

## Lecture Transcripts

# Rapid Process Development and Scale-Up Using A Multiple Reactor System

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### Abstract:

This article presents case studies that show how computer control involving parallel synthesis in specially designed reactors, particularly on the 25–100 mL scale, can provide significant benefits to the development cycle of new synthetic compounds of commercial interest. The application of computer control to a variety of processes is discussed, particularly the combination of automation with statistical design packages for process optimisation. By employing a combination of calorimetry data and other analytical measurements, it has been demonstrated that small-scale experimentation can produce data that is both representative and scaleable.

### 1. Introduction

The uptake of computer controlled processes in the chemical development laboratory has been much slower than in many other areas of the industry, with manual experimentation the predominant method of choice in many small and medium sized companies, worldwide. Even up until the mid-1990s (or even later), the limited automation that existed for process development was principally focused on bench scale reactors, typically with a volume of around 1 L with dedicated control systems for each reactor employed.

The last three or four years have seen a rapid change in this situation, especially in terms of small-scale (around 10 mL) process screening. This reflects the increasingly competitive pressure to develop new products or variants of existing ones in the shortest time possible and then take them to market as fast as possible. This driving force is particularly highlighted in the pharmaceutical industry where the current market pressures are extreme and there is a constant necessity to generate hundreds if not thousands of potential candidate compounds for screening. Recent developments in robotic systems and the upsurge in combinatorial chemistry now allows a much greater throughput of many of these potentially interesting compounds, but this has had the effect of moving the bottleneck in new product development to the stage of process scale-up and refinement. It is the subject of this paper to examine one method for addressing this problem in detail and to show how multiple automated calorimeter/reactor systems are ideally suited to reducing the time spent at this stage of product development.

### 2. Current Automation Tools

**2.1. Robotics.** The majority of off-the-shelf robotic systems that have evolved for process research in the chemical industry consist of a “moveable arm” that can orientate itself in either the  $x$ ,  $y$ , or  $z$  plane, enabling it to locate test tubes or similar sized containers, serving for example as a reactor. By augmenting the design further and incorporating an automated syringe pump, it is also possible to add or remove reagents as part of a chemical synthesis or perform simple chemical sampling. As such, these robotic systems are commonly used in industry and are generally described as “liquid-handling units” reflecting their widespread use and application. It is also possible to incorporate two or more pumps in such a system to serve a large number of receivers perhaps dispensing more than a single reagent. This, however, can lead to complex scheduling and sequencing problems, making their use by a nonspecialist operator extremely difficult, although many commercial systems have sought to provide software solutions to these difficulties.

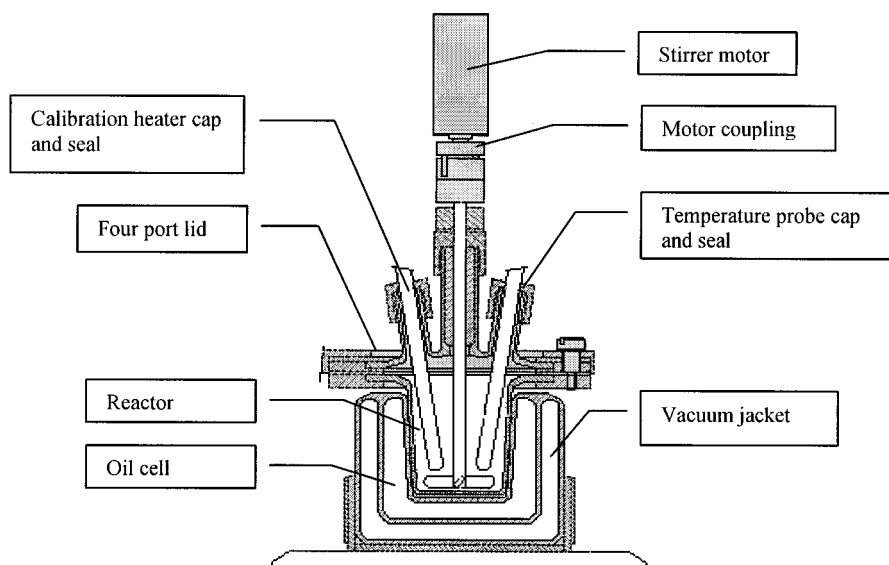
In reality chemical process development using these “standard” robotic systems is frequently limited to the simplest of chemical synthesis with actions, such as controlled reagent dosing, in response to a measured process variable (temperature, pH, pressure, turbidity, etc.) not feasible. More demanding needs such as working with solids (pastes, slurries, and suspensions) or performing the reaction at elevated pressure (in excess of 50 bar) in conjunction with agitation go largely unanswered by the typical robotic system. It is for these reasons that robotic systems are principally employed at the initial screening stage of product development where the complexity of the required tasks and unit operations is limited.<sup>1</sup>

This is not to say that all robotic systems are the same, and indeed some novel ones have been developed recently. Schering<sup>2</sup> have developed a fairly complex system for process screening which can in certain cases also be used for process development. Glaxo<sup>3</sup> have also recently presented the “PROSPER” system which has over 50 reactors that are individually controlled with excellent features to enable rapid process development.

(1) Harre, M.; Tilstam, U.; Weinmann, H. *Org. Process Res. Devel.* **1999**, *3*, 304.

(2) Weinmann, H. *Symposium presentation at The 3rd International Symposium, The Evolution of a Revolution: Laboratory automation in Chemical Process R&D*; Boston, 2000.

(3) Owen, M. *ibid.*



**Figure 1.** Schematic representation of an auto-MATE system.

**2.2. Automated Laboratory Reactors.** Larger scale (1–10 L) fully controlled reactor systems/calorimeters for the accurate simulation of batch and semi-batch process chemistry and the continuous measurement of reaction heat output are well accepted as the *sine qua non* tool for process scale-up. Such systems can be highly specialised and include good mechanical stirring, multiple liquid dosing, accurate temperature control, reflux, and high-pressure facilities.<sup>4</sup>

However, when the process has not been fully optimised or where there may be several possible synthetic routes to choose from, then large-scale systems may, at best, only provide a partial solution. This is essentially due to the considerable quantities of chemicals that are required for such experiments and the difficulties associated with the waste disposal. These difficulties are particularly highlighted if the process involves an expensive reagent or a difficult-to-synthesise intermediate. The time requirement for performing a series of process optimisation experiments must also be taken into consideration especially since the time to market for a new product is crucial. Typically it is found that large-scale automation experiments involve long “turn-around” times between experiments, and this in conjunction with only one reactor available to the researcher means that true optimisation may take weeks or even months to complete.

**2.3. The Auto-MATE.** It is clear that although rapid experimental screening with robotic systems provides a convenient route by which many hundreds of potential target compounds can be synthesised they are often unsuitable for the more complex task of process optimisation (with notable exceptions, see for example refs 1–3). Bench-scale reactors on the other hand, particularly those able to perform calorimetry are able to generate extensive data for direct scale-up, but with the drawback of large sample sizes and slow optimisation times.

This leaves an important gap in the product development cycle, how to take a potential target compound from the screening stage to the point where it has become a well-

defined process of commercial importance. The auto-MATE<sup>5,6</sup> has the attributes of a system that addresses many of these problems and has been used with considerable success on a wide range of processes.

The auto-MATE is a miniature (25–100 mL) computer controlled multiple reactor system equipped with all the features commonly associated with a bench-scale or larger reactor. A key feature of the system is that up to 16 independent reactors can be controlled simultaneously from a single computer interface, although in practice four appears to be the most common choice. The system is designed to address the gap present in the process development cycle and consists of a small container that constitutes the oil jacket, normally made of glass (but it can also be metal), with a central recess into which a close-fitting miniature reactor is placed. A schematic diagram is shown in Figure 1.

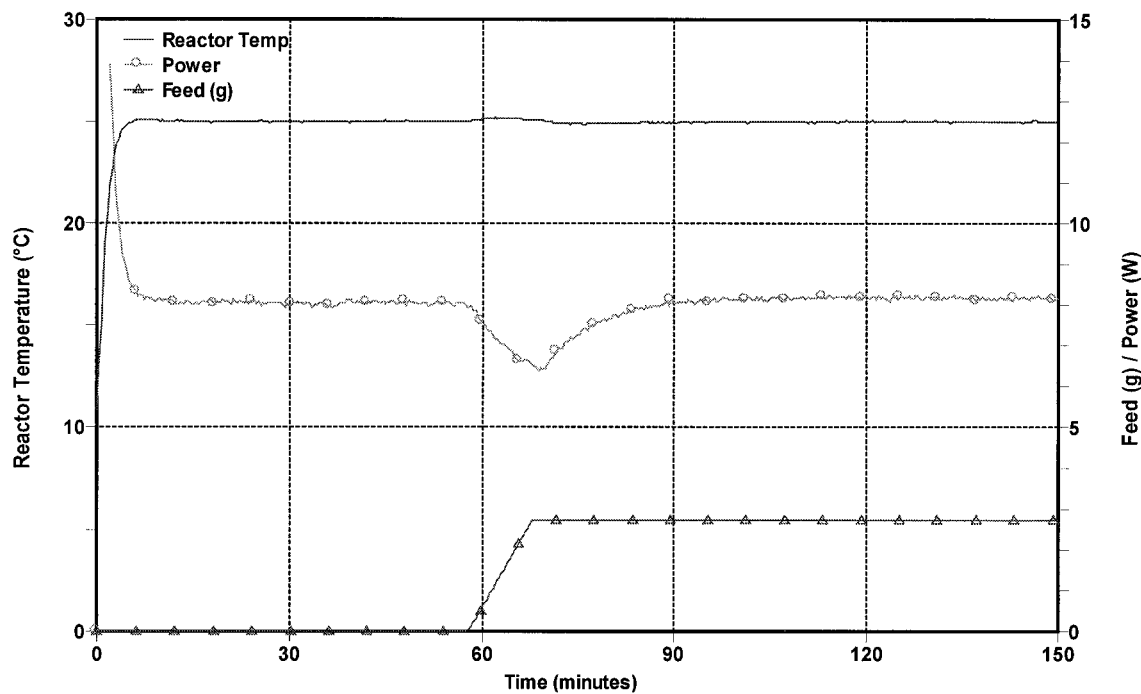
Reactors of different volumes and materials can be used interchangeably with the jacket and by employing a reactor cover with integral stirrer mounted on it with ports for a thermocouple, pH probe, heater, reflux condenser, etc. all of the features of a larger reactor system are present. To increase material throughput and reduce experimental “down time” on termination of an experiment the entire reactor insert can be removed and replaced in a matter of minutes.

Temperature control (both isothermal and non-isothermal) is maintained by means of an electrical heater placed within the reactor. This enables both precise and rapid control of the desired reactor temperature and optionally allows calorimetric data to be acquired using the power compensation technique.<sup>4,6</sup> Using this information it is possible to determine reaction end points and act as a first pass screen for hazard assessment in scale up.

(5) Evens, N. *Symposium presentation at The Evolution of a Revolution Laboratory Automation in Chemical Process R&D*; : Chester, 1998, Abstract book.

(6) Singh, J. *Eur. Pharm. Contractor* **1997**, 157–160.

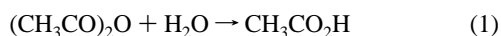
(4) Singh, J. *Process Safety Progr.* **1997**, 16, 1.



**Figure 2.** Isothermal calorimetry of the hydrolysis reaction between water and acetic anhydride.

### 3. Applications of the Auto-MATE to Simple Organic Synthesis

The basic utility of the auto-MATE can be illustrated by examining the model hydrolysis reaction between water and acetic anhydride. The reaction proceeds quite readily at ambient temperatures with the formation of acetic acid as outlined in eq 1.



The reaction is exothermic and therefore results in a decrease in the power supplied to the internal heater to maintain isothermal conditions. By examining the power output from the reaction, it is possible to determine the maximum heat output rate (which will be proportional to the maximum cooling duty required on scale up) and the total heat release from the reaction. A typical isothermal calorimetry trace for the dosing of 2.5 mL of acetic anhydride at 0.25 g/min into 30 mL of water is shown in Figure 2.

As can be seen from Figure 2, at the start of the experiment the reactors and their contents need to be raised to their set point values. To achieve this as quickly as possible the heater is turned on at a near to maximum value (just over 15 W). After the desired reactor temperatures have been achieved, the power then falls and stabilises at approximately 8 W (since the heater is now only required to make up the temperature differential between the oil jacket and the desired reactor temperature). On dosing of acetic anhydride after 58 min the heater power is observed to fall further as it compensates for the energy that is liberated by the reaction, whilst maintaining isothermal conditions. By integration of the power-time curve by selection of two suitable baseline regions before and after the reaction period, it is possible to evaluate the heat of reaction. For the reaction between water and acetic anhydride, this is typically

found to be in the region of  $-60$  kJ (per mole of acetic anhydride).<sup>7</sup>

In addition to providing important data regarding the magnitude of heat release during the reaction the shape of the heater power profile also provides useful information regarding the global kinetics. It is observed that on termination of the acetic anhydride feed the heater power returns very quickly to a new baseline value. This is indicative of almost feed rate limited kinetics, in which the heat release profile is almost entirely determined by the feed rate of acetic anhydride into the reactor. This information is especially important when you want to scale up your reaction within the confines of your existing plant capacity. These kinetic effects are more clearly shown in Figures 3 and 4.

In Figure 3, the feed rate of acetic anhydride is kept constant at 0.125 g/min, and the isothermal reaction temperature increases from 25 to 35 °C. Examination of the heat release profile under these conditions shows that as the reaction temperature is raised the rate of heat release increases and the reaction terminates more quickly. In Figure 4 the effect of feed rate on the heat release power profile is investigated, and again a similar effect is observed with the heat release rate becoming greater as the feed rate is increased.

Clearly, it is important to determine the reproducibility of the calorimetry data obtained on this scale and to compare it to data obtained from larger bench-scale reactors, especially since these data can be used to give vital information on process scale up. Table 1 summarises the results from 24 experiments between water and acetic anhydride performed in a four-reactor system in six experiments. All reactors were glass atmospheric vessels maintaining isothermal reactor temperatures of 25, 30, and 35 °C. Acetic anhydride

(7) Amende, D. Pfizer, Inc., private communication, 1998.

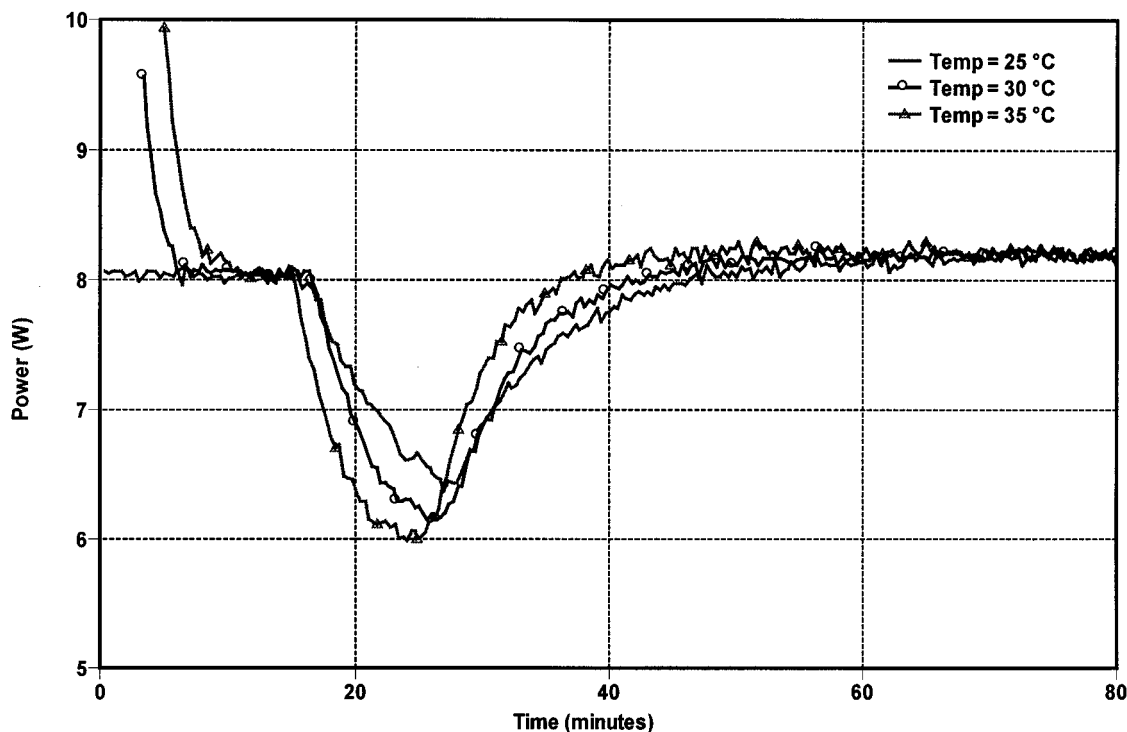


Figure 3. Variation in the power profile with temperature for the reaction between water and acetic anhydride.

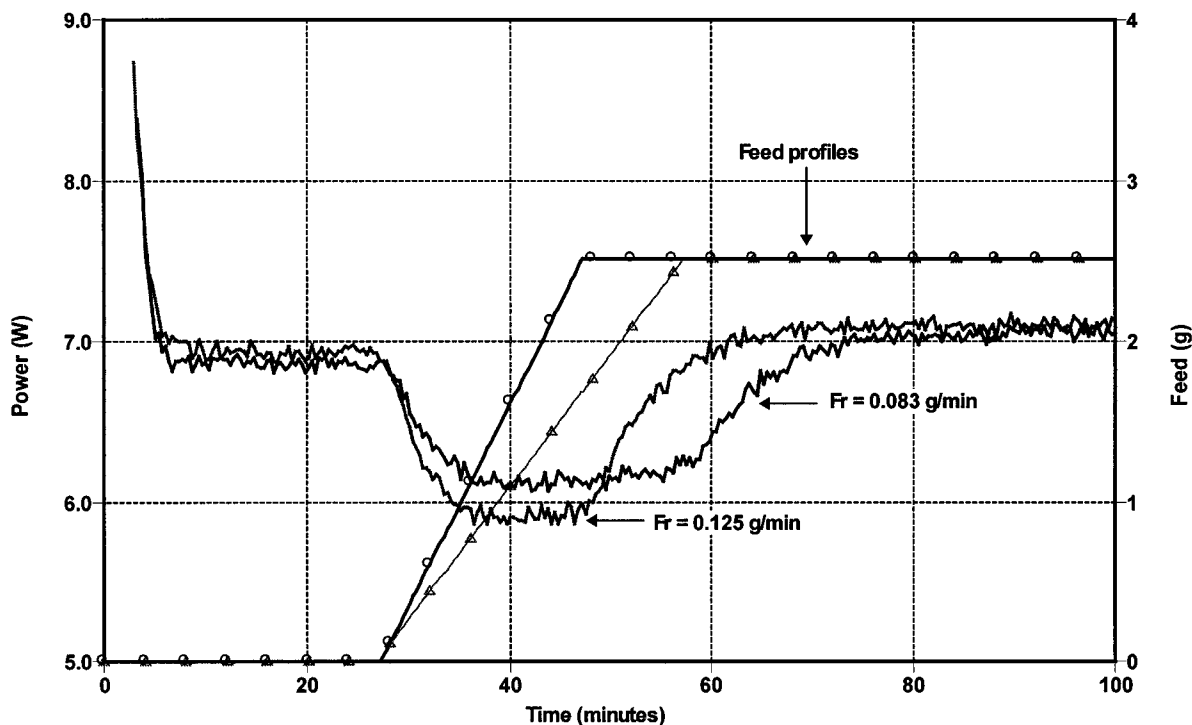


Figure 4. Variation in the power profile for the reaction between water and acetic anhydride with feed rate.

(2.5 g) was charged via four computer-controlled syringe pumps at rates of 0.088, 0.125, and 0.25 g/min, respectively.

Analysis of the 24 experiments reveals a mean enthalpy release of  $-62.4 \text{ kJ mol}^{-1}$  with an enthalpy spread of  $\pm 6.7 \text{ kJ}$ . This constitutes only a 5.8% error in the enthalpy measurement even on consideration of the experimental error involved in setting up the experiment. This compares well to data from larger (1 L)-scale calorimeters which have

been reported to measure a heat of reaction of between  $-57$  and  $-64 \text{ kJ mol}^{-1}$  for the same reaction under similar conditions.

An analysis of variance (ANOVA, one way with replication) illustrates that data from reactors 1, 2, 3, and 4 for tests 3, 4, and 6 show no statistical difference, by way of the  $F$ -test, at the 95% confidence level, when:

- analyzed as three replicated measurements (same temperature) on four reactors ( $F_{3,8} = 4.07$ ,  $F_{\text{obs}} = 0.87$ );



**Table 1.** Analysis of auto-MATE enthalpy data from the reaction between water and acetic anhydride

	calculated enthalpy (kJ Mol <sup>-1</sup> of acetic anhydride)			
	reactor 1	reactor 2	reactor 3	reactor 4
test 1 (25 °C, 0.25 g min <sup>-1</sup> )	61.7	59.6	58.9	67.6
test 2 (35 °C, 0.25 g min <sup>-1</sup> )	59.3	63.6	64.0	62.8
test 3 (30 °C, 0.125 g min <sup>-1</sup> )	62.5	63.3	61.7	64.1
test 4 (30 °C, 0.088 g min <sup>-1</sup> )	63.1	63.3	66.1	69.1
test 5 (25 °C, 0.25 g min <sup>-1</sup> )	56.8	60.7	60.7	60.5
test 6 (30 °C, 0.25 g min <sup>-1</sup> )	59.0	60.6	59.3	64.8

• analyzed as four replicated measurements (four reactors) for different test conditions (same temperature, different feed rates) ( $F_{2,9} = 4.26$ ,  $F_{\text{obs}} = 3.14$ ).

ANOVA (two way without replication) on all of the data of Table 1 shows no statistical difference in the data from any of the reactors ( $F_{3,15} = 3.28$ ,  $F_{\text{obs}} = 2.57$ ); statistical variation in the data from each test condition ( $F_{5,15} = 2.90$ ,  $F_{\text{obs}} = 4.08$ ) which is not surprising, given the changes in the conditions for the set of six tests.

Common to all calorimetry experiments, the uncertainty in the enthalpy determination will be directly related to the heat output during the reaction, with strongly exothermic reactions providing smaller relative errors than less exothermic reactions. In principle the calorimetry information recorded on this scale is not intended to be used for direct scale up and should be confirmed once a process has been optimised with a bench-scale calorimeter. In practice, however, this caution is only important for reactions with low heat outputs where the error can be much higher.

#### 4. Application of the Auto-MATE in Conjunction with Experimental Design

After a new product of commercial interest has been identified, the next stage of development is the refinement of the synthetic route, with care taken to consider the implications of any changes on the economics both in the batch production time and raw material costs. It is also necessary at this stage to consider the ease and practicability of scale up and the plant capabilities, such as cooling duty that will be used for production.

This refinement task is both expensive and time-consuming, and it is essential that a process operates with maximum efficiency to ensure profitability. For these reasons statistical design techniques are becoming an ever increasing tool to the development chemist to ensure desired process optimisation occurs, employing the least number of experiments. By the use of a formal statistical design method in addition to optimising the process it is also possible to examine the interactions between the process variables, such as feed rate, agitation, temperature, or residence time. This knowledge is invaluable since it enables the operator to decide which variables must be controlled within tight limits and which variables have very little effect on the process.

The auto-MATE's ability to perform multiple experiments together with the ability of multi-variable control renders this an ideal tool for process optimisation studies. These

capabilities coupled with the additional calorimetry data enable an investigation into both the synthetic chemistry as well as an evaluation of the reactor design. A case study demonstrating the application of combined statistical design techniques and automated reactor systems in process optimisation is presented below.

The example consists of work performed between the Hazard Evaluation Laboratory, UK, and a flavourings company. The object of the research was to employ statistical methods in conjunction with automated reactor systems to reduce the batch cycle time of a product whilst maintaining it within a stringent specification. Although the exact chemistry cannot be discussed in any detail for commercial reasons, the underlying process consisted of mixing three components A, B, and C to form a product D, as outlined in eq 2.



On employing the current processing methods it was found that operating the reaction at temperatures above 12 °C resulted in formation of an undesired side product that caused failure of the entire batch (1800 kg).

The first stage of the optimisation strategy, as in any statistical design analysis, was to identify the key variables in the process and quantify them. It was found that four variables were important, these being reactor temperature, feed rate of component B, the presence or absence of component C at the start of the reaction, and agitation. Allowing for scaling differences between plant scale production and the auto-MATE, it was chosen to investigate the four variables at 50% higher and lower values than those currently being used on plant. This involved looking at a temperature range of 4–16 °C and feed rates of 0.1–0.18 g/min (4.86–8.74 kg/hr of component B industrially).

Initial studies focused on a full 2-factorial screening design in which the importance of the four variables was established. This was performed using "Stat-Ease Design Expert 5" software package although there are many other commercial programs available.<sup>8–10</sup> In a 2-factorial experiment each of the chosen factors are studied at their extreme values and their effect on the objective function(s) statistically analysed. Table 2 shows a typical table of data from a 2-factorial design. As can be seen a casual glance at the data does not provide any immediate trends, and only analysis by statistical techniques enables the single- and multi-factor interactions to be determined.

Figure 5, shows the 2-factorial results for temperature and feed rate on batch cycle time. The results of the screening experiments revealed that both agitation and the presence or absence of component C at the start of the reaction had no effect on either the batch cycle time or the percentage of undesired side product formed. This allowed the number of

(8) Davies, L. *Efficiency in Research Development and production: The statistical design and Analysis of Chemical Experiments*; Royal Society of Chemistry: UK, 1993, ISBN 0-85186-137-7.

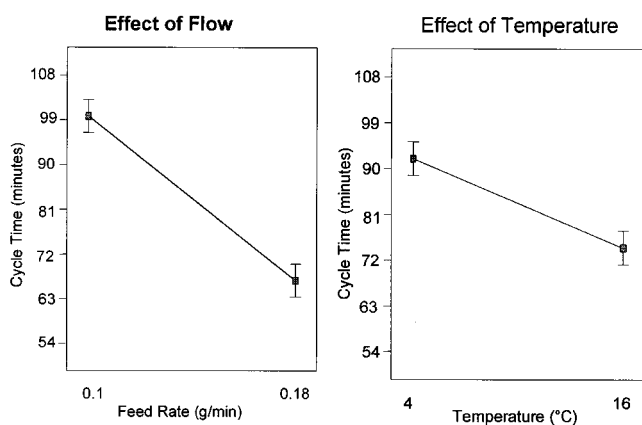
(9) Deming, S. N.; Morgan, S. L. *Experimental Design: A Chemometric Approach*; Elsevier Science Publishers: New York, 1987.

(10) Box, G. E. P.; Hunter, W. G.; Hunter, J. S. *Statistics for Experimenters*; John Wiley & Sons: New York, 1978.

**Table 2.** Typical data from process optimisation experiment<sup>a</sup>

Conditions				enthalpy release (kJ/mol)	accumulation (%)	batch cycle time (min)
T (°C)	FR (g/min)	SS	C present			
16	0.1	high	no	-4.15	6.1	89.0
4	0.18	high	no	-3.96	34.4	77.1
16	0.18	low	yes	-4.56	25.9	56.1
16	0.1	low	no	-4.96	10.9	94.2
4	0.18	low	yes	-4.05	36.7	80.5
16	0.18	high	yes	-4.12	17.4	57.0
4	0.1	low	no	-4.88	19.4	106.9
4	0.1	high	no	-3.62	19.4	105.2

<sup>a</sup> Where: T = temperature, FR = feed rate, SS = stirrer speed, C = component C.

**Figure 5.** Full 2-factorial design results examining the effects of feed rate and temperature on process cycle time.

variables required to optimise the process to be reduced to two, feed rate of component A and the process temperature.

Analysis of the calorimetry data revealed an enthalpy release of  $-116.1 \text{ kJ (kg of reactants)}^{-1}$  ( $\pm 5.2\%$ ) for reactions with component c present, which compares well to larger scale 1 L reactor data that have been quoted as  $-116.7 \text{ kJ (kg of reactants)}^{-1}$ .<sup>11</sup> From the calorimetry data it was also possible to use the enthalpy release curve to determine the batch cycle time, since clearly once the enthalpy release had returned to zero the batch could be considered finished. The only difficulty with this approach, however, was the determination of the zero enthalpy release point taking into account the noise in the power measurement. To minimise this uncertainty it was decided to choose an arbitrary enthalpy release value to act as a representative measure the batch cycle time. Several values were investigated, 92, 95, and 98% enthalpy release, and it was found that 95% enthalpy release provided the most reliable measure of the batch end point and was used in conjunction with the optimisation software, Figure 6.

Accumulation can be estimated from the enthalpy release after the end of the feed stage, as a percentage of the total enthalpy of reaction and can essentially be considered as the competition between the addition and depletion of reactants. This was determined to be 24.6% for the above reaction at 10 °C with a feed rate of 0.14 g/min, again comparable to

data from larger calorimeters.<sup>4</sup> Interestingly, the product analysis performed with GC revealed that all of the experiments gave a product that was within the required specification. On consideration of the screening experimental conditions that were 50% higher and lower than those used on plant this was surprising since a proportion of samples were expected to fail and consequently new screening experiments had to be performed at higher temperatures and feed rates.

It was found that operating the process within the temperature regime (8–24 °C), and with feed rates of 0.15–0.25 g/min produced an optimisation window in which there was a gradient from no side product to complete sample failure. By using this window it was possible to perform additional experiments and augment the 2-factorial design into a central composite design to generate a response surface for the process. The results from this response surface are shown in Figure 7.

The analysis of this response surface clearly reveals that as the feed rate and temperature are increased the batch cycle time decreases. This is also mirrored in the calorimetry data which reveals that the increasing temperature causes a reduction in the accumulation value to the point where the kinetics are feed-rate limited. However, although the increase in process temperature and the feed rate of component B both significantly reduce the batch cycle time, it is necessary to consider these data together with the product specification information. By incorporating the product specification boundary into the response surface it was possible to determine the most profitable region to operate the process and reduce the batch cycle time from over 8.5 h to just below 1 h. (The constraint imposed by product specification on the batch time, is not shown in Figure 7 due to difficulty in plotting a large number of variables clearly on the same plot).

This case study demonstrates the real value that statistical design techniques can make to the refinement of chemical processes. Couple this ability with a fully computer-controlled multiple reactor system, and rapid/optimised process development becomes a readily obtainable goal.

## 5. Application of the Auto-MATE in Hydrogenation Reactions

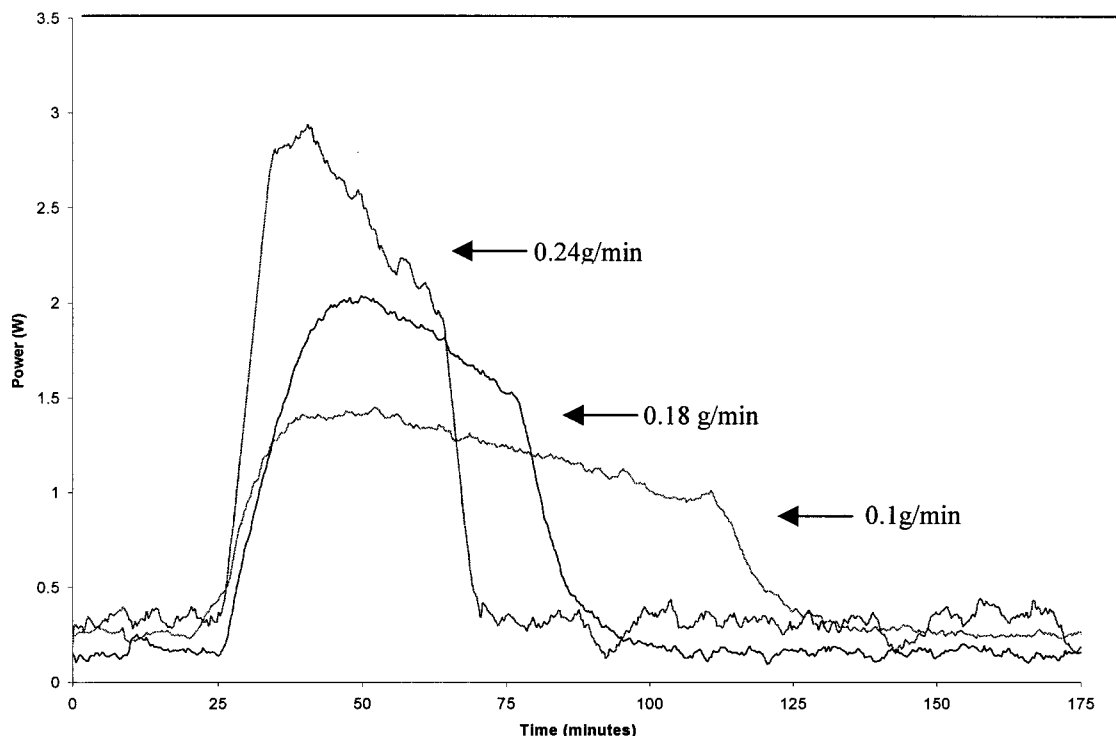
The hydrogenation reaction of 2,4-dinitrotoluene to 2,4-diaminotoluene over a palladium-on-carbon catalyst has been well-studied.<sup>12–14</sup> It is now well accepted that the reaction follows a Langmuir–Hinshelwood kinetic model with a noncompetitive adsorption of the organic species and hydrogen on the active sites with the formation of a 2-(hydroxyamino)-4-nitrotoluene intermediate. It has been shown that both the specific activity and selectivity of the reaction is dependent on the Pd particle size and loading. A high-pressure auto-MATE unit has been used to follow the heat release profile of this and other aromatic nitro hydrogenation reactions.

(12) Rajashekharam, M. V.; Jaganathan, R.; Chaudhari, R. V. *Chem. Eng. Sci.* **1998**, *53*, 787.

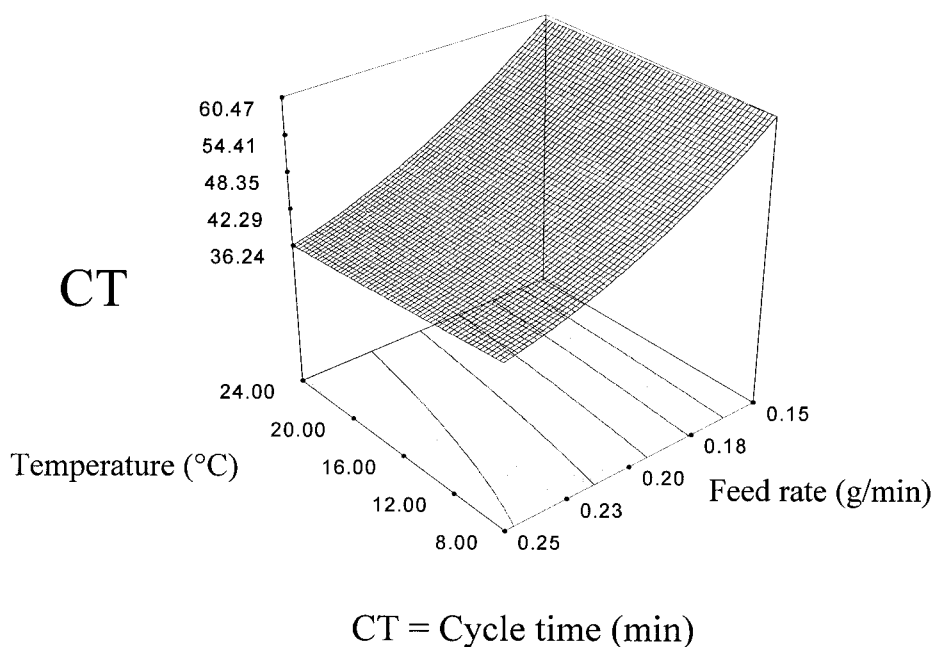
(13) Musolino, M. G.; Milone, C.; Neri, G.; Bonaccorsi, L.; Pietropaolo, R.; Galvagno, G. *Stud. Surf. Sci. Catal.* **1997**, *108*, 239.

(14) Neri, G.; Musolino, M. G.; Milone, C.; Galvagno, G. *Ind. Eng. Chem. Res.* **1995**, *34*, 2226

(11) Simms, C. Hazard Evaluation Laboratory, internal report, 1999.



**Figure 6.** Employing the enthalpy release curve to determine the batch cycle time.



**Figure 7.** Central composite design response surface for the optimisation of a flavourings process.

For the reaction of 2,4-dinitrotoluene it can be clearly seen that both of the nitro groups present on the ring are hydrogenated and that the hydrogenation reaction occurs in two distinct steps, consistent with the mechanism proposed above, see Figure 8. From the shape of the heat release profile it is apparent that hydrogenation of the first nitro grouping occurs much quicker than that of the second. This is identified by the sharp fall in the power profile over approximately 10 min on the addition of hydrogen to the system followed by the shoulder corresponding to the reaction of the second, grouping over several hours. On determining the total enthalpy release for this reaction for

both nitro groupings, we obtain a value in the range of 250–300 kJ mol<sup>-1</sup>. This is in good correlation with data from larger calorimeters (1 L and above) that have been found to give similar values.<sup>15</sup>

It should be recognized that calorimetry is not a very specific tool for identifying reaction mechanisms and the above interpretation is not necessarily a complete one. The objective here is simply to indicate the fact that it can contribute usefully in such a discussion.

(15) Simms, C. Hazard Evaluation Laboratory, internal communication, 1999.

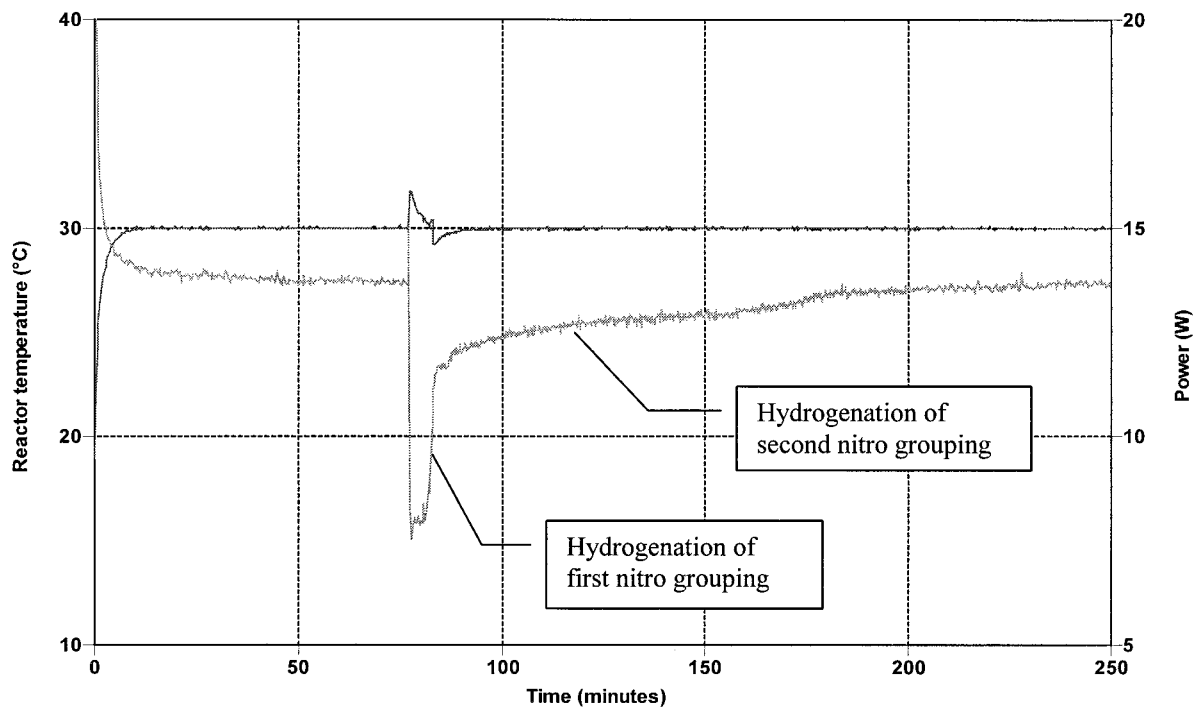


Figure 8. Power compensation data for the hydrogenation of 2,4-dinitrotoluene in methanol.

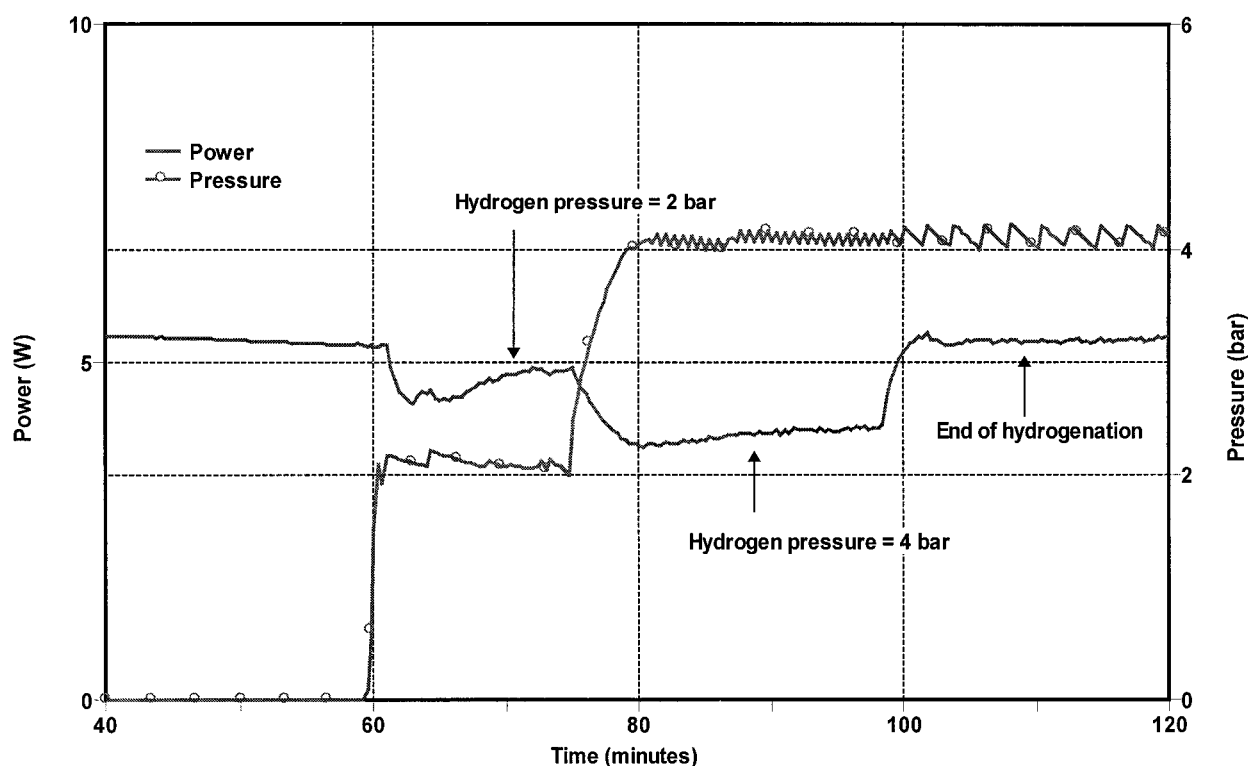


Figure 9. Hydrogenation of a 6 wt% solution of nitrobenzene in methanol over a palladium-on-carbon catalyst.

The auto-MATE has also been used to investigate the hydrogenation of a 6 wt% solution of nitrobenzene in methanol (again employing a palladium-on-carbon catalyst). In this reaction, the influence of hydrogen pressure on the reaction was investigated, see Figure 9. Initially, the reactor and contents were heated to their isothermal set point of 55 °C (in the absence of hydrogen), and the heater power was allowed to stabilise, giving a value of approximately 5.3 W.

On the introduction of hydrogen at a constant pressure of two bar, it is found that the reaction starts immediately and the heater power falls to a new value of around 4.5W in order to maintain isothermal conditions. Then, on increasing the hydrogen pressure to 4 bar, the power is observed to fall further to 4.0W, reflecting the increase in reaction rate at higher pressures. Completion of the hydrogenation is also quite marked with a sharp rise in the heater power (com-



pensating for the absence of heat release by the reaction) to a new baseline value. By extending this study further and examining different catalyst loadings and the influence of particle size, it is hoped to investigate the limits of heterogeneous reactions on this scale and evaluate how these small calorimeters can act as a rapid catalyst screening tools.

## 6. Conclusions

This paper describes just a few of the many potential applications of multiple reactor systems used in conjunction with calorimetry data for process analysis, refinement and scale-up. The combined application of multiple reactor systems and calorimetry data not only provides a new investigative tool to the process chemist but also represents one way of bridging the gap in the process development cycle. These applications of the auto-MATE can be split into a number of broad categories.

The first is its application to the process development cycle, since it provides the next logical step after the use of a robotic system, in which an interesting material or potential target can be converted into a process of real commercial importance. However, in addition to supporting robotic systems the auto-MATE in some cases provides an interesting alternative, since it has many desirable and highly controlled features such as; good mixing, pressure operation, accurate temperature control and liquid/gas feeding. These are facilities that “standard” robotic systems developed for process screening or standard “liquid handling” operations cannot normally provide.

These features combined with a statistical design package for process optimisation make the auto-MATE an attractive option for rapid process development and scale-up.

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