *Introduction to Chemical Sensing with Applications to Micro-Reactors*. He stated that the special needs for microreactors as applied to industrial processing are: small size; multiplexed input/output; and low cost. The advances in nano-sensors provide a good way to discuss the interface of sensors to microreactors as well as what is new in sensor science and engineering. He concluded with the thought that microreactors will integrate sensors as both technologies advance together in providing new analytical capability to industrial applications.

Nien-Hwa Linda Wang of Purdue University presented her cutting edge research in her paper titled *Simulated Moving Bed Technologies for High-Purity and High-Yield Multi-component Separations.* She stated that while continuous adsorption process (or "Simulated Moving Bed" process – SMB) can produce high-purity chemicals with significantly higher yield, higher throughput, and lower solvent consumption than batch chromatography, there are significant barriers to its implementation for large scale separations of complex mixtures. New technologies have been developed at Purdue to overcome these barriers and have been successfully applied to development of tandem SMB to recover insulin from a ternary mixture and a five-zone SMB to recover six sugars from corn stover hydrolyzates.

The final presentation of the workshop was made by David Ross of the National Institute of Standards and Technology. His paper was titled *High Performance Biochemical Analysis with Simple Microfluidic Devices.* He described efforts to develop microfluidic techniques for biochemical analysis that are very simple and that combine multiple analysis steps into one operation. Examples of these new techniques include gradient elution moving boundary electrophoresis (GEMBE), gradient elution isotachophoresis (GEITP), and temperature gradient focusing (TGF). They can provide high resolution separations with very short channel lengths so that the microfluidic chip can be much smaller than and therefore much less expensive than a conventional capillary electrophoresis chip.

At the conclusion of all the technical presentations, the entire workshop was summarized by Ray Chrisman who is retired from The Dow Chemical Company after a career in R&D in Analytical Chemistry and Chemical Sciences, and is a visiting Scholar at the Center for Process Analytical Chemistry, at the University of Washington. The goal of this summary was to frame the final discussion period, which was to include a path forward. He targeted three main areas in his summary:

1. Potential advantages of microreactors;
2. Key potential problems of the technology and some solutions; and
3. Key application areas.

The details around the three main areas are described below.

1) ***Potential advantages of microreactors as articulated by the presentations.***

Reaction control was demonstrated in multiple talks as microreactors were shown to enable unique control sequences for better reaction optimization. The control was often enhanced by real-time analysis for more precise control strategies.

- Temperature control above boiling points was demonstrated to give enhanced reaction rates with only modest back pressure control.
- Purity of desired products was pushed to essentially 100%, as described in one presentation, with very selective control of reaction sequence by multiple reactant addition points, temperature, pressure, and residence time. The use of multiple catalyst beds provided access to an even greater array of potential chemistries.
- Yield was enhanced in every example though it was pointed out that we would not be talking about reactions that were not improved. One comment was made that a review of currently practiced chemistries at one corporation indicated that 15-20% of their reactions would be significantly improved in a microreactor. An additional comment added that as more capabilities are understood more chemistries would benefit and/or the same products could be produced with chemistries that are not normally commercially practiced due to current control limitations in batch reactors.
- Exothermic and endothermic reactions were demonstrated to benefit from the improved high heat transfer rate control possible with microreactor designs.
- Exotic chemistries or more correctly very reactive chemistries were demonstrated to be a very useful place to start the introduction of microreactor technology to manufacturing as the enhanced safety and control made it easy to demonstrate improved economics.
- Photochemical reactions were suggested as possible and advantageous in glass microreactors but little data was currently available to be presented.

The continuous microreactors were very compatible with continuous separation approaches such as membrane separations and simulated moving bed chromatography, SMB, as well as several other continuous extraction techniques. At this stage very few complete processes were described that utilized these new tools from end to end but the components are being developed and implemented which should enable these approaches to be used.

Low solvent usage was a key feature that was noted due to the potential to reduce the environmental impact of chemical production. Many reactions could be run neat or with melts which means much less separation is needed after synthesis and less solvent to recycle or destroy.

Enhanced safety inherent in microreactor operation was pointed out in several presentations. These are a result of the small volume of material in the reactor and the high surface to volume ratio which can moderate temperature excursions and quench reaction run away. One presentation did show a reaction that got out of control but the author pointed out that it was more of an irritant than a safety issue. However, it appeared that the reactor was destroyed.

- This same small intrinsic volume in microreactors made it much safer to work with highly toxic reactants since the small volumes produced could be consumed as they were generated.

2) Key potential problems of the technology were discussed with multiple solutions offered.

Equilibrium driven reactions were discussed at length as many chemistries use precipitation, second phase formation or gas evolution to drive reactions. The key seemed to be the choice of reactor design or new modes of reactor operation. One novel approach is the utilization of slug flow which is segmented flow with gas or other phases between segments. Gases or liquids could partition into or out of the other phase as needed. Several approaches were used to separate the slugs post reactor. Solids required careful reactor design to insure particles did not drop out in dead zones and form plugs. The high shear rotating drum design seemed much less sensitive to solids.

Solids processing was considered a key problem. No work was described related specifically to solids processing though multiple presentations dealt with solids present at various stages of the reaction. Examples of solid product formation were nanomaterials or polymer melts. Solids were used as catalysts and their use as reactants was demonstrated in cases where it would melt or could be slurried. In most cases it seems that solids can be dealt with for continuous operation but they are a problem that requires additional thought for plug free operation.

- The special case of organism mediated production in microscale equipment was mentioned. However, there was only one known research reactor design in the field which was from Seahorse and not much was known about the general utility of such an approach.
- Approaches for the use of solid catalysts were described. These included the use of fixed bed columns and also suspensions of catalysts particles. Both seemed efficient and advantaged for the demonstrated reactions probably due to the use of small, high surface area catalysts and precise temperature control.
- The production of polymers was described and it demonstrated that high molecular weight materials could be processed. This suggested that microreactors could be advantaged in post translational modification of proteins since there can be a low shear environment with high mass transfer and precise temperature control. While this was suggested it was not demonstrated.

The final concern was scale up of microscale equipment for commercial production. Almost from the beginning with the introduction of microreactors it has been suggested that they could be numbered up by adding more reactors and keeping the column conditions the same as in the lab. Work is now being described where this concept is shown to be very viable. The advantage of the approach is that the reaction proceeds in the same manner in the parallel systems as it did in the lab studies that used the same channel dimensions. This makes scale up much less expensive and much more efficient. Work was also described where more channels were added per chip and in some cases slightly enlarged for higher volumes.

- One issue was the amount of material that is needed for lab scale testing. This is an important issue as not all reactants are readily available during early phase process development. Several approaches were demonstrated. In one case smaller scale channels were used for early testing, in another slug flow and finally pulsed operation. Each seems workable though care must be used to transfer results to a larger scale.
- In one presentation commodity scale operation was described which demonstrated that the principles of high mass flow and good temperature control can work to advantage to control really active catalysts or for getting heat into very endothermic reactions.

3) Several key applications were described which demonstrated the power of the technology.

Several good examples were given where reactive and toxic chemistries were scaled very efficiently in microreactors. This demonstrated that the potential of the technology could be realized at scale for commercial production.

There was discussion of the concept of using them for distributed production to reduce storage and handling issues with reactive materials such as ethylene oxide. Distributed processing of biomass to reduce shipping bulky raw materials was described but commercialization has not occurred.

- Small volume production of medical tracers that use radionuclides was briefly mentioned as an efficient and effective example of using microreactors for distributed production.

A strong case was made for the use of the technology to reduce environmental costs by more efficient production as well as by reduced solvent utilization for lower energy needs. It was pointed out that distillations uses up to 3% of the total energy consumed in this country. Thus less solvent use and cleaner products could have a significant impact on energy usage. It was stated that a significant reduction in waste is possible with smaller scale production as the waste per pound of product is very high. The comment was that refinery production generates about 0.1 pound of waste per pound of product while pharmaceutical production can generate more than 100 pounds of waste per pound of product.

A general comment was made that continuous production generally has lower operating costs as well as lower capital costs which is why most bulk chemicals are made that way.

This would suggest that longer term many processes could be more efficiently operated as continuous processes but it was felt that the savings would not cost justify converting existing processes. The capital cost side of scaling microreactors is much less clear. Bulk materials have an economy of scale related to the fact that by doubling the diameter of a pipe increases flow by a factor of 4. Thus much less steel is used per pound of material processed as the scale increases. Microreactors maintain the same size channels which mean that the material costs go up almost linearly with scale. There is some expectation that just as micro-electronic chips are cheaper with volume production microreactors will be cheaper with volume production. However, this has not been demonstrated.

A presentation on SMB for continuous separations suggested that chemical production in microreactors could be very compatible with this efficient general purpose separation procedure. While it has been cost justified to develop the methodology to commercially separate high volume materials like xylenes and high fructose corn syrup, most processes that would benefit have not been studied. The presentation stated that SMB is now much easier to optimize and is applicable to the separation of multiple components. Historically its use has been limited to the separation of two components such as optical isomers. The separation of multiple components will be important for general purpose utilization.

Finally, microreactors were demonstrated to be very compatible with real-time analysis.

- Several presentations demonstrated that very fundamental data about a chemical reaction could be determined in a microreation environment. This data could be used for reaction optimization for scale-up or for reaction understanding for process model development. It was pointed out that if the rate expression for the intrinsic chemistry is determined then this information can be used to speed the optimization of scale-up using batch or continuous processing.
- A special case of reaction understanding is the data required for the FDA program of quality by design, QbD. It was demonstrated how this data could be generated in a microreaction system to provide the FDA envisioned process understanding. However, no one was aware if anyone was currently doing this.
- Much discussion was held concerning whether each channel needed to be monitored or whether analysis of the collected streams was sufficient. It seemed that data on the combined streams would work but the potential to have much tighter control by individual stream monitoring seemed useful. Several sensors were described that had the potential to be deployed on the large number of channels that are needed for commercial production.
- The ease of sensing and the responsive nature of microreactors suggest that much more precise control of microscale systems will be possible and should provide enhanced control strategies for more efficient chemical production.

Session 4 Discussion Period; and Future Directions

Discussion period 4 opened with a question and answer period relative to Session 4 which focused on cutting edge sensing and separations technologies, and new developments in micro-analytical measurement science. Then, based on the ***Summary of Conference and Issues*** presented by Ray Chrisman and shown above**,** an in-depth technical discussion of the entire workshop followed to include discussions of future directions. This discussion was facilitated by Ray Chrisman (Dow, retired), Michael Gonzalez (EPA), and Hratch Semerjian (CCR).

Some key advantages of the use of microreactors were cited:

- Safety is a big driver; any explosion is small
- Temperature control is a big advantage; exothermic reactions are not problematic
- Can operate at a higher temperature in a microreactor
- There is general reaction control; temperature profiles can be monitored
- There is greater access to exotic chemistries; such as reactions that use or produce hazardous materials
- Microreactor equipment is compatible with separations technology such as simulated moving beds (SMB)
- Environmental footprint is reduced
- Reduced solvent utilization (green and sustainable)
- Scale up scenarios are feasible

Some issues/topics identified:

- How to handle equilibrium controlled reactions
- Controlled formation of products; can control the reaction, temperature etc.
- How to handle solids – catalysts – how to load and drive reactions
    - In some cases solids can form but don't have a chance to aggregate, but need a well designed reactor
- Can achieve very high volume output (1.7 Tonnes per hour) through these devices by adding more and more microreactors ("number up" concept). However this large scale is not yet "commodity level"
    - Velocys and Corning are pushing to large scale. There is every reason to think that we can get there, but it has not been demonstrated.

Some areas where microreactors could have the greatest impact:

- Reactions that can't be done another way (new chemistries)
- Continuous reactors are considered more cost effective than batch style.
- On demand production; examples include specialty chemicals, distributed production materials, small volume needs, radionuclides for medical diagnostics
- In the production of pharmaceuticals often the waste per pound of product is very large. This is a great opportunity for microreactors.

General Discussion: the general discussion that followed was "free form" and a summary around major topic areas that were brought up are provided below.

Some Technical Issues:

- **Sensor Technology*:*** microsensors, MEMs, would allow monitoring and optimizing separations in realtime as part of the process
  - One of the major advantages of microreactors is that you can measure and provide feedback control in inline in real time. The parameter space gets much bigger because of the control.
- **Fluid Mechanics:** Is the fluid mechanics understood? What happens to fluid flow in the twists and turns within the device, pressure drops etc.
- **Reactions Rates:** We need to better understand why we see enhanced reaction rates in microreactors. Mass transfer was identified as a key factor.
  - The diffusion time is short and domain sizes are small.
  - There are increased collisional frequencies, and collision rates are in a uniform field.
  - What are the shear energy contributions? Shear is not much of an issue in low viscosity materials.
- **Intrinsic chemistry** becomes the limiting step
  - Knowing about the ***intrinsic properties*** of the reaction and device, the system can be fine tuned.
- You can ***avoid large scale mixing*** issues at the microscale.

From an analytical perspective:

- Continuous reactors are easier to sample, time-resolved information can be obtained, with a possibility of making adjustments in realtime for higher yield, higher purity products.
  - Issues around "how representative is the sample" needs to be addressed.
- Mixing is a function of temperature, molecular weight, as well as the mixing device. If the reaction is dependent on fast mixing – the microreactor has to be well characterized.

Example of an Application Area – biorefinery:

- It is likely that simulated moving bed technologies (SMB) can be applied to biomolecules. It is feasible, but it is cost effective?
  - SMB was applied to the production of biofuels – in a demonstration, 6 sugars were recovered from a 10 component mixture. Costs were a few pennies for a gallon of feed. Feedstock costs about 9 cents per pound. In the demonstration of feasibility there was no effort to reduce costs.
- Clearly the use of microreactors is cutting edge for industrial processing at the commodity scale. **However, its value and versatility is not widely appreciated.**

Gaps and Barriers identified that hamper more widespread implementation.

- There is subset of separations and sensors are amenable to microreactors. However, multi disciplinary teams are needed to bring everything together. To get to the fruit of automated control of systems will need a funding source. NSF does not tend to fund this type of research
- Extensive work in combinatorial chemistry going on to help with the understanding of the reactions on the microscale
- Some implementations require advanced reactor designs, which are not commercially available.
- Organizational alignment within companies may be the crux of the problem. Technical and business worlds need to communicate better.

Gaps and Barriers due to Education:

- Education was cited as a key barrier to the implementation of the use micro-reactors in industrial applications. One speaker emphasized that an analytical lab from 100 years ago is quite similar to the lab of today. Many participants felt that microreactors and the new chemistries required to make the best use of the new technologies should be taught at universities. The absence of a new generation of scientist coming through the education system, will result in a lack of creativity in the workplace.
- Changes in education are not only required in academia, but also within companies in order for the companies to be more receptive to new processes and new ideas.
- There are clear industrial applications for continuous reactions that are fast, exothermic. However, there are also cases for much slower reactions. We need to understand advantages/disadvantages of batch vs continuous processing from both a business and a scientific perspective.
    - Scientists must have fundamental data to understand the intrinsic properties of each part of a complex reaction. Chemists and chemical engineers need to work together.
    - If it is fundamentally more economical, then the case can be made to industry management.
- Some academic participants noted that in the US, it is difficult to publish work on microreactors in traditional chemistry journals since the reactions are not new. The methods are new, but this can be difficult to convey.
- **NSF funding** and the academic system in the US is built around single investigators, and fundamental, not applied science. **Europe** has pure and applied chemistry degrees, this works well for the advancement of new technologies.
    - Universities and industry work closer in EU.
    - Many of the professors in EU work in both industry and university. Academics are looking for what is the problem to be solved.
- **US EPA** interest in microreactors centers around environmental issues (sustainability)
    - We need better understanding of microreactors – we understand batch reactors – but not microreactors.
    - We have to redesign chemistry for smaller scales.

Potential Role for CCR:

- CCR could put a bibliography on the web – serve as a hub and link to other existing references and publications.
  - Mettler Toledo's Organic Process Research and Development Division has published special issues on this topic, and
  - CPAC has recently released a book.
- CCR could provide case studies on the web that describe issues that were encountered – and how they were solved or not solved.
- CCR could prepare a white paper to summarize this workshop.
- CCR could provide a venue for a forum such as this to be repeated. In what timeframe?
- CCR is working with V2020 to develop roadmaps – would microreactors be suitable to study?