Emerging Technologies Supporting Chemical Process R&D and Their Increasing Impact on Productivity in the Pharmaceutical Industry

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1. Introduction

Over the past 30 years process R&D functions within the pharmaceutical industry have undergone a remarkable transformation. At one time the bulk of investment of time and resources required to develop and fine tune a highly efficient drug substance manufacturing process could be delayed until a product was launched and its prospects for commercial success were assured. With the passage of the Waxman−Hatch Act in 1984, however, the industry began an era of shortened product life cycles and greater reliance on new product innovation. Accompanying the change was the need for at-risk process development at increasingly earlier stages of product development and movement from a "learn-while-doing" approach toward a "learn-before-doing" approach, as described by Pisano in *The Development Factory*.[1] Advances in analytical instrumentation and greater accessibility to analytical tools also played important roles in helping to shift the emphasis of modern pharmaceutical process R&D functions from one of *making material* to one of *creating knowledge*.

As the major pharmaceutical companies gradually increased their number of products over the years, earnings growth potential began to level off as revenue growth from new products and revenue losses to generic competition approached steady state. By the late 1990s many companies had intensified their investments in internal drug discovery capacity and technologies while concurrently increasing their in-licensing efforts in an effort to reach and sustain an increased number of new product introductions per year. Consequently, there has been increased pressure on process R&D functions to efficiently deliver cost-effective manufacturing processes for an increasing number of candidates in development pipelines while simultaneously increasing productivity.

The goals of process R&D vary according to the stage of a given product's development (Figure 1). When projects are first transitioned to development, relatively small quantities (1−5 kg) typically are needed and the probability for overall project success is still quite low. At this stage, process R&D organizations frequently employ an expedient variant of the synthetic route used during drug discovery to make initial development supplies. Thereafter, however, they seek to identify a future commercial route and develop and demonstrate a reliable and cost-effective manufacturing process—usually at risk and in the shortest time frame possible. The generation of pharmaceutical chemical process technology can be represented as occurring in three stages involving (1) exploratory process research and route selection, (2) process definition and knowledge generation surrounding control parameters (development), and (3) process verification/parameter range setting (Figure 2). The purpose of this paper is to review advancements in research-supporting technologies that have established footholds of acceptance in advancing productivity to support these stages and have the potential to change the future landscape of process R&D within the pharmaceutical industry. Rather than being comprehensive in its coverage of all possible technologies, this review will

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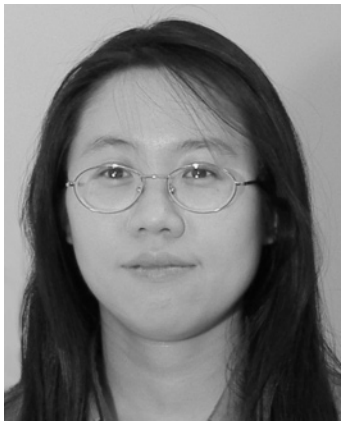

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	DRUG DISCOVERY	Early Development		Late Development	PRODUCT LAUNCH
		Phase I	*Phase II*	*Phase*	
Number of agents produced	$> 10^4$	10	6	2 - 3	1 - 2
Candidate Requirements	10 g	1 kg	25 kg	300 kg	1000 kg

expedient → practical → efficient → optimal

Figure 1. Process research and development cycle.

focus specifically on four particularly important and interrelated fields: 1) technology-assisted parallel experimentation and screening, 2) developments in analytical chemistry impacting process research, 3) kinetic analysis and reaction modeling, and 4) continuous processing/process intensification.

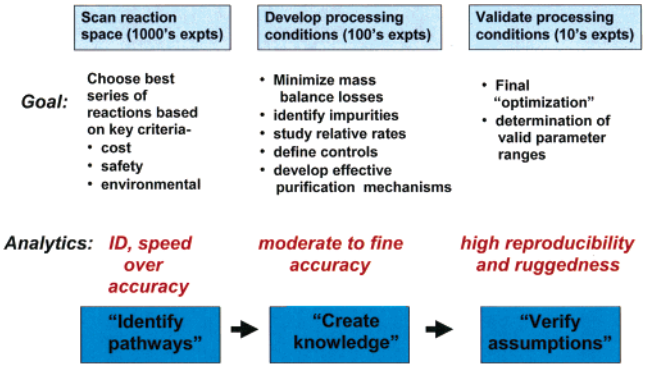


Figure 2. Process research and development cycle.

2. Technology-Assisted Parallel Experimentation and Screening

2.1. Historical Development

Among the pioneering efforts to automate chemical reaction optimization using computer-controlled robotic equipment were those reported by Fuchs and Kramer at Purdue in the 1980s.[2] The Purdue team's approach was to use a Zymark robotic arm that was programmed to carry out repetitive tasks to support multiple experiments in a manner analogous to the way a chemist would conduct them by hand. Using this strategy, the team successfully optimized conditions for the preparation of an intermediate that was required in large amounts for one of their synthetic programs. An earlier review provides a summary of this and other early attempts to introduce automation into chemical development and reaction optimization.[3]

It was not until the early1990s that the use of automation in a pharmaceutical process research setting was reported by Boettger at Bristol-Myers Squibb.[4] This work also employed a customized Zymark robot, in this case configured to carry out unit operations to support optimization of a palladium-catalyzed coupling reaction. While this report emphasized some of the essential features of an automated system for process development activities—including accuracy and precision, equivalent agitation of each reaction vessel, and careful temperature control of the reaction vessels—subsequent use of a programmable robotic arm was not embraced broadly as a strategy to support technology-assisted experimentation. However, as more sophisticated technology became available commercially to support drug discovery and enable high-throughput screening and combinatorial chemistry in the mid-1990s, the extended application of those tools to process R&D began to follow. As a result, the late 1990s marked the start of an era of serious exploration and innovation surrounding the use of automation and other research-supporting technologies in Pharma process R&D settings.[3]

Among the earliest possibilities recognized was the use of automation tools (developed initially to support parallel synthesis activities in drug discovery) toward chemical reaction optimization. For example, in a 1999 article Glaxo researchers reported the development of an automated workstation to support solution-phase parallel experimentation.[5] The Glaxo system, called DART (Development Automated Reaction Toolkit) by its developers, was assembled from commercial hardware components and tied together with custom software. DART was designed to allow for up to 20 reactions to be carried out simultaneously. The reactions could be prepared "automatically" with the use of an "on-board" interfaced robotic liquid handler. In addition, the robotic liquid handler could be configured to automatically prepare samples from the reactions and inject them directly into an on-line HPLC for "near real-time" analysis. The later feature enabled the researchers to monitor their reactions over time, which provided essential clues to the reactions' progression and their kinetics. Interestingly, the Glaxo concept was ultimately commercialized as the SK233 workstation, and a thorough evaluation of the SK233 workstation was presented in a report by SmithKline Beecham scientists thereafter.[6] In this report the authors highlighted the system's versatility to carry out both screening and development studies (including DOE and kinetic profiling of reactions), while they also noted a limitation in the SK233's ability to handle reactions under inert atmosphere. In response to this limitation, the SmithKline Beecham team redesigned the reaction vessels (Figure 3). Their design

Figure 3. ReactArray reaction vessel.

included a cold finger that connected to the reactor tube via a tapered ground glass joint. The cold finger could be cooled with chilled circulating fluid, and the cooling path could be connected serially to the other reactors so that several reactor cold fingers could share the same cooling fluid. The cold finger assembly also had a hollow center through which the needle from an automated liquid handler could travel for reagent addition or sample withdrawal. This hollow center was also connected to an inlet/outlet pair so that inert gas could be used to flush the reactor. The authors successfully demonstrated that their reactor design in conjunction with the original SK233 framework could be used to study reactions that were air or moisture sensitive at reflux. The current commercial version of the SK233 includes this reactor design and is marketed as the ReactArray workstation (Figure 4).[7]

The Glaxo DART concept was representative of the handful of systems that were initially made available by commercial technology providers, many of which are described in an earlier report.[3] A thorough description of the use of the Bohdan market entry, the process development workstation, can be found in a report by Schering researchers.[8] In addition to the commercial implementations, many home-grown systems, such as those in the author's own laboratories[9] and in other's laboratories,[10] were founded on the same basic concepts. Collectively, these workstations

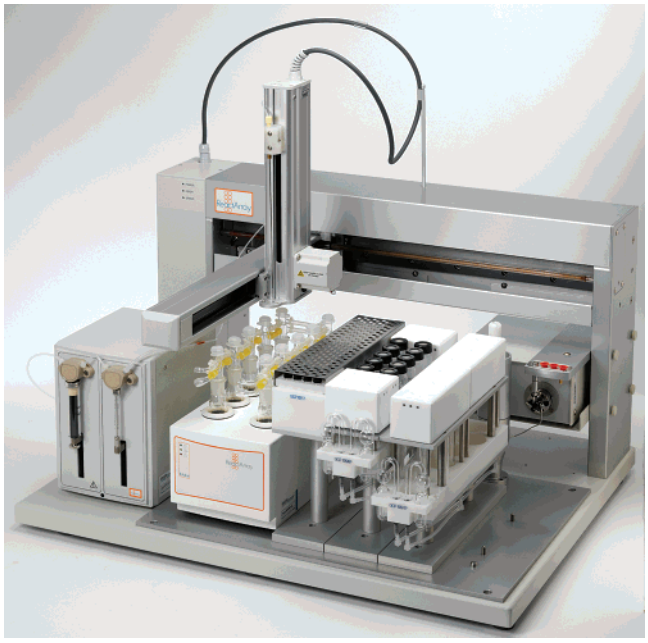


Figure 4. ReactArray workstation.

aimed to enable a handful of common unit operations: (1) the ability to heat, cool, and stir multiple reactions in parallel, (2) the ability to add liquid reagents and withdraw reaction aliquots automatically, and (3) the ability to analyze samples of the individual reactions by HPLC or GC (either on-line or off-line).

2.2. Application of Technology To Assist Design of Experiments (DoE)

Statistical design of experiments (DoE) is a well-established method that allows an experimenter to determine an optimal outcome (e.g., yield, impurity minimization, etc.) based on specifically designed studies of the variables (e.g., temperature, pressure, stoichiometry, etc.) on which the outcome is dependent in conjunction with statistical analysis.[11] DoE techniques have been routinely applied in other industries and settings, and the value of DoE in chemical process research in the pharmaceutical industry has been recognized for decades.[12,13] A good reference book covering DoE applications for chemical reaction optimization was written by Rolf Carlson and has recently been updated.[14] Carlson has been influential in demonstrating the power of DoE to process R&D chemists, and in two very recent lecture transcripts he outlined in detail the opportunities that DoE provides for reaction optimization[15] and reaction condition selection (e.g., solvent, catalyst, etc.).[16] Yet, even today application of DoE to process development activities is far from routine. This may be because DoE experiments require a great deal of structure with assurance of consistency across experiments and are tedious to perform manually. Automation tools, however, are perfectly positioned to assist with this work, and as technology to assist with parallel experimentation was developed, documented demonstration of this point soon followed. For example, the Glaxo report that introduced the DART system also described its application to DoE studies.[5] In this report, the researchers state that within 3 years thousands of reactions had been carried out with the assistance of DART and describe three examples in detail. In one of these examples, the team describes the application of DoE to optimization of a Mitsunobu reaction that resulted in a yield enhancement from ~70% to 89%. With the help of automation, this work took just under 2 weeks to complete. GSK scientists followed up their report on DART with two often-cited and influential papers that served as veritable primers for process scientists who seek to apply the power of DoE in their own work.[17,18] One of the GSK reports[18] even offered a perspective on negotiating common roadblocks encountered when introducing DoE concepts into an organization. A summary of additional recent applications of DoE to pharmaceutical process R&D through 2003 has been published.[19]

Since the initial report on DART, progress on the coupling of automation tools and DoE was reported by technology vendors who were introducing a new product,[20,21] researchers who had evaluated and selected a particular commercial technology,[8,22] and organizations that wanted to communicate their labors in assembling custom workflows.[10,23−26] Two specific articles were even written with the sole purpose of comparing and contrasting commercial technology vendors' offerings for the assistance of parallel experimentation and DoE.[3,27]

While the commercial version of the GSK DART workstation (the SK233 or ReactArray workstation) appears to be the system most often cited to be used to enable DoE as described above,[28−30] reports highlighting the role of DoE in reaction optimization without the aid of automation have also increased in frequency.[31−37] Equally interesting, reports of the use of DoE in the optimization of chemistry for parallel synthesis of libraries for discovery chemistry have also appeared in the past few years.[38−40] Although the identification, understanding, and control of key parameters is of great importance to both drug discovery and process chemists, the difficulties inherent in gaining widespread adoption for any new technology cannot be underestimated. To become readily accepted it must be user friendly, easily learned and retained, and inexpensive enough to become fully available to each process scientist. A relatively simple advance that has made headway in this arena is the development of reactor blocks, such as the Mettler-Toledo Autochem MiniBlock XT (Figure 5).[9,41] Such devices are available in a variety of commercial formats and provide an inexpensive tool that allows multiple experiments to be carried out simultaneously. They can easily be employed with heating/cooling devices and stir plates in conjunction with liquid handler dispensing of reactants, but they can also be manually charged. For situations where control of temperature for individual parallel experiments is important, the STEM RS2 reaction block offers separate temperature control of two zones, each containing five reactions cells, while the RS10 block provides independent temperature control for 10 individual reaction cells (Figure 6).[42] Overall, reactor blocks are lowering the bar for chemists to take meaningful steps toward reaction screening and structured forms of parallel experimentation.

It may be worth noting that the GSK DART strategy coupled with DoE is particularly well suited to facilitate the earlier two phases of process R&D (Figure 2) in which key variables and their impact on response directionality are identified. Frequently, the information derived from these studies provides clues on physical or mechanistic subtleties that guide the direction of further research and process design decisions. However, the strict control of critical reaction parameters such as temperature and agitation are not usually adequately managed with such screening instrumentation, as clarified in a review of commercial equipment that facilitates parameter range setting and robustness studies.[27] Automated

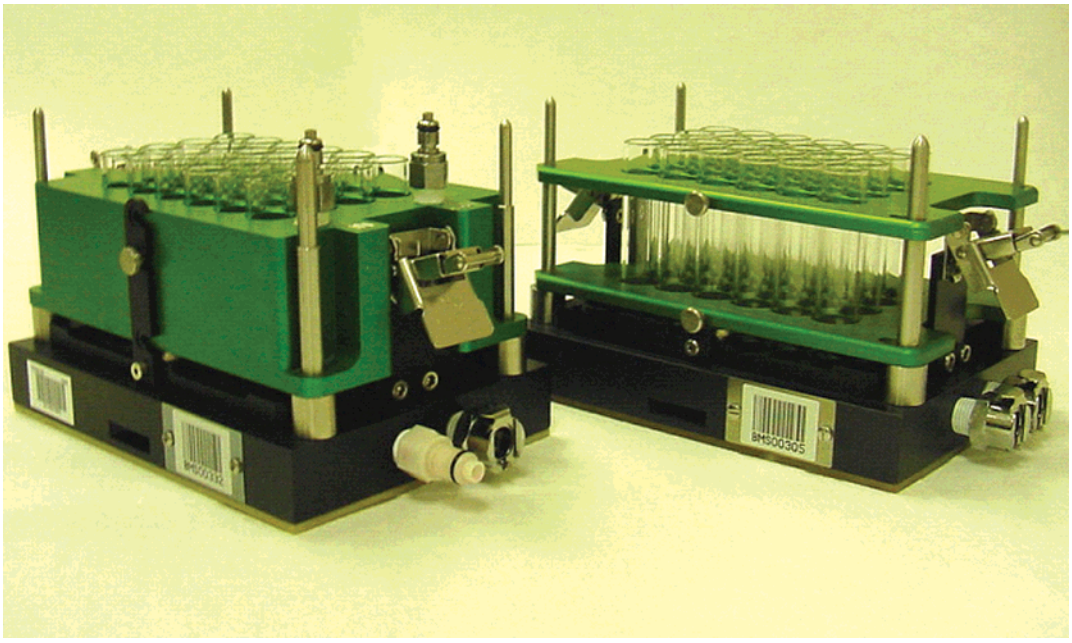


Figure 5. MiniBlock XT from Mettler−Toledo Autochem.

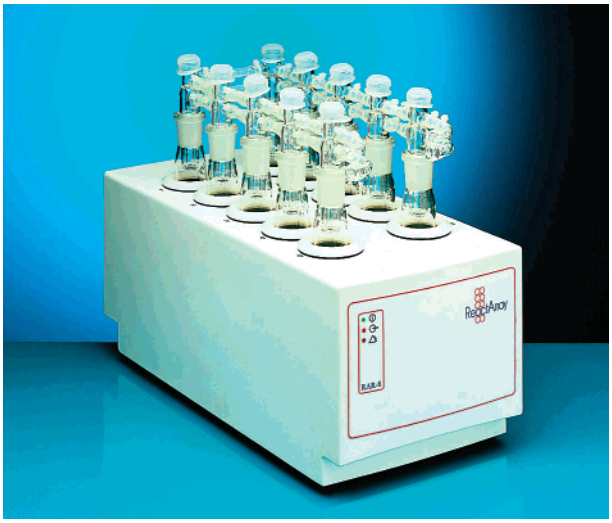


Figure 6. Stem reaction blocks.

technologies used to support late-stage process development have been appropriately referred to as "plant reactor mimics" in order to highlight the connection of this stage to scale up and manufacturing.[24] Two plant reactor mimics which also allow the execution of simultaneous parallel reactions stand out as emerging industry standards for late-stage reaction studies. They are the Mettler-Toledo MultiMax[41] and the HEL Auto-MATE.[43] These two systems are small stirred tank reactor mimics that can each handle 4−16 simultaneous reactions. The systems require moderate reaction volumes (50−100 mL), allow careful control of temperature and agitation, and even enable reactions to be monitored or studied using calorimetry. A 2002 review describes both systems in detail.[27]

The MultiMax, which in its most common configuration allows for four simultaneous reactions, has been used extensively to study crystallizations.[44,45] The MultiMax is well suited for this task since it can be interfaced with in-line monitoring techniques such as FTIR, Raman, and particle size measurement devices (e.g., Mettler-Toledo's Lasentec). The use of Raman and particle size measurement coupled to a MultiMax is exemplified in a recent report by Pfizer scientists where the system enabled a form change to be precisely monitored and crystallization kinetics to be elucidated.[45] The HEL Auto-MATE, which is similar to the MultiMax in its approach, has been used to study carefully control reaction parameters for DoE and hydrogenation reactions.[20] In addition, a report from a Roche discovery scale-up laboratory describes their use of the HEL device for the rapid screening of conditions for a Vilsmeier formylation scale-up.[46] The Roche report also illustrates the use of calorimetric data obtained from the Auto-MATE to derive kinetic rate constants which allowed the team to predict temperature profiles on scale, thus enabling a safe transition to scale up.

2.3. High-Throughput Screening and Measurement Technologies

Commercially available automation technologies have also been applied toward high-throughput screening activities to support pharmaceutical process development with significant impact, particularly in the area of catalyst and transition-metal/ligand screening, where companies have developed specific technologies to meet the demand for innovative leads for specific synthetic transformations.[47] An additional and significant recent example is high-throughput screening technology to uncover new and unexpected crystal forms (polymorphs) and salts of active pharmaceutical ingredients (APIs). The motivation for developing this technology has a surprising origin. After the primary composition-of-matter patent for a drug expires, an innovator pharmaceutical company normally maintains exclusivity in the sale of its product through an extension granted under the provisions of the 1984 Waxman−Hatch Act. However, in recent years generic companies have been aggressively challenging the intellectual property positions of innovator companies from this and every other angle possible.

In one recent case, a court ruled that when another form of the drug (salt or polymorph) is discovered to have the same or improved bioavailability as the marketed form, the holder of the patent of this new form can enter the generic

market immediately following expiration of the innovator's primary patent.[48−51] This situation can result in the loss of years of exclusivity for the innovator company under the Waxman−Hatch provisions and potentially billions of dollars in lost revenue. To protect against this threat, pharmaceutical companies have increasingly embraced high-throughput screening to search for crystal forms that should be protected by patents. Very sophisticated automated workflows have been developed for high-throughput polymorph and salt screening, enabling the evaluation of hundreds to thousands of crystallization conditions.[52−58] A particularly informative review of high-throughput crystallization and its impact on the pharmaceutical industry has recently appeared.[59]

Patent protection of unique crystalline forms is not the only role of high-throughput crystallization however. The unexpected appearance of a new, unexpected polymorph late in development can be highly problematic for a pharmaceutical company. An extraordinary illustration of this was a problem involving Abbott's HIV protease inhibitor Norvir.[60] Two years after the company's launch of Norvir, the product had to be recalled from the field since crystals of a different, much less soluble polymorph of the API had appeared in the semisolid formulation. The Abbott team was forced to race against the clock to understand the problem and reformulate the drug before it could be returned to the market, and more important than reducing Abbott's revenue, the problem left patients without the drug that they needed. Pharmaceutical companies have therefore turned to high-throughput screening to identify potential problems (such as alternate polymorphic forms) as early as possible.

It is worth noting that high-throughput screening and measurement experimentation workflows differ from the structured experimentation (e.g., DoE) workflows described earlier in two key respects. First, high-throughput workflows are typically highly differentiated to address a specific need and frequently include sophisticated combinations of robotics and software. Second, although an organization may have to carry out 50−100 crystallization screens per year, a given researcher may only be responsible for one or two per year. For these reasons, high-throughput workflows are normally operated by dedicated expert groups within an organization or outsourced to a contract research organization.

Expert groups do not typically encounter the same roadblocks that entire organizations do when faced with new technology. This fact has spurred innovation in many high-throughput screening areas in the past few years,[61] much of which has not yet appeared in the literature but has inundated the patent and trademark office. Some of the leading examples that have been published, in addition to crystallization, are solubility measurements[45,62−66] and chemical reaction and degradation kinetics.[67−69] More recently, high-throughput homogeneous and heterogeneous catalyst screening, which has been impacting the chemical industry for years,[70] has begun to permeate the pharmaceutical arena.[71−74] Catalytic reactions can be extremely challenging on a small scale because of the very small amounts of catalyst required and sensitivity of the reactions to environmental and reaction parameters (e.g., mixing, pressure, temperature, oxygen and moisture in the air, etc.). This is especially true for heterogeneous catalytic hydrogenations because the reaction mixture exists as three physical phases. The multiple phases make careful control of mass transfer effects essential.

One recent report by Merck scientists serves to illustrate the impact of catalyst screening on pharmaceutical process

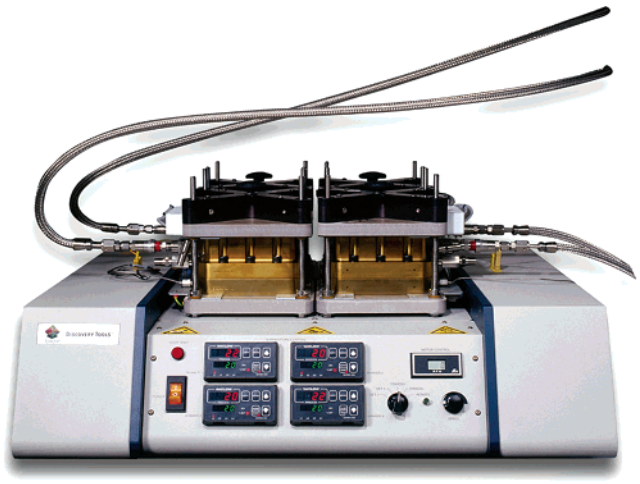


Figure 7. Symyx high-pressure reaction blocks.

research.[74] In their paper, the Merck team describes the use of technology from Symyx Technologies, Inc.[75] for their catalyst screening work. They make use of two of the technology provider's products: the high-pressure reaction block (Figure 7) and the 48-reactor parallel pressure reactor (PPR) system (Figure 8). The latter is a 96-well reactor block

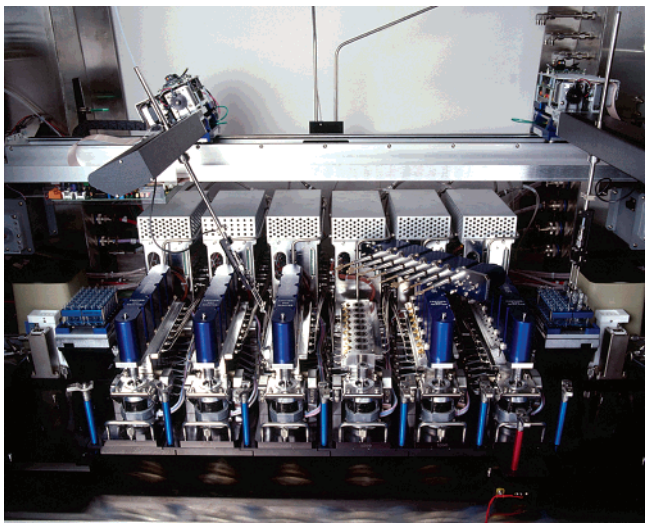
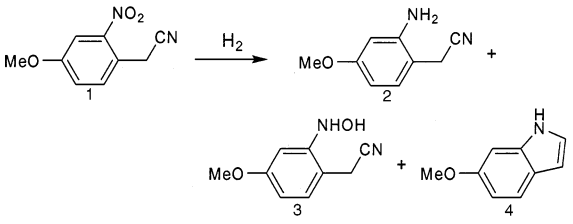


Figure 8. Symyx parallel pressure reaction (PPR) system.

that can be used along with other conventional automation equipment, such as liquid handlers and powder dispensers, for preparation of the individual reaction mixtures. The block is rated to operate in a temperature range from −10 to 200 °C and at pressures up to 1500 psi. These constraints provide an ample range for pharmaceutical process research. The PPR, on the other hand, is a fully automated system that is comprised of six, eight-reactor modules that each has independent stirring, temperature (25−200 °C), and pressure (up to 500 psi) control. Each reactor also enables pressure monitoring for gas uptake measurements, and the group of modules is interfaced with a robotic liquid handler for sample processing and reagent handling. The entire system is housed in an inert atmosphere glovebox.

The Merck report highlights three examples in which catalyst screening and optimization had a measurable impact on their development programs. In one example, they present the challenge of the selective reduction of nitro compound **1** (Scheme 1). During the hydrogenation of **1**, hydroxylamine

Scheme 1



(**3**) and indole (**4**) byproducts are formed in addition to the desired aniline (**2**). For this and other reasons, the researchers chose V-doped Pt/C as the catalyst. The authors used the Symyx PPR to carry out a DoE which was aimed at optimizing the yield of **2** as a function of catalyst loading (1−10 wt %), temperature (25−45 °C), and pressure (20−80 psi). Their work resulted in a statistical model that revealed a strong dependence of yield on catalyst loading and minimal dependence on pressure and temperature. With only 18 experiments carried out in a single PPR run, the Merck team was able to find optimal hydrogenation conditions for **1** in a short time and using minimal material. The conditions that were identified were successfully demonstrated on multi-kilo scale.

The PPR represents the state-of-the-art in high-tech systems for catalyst and reaction screening. It must be pointed out, however, that another Symyx innovation and ancestor of the PPR, the Endeavor (which is sold by Biotage and formerly by Argonaut),[76] is a less intricate system that is akin to a single one of the PPR's modules without the interface to a liquid handler. Nonetheless, because of its ability to follow gas uptake and support high-pressure development studies, the Endeavor has found much support in the pharmaceutical process research community, and several reports of its use have appeared in the literature.[22,71]

2.4. Future Trends

The application of automation equipment to support structured forms of experimentation (such as DoE), the existence of a number of important high-throughput workflows, and the expected introduction of new workflows going forward leaves Pharma process R&D functions begging for software and hardware standardization. Integration of the technologies that make up the workflows is crucial such that (a) common hardware can be shared among workflows, (b) upgrades and updates of software are simultaneous for all systems, (c) learning curves for operating new equipment are easily climbed, and (d) data are stored and can be mined from common locations. Some forward-thinking technology providers are developing in this direction already. For example, a recent report from Symyx describes the Extended Core Module, which is a modular platform for assembling automated workflows and allows addition and removal of hardware components (e.g., liquid handling, powder dispensing, stirring, weighing) using a plug-and-play style common interface.[77] In addition, a recent report from researchers at Pfizer illustrates one attempt at streamlining data mining and visualization.[78] Regulatory influence will also impact how informatics will play a role in pharmaceutical process research. Moreover, a modern, holistic approach to process research, in which knowledge is the key deliverable, is inconsistent with traditional paper notebooks for recording data. Electronic laboratory notebooks (ELNs) are increasingly replacing the traditional pen and paper approach while promoting experimental data sharing and searching capabilities across entire organizations.[79] It is also not unreasonable to assume that software used to develop integrated HTE workflows and ELNs will one day interface, providing a direct connection between automation technologies and the bench scientist.

3. Developments in Analytical Chemistry Impacting Process Research

Improvements in the speed and depth of process knowledge acquisition will continue to be highly dependent on advances in analytical technology. For the purpose of evaluating the output of high-throughout screening studies, a number of techniques have been employed including IR thermography,[80,81] capillary electrophoresis,[82] thin-layer chromatography,[83,84] mass spectroscopy,[85] fluorescence,[86] and even enzyme immunoassay.[87] These and other methods are increasingly being developed to enable high-throughput screening studies for the qualitative or semiquantitative identification of catalysts and specific reaction possibilities. During the subsequent stages of process research (route definition, early process development), the most important aspect of analysis involves recognition of reaction side products and mass balance issues, such that the impurity profile of isolated intermediates and drug substance can be established (Figure 2, area shown on left). As process scientists work to establish control over a set of chemical steps chosen for development, according to accepted regulatory guidance they are required to identify each impurity present at 0.10% or greater and ensure API used in clinical studies have comparable or lower levels to those lots previously employed in animal safety studies.[88] Therefore, an important target for technological advance is the efficiency with which "impurity profiling" can be accomplished and impurity profile changes monitored throughout development.[89]

3.1. Technological Advances for Impurity Profiling

The most visible effort to increase impurity profiling efficiency has occurred among the so-called "hyphenated" techniques, of which LC/MS[90] and GC/MS have shown the most dramatic progress. The ruggedness of modern LC/MS and GC/MS instrumentation has been thoroughly demonstrated both as a tool to assay drug and metabolites from pharmacokinetic studies and as a method to support high-throughput analyses of drug discovery combinatorial libraries.[91] With steady reductions in instrumentation size and cost, mass spectrometry, once the domain of specialists, has been made directly available to process chemists and engineers in convenient open-access "walk-up" settings. A recent report from one pharmaceutical company describes a systematic workflow that enables aggressive impurity profiling and monitoring through walk-up HPLC and LC/MS instrumentation and custom targeted software.[92]

Analysis cycle time reductions have been most impressively gained in the GC/MS field, where "fast" GC methods have been shown to provide sharp, rapid resolutions of analytes showing very narrow peak widths.[93] Recent reviews have been published that describe the methodology employed.[94] Fast HPLC methodology also continues to gain acceptance. While most HPLC analyses continue to rely upon columns containing 3−5-μm particle sized stationary phases, fast and ultrafast HPLC separations employ columns packed

with 1.8 μm particles. With the advantage gained in mass transfer, however, comes the disadvantage of increased backpressure, which ultimately requires special ultrahigh-pressure pumps and flow cells. Monolithic HPLC columns offer a promising alternative. The stationary phase of these columns is comprised of a single, highly porous rod that allows high flow rates at lower backpressures while retaining equivalent resolution to small-particle packed columns.[95] These columns are increasingly being applied in situations requiring high throughput, including quality control testing[96] and pharmaceutical process development.[97]

Supercritical fluid chromatography (SFC), although more than 20 years old, has gained ground as an important modern analytical tool in pharmaceutical process research. In SFC, supercritical carbon dioxide along with an organic modifier (e.g., methanol) replace the solvent mixtures used in traditional HPLC. Owing to the high diffusivity and low viscosity of supercritical carbon dioxide, SFC benefits from fast mass transfer which results in high flow rates and fast on-column equilibration.[98] The most successful modern application of SFC is toward enantioselective separations. Traditional enantiomer separations using HPLC are plagued by lengthy run times and equilibration times, and both of these challenges are overcome by SFC.[99,100] One pharmaceutical process research organization has capitalized on the rapid column equilibration provided by SFC and reported an automated SFC method development workflow.[101,102] Because of the fast runtimes, SFC has heavily impacted high-throughput synthesis in drug discovery, both as an analytical tool for chiral analysis and as a preparative technique to obtain pure enantiomers from racemates.[103−107] In pharmaceutical process research, SFC holds the potential to broadly support on-line monitoring of parallel experimental reactions, and it has been shown to facilitate high-throughput experimentation by providing a rapid tool for monitoring chiral selectivity during enantioselective screening studies.[74,108] In addition, preparative chiral SFC is proving itself an important "green" alternative to traditional chromatography for rapid access to enantiopure pharmaceutical materials.[109]

While mass spectral molecular ion and fragmentation data may yield sufficient information for certain screening applications in process development, NMR data are generally also required to unequivocally elucidate the structure of reaction byproducts that have the potential to become process impurities. LC NMR offers the potential for streamlining the acquisition of NMR data directly following HPLC separation of individual impurities from complex mixtures, but earlier work fell short for high-throughput applications owing to inadequate sensitivity and the need for solvent signal suppression techniques and impractical volumes of deuterated solvent.[110]

Advances in NMR sensitivity gained from higher magnet fields and cryoprobe technology appear poised to overcome these limitations, however, particularly when used in conjunction with the technique of in-line, solid-phase extraction (SPE-NMR). In this method, a SPE device captures the HPLC effluent and concentrates the impurity of interest, whereupon it can be backflushed into an NMR flow probe using deuterated solvent. Further improvements such as a semipreparative version of LC-SPE-NMR have increased sensitivity some 30-fold compared to LC NMR.[111] Excellent reviews on the subjects of LC-SPE-NMR and LC NMR have been published recently.[112,113] In the future, automation of sample collection and introduction from SPE cartridges can be expected to improve NMR data throughput for impurity profiling work in support of route-scouting and process development.

3.2. On-line "Real-Time" Analysis

Alongside advancements in hyphenated analytical technologies, in situ, "real-time" analysis has become a very important contributor to pharmaceutical process research and development. Although on-line technologies such as FT-IR, near-IR, and Raman have been in use for years, gradual refinements to instrumentation and software have substantially improved their utility over the past decade. As a result, real-time analysis technology has increasingly allowed process research scientists to follow reactions and reaction pathways in ways that were once difficult or impossible (vide infra). Beyond use for the in-depth study of chemical reactions, these and other instruments capable of real-time data acquisition are becoming increasingly important in the monitoring and control of manufacturing processes. Although a detailed discussion of the field of process analytical technology (PAT) extends well beyond the scope of this review, the reader is referred to a very recent book on this topic[114] and a special issue in *Organic Process Research and Development* that highlights the impact PAT is having on the control of chemical processes on scale.[115−117]

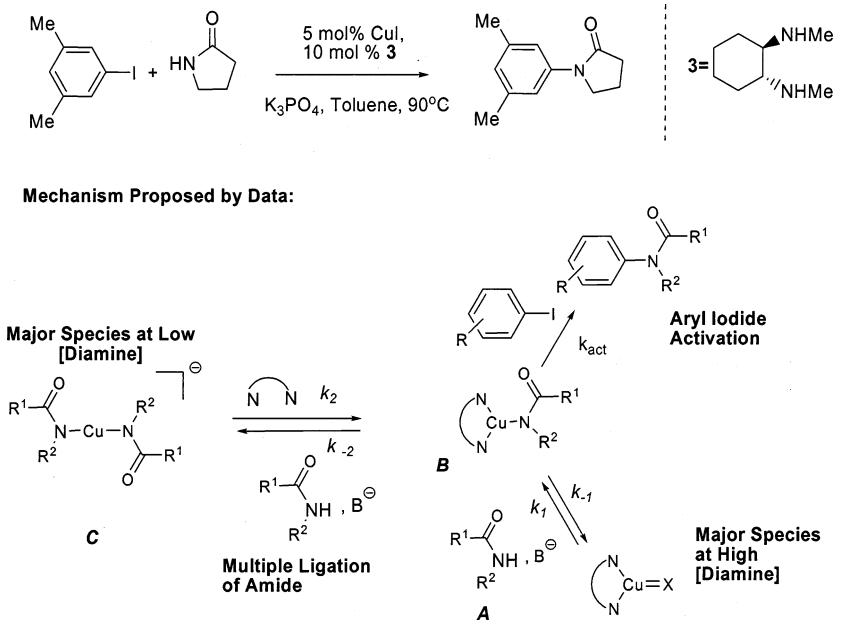
Finally, it is worth noting the ongoing efforts of the Center for Process Analytical Chemistry (CPAC), a university−industry cooperative research center that has been dedicated toward the development of new process analytical technology since 1984. A recent review covers their ongoing innovative work to develop new sensor technology to support PAT and microinstrumentation to support high-throughput experimentation.[118]

4. Kinetic Analysis and Reaction Modeling

4.1. Drivers for Kinetic Analysis and Reaction Modeling during Pharmaceutical Process Development

While the basic principles that enable elucidation of mechanistic details for complex, multistep reactions have been available for many decades, the translation of theory to practice has not displaced traditional empirical approaches to problem solving within the pharmaceutical industry. In recent years, however, applications of in-depth kinetic analysis to problem solving have been expanding steadily with the development of more rigorous analytical methodology, development of computational tool speed and sophistication, and growing awareness of two overlapping fields—Physical Chemistry and Reaction Engineering.[119] Inevitably, most reactions turn out to be more complex than initially anticipated, and a number of examples can be cited where detailed kinetic analyses have resulted in greatly enhanced levels of reaction understanding and control.[120,121] An equally important potential outcome of in-depth mechanistic studies is the prediction and achievement of reaction possibilities that might otherwise be overlooked or viewed as implausible based solely upon empirical "chemical intuition" and the absence of literature precedent.[122] However, the perceived mathematical rigor involved in carrying out such work continues to pose a barrier to research investigators who would gain from its power but lack the underlying skills and/or aptitudes required. Thus, pathways that can lower that

Scheme 2



barrier would serve to broaden accessibility to these tools. An article recently published by Blackmond outlines a systematic approach for carrying out mechanistic studies on complex catalytic reactions and is a significant step in that direction.[123]

Recognizing more generally that advances in analytical technology are increasingly enabling pharmaceutical companies to control their API production processes based upon higher levels of background knowledge and greater depth of understanding and control of critical process variables, the US Food and Drug Administration (FDA) has been encouraging companies to move beyond existing validation practices while promising to adopt a "risk-based approach" in its review of new product applications.[124] In taking this approach, the FDA seeks to put more focus on the identification and control of processing parameters that are most critical to quality and safety from the viewpoint of the patient. Similarly, it proposes to base its future approach to current good manufacturing practice (cGMP) regulation on its evaluations of systems a company puts into place that ensure *quality by design* (based on that underlying knowledge and systematic monitoring of critical process parameters) while deemphasizing requirements to carry out extensive end testing of materials against specifications.[125]

There are two important elements to minimize the risk of unintended quality deviations associated with scaling up a chemical reaction. The first is to obtain a sufficiently thorough understanding of the reaction's mechanistic dynamics in such a way that specific protocols can be designed to control all variables that could affect a reaction's rate and product ratios. The second is to obtain knowledge of the ranges over which the protocols should be effective, particularly in controlling variables that are most critical to achieve the desired outcome. Thus, through establishment of a valid reaction/reactor model, critical sources of variability can be identified and explained and product quality attributes can be accurately predicted over a "design space" established for various process variables. Further, creation of a valid process model allows one to perform virtual experiments to help ensure an efficient, safe scale up and efficient transfer of a process from one site to another.

4.2. Approaches to Kinetic Analysis

All kinetic studies are based on the fit of experimental data against mathematical rate expressions derived for one or more proposed reaction mechanisms, but the methods involved may be classified into two approaches—integral and differential—according to the manner in which data is acquired and treated. In the classic integral approach, a particular rate expression is assumed based on a proposed mechanism, and in conjunction with appropriate integrations and mathematic manipulations, the experimentalist ultimately seeks to establish a linear relationship between concentration and time. The mathematically treated data are plotted, and if linearity is demonstrated, the rate equation is said to satisfactorily fit the data and support the mechanism proposed. The integral approach is direct and can be recommended to confirm relatively simple rate expressions, but it can only test the rate expression for a specific mechanism proposed by the experimentalist.

In the differential approach the direction is reversed—the experimentalist tests the fit of various proposed rate expressions to data directly without integration. This approach is more useful in studying complex reactions and with sufficient data quantity and quality may be employed to accurately discern one complex rate expression among many possible while allowing the experimentalist to test hypotheses for any mechanistic nuances that may be involved. A recent report exemplifying the differential method to gain deeper insights into a complex chemical reaction is the kinetic study of the copper-catalyzed amidation of aryl iodides reported by Strieter et al.,[126] as described in Scheme 2. On the basis of an observed nonlinear relationship between the diamine ligand **3** and reaction rate, the authors confirmed a fit of simplified rate relationships to rate data collected using high and low levels of **3** and in doing so provided compelling evidence indicating that the amination reaction proceeds almost exclusively through intermediate B. This example illustrates an essential point about the value of kinetic measurements. The need to include excess diamine to ensure a reproducible reaction rate can be learned purely based on empirical trial and error experimentation, but a deeper

mechanistic understanding in many cases enables the process development scientist to ask more insightful questions and design process conditions in conjunction with knowledge obtained on other related dynamics present (e.g., how little excess of diamine is actually required to ensure intermediate B is favored, and if the multiply ligated catalyst is only partially soluble under the existing conditions, what impact might temperature, solvent modifiers, and agitation have on the rate of equilibrium achievement?).

The accuracy of conclusions that can be drawn using the differential approach is highly dependent on the quality and quantity of data that can be acquired. While traditional sampling techniques (HPLC, GC, and NMR) are valuable in providing conversion trends, they possess two fundamental shortcomings for use in more rigorous forms of kinetic analysis. One is the limited number of samples that may be taken per reaction (while high sampling frequency may not be critical when analyzing simple systems, it is of much greater importance when mechanistic complexity is present). The second shortcoming is the loss of accuracy frequently observed when reaction samples are drawn and quenched for off-line analysis (e.g., a cryogenic reaction where the sample is sensitive to temperature).

4.3. Modern Experimental Techniques To Obtain Kinetic Data

Over the past decade there have been significant advances in the sophistication of commercial instrumentation capable of gathering high-quality kinetic data in situ and in "real time". These advances have changed the landscape for both reaction and reactor modeling. One such development is the application of isothermal reaction calorimetry. A history of the early development of isothermal calorimetry was reported by Karlsen and Villadsen[127] and outlines the pioneering efforts of researchers at Ciba-Geigy that led to significant development of automated reaction calorimeter technology. At that time these instruments were used primarily to conduct safety studies to project thermal events of processes at scale, and a widely accepted commercial product that evolved from these efforts was Mettler-Toledo's Reaction Calorimeter, RC1, which measures the rate of heat flow into or out of a reactor while maintaining precise control of the temperature of its contents during a reaction. Using the RC1, heat flow data (which is a direct measure of reaction rate) can be obtained at high sampling rates and with high accuracy. Reaction calorimetry therefore provides direct data that is eminently suitable for the differential method of analysis.

One of the early adopters who applied the RC1 instrument to pharmaceutical process development is Landau et al., who in a series of papers demonstrated the use of calorimetry for both mechanistic pathway analysis and predicting behavior on scale. The past decade has witnessed a significant increase in the use of reaction calorimetry for kinetic parameter estimation, and the reader is referred to an extensive review by Landau et al.[128] and a more recent review by Zogg et al.,[129] which describe in detail the principles of reaction calorimetry and its role in kinetic analysis.

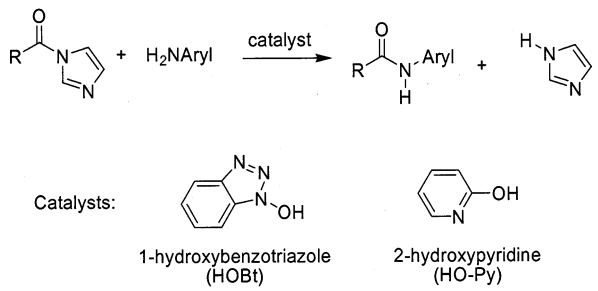
The advancement of in-line spectroscopic instrumentation has also had a major impact on the potential to study chemical reactions in depth. For example, the development of attenuated total reflectance (ATR) technology for FTIR[130] has greatly expanded the versatility of the use of in-line IR for reaction monitoring. Another popular technique employed within the pharmaceutical industry to obtain reaction kinetic data is Raman spectroscopy. As in the case of FTIR, the use of in-line Raman spectroscopy for reaction monitoring was facilitated by advances in technology such as the development of holographic filters.[131] In both cases, high sampling rates and excellent measurement accuracy enable mechanistic details to be teased out via experimentation.[132,133]

Reaction calorimetry and in situ spectroscopic monitoring are complimentary techniques that are often used synergistically to obtain reaction rate data and enable a better understanding of reaction dynamics. It is also important to note that kinetic models based on off-line measurements can also prove valuable, particularly in providing confirmatory evidence to conclusions drawn from "real-time" data analyses.

4.4. Reaction Modeling

The availability of high-quality kinetic data in recent years has spurred interest for the development of commercial packages to enable reaction modeling in batch reactors (e.g., Batch CAD, ChemCAD, and DynoChem). The availability of these commercial packages to simulate reaction outcomes based on data from a few concentrated experiments has greatly reduced barriers to modeling, and these tools have been gaining popularity.[134] An example of the potential predictive power of reaction modeling was reported by Bright and co-workers,[135] who applied the features of DynoChem to evaluate the use of 2-hydroxypyridine (HOPy) as an alternative catalyst to 1-hydroxybenzotriazole (HOBt) in promoting an imidazolide coupling with an aniline derivative (Scheme 3).

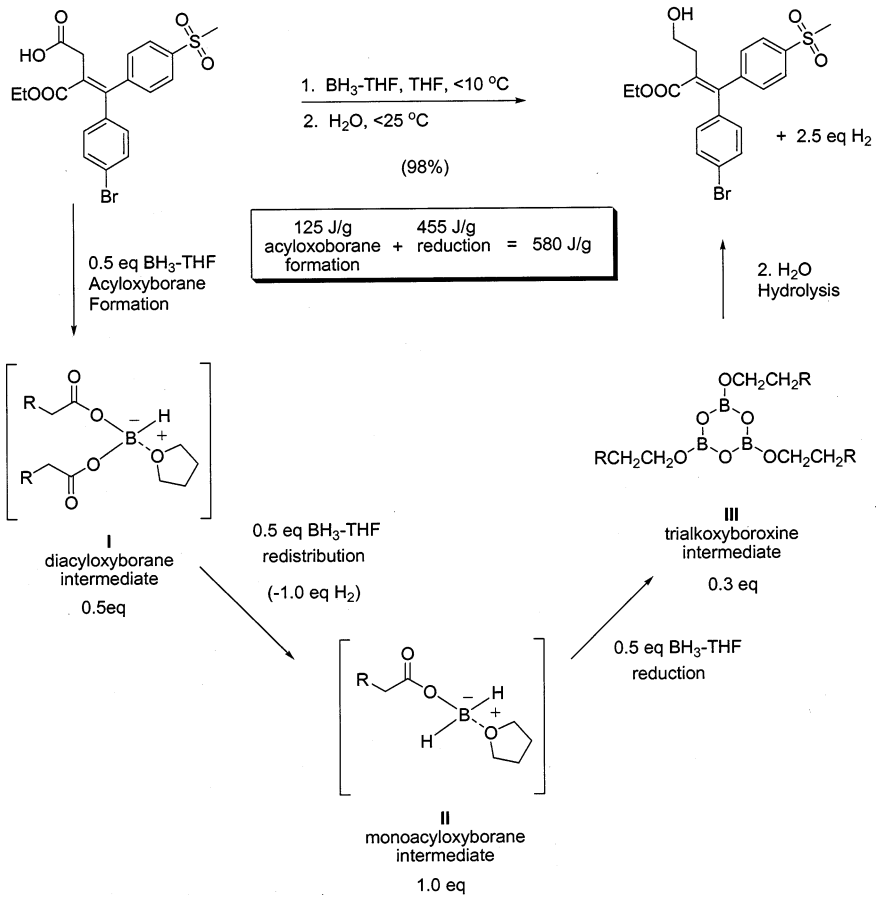
Scheme 3



Although HOBt is capable of catalyzing the reaction when run at reflux in ethyl acetate (78 °C), alternatives were sought since shipping restrictions exist with this catalyst as a result of its explosion potential. Using off-line HPLC sampling measurements, conversion data as a function of time were obtained for various charges of HOBt at 78 °C and similarly for HOPy at two different temperatures (78 and 102 °C). From that limited data a model was constructed, and the kinetic constants and the activation energies were estimated. Using the power of computer simulation the optimal reaction conditions (i.e., catalyst quantity, reaction time, and reaction temperature) were predicted, and subsequent experiments confirmed that the predictions were accurate.

In a second report,[136] the BatchCAD software package was employed to study the detailed mechanism of the borane reduction of a carboxylic acid and establish control over a potentially dangerous exotherm. From published reports and an experiment designed to confirm the rate-limiting step, a detailed mechanism for the reduction of carboxylic acid **1** was proposed (Scheme 4). The proposed mechanism and the

Scheme 4



exotherm data were used to develop a five-step kinetic model, and based on the measured heats of reaction, off-gas data, and in-line FT-IR data, the kinetic rate constants were obtained by regression from the experimental data of a 90-min addition experiment. The model created from these data allowed further simulation of temperature profiles and addition protocols and led to the determination of an optimal addition rate of the borane reagent. Both the five-step kinetic model and the exotherm control protocol were subsequently verified with follow-up experiments.

The two examples above illustrate the benefits of using an integrated approach to kinetic analysis by employing reaction calorimetry in conjunction with in-situ FTIR monitoring and other orthogonal methods and then using the data to construct reaction models from which the mechanism and kinetic parameters for a complex reaction may be elucidated. The combination of such kinetic models with the heat transfer characteristics of a given reactor enables one to perform 'virtual experiments' that lead to optimal protocols that are well understood and readily transferable from one process implementation site to another.

5. Continuous Processing/Process Intensification

5.1. Motivations and Opportunities

Process intensification is a general term used to describe process development efforts aimed toward dramatically reducing processing cost, time, waste, equipment size, or land use while maximizing overall efficiency.[137,138] In its most direct form, process intensification relates to objectives that have been embraced by process chemists within the pharmaceutical industry for many years. The development of reaction chemistry in sufficiently high yield and quality to eliminate specific purification steps, the choice of common reaction solvents enabling direct "telescoping" of chemical steps, and the choice of solvent conditions allowing direct crystallization[139] are all examples of process intensification, and the parallel screening and measurement technologies discussed earlier in this review are increasingly being used to more rapidly identify and capitalize on such opportunities to improve overall process efficiency.

More extensive opportunities exist however. Continuous processing, one of the cornerstones of process intensification, has been employed for many years by petrochemical and bulk chemical producers to increase efficiency and overcome challenges inherent to specific reactions. In contrast, batch processing predominates in the pharmaceutical and fine chemical industries and in the near future will likely continue to do so in situations where (1) product life-cycles are relatively short, (2) overall product demand is limited, (3) production volumes are relatively low, and (4) capital investments required to implement continuous processing are high or unique to a given process.

While the time and cost of research and development is also a consideration, advances such as those described in earlier sections of this review are lowering the barriers and increasing the speed with which continuous processing may be developed and applied. Moreover, significant advantages from the standpoint of cost, safety, efficiency, and environmental impact can often be gained by applying continuous processes with minor modifications to existing processing infrastructure despite the above constraints.[140] Relevant

opportunities reported recently involve (1) fast reactions (i.e., complete within seconds to minutes) with unstable intermediates or products that would otherwise degrade over extended reaction times of batch processing,[141−143] (2) reactions involving hazardous reactants prepared and consumed in situ,[144] (3) reactions possessing potential for runaway exothermic hazard,[145,146] (4) batch reactions requiring intimate mixing of reactants in multiple phases,[147] and (5) reactions occurring rapidly upon close contact with specific energy sources (e.g., microwave,[148,149] UV irradiation,[150] and sonication[151]). One company that commercializes equipment specifically to support process intensification is Protensive, in the United Kingdom.[152]

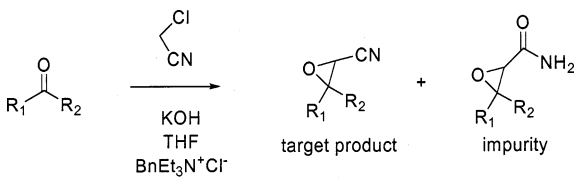
The use of simulated moving-bed (SMB) chromatography for separation of enantiomers represents another example of process intensification that increases separation efficiency and reduces solvent usage. SMB technology is increasingly being employed by the pharmaceutical industry, particularly in situations where an initial supply of enantiomerically pure intermediate or API is required rapidly during the earliest stages of clinical study and product development or in cases where low production volumes of highly potent compounds are needed. Specific articles covering SMB use in the pharmaceutical industry have recently been published by Miller[153] and Toumi.[154]

5.2. Emerging Applications of Engineering Technologies

5.2.1. Spinning-Disk Technology

While the simplest representation of a continuous reactor is a tubular plug-flow system, advances in reactor design and enhanced understanding of micromixing[155−157] and microfluidics[158] are opening doors to highly effective processes based on reaction control that many synthetic organic chemists would not currently recognize as being feasible. Spinning-disk reactor technology, for example, features greatly enhanced mixing, heat transfer, and residence time control, all of which allow for intrinsically fast and exothermic reactions to complete within the brief contact time of the spinning disk.[159] On the basis of the technology, Oxley et al. reported an impressive illustration of process intensification as applied to a phase-transfer-catalyzed Darzen's condensation in which reaction times were dramatically reduced and an impurity that would have been unavoidable in a batch process was readily controlled. Moreover, the reaction stream from the spinning-disk reactor was coupled directly into a designed continuous crystallization that provided readily filterable crystals of narrow particle size distribution (Scheme 5).[160]

Scheme 5



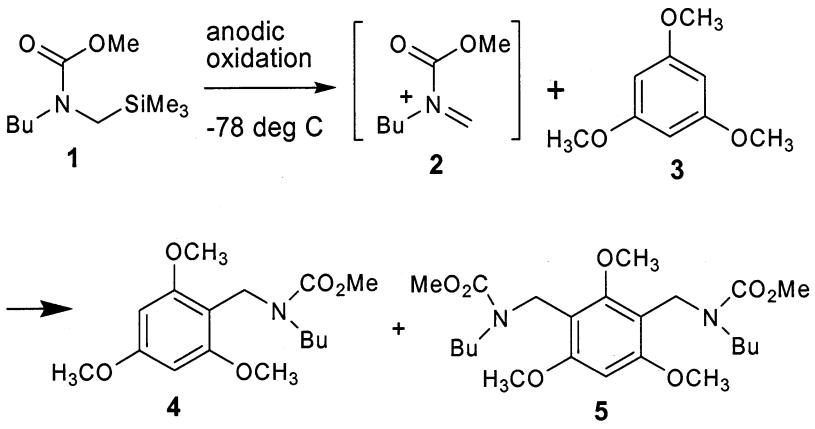
5.2.2. Microreactor Technology

The potential for significant process productivity gains has also generated considerable interest in *microreactor technology*. Microreactors are continuous flow systems with internal channel widths in the 50−300 μm range and volumes most typically in the microliter range. Thanks to modern advances in microfabrication technology, microreactors with precise and complex internal geometries and connections can be constructed, and specific devices, such as micropumps, micromixers, microheat exchangers, microextractors, etc., have been designed for various unit operations.[161] Current techniques to fabricate microreactor components include dry and wet chemical etching, micromolding, laser ablation, mechanical micromachining, microelectrodischarge machining, and LIGA technology, all of which allow microreactor components to be constructed from silicon, metals, glass, ceramics, and polymeric materials.[161,162]

Extensively reduced dimensions for reactant mixture flow within a microreactor dramatically improves heat transfer and mass transport, and enhancement of the surface-to-volume ratio may be used to advantage in (1) controlling reactions that are highly exothermic, (2) allowing reactions normally conducted at cryogenic temperatures to be run at substantially higher temperatures, and (3) minimizing undesired secondary reactions. Generally the flow characteristics in a microchannel lie in the laminar regime, where mixing is dominated by molecular diffusion. Fast mixing can be achieved at scale, however, through multilamination and recombination, where shortened diffusion paths and increased fluid interfaces are made possible. Thus, in situations where reaction rate is diffusion limited, the domain for reaction is essentially reduced to a series of parallel planes between the two reactant streams. With zoned control of localized temperature within the microreactor and short, controlled reaction times, secondary reactions that would normally be evident under batch conditions can frequently be minimized or eliminated. Moreover, the limited volume of active chemistry within a continuous flow microreactor provides greatly improved process control and safety. In principle, an additional benefit of microreactor technology is also scalability, since the technology is amenable to "numbering-up" effective microreactor channels rather than "scaling-up" vessel size. An excellent article covering microstructured mixer devices and principles to support scale up of the microreactor concept with miscible liquids and/or gases has been published by Hessel et al.,[163] and a two-volume set has been published by the same authors on chemical microprocess engineering.[164]

An impressive example of the potential for micromixing control to detect and enable nonobvious reaction selectivity potential was very recently described by Nagaki et al. in their study of rapid, consecutive Friedel−Crafts reactions using highly reactive aromatic compounds with *N*-acyliminium cation pools (Scheme 6).[165] When the reaction was carried out in batch mode, poor selectivity for monosubstitution was achieved independent of the manner in which the two substrates were mixed, and overall mass balance recovery of the two products remained below 70%. When the two reactants were mixed through a 25 μm channel and quenched following a 30 ms contact time; however, selectivity for monosubstitution over disubstitution increased to 92:4, and an overall mass balance of 96% was achieved. The application of microreactor technology is also not limited to reactions that complete rapidly at low temperature. For example, a process involving the monochlorination of acetic acid was recently patented in which case levels of dichlorinated byproduct (which normally complicates batch reactions) were suppressed to <0.05% when chlorination was

Scheme 6



method of addition (-78 deg C)	4(%)	5(%)
addition of 2 to 3	37	32
addition of 3 to 2	33	33
simultaneous addition	34	30
simultaneous addition (micromixer)	92	4

purposely conducted at 190 °C using microreactor technology.[166]

The application of microreactor technology toward a wide range of reaction types is now well documented in the literature, and the reader is directed to a recent review in which a number of microreactor applications were benchmarked for efficiency relative to batch processing[167] and a second review by Hessel et al. detailing examples where organic transformations can be effectively improved.[168] Additional general reviews on microreactor principles and opportunities have been written by Pennemann et al.[169] and Fletcher et al.[170]

An essential point to be made regarding microreactor technology is that many synthetic chemists are likely to miss attractive processing opportunities if they rely solely on standard methods of reaction screening, particularly in cases where reaction performance is complicated by undesired, consecutive secondary reactions. In many such cases reaction selectivity potential is not recognized and may simply be written off as being plagued by lack of selectivity or "mass balance issues". In that regard, greater utilization of small microreactors as screening tools should help "unmask" inherent kinetic rate differences that can be used to achieve high reaction selectivity in conjunction with appropriate micromixing technology at scale. In a recent report on microreactor technology Roberge et al. estimate that as many as 50% of reactions in the fine chemical and pharmaceutical industry could benefit from development of a continuous process based on microreactor use.[171] However, these authors also point out that the inability to handle solids is a potential limitation in many cases and that processing reactors represent only 15% of the equipment overhead cost. Thus, the investment in continuous processing cost involving microreactor technology needs to be offset by yield improvements, efficiencies gained, and overall cost-of-goods advantages realized.

5.2.3. Monolithic Columns and Catalyst Immobilization Strategies for Continuous Processing

To simplify processes and ensure reproducibility, process chemists within the pharmaceutical industry generally gravitate toward reaction chemistry that can be run in a single common liquid phase. However, significant productivity advantages can frequently be achieved by employing multiple phases (i.e., liquid−liquid, gas−liquid, solid−liquid),[172] and many of the hardware and software tools described earlier in this review should serve to catalyze more general development of process technology based upon multiphasic reactions. For example, Kobayashi et al. recently demonstrated a system for continuously carrying out triphasic hydrogenation reactions via immobilization of palladium onto the surface of a microchannel.[173] In relatively recent reviews by Ley[174] and Kirschning[175] advances were also outlined for the use of immobilized catalysts and reagents for parallel synthesis applications in support of drug discovery, but opportunities for industrial processing were also made obvious. In this regard, yet another emerging process intensification technology worth highlighting is that of the monolithic column as process reactor.

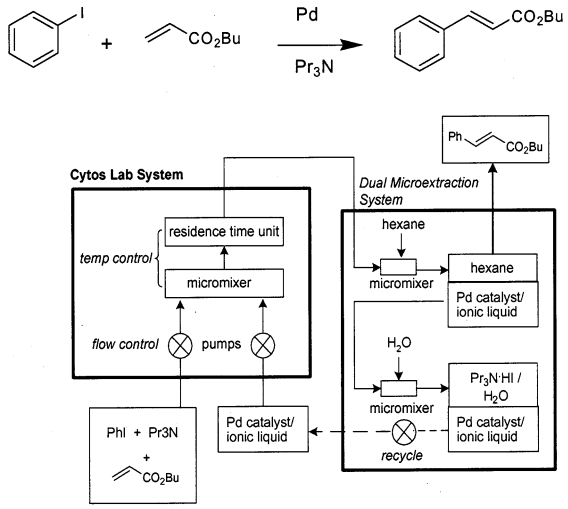
Reactors that employ fixed or moving beds of solid catalyst have been used in other industries for many years with specialized hydrogenation reactors representing a primary example. However, randomly packed catalyst beds are accompanied by uncontrolled fluid dynamics that cause drawbacks, including mass and heat transfer limitations, limitations on effective catalyst surface area, and high-pressure drops.[176] A monolith is a highly structured material formed by controlled copolymerization of specific monomers in the presence of porogens or degradable polymers embedded in the polymer being formed.[177] With technologies developed over the past decade, the porosity of the polymeric material formed can be carefully controlled and a polymeric structure can be produced as a single continuous rod within

a reactor column housing or alternatively cut into disks. Properly formed, the channels formed in a monolith provide for high surface area, short diffusion paths, excellent mass transfer rates, and low-pressure drop across a designed reactor column. As such, they possess significant advantages over existing technology involving fixed-bed or fluid-bed catalysts.[178] The use of monolithic columns as supporting structures for immobilized catalysts has been demonstrated more generally, and the reader is referred to two recent reviews that cover an array of applications recently published.[179,180] Although such sophisticated catalyst immobilization strategies have not yet reached the stage of general commercial use, future potential for process productivity enhancement from these techniques should become more clear as further development proceeds.

5.3. Future Trends

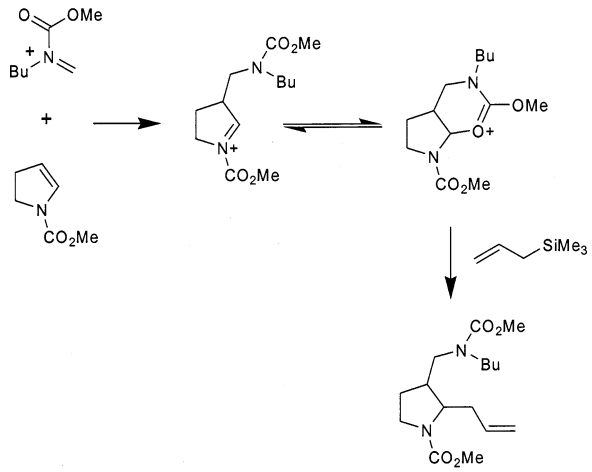
As the advantages and limitations of specific reactor and workup technologies become more widely recognized, one could readily predict that specific types of reactions (particularly those based upon catalysis) will be designed in an integrated manner with the safest and most economically advantageous *physical* means to carry them out on scale. With the aid of microfluidics engineering technology, biphasic reaction systems are now capable of being designed in which *homogeneous* catalysts are localized in ionic liquids in a manner that allows them to be cleanly separated from product streams and recycled.[181] Accordingly, it is interesting to note a recent paper in which a low-viscosity ionic liquid was specifically screened for effectiveness as a catalyst carrier with enhanced flow and mixing properties for improved utility in a continuous microreactor application while allowing downstream integration with a continuous workup strategy (Scheme 7).[182] Employing the "cation pool"

Scheme 7

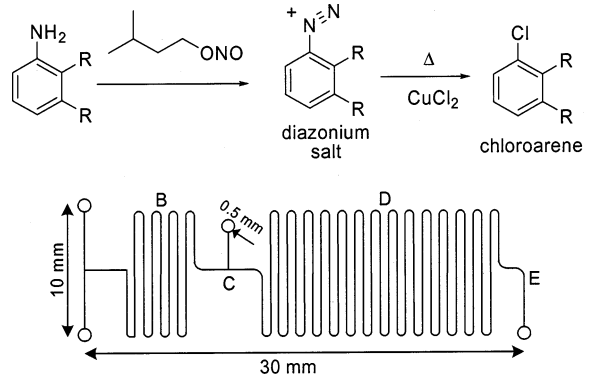


method described in Scheme 6, Suga et al. demonstrated the integration of two chemical transformations with the aid of a micromixing device (Scheme 8).[183] Similarly impressive is the recently reported design and demonstration of the successive diazotization and chlorination steps involved the Sandmeyer reaction in successive chambers of a microreactor with a high level of control (Scheme 9).[184] As such reaction/reactor combinations are designed, technology patents are sure to follow, as exemplified by the Clariant patent for diazotization/coupling technology cited in the latter report.

Scheme 8



Scheme 9



A) Diazotization inlets
B) Primary (diazotization) reactor (80 mm)
C) copper chloride inlet
D) Secondary (Sandmeyer) reactor (280 mm, higher temp.)
E) chloroarene product outlet

6. Rate-Limiting Steps to Technology Uptake and Adoption within the Pharmaceutical Industry

The breadth of literature cited in this review illustrates the range of productivity enhancement opportunities available to the pharmaceutical and fine chemical industries, all made possible by recent innovations in research and development technologies. The advancement of process intensification methodologies shows great promise for increasing process reliability while lowering manufacturing costs. Evolving hardware and software tools can be brought to bear, potentially to accelerate research and development of those methodologies. Regulatory bodies such as the US FDA are applying pressure to take greater advantage and yet the overall rate of uptake remains (arguably) slow.

What is missing? Inertial barriers to the adoption of new technology are certainly present but are not insurmountable. First and foremost, any new technology must be sufficiently attractive economically to displace existing technology that is familiar, trustworthy, and firmly established. Just as a net gain in free energy is required for a chemical reaction to proceed forward, the level of investment required for new technology adoption ultimately must be matched by potential for high economic return. It should also be recognized that early adopters within industry must explore new technology while facing project delivery timelines with a greater level of risk. Consequently, the patenting of new technology can

frequently increase the inertial barrier and depress incentives to explore the technology, particularly when other cost-effective alternatives exist.

Second, to take maximum advantage of the technologies cited, the personnel traditionally responsible for process R&D (synthetic organic chemists, chemical engineers, and analytical chemists) will need to gradually increase their versatility as scientists. An infusion of experts from previously unfamiliar fields, such as reaction science, automation technology, and informatics, is also needed. An industrial process R&D project, by its nature, is an interdisciplinary team effort. However, an increased comprehension of each of the above fields by all would greatly facilitate the transformation of industrial process R&D into a discipline that is more fully capable of capitalizing on new technology's potential. Yet, there are also practical limits to the scope of working knowledge over which a typical scientist can maintain competence. Tradeoffs need to be weighed on the extent to which specific technologies should be more broadly dispersed or remain within the hands of specialists. Advanced research technologies involving high-throughput experimentation, measurement, and screening, for example, appear to be falling into the latter category.

Finally, for the technologies cited to have greater economic impact, managerial and scientific leaders within the pharmaceutical industry will need to more actively sponsor internal productivity enhancement objectives as strategic priorities. Similarly, senior business leaders will need to be convinced to approve the necessary investments in training and infrastructure and sometimes even need to allow other short-term opportunities to be sacrificed in order to realize the long-term productivity gains made possible by technological innovation. Even in today's challenging business climate those are difficult but not impossible things for pharmaceutical and fine chemical companies to do.

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