

Part II
Sensing, Analysis, and Control

5 Microtechnology and Process Analytics

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5.1 Introduction

Microtechnology has been important in the continued evolution of process analysis instrumentation and has led to significant reductions in the size of process analyzers. The technology has also improved the reliability and lowered the cost of analyzers. A more complete overview of the technology used in the field of process analytical technology (PAT) can be found in a book chapter by Blaser and Chrisman [1]. However, the focus of this chapter is on the interface of process analytics with the microtechnology used in the processing of materials. A brief mention of the impact of microtechnology on the actual measurement instrumentation will be described at various points in later sections, but this aspect of advances in process analytics is not a major topic of this chapter.

PAT has been an important part of industrial manufacturing for many years in the application of measurement science and technology within a production environment. Sophisticated measurement technology, such as spectroscopy, was first demonstrated within the German chemical industry in the late 1930s [2, 3].

The beginning of PAT was driven by problem-solving reasons to understand the composition of the material of interest in the process. The measurements were often part of a trouble-shooting effort that was trying to optimize reaction conditions and to understand process factors that influenced the success of the desired reaction. Initially, process analysis was carried out by taking samples from the process in the production plant and transporting them to the analytical laboratories. As a way to optimize time, many analytical laboratory measurements were eventually moved to the production plants (Figure 5.1).

In order to improve further the time needed to receive results, there is now an emphasis on achieving a real-time response, almost like a sensor, with an expected high level of accuracy and reliability.

As the recognition that the use of measurement technology enhances productivity, improves product quality and reduces environmental impact has grown over the past



Figure 5.1 Laboratory mass spectrometer modified for data gathering in a plant environment. Courtesy Dow Chemical.

30 years, there has been increasing emphasis on improving the technology. The early, traditional approach to implementing PAT was to modify selected laboratory analytical technology to create instrumentation suited to the production plant environment (Figure 5.2).

PAT was able to provide an insight into the process that gave information on real-time composition and concentrations. It is also a very valuable way to study reaction pathways and reaction kinetics for the purpose of understanding the reaction mechanisms. This has proven to be very important to developing an effective process control system. As the desired needs of measurement in the production environment became understood, technology has been developed to respond to this need, without

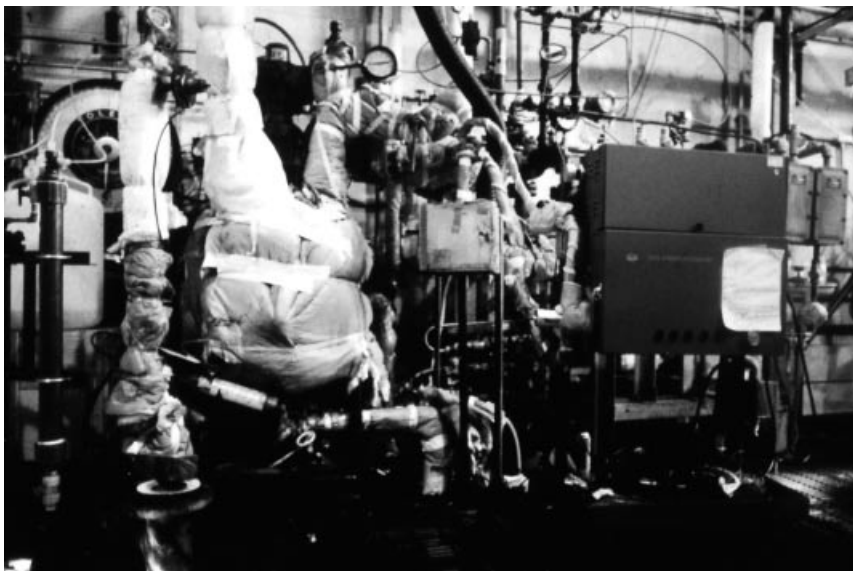


Figure 5.2 Laboratory vibrational spectroscopy instrument modified for production use. Courtesy Dow Chemical.

regard to whether it was practiced in the laboratory first. In this area, microinstrumentation has shown particular advantages.

PAT is different from traditional analytical chemistry in that the goal is to characterize a material undergoing a transformation and to measure the progress of the transformation. An additional difference is that, in modern PAT, the composition of the material is known. The exception is when real-time analysis is used in R&D in the discovery phase, where unexpected reaction routes may occur, or in the process development phase, where unexpected by-products may form.

In modern commercial production, the only time an unknown material should be present is when there is a change in the quality of the raw material or a change in process operating parameters or if there is a mechanical problem with the process. Hence the main problem for process analytics is to determine the concentration of known materials that are in a state of change. This requires good precision in the measurement and an analysis method, including the sampling system, that does not drift during months of use. As no drift is a difficult requirement to satisfy, the method will usually include a calibration procedure that must be performed at some frequency.

A key requirement is that the plant operators believe the measurements and have a process model such that if the process measurements are out of range they know how to modify the process parameters, such as temperatures and flows, to bring the measurements back into range.

There are various terms that describe the approach that is used to make the process measurements. The terms usually include in-line, on-line and at-line. The “take a sample back to the laboratory for analysis”, off-line analysis, is the most traditional method and is generally not considered a real-time measurement since most often the results are not rapidly available to make process corrections. However, some elegant pneumatic sample transport systems coupled with rapid feedback have been used, but are not within the scope of this discussion.

The in-line method seems to be the most straightforward in that the sensing device is embedded within the process such as is the case with a thermocouple. The problem with in-line analyzers is that except for the most rugged and reliable measurement devices, there can be problems when the analyzer fails. With an in-line analyzer the process typically must be shut down to calibrate, fix or change the analyzer. This may not be a major problem for batch processes whose cycle times are fairly short, but is a major problem for continuous processes, which are designed to operate for years without a shutdown.

The on-line system is the most commonly used system for compositional analyzers. In this approach, the sampling system is automated and directly interfaced to the analyzer. With the analyzer system external to the process, it is fairly easy to repair and/or calibrate the system without the need to shut the process down. As this is the most common real-time analyzer approach, it will be discussed in more detail later in the chapter. The at-line process is similar to the old laboratory analysis in that a manual sample must be taken out of the process but in this case the analyzer is rugged enough to be located in the process area to do an immediate analysis once the sample is obtained. This method is labor intensive to do but does solve the sampling

system problem, which tends to be the cause of the majority of failures with real-time analytics. The distinction between at-line and on-line is beginning to fade away, with both terms being used for the historical on-line concept.

A slight variation is the real-time analyzer that is used to detect emissions from a process. This is an important class of process analytics but it will not be covered in this section since it is not directly interfaced to the chemical reactor and does not really change with microtechnology systems. However, the use of emissions monitoring can be every bit as important in the protection of plant personnel and the environment with microtechnology systems as with macroscale plants.

As already mentioned, process analytics is designed to help track the composition of materials that are undergoing some transformation. Although speed is important, the measurement usually does not need to be instantaneous. However, the speed required is related to the time constant for change of the process being monitored. Thus, given the responsiveness of microtechnology equipment, there is potential to profitably use faster analysis times compared with large-scale reactors. In large-scale equipment, precision of the measurement is usually more important than the accuracy and this appears to be true in microscale equipment also. While high accuracy is useful, systematic errors can be corrected at various times during the process. High precision, on the other hand, enables control parameters to be tightened in real time to produce less product variation.

Another facet that is often not appreciated is that to use real-time data effectively the process must be well understood. This is required because it must be clear what operating parameters must be changed and by how much to keep the process in the desired operating range. As an example, in an automobile a sensor provides information about the speed of the vehicle. From this information, the driver then alters the feed of gasoline to the engine to increase or decrease the speed. Although this seems simple, it is based on experience that has been developed by the driver to relate fuel pedal pressure to fuel flow to vehicle speed. The relationship needs to be relearned for each vehicle and is very different for a large truck than for a small racing car. In a like manner, the plant operator must know what controls need to be altered and by how much to keep a process in a desired operating range.

5.2 Information Sharing in the Process Analytics Field

As the importance of developments in PAT was recognized by industry and government groups, there was interest in establishing forums where the needs for advances in this field could be discussed and prioritized. It also became obvious that no one organization had the resources to assemble a critical mass of personnel to develop the tools that were necessary. In the mid-1980s, several consortia were established. These included the Center for Process Analytical Chemistry (CPAC) at the University of Washington and the Measurement and Control Engineering Center (MCEC) at the University of Tennessee in the USA and the Centre for Process Analysis and Control Technology (CPACT) at the Universities of Newcastle,

Strathclyde and Hull in the UK. Each of these centers was based on industry members who would contribute funds that could be leveraged to fund academic research activities in PAT.

In subsequent years, other centers and associations have been established, such as the Center for Advances in Manufacturing of Pharmaceuticals (CAMP) at Purdue and MIT. Many of these have been addressing areas within the definition of PAT (data handling, miniaturization, solids handling, etc.) One such activity has been the proposed National Institute for Pharmaceutical Technology and Education (NIPTE), involving several universities (including Purdue, Rutgers and Puerto Rico), in preparing a roadmap for processing of pharmaceuticals – largely solids handling concerns. There has been activity within the German chemical industry to focus on process analysis in general and enabling technology such as micro-unit operations in particular. These include: Dechema's Microchemtec and discussion group concepts (http://www.analyticjournal.de/aj_navigation/ak_pat.htm). Within Scandinavia, there have been activities sponsored by the Danish Agricultural University and the University of Southern Denmark at Kolding, several Swedish organizations emphasizing chemometrics and sensors and Norwegian activities at the Food Research Institute (Matforsk) and the University of Bergen in chemometrics and spectroscopy. Additional activities in The Netherlands, the UK, Japan and the USA have highlighted the advances in miniaturization, particularly the symposia on Micro Total Analytical Systems (MicroTAS).

There was interest in presenting the technical developments from research efforts within these centers at industrial sites and government agencies at open, international forums. Such venues were initially at established technical conferences and symposium such as the Pittsburgh Conference (Pittcon) and the Federation of Analytical Chemistry and Spectroscopy Societies (FACSS), where occasional sessions on PAT were organized. In the late 1980s, the International Forum for Process Analytical Chemistry (IFPAC) was organized as a symposium and vendor display venue dedicated to PAT and it has steadily grown in importance in reporting developments in the PAT field and vendor exhibitions of new commercial offerings. The participation has increased from an initial gathering of chemical and petrochemical industry researchers to one that includes almost all industries and many government agencies. One of the reasons for the multi-industry interest is the recent emphasis that the US Food and Drug Administration (FDA) have put on PAT by issuing a Guidance on the use of PAT. The Guidance is intended to help in improving the quality and productivity in pharmaceutical and biological products. The FDA is promoting a Quality by Design (QbD) approach to develop process understanding and indicates that PAT can help achieve this. Global regulatory agencies have encouraged this activity and significant efforts are being made to the development of international harmonization in this field. The US Pharmacopeia (USP) has also begun an effort to emphasize incorporating PAT approaches in their monographs.

A number of conferences and symposia have been offered with PAT and QbD themes during the past 5 years, as industry is responding to new developments in the PAT tools available to optimize and monitor processes. Conference organizers such

as IBC, Global Health and IQPC have been highlighting the PAT theme globally. The number of sessions and the vendor displays at IFPAC and the other conferences that feature developments in microanalytical methods is increasing in number and in level of interest. This is due to the successful demonstration of these devices in industrial applications.

Along with an increase in PAT-related presentations there has been a dramatic increase in the number of publications documenting the technical developments and their impact. A journal of PAT has been established (www.patjournal.com) and a number of trade journal articles have also been published on the importance of microinstrumentation developments for PAT. These trade journals include *Control Magazine*, *Chemical Processing*, *Chemical and Engineering News*, *American Pharmaceutical Review* and *European Pharmaceutical Review*. There are also periodic reviews of the PAT field in the journal *Analytical Chemistry* [4, 5].

To emphasize further the importance of this field, an ASTM Committee (E 55) on Pharmaceutical Applications of Process Analytical Technology has been formed and there are several subcommittees of the ASTM E-55 that address particular issues such as nomenclature and applications.

5.3 Characterization Needs for Microsystems

As microtechnology for chemical processing continues to develop, there are both traditional and new types of characterization needs. The traditional needs are comparable to what is needed for any real-time analysis of a process unit operation, which is an analysis of the state of the transformation that has occurred or is occurring in a unit operation. For a chemical reactor, the required information may be a composition analysis or a polymer molecular weight or particle size. However, for microtechnology-based unit operations there are several additional characterization needs. These analyses are somewhat different to what is needed in traditional processing equipment. First, since microreactors are still very new, it is important to understand the performance of the microtechnology-based hardware component. For example, it is important to understand the true quality of mixing of the equipment or to understand if there are poorly swept regions where solid may drop out of solution. Second, since many of the implementations of microreactors are based on scaling up by adding more channels or numbering-up, it becomes important to know what is going on in each channel. For example, is one channel beginning to plug or is it experiencing a changing heat transfer rate?

In a general sense, the characterization of the performance of the microtechnology-based equipment is not a process analytical problem and is the responsibility of the hardware developer since there are many variables that need to be characterized for proper design and operation of the device. These include flow distribution to the multiple channels, chemical component mixing and heat transfer rates, to name just a few. For example, Schouten has demonstrated the care needed to characterize and model gas-phase reactor systems that he and his colleagues design (e.g. [6]).

However, as more systems become commercially available, the user will need to be aware of the potential for problems and understand measurements that can be used to characterize performance. As noted by Hickman and Sobeck in a recent chapter, in which they were interested in generating laboratory-based kinetic information for process development applications, the mixing characteristics in the microreactor need to be characterized to model the reaction chemistry [7].

Hickman and Sobeck [7] described an elegant automated system that was designed to determine the kinetics of reaction. They analyzed the requirements of a reactor system that would be needed to enable reactions to be characterized over a range of reaction rates. During the course of their analysis and testing to determine optimum performance parameters, they had to rule out the use of commercial microreactor systems due to system characteristics that were not compatible with the high degrees of performance required for reaction characterization. While the current group of solution-phase microreactors are not sold to do the exacting work that the authors desired, their analysis approach also determined that the microreactors did not perform as expected. Thus, if precise control of reaction chemistry is required for optimum yield, the operating performance must be measured. The issues that the authors were most concerned about were rate of mixing and deviations from uniform flow through the system.

The reasons why users may want to understand these characteristics of their chosen reactor are related to the types of chemistry that can be run efficiently in the system. For example, poorer mixing means longer residence times in mass transfer-limited reactions. Uniform flow in this context is similar to dead volume in chromatographic systems. One impact is that if more back-mixing can occur in the system, there can be a problem with control of processes with multiple sequential reaction steps. For example, in cases where one reactant can react further with the product, the higher the plug flow characteristics are the better the reactor is at minimizing unwanted reaction by-products. The reason is that to minimize a reactant reacting with a product it is important that they each be as low in concentration as possible when in the presence of the other. Thus, if a reactor has unmixed domains where the concentration of reactant is high and the domain comes in contact with regions where product concentration is high, a product of the two is more likely to form.

Also, operationally, dead volume issues can make it much more difficult to change from one reaction chemistry to another due to long clean-out times. In addition, it is possible to have particles drop out and ultimately plug the system in areas with low flow relative to the bulk of the stream. Hickman and Sobeck also mention thermal requirements for a system to achieve the isothermal characteristics that they needed. Operationally, reduced heat transfer limits the types of reactions that can be efficiently controlled and also hot spots can lead to an increase in alternative reaction pathways with the formation of impurities. Finally, another problem that they encountered was that given the high surface to volume ratio of the equipment, the materials of construction caused a problem for some chemistries that they wanted to study. It is not clear if the material of construction issue would be a problem for routine operation. Again, these are not really process analytical problems but they can

impact the chemistry that is being performed and it is wise to understand the details of the reactor's performance. It is expected that in the future there will be agreed-on performance tests developed or supported, hopefully, by the device producer associations that will reduce the need for the user to test the system characteristics.

The second type of problem, which is the characterization of the performance of each individual channel, is unique to microtechnology which can scale up by adding more reaction channels. The current general thinking is that by monitoring back-pressure, bulk chemical composition or some other characteristic of the combined inputs or outputs, variations in individual channel performance can be detected. Although this approach is reasonable, the multi-channel format offers the potential to detect operating changes long before they have a negative impact on product quality.

Methods for individual channel monitoring do not yet seem to be cost-effective. However, new methods for large-scale self-assembly of electronic components seem to offer an approach that may make individual channel monitoring possible at an affordable cost. The assumption is that early detection of device performance changes should allow more precise control of product quality.

5.4

Sampling Specifics for Microscale Systems

Sampling of a chemical process is an unappreciated aspect of process analysis that often leads to problems. The general sense is that the bulk of the on-line analyzer problems, about 80%, occur in the sampling system and it is not uncommon for the sampling system to cost as much as the analyzer and have a much higher cost of ownership (mostly repair costs). The difficulty arises from the fact that the sampling system must take a sample from a process stream operated under one set of conditions and prepare it for introduction into an analytical device that often requires samples with very different conditions. This means that the sample must be transported to the analyzer location, particles must be removed, the reaction quenched, the chemical composition, such as pH, adjusted and the overall concentration usually diluted, the temperature and pressure altered and the flow rate controlled. The sampling system must do these tasks rapidly and reproducibly without plugging. To make matters worse, the process may be multi-phase.

The general requirements for an on-line analyzer sampling system have been described by Blaser and Chrisman [1]. A typical system uses a fast loop to bring sample from the process. The sample stream is conditioned and a sample is taken for introduction into the analyzer. The cost and complexity of these purpose-built systems have led to the development of a standardization scheme to reduce the design, installation and maintenance costs of sampling systems. The overall standardization concept is known as the New Sampling and Systems Initiative (NeSSI). More information of the approach will be described later in the chapter but the general approach is very compatible for use with microtechnology-based processing.

On-line systems are the normal approach for large-scale chemical processes due to concerns about system failure and calibration of an analyzer that is in direct

contact with the chemical process. In-line analysis, which is often very fast, seems much more compatible with the faster response characteristics of microtechnology-based equipment than on-line analysis in which a sample needs to be removed from the process stream for analysis. The problem with in-line analysis is that it is still difficult to do composition analysis on a process stream, which contains many components. The expectation is that, with all the positive features from in-line analysis, such as speed, simplicity of interface, representative sampling and sampling system cost, there may be more emphasis on using advanced data analysis approaches to extract the needed information from overlapping measurement features. However, for now, composition analysis of a complex stream still requires some separation type of analysis, which means that a sample must be extracted from the process. Fortunately, separation systems are getting very fast, which means that the fine control possible with microscale systems can still be utilized for quality production or for advanced control techniques such as various types of pulsed operation.

Again, given the rapid response of microreactors to parameter changes, it becomes even more important, for sample extraction approaches, to insure that the sample that reaches the analyzer represents the process at the time the sample was taken. This means that the process sample quench needs to be very rapid. This may mean that a micromixer needs to be used for quenching. Otherwise, the reaction may proceed for some time in the sampling lines.

Just as with normal process analysis, the sample will need to be prepared for the analyzer. While the quench stream should be able to adjust the chemical characteristics such as pH, it may still be important to dilute the sample to get it into a range that is compatible with modern high-sensitivity instruments. This can be done by a technique that is known as dynamic dilution. This approach requires that the sample plug passes through an area with intentional dead volume. This will broaden the sample plug flowing through the lines in a reproducible manner such that the plug can then be sampled at a constant time from the plug maximum concentration to give the desired dilution.

Normally, filtering would also need to be done, but this seems to be less of a problem as the whole system requires particle control to avoid problems with the small channels in the microtechnology-based processing equipment. Still, some type of filter on the analytical stream is recommended as particles can originate from the sampling system itself.

One other feature that is different is that the process stream is a fairly small-volume continuous stream. This is mostly not a problem but there can be unexpected side-effects. For example, the whole process stream can be routed through the analytical valve, which is good for representative sampling. However, the speed of actuation of the valve can cause process upsets as the valve momentarily deadheads the process. Also, depending on design, the analytical valve can put a small amount of the analytical quench stream into the process stream. This plug may cause difficulties in another part of the process if, for example, it is designed to alter the sample pH rapidly. Although problems can arise, most microtechnology-based processes are very compatible with on-line analysis.

5.5

Advantages of Using Microscale Systems for Process Development

The high compatibility of microtechnology-based processing with process analytics means that not only is it very convenient to do process monitoring but also to study the chemical process with the equipment. Mills and coworkers [8] recently described a gas-phase microtechnology-based system for the characterization of catalysts. The integrated system that contains the process analytics needed for reaction characterization demonstrates that high-quality data can be obtained from laboratory-based systems.

Vanden Bussche has pointed out [9] that it is possible to use information from microscale laboratory equipment for the scale-up of gas-phase catalysts in the petroleum industry when the microreactor is well designed and there are also good models for production-scale equipment. This is very significant in that the construction of intermediate units to develop process information is very expensive and time consuming. Therefore, if usable process information can be developed at the laboratory scale, then significant amounts of time and money can be saved. In addition to good design of the microscale equipment, high-quality on-line analytical data must be obtained to insure that there are precise data to feed into the models. He also added that they still confirm the data in larger scale facilities but that takes much less time to do.

The system that Hickman and Sobek described was for liquid-phase work. Their system was designed to collect real-time analytical data with the goal of determining the rate expressions for chemical reactions they wished to scale up. They used a continuous microreactor for their system, which can be a good model for a batch reaction. The system they designed had automated control of temperature, residence time, pressure and concentration. Thus, in an automated fashion, the device could step through an extensive range of variables to characterize a chemical reaction fully. Their system had a sampling loop that enabled high-performance liquid chromatography (HPLC) or gas chromatography (GC) to be used for reaction characterization.

Nielsen *et al.* described an automated system for the characterization of liquid-phase ethylene polymerizations [10]. The system had control of residence times, concentration of catalysts, temperature and pressure. In real time with in-line sensors, it was possible to determine the heat evolved from the reaction and to determine catalyst performance. Thus, by using a carefully controlled microscale reactor with in-line analysis capabilities, a complex polymerization reaction could be characterized in the laboratory setting.

5.6

Overview of Chemometrics in Process Analytics

To take full advantage of the capability of microtechnology-based processing, it is important to be able to understand in real time how the unit is performing.

For example, GC is in broad use for on-line analysis due to its ability to quantitate the composition of mixtures. While inherently a rather sophisticated instrument, yielding hundreds or even thousands of data points on multiple analytes per analysis, in process settings gas chromatographs are typically operated through a series of “heart cuts”, such that most of the information is discarded until only a few peaks related to one or two chemical species are reported. The main reason for this is that interpretation of the full chromatogram requires expertise that is becoming more and more difficult to find and justify on the process floor. Furthermore, most process control systems would be overwhelmed by a data stream consisting of a full chromatogram – one or two key variables per analyzer are typically the limit even for relatively complex data control systems. Consequently, most on-line applications are relegated to rather simple measurements with more complex problems still done off-line in the laboratory. Thus, to monitor complex processes more fully, be it by GC or with another process analyzer, and make more use of the information-generating capability of these instruments to achieve greater process understanding and/or control, new data handling approaches are needed.

One possible solution to these problems is to leverage advances in chemometrics to aid in the extraction of important information from on-line analyzer data streams in an automated way. Chemometrics is defined by IUPAC as “The application of statistics to the analysis of chemical data (from organic, analytical or medicinal chemistry) and design of chemical experiments and simulations”. The International Chemometrics Society (ICS) defines chemometrics as “The science of relating measurements made on a chemical system or process to the state of the system via application of mathematical or statistical methods”. Both definitions illustrate the breadth of application for chemometrics techniques – all the way from experimental design through signal processing, modeling and calibration stages with the ultimate goal being the extraction of useful chemical information from observations of chemical systems. In the context of this chapter, it should be clear that chemometrics does, and should, play an important role in process analytics of microtechnology-based unit operations. In fact, the FDA’s PAT guidance specifically mentions chemometrics as a key technology to be applied as part of the mechanism of achieving “process understanding” from process measurements.

What, then, does chemometrics really provide? Workman [11] offers some desirable advantages of chemometrics that include the following:

- Chemometrics provides speed in obtaining real-time information from data.
- It allows high-quality information to be extracted from less resolved data.
- It provides clear information resolution and discrimination power when applied to second-, third- and possibly higher-order data.
- It provides methodology for cloning sensors – for making one sensor take data as “precisely” as another sensor.
- It provides diagnostics for the integrity and probability that the information it derives is accurate.
- It promises to improve measurement quality.

- It improves knowledge of existing processes.
- It has very low capital requirements – it is inexpensive.

Kourti recently published a very readable review titled “Process analytical technology beyond real-time analyzers: the role of multivariate analysis”, where she gives an overview of the most relevant chemometrics techniques and some demonstrations of their application [12].

As previously mentioned, often the amount of data from advanced sensors (such as chromatographs) is large and a fast algorithm-based system is important to allow the use of these instruments in process optimization and/or process control. Expertise in chemometrics, access to commercial pattern recognition engines for laboratory-based instruments and process sensor development are key to advances here. A goal is to develop robust instrumentation (such as GC) that performs a consistency check to determine that the data generated are valid and then processes the data at that location into information for control of the desired application. This then allows for the traditional complex laboratory to be moved on-line. Instruments that utilize these approaches bring a significant cost advantage when operating microsystems.

5.7

New Sampling and Sensor Initiative

Both in-line and on-line methods are reasonable to use with the microtechnology-based systems for composition characterization. However, unlike the case with large-scale chemical processes, it seems like the in-line approach has an advantage for composition analysis in microscale equipment due to speed. The problem with in-line systems, as mentioned above, is that with complex multi-component streams it is often not possible to achieve good component quantification without a separation. Hence an extractive sampling approach needs to be taken to move the sample to the analyzer. While an extractive sampling approach seems simple, it is generally agreed to be the source of 80% of the analyzer problems and often costs as much as the analyzer. Therefore, the chemical processing industry has been looking for an approach to reduce the costs and problems with sampling systems.

The key requirements for the new approach were a system that was modular, miniature and smart. To understand more about the background of the concept, how it grew into commercially viable hardware and to learn details of operation, see a recently published chapter by Veltkamp [13] and the CPAC web site [14]. The growth of the hardware concept, which is covered by the general name NeSSI (New Sampling/Sensor Initiative), is assured since several large global companies have mandated within their organizations that the technology be used in all their on-line applications.

The key requirements of being modular, miniature and smart for this hardware concept make the hardware very compatible with microtechnology-based processing equipment. The major facet of the concept is that all components have a standard surface mount configuration, which was based on technology that was developed in

the semiconductor manufacturing industry. It should be pointed out that the concept also extends to the mounting of the analyzers. Hence it suddenly becomes possible to change the system configuration very quickly.

The surface mount hardware, which can be valves, flow controllers, filters, gauges and analyzers, which now constitutes a long list of components, has the fluid fed from below. Three major vendors provide different flow path systems but all surface mount components are interchangeable. Many analyzers that are often used for in-line analysis can also be mounted in the flow path of the NeSSI-based hardware.

The advantage for the microtechnology-based equipment is that the high degree of compatibility means that inclusion of the analysis system from the start is very easy. In addition, it is also very easy to add or modify both the sampling system and the number and type of analyzers. For example, as the system is being studied several analyzers may be employed to develop process understanding, and as the process moves to production a subset of analyzers may be used for control.

Another feature of the NeSSI approach is that since there is easy control of the flow path, it is possible to mount or connect the microtechnology-based processing equipment to the backbone system. This makes it easy to have the analyzer components in the system for analysis as soon as the reaction pathway is designed. Some users have actually integrated the chemical processing and the analyzer components on to the same NeSSI backbone system whereas others have just interconnected the two types of flow systems. Either approach makes it easy to have significant flexibility available to characterize a reaction.

In addition to the technical advantages listed above, there are also some less direct benefits to adopting and promoting miniature modular sampling/sensor systems. It is an unfortunate fact of life that much of the time spent conducting research is spent assembling systems and apparatus needed to support the planned experimentation. While some of this setup effort is unavoidable due to the nature of research, having a standardized toolkit of fluidic and sensing components that could easily be assembled for specific tasks or rapid prototyping would certainly reduce the burden and increase researcher productivity. The “plug and play” nature of modular sampling/sensor systems implies that a relatively small toolkit of such components could be reassembled and reconfigured by students and relatively untrained personnel to perform a variety of analytical tasks typically taught in the laboratory. Finally, the reduced volumes and closed, leak-free, nature of a modular sampling/sensor system may reduce exposure risks and waste generation, thereby increasing overall safety.

5.8

Various New Analytical Approaches that are Suited to Microscale Systems

A range of new microanalytical techniques that are useful for interfacing with microtechnology-based unit operations has been described at length recently by Koch *et al.* [15]. One of the selected examples is Raman spectroscopy, which demonstrates the potential of the new developments.

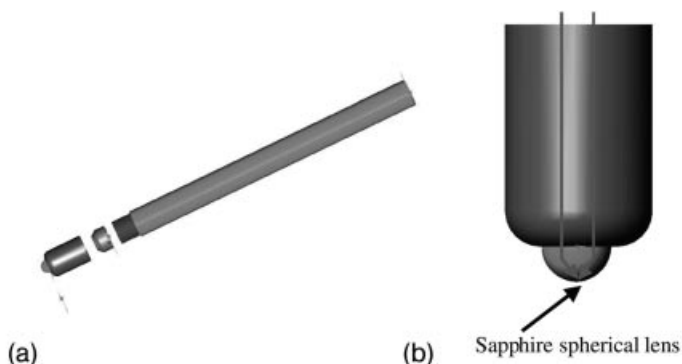


Figure 5.3 (a) Sketch of the Raman immersion probe. (b) Sketch of the immersion probe tip and spherical lens.

Raman spectroscopy is an accepted vibrational spectroscopic technique for determining and monitoring both qualitative and quantitative molecular information of organic and inorganic molecular species from almost any type of sample (i.e. as a solid, liquid or gas) [16, 17]. Raman spectroscopy is attractive for on-line analysis due to the relatively short analysis times (1–30 s on average) and ease of optical sampling.

Raman spectroscopy has been used to monitor a variety of industrial processes to improve product quality and process understanding [18, 19]. The same features that make Raman spectroscopy a useful technique for traditional process monitoring, such as the short analysis time and ease of optical sampling, mean that it can also be a useful tool for analyzing and understanding chemical reactions performed in continuous microreactors.

A key element to monitoring any chemical process on-line is to sample the system effectively and reproducibly. To address this concern, an immersion probe has been developed at the Center for Process Analytical Chemistry (CPAC) [20, 21] for the analysis of single- or mixed-phase chemical reactions. This immersion probe (Figure 5.3a and b) incorporates a spherical lens that was designed and optimized for the purpose of performing Raman measurements in both laboratory and industrial reactor environments [3–5]. The spherical lens of this probe is an efficient sampling interface for the analysis of heterogeneous samples, including solids, liquids and gases. The probe design is compact, durable and straightforward with no moving or easily fouled components. The design of this probe has also been shown to be effective with other types of spectroscopy, including UV–Vis, near-infrared (NIR) and fluorescence. The improved measurement precision of the probe is attributed to the use of the spherical lens as both the focusing element and the optical sample interface.

To illustrate the concept of using analytics to improve process understanding, an example chemical reaction was run. The reaction was performed in a Cellular Process Chemistry Systems (CPC) continuous feed microreactor which was configured to operate as a small-scale chemical production plant. The initial goal of this microreactor project was to couple effectively an in-line Raman probe to the continuous



Figure 5.4 CPC continuous feed reactor with online Raman detection utilizing a commercial Raman probe equipped with a Raman ballprobe (circled) at the outlet port of the reactor.

reactor system both to evaluate reactor performance and to apply Raman spectroscopy as a process control tool for the screening and optimization of reaction parameters. To accomplish this, the reactor was initially fitted with a custom-designed low-volume flow cell incorporating the Raman immersion ballprobe at the outlet port of the residence time module as highlighted (Figure 5.4). Due to anticipated problems with bubble formation in the sample line, a back-pressure regulating valve was installed downstream of the Raman probe to improve the sampling precision.

The reaction describing the esterification of acetic acid with methanol to produce methyl acetate is shown in Figure 5.5. Since the objective of this study was to develop a general chemistry test bed for evaluating and optimizing various chemistries and on-line analytical sensors, this reaction was selected. This reaction has been well studied, it is temperature sensitive and it is of minimal toxicity. The formation of methyl acetate was monitored using the modified flow cell equipped with a Raman ballprobe and a back-pressure regulating valve to reduce perturbations in the flow. The experiments clarified that one could change and control the microreactor parameters in real time and monitor the chemical response to that control variable change with Raman spectroscopy.

Using the on-line Raman instrumentation, changes in reaction yield as a response to temperature enabled the reaction kinetic profiles to be monitored. The research project was expanded to study the effect of multi-phase products. Further experiments were performed after this initial reactor profiling work to react butanol and acetic acid to form butyl acetate and water. Immediately problems were encountered with the original optical sampling apparatus due to the multi-phase products resulting from this reaction system. This optical sampling problem was solved by using the previously mentioned modular sample handling components better known as NeSSI. As this new approach to process sampling hardware components has become available over the last few years, it has offered flexibility in design and implementation of complicated flow systems for process sampling and analysis [22].

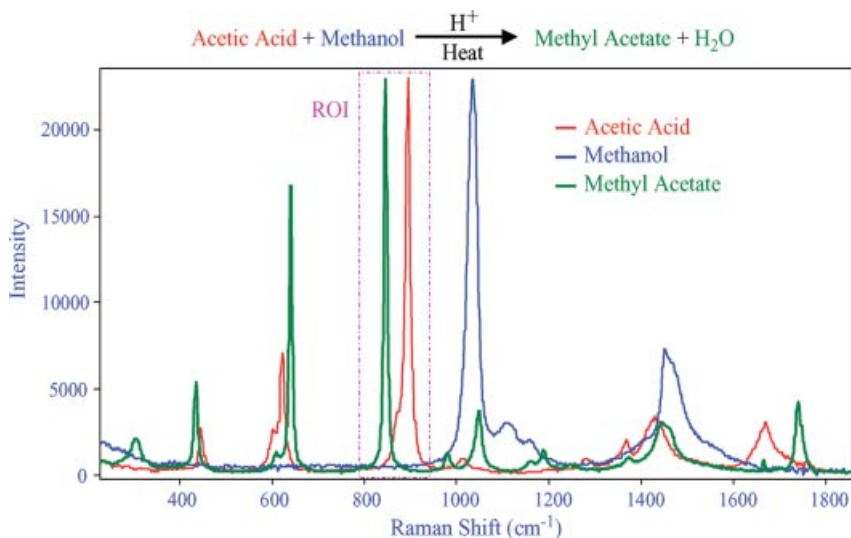


Figure 5.5 Methyl acetate reaction data; including standard Raman spectra of acetic acid, methanol and methyl acetate. The acid catalyst used in this reaction was concentrated sulfuric acid.

Just as is being found for laboratory-scale work, the technology has been successfully adopted by numerous industries as a cost-effective way of sampling both gas and liquid streams for process analysis.

The optical sampling problem encountered during the butyl esterification reaction can be seen at the far right in Figure 5.4. The problem was due to the phase separation of the products between exiting the heated reactor block and reaching the room temperature Raman ballprobe tip in the sampling apparatus.

The solution to the sampling problems was a simple NeSSI sampling system purchased from Parker–Hannifin and shown in Figure 5.6. The Raman ballprobe is the second component from the left with the fiber-optic cable attached at the top.

Heating the sampling system with the reactor heating source eliminated the multi-phase sampling problems that occurred in the original system and allowed for reproducible continuous analysis of the butyl acetate and water products. The rest of the sampling system consisted of only two modular face mount components to monitor the continuous microreactor effectively. A 0.5-in i.d. pressure fitting was used to mount the Raman ballprobe into the sampling system. An illustration of the probe mount component and the reaction flow path are shown in Figure 5.7. After the probe coupling component, a surface mount needle valve component was installed. The needle valve was used to increase the back-pressure of the system at the Raman ballprobe interface to reduce greatly the formation of gas bubbles in the sampling system. This simple commercially available sampling system allowed for increased control of the sample stream at the Raman probe interface and therefore greatly improved the reproducibility and accuracy of the Raman analysis.

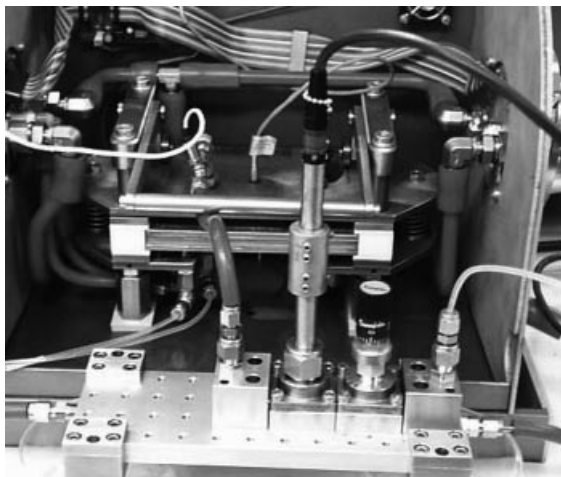


Figure 5.6 A NeSSI sampling system designed to reduce optical sampling variables for performing on-line Raman analysis.

Just as the preceding example demonstrates that Raman spectroscopy is very compatible with microscale unit operation characterization, the whole range of traditional spectroscopic (IR and NIR) and chromatographic (GC and LC) techniques are undergoing changes that will make them even more useful for this application. All of the techniques are being miniaturized for a range of reasons from cost and performance improvements to needs for portable applications. Many of these changes have led to smaller, faster, cheaper instruments with a broad range of features that can be easily interfaced with the microtechnology-based unit operations.

There is a growing list of analytical devices that can provide information on the physical properties required for the understanding of aspects such as flow, texture,



Figure 5.7 NeSSI top mount component for use with Raman ballprobe. Raman ballprobe inserted into component indicating flow channels to probe optic (sphere in right-hand illustration).

moisture, particle size, coatings, mixing consistency and bioassay are being developed in microtechnology-compatible packages. These often employ non-traditional analytical laboratory technologies such as

- dielectric (fringe field) spectroscopy
- surface plasmon resonance
- acoustics
- radiofrequency
- light scattering
- microfluidic properties
- imaging technologies
- membrane technologies
- vapochromic sensors.

These various measurement techniques will provide a greater understanding of the performance of microtechnology-based unit operations. Also, since they are being produced in microscale packages, they can be easily added to the NeSSI fluid handling backbone. Hence they can be utilized in various combinations to maximize process understanding.

One additional area that is on the horizon is the potential to optimize biologically based processes with microscale equipment. An approach developed by BioProcessors is a Simcell platform, which is an automated miniaturized system for cell culture development. This platform is capable of running and monitoring hundreds of complex bio-reactions. This automated platform has been used to conduct high-throughput cell culture experiments for process development purposes. The system performs bioreactor operations such as cell inoculation and culture monitoring and control.

5.9

Conclusion

PAT has become a field of measurement science that recognizes the contributions from a variety of technical disciplines, including chemistry, engineering, biology, data handling and control strategies. The developments coming from MEMS (micro-electrical mechanical systems) technologies and related microtechnologies have been valuable to the measurement field. The outcome has been an ability to achieve an increasing amount of knowledge about the process being operated.

As the demand for process analytical tools expands, the analytical instrument vendors will need to develop and market instruments that are conducive to responding to the goals of PAT. The instruments should be flexible, modular and have the capability to be integrated into analyzer systems. The analyzer system needs to incorporate sampling, sample conditioning, detection, data gathering and information generation. The measurement technologies applied to processes also need to expand from the traditional compositional characterization to include also more physical characterization tools. This is important, as it is increasingly necessary in

order to develop measurements that correlate with, or even predict, final product properties.

As approaches to high-throughput experimentation, process intensification and process optimization continue to develop and show value to the researcher, then the engineer or the analytical chemist will be under increased pressure to use microanalysis tools. This will be to evaluate the operations of the microreactors (such as diagnostics of the microchannels and composition of the reactor). The results of these applications will be seen in distributed manufacturing approaches and number-up versus scale-up of processes. These successes in engineering will also increase the demand for the effective use of microanalytical instrumentation.

For the most part, analytical instrumentation has been at a micro-level for some time already, particularly the electronics related to detection and so on. As the instrument vendors see the market developing, the interfaces between the instruments and the microprocess unit operations will need to be retrofitted. Because reactions are so rapid in microreactors, one can explore more unique types of chemistries. In particular, the ability to remove heat so effectively allows complex condensation reactions to be carried out.

As microtechnology in general and particularly microanalysis evolve, more unit operations can be monitored and optimized. Operations such as separations, reactive distillations and extractions will benefit from feed-forward and feed-backward control schemes once the data are available to generate effective models. In the longer term, the challenge of miniaturizing solids handling operations will need to be addressed and assessed as to whether there are benefits to be realized.

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