

Parallel Synthesis of High Pressure Reactions – including catalyst development

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The rapid growth in research activity, especially in the pharmaceutical industry, has led to an expansion in the range of tools that can be used to quickly identify, screen, optimise and scale up new processes. This paper will describe two new parallel synthesis systems for high-pressure applications, one for rapid screening and the other for more detailed process development. The differences in specification for these very different applications and the types of data obtained will be highlighted with examples and a range of potential applications will be discussed.

1 Introduction

Rapid identification of new chemical routes and the subsequent development of scaleable processes are the overriding objective of many fine chemical and pharmaceutical companies. This includes identification of new catalysts (especially for hydrogenation), development of improved methods for making chemicals for which there is an existing demand and evaluation of the best reagents/routes for new active ingredients that have been identified by one of many “discovery” methods.

These and many seemingly similar applications, in fact, encompass a wide range of different needs. There are the obvious differences in the sense that operating conditions (pressure, temperature etc) may differ widely between different applications but more importantly, the final objective can be very different too. For example, in the case of high throughput screening the objective is to distinguish between a large number of options – for example lots of candidate catalysts. In this case only relative values (of yield for example) are important – allowing easy ranking of different materials. At the other extreme, accurate control and the ability to operate under “realistic” conditions is much more important than a large numbers of samples, if the objective is reliable and safe process scale-up.

2 Requirements of Discovery, Screening and Development

The large number of the commercial systems available for parallel synthesis involve the use of a robotic x-y-z arm to move reagents to different “reactors” and take samples. Applications can typically be divided into three categories:

- **Discovery:** This might include the commonly referenced “combinatorial” method of looking for “hits” in terms of compounds that might indicate a positive response to a specific application. This can benefit from hundreds of reactor vials with milligram quantities of material. The vials are normally held at room temperature and pressure without any real control of the conditions.
- **Screening:** The ideas or synthesis options that need to be screened might originate from any number of sources but normally this will follow on from the discovery stage. The objective is to find, quickly, possible ways of making an identified compound and therefore, some moderate control of process conditions (often only temperature) is sufficient.
- **Development:** Ultimately the process needs to be scaled up – at the very least to pilot scale so that material for preliminary trials can be produced and if these trials are successful, a production plant will need to be built. The number of processes coming through for development and scale up will be much less than screening candidates and so the number of experiments necessary is reduced but each is more demanding of resources.

Discovery of candidate molecules can emerge not only from experiments but also theoretical predictions are possible as well as the more traditional route – the chemist’s experience or know-how. This is a field that employs clinical and medicinal chemists, biochemists as well as organic and inorganic chemists but rarely process chemists or engineers.

Chemical screening is really the first step where anything approaching process chemistry is carried out, albeit in a fairly crude manner. When true process development is needed, very few robotic systems are of much value due to explicit design limitations and this aspect needs to be better appreciated. The differing objectives of screening as compared with process development are summarised in table 1.

<i>CHEMICAL SCREENING</i>	<i>PROCESS DEVELOPMENT</i>
Screening Chemical Routes	Develop Route into Process
Solvent Selection (Crystallisation)	Crystal Growth (Cooling rate, concentration, agitation rate polymorphs)
Proof of Concept	Scaleable Process
Reduce Time in “early” Research	Reduce/eliminate time in bench or pilot scale testing
Find most “Active” or “Selective” Catalyst	Optimise conditions of use – Establish Actual Batch Times, Selectivity etc.

TABLE 1: Distinguishing Objective of chemical Screening and Process Development

3. High pressure Reaction screening

3. 1 Gas-Liquid Reaction Screening

Where high-pressure reaction screening is needed, the choice of commercially available systems is limited – robots are not able to play any meaningful role. Applications are frequently gas-liquid reactions often with solid catalysts, requiring control of gas addition plus good mixing. High-pressure liquid addition can also be an important feature in some cases – polymerisation and other high volume applications being cases in point. In screening catalysts, it is important to determine selectivity towards the desired product and activity (i.e. rate of reaction). Mixing can crucially influence the latter.

In a typical experiment, the reactors are assembled after charging the catalyst plus solvent and liquid reactant. Then, after a suitable purging procedure, reaction is started by charging the reactant gas (e.g. hydrogen) at the selected pressure.

Two systems that offer scope for this type of application are the “Endeavour” and the high-pressure chem-SCAN. They are both based around a heated block containing 8 metal reactors into which gas is dosed.

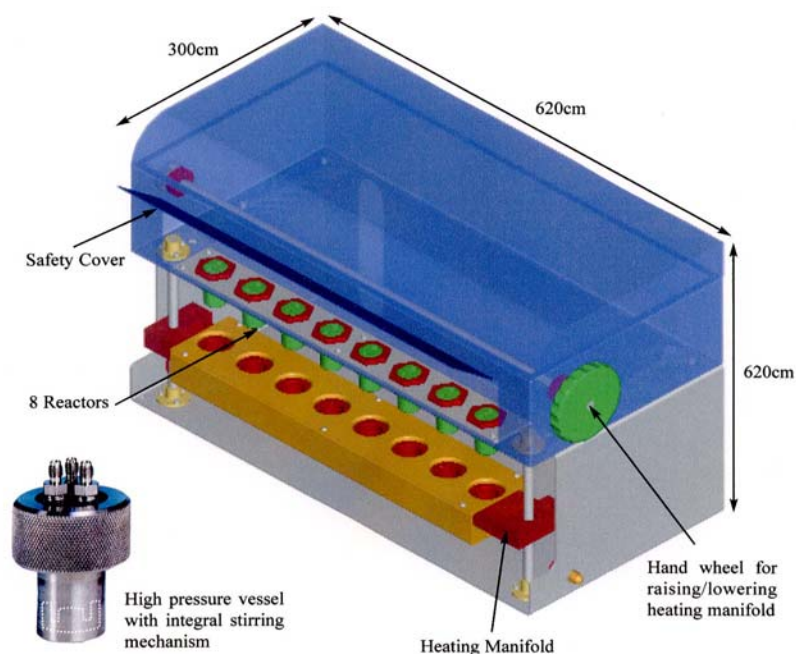


Figure 1: A schematic drawing of the high pressure Chem-SCAN

An overview of the chem-SCAN is shown in table 2 with a drawing of the layout in figure 1, indicating that each reactor, rated to 100 bar, is individually stirred incorporating a conventional anchor or propeller blade agitator. A drawing of the unit is shown in figure 1. Reactors can be run at different pressures and the rate of gas uptake (semi-quantitatively) is calculated on line. This system is totally computer controlled with data logging. The underlying winISO software is fully able to cope with all variations of experiments but “standard” experiments can be run simply by completing an input form.

- ▲ Supplied in blocks of 8 reactors
- ▲ Reactor volume ~ 10 ml and ~ 15 ml
- ▲ Pressure rating to 100 bar
- ▲ Temperature range – 20 to 200°C (or wider)
- ▲ Evaluates gas consumption rate
- ▲ Evaluations total gas consumption
- ▲ Automated high pressure liquid addition

Table 2: Chem-SCAN High Pressure Reaction Screening Unit

In any given experiment, the reactors can be run at separate pressures – a range of nearly 100 bar can be covered in one test. The temperature of each reactor is generally the same but variations are possible. In general, the influence of temperature can be evaluated in different ways:

- In the same experiment, raise the block temperature in steps, covering up to eight different values if necessary. At each step, a different reactor can be run.
- Repeat experiments at different block temperatures, at each temperature different pressures can be screened.

These procedures are totally automated.

3.2 High pressure Liquid Addition

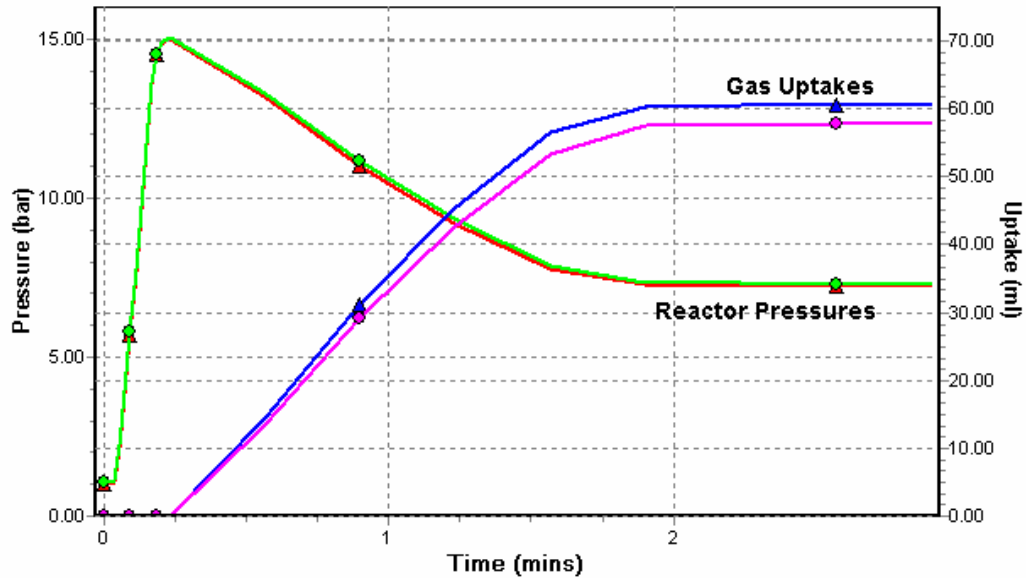
The common applications of the chem-SCAN involve charging of liquid and powder reagents to the reactors before the system is heated and pressured. There are however important examples where a key addition must be carried out after the reactors are sealed and under pressure. This includes temperature sensitive catalysts where charging at the outset would lead to their deterioration.

The chem-SCAN is able to handle high pressure liquid additions of up to 100bar in a totally automated manner, with an accuracy of around 0.05ml or better. If necessary, such additions can be performed at a predefined rate – representing for example a semi-batch reactor.

3.2 Hydrogenation Catalyst Screening with Chem-SCAN

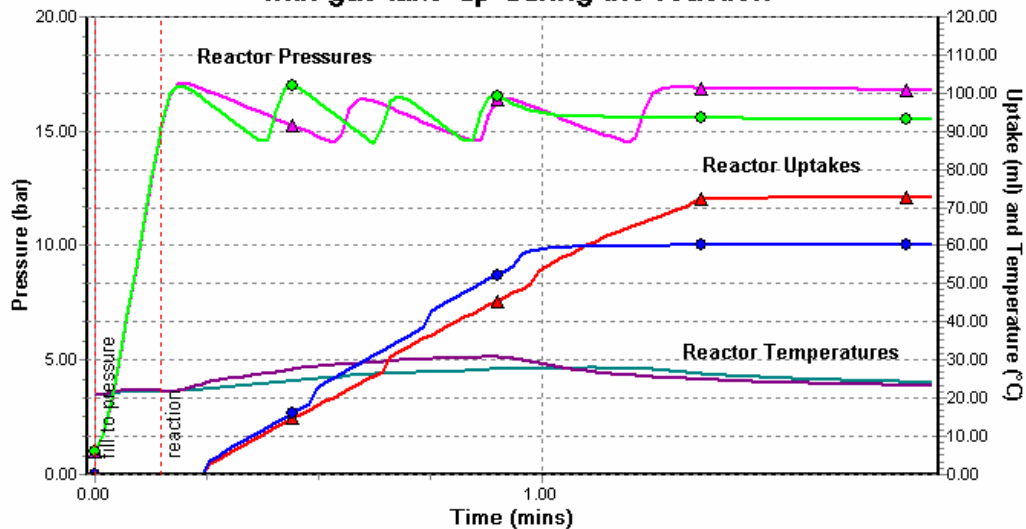
The simplest way to run a gas-liquid reaction test is to pressurise the reactors to a given value – different pressures if necessary – and then turn on the stirrers to initiate reaction. An example is shown in figure 2, for just two reactors, both at a starting pressure of 15 bar. As the pressure falls due to reaction, the gas consumption rate is calculated and displayed. In this way, performance can be easily compared both from the pressure data and the consumption.

Fig. 2: Chem-SCAN operating in batch mode from initial pressure of 15 bars



A more typical set of data is shown in figure 3, where the reactions are run at constant pressure (around 16 bar). This shows the control system allowing the pressure to drop and then making up the consumption in steps. This is a particularly fast reaction – taking only around 1 minute – but in spite of this, the data is quite reasonable. The change in temperature is also shown – the variation is relatively small due to the large thermal mass of the high pressure reactors.

Fig. 3: Typical chem-SCAN data with gas take-up during the reaction



Reactors and different pressures can be run at the same time, to simultaneously determine the affect of pressure. Running different reactors at the same condition (as in figure 2) is useful for showing the reproducibility.

4 Rapid Process Development – basic requirements

Much confusion exists when tools for process development are discussed – virtually all manufacturers use the terms screening and development interchangeably. As a result, a relatively simple tool such as the SK233 is sometimes described as a process development platform. The problem may be a matter of definition: since screening of process options is the step that precedes development, it might legitimately be regarded as a part of the development effort.

The definition most commonly used is that a developed process is one that is ready to scale up – it has been optimised (within the time available) and conditions of temperature, feed rate, pressure etc is precisely known. The importance on the results of mixing and other key operating variables such as batch time should be known. While accurate calorimetry data is not necessary, there needs to be a clear understanding that the process can safely be scaled up and at least an idea of the relative heat release.

To meet these objectives, computer controlled bench-scale reactors and calorimeters have traditionally been used to prepare a process package. These are regarded as scaled-down pilot plants and data produced has been shown to scale up reliably. In the context of rapid process development, these tools are not appropriate. The growing use of statistical experimental design, where some 20 or more runs at different conditions might be required, would take months using a bench scale unit. In addition, large amounts of reagent are needed (which may not be available in such quantities or could be very expensive) and will certainly generate a lot of chemical waste.

5 Parallel Syntheses for Process Development

5.1 Available Equipment

The key requirements for rapid process development are therefore a combination of two systems:

- degree of control and precision normally associated with bench scale computer controlled reactors, possibly with some indication of calorimetry combined with,
- significantly reduced working volume
- multiple reactor (parallel) operation, including parallel dosing of liquids, gas etc. in a manner anticipated after scale up.

There have also been attempts, with limited success, to integrate robots with conventional stirred and jacketed reactors. This has not been done with multiple reactors but the idea is that the vessel can be automatically drained and washed after each batch and the robot can then re-charge it. In this way, although there is only one reactor, the fact that it can be operated continuously will give productivity gains. If this idea is successfully combined with a good reactor control package, a great deal can be accomplished. Recently, the “surveyor” has been launched using 10 parallel reactors of around 60ml volume each. This has some features listed above but certainly cannot be used at pressure.



Figure 4: High pressure auto-MATE

A commercial system that does meet these requirements is the auto-MATE, first introduced in 1998, and this is available in both atmospheric and high-pressure versions. The high pressure version – see figure 4 – has a standard rating of 100bar and can be equipped with both high pressure gas and liquid addition (in parallel). It is based around a four-reactor block, each reactor with a volume of 50ml to 100ml and mechanically stirred. The agitation speed is individually adjustable and a wide choice of stirrers is available, including gassing stirrers for high-pressure versions. Each reactor is independently controlled and monitored; duplicate blocks with up to 16 reactors can be controlled in this way from a single computer interface. The main features are summarised in table 3.

- ▲ Supplied as single reactor or blocks of 4
- ▲ Reactor volume 50 or 100 ml (standard)
- ▲ Pressure rating 100 bar
- ▲ Temperature range – 20 to 200°C (or wider)
- ▲ Individual temperature and pressure control
- ▲ Gas consumption by mass flow sensor
- ▲ Mechanical stirring with individual speed control
- ▲ Range of stirrer designs
- ▲ High pressure liquid addition
- ▲ Reaction calorimetry data

TABLE 3: Features of High Pressure auto-MATE

An interesting feature of the auto-MATE, which adds significantly to its value as a development tool, is the ability to make calorimetry measurements. This capability is implemented in a manner that does not place an extra burden on the operator and requires no specialist knowledge of the subject. This will become clear from the applications discussed below.

5.2 Calorimetry in Process Development

5.2.1 Tool for non-experts

Calorimetry in relation to process development is often referred to as “reaction calorimetry” and employs the method of heat flow, to evaluate reactions. This method is quite accurate and has been widely used in larger scale calorimeters but it is also a rather complex method of calorimetry and is used mostly by specialist groups. The method would be totally inappropriate for rapid process development where synthesis or organic chemists are working.

A calorimetry method that has found widespread acceptance in this type of situation is power compensation, as used in the auto-MATE for example. The operating principle is illustrated in figure 5 where the reaction is carried out at constant temperature. Temperature control is achieved by automatically adjusting the heating power delivered through the electrical heater, as conditions change. Thus, starting from a steady state condition before the reaction begin (requiring a heater power of 5W to maintain constant temperature), simply monitoring the power changes during the reaction gives a direct measure of the heat release.

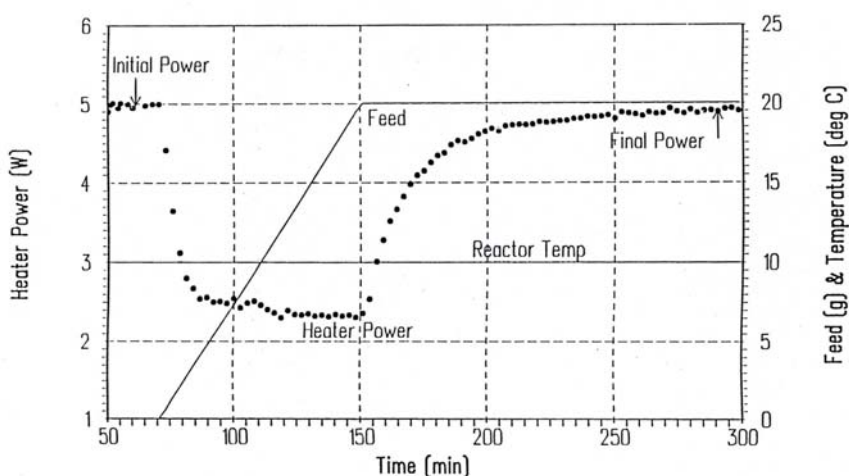


Figure 5: Basic data from power compensation test

In figure 5, the baseline power before reaction starts to fall to compensate for the heat released by the reaction and when feed is stopped (after 150 minutes into the experiment), it gradually rises as the reaction is completed. The data in figure 5 would be visible in real time as the experiment proceeds and available to the user, without any calculation being necessary.

5.2.2 Reaction monitoring

Most chemical reactions in industry involve a release of energy as they proceed (ie are exothermic) and if this energy can be measured as the reaction proceeds, it becomes an extremely useful monitor of activity. The rate of heat release can be used as a measure of kinetics - comparison of the activity level of two different catalysts, can simply be done from this alone. Heat release can be a very direct and on-line measure of end-of-reaction – this simple indicator can be extremely valuable.

The influence of temperature on reaction rate and hence batch time, in the simple reaction between acetic anhydride and water, is illustrated in figure 5. This shows that at the selected temperature for the reaction, there is accumulation of unreacted anhydride and this has to “react out” over a period of nearly 2 hours after feed has stopped. End of reaction is easily established from the heat output trace.

5.2.3 Hazard Assessment

An important and commonly accepted application of calorimetry is in terms of hazard assessment. Reaction calorimetry provides, among other things, the total heat release when the process is carried out in the prescribed manner. If this energy were not removed (for example due to cooling water failure), it would lead to a rise in temperature that can be calculated from:

$$\text{Temperature rise (K)} = \text{energy release (J/g)} / \text{mean heat capacity (J/gK)}$$

It is also possible to relate this temperature rise to pressure rise. For atmospheric pressure operations, simply knowing if the reagents can be taken above the boiling point is useful.

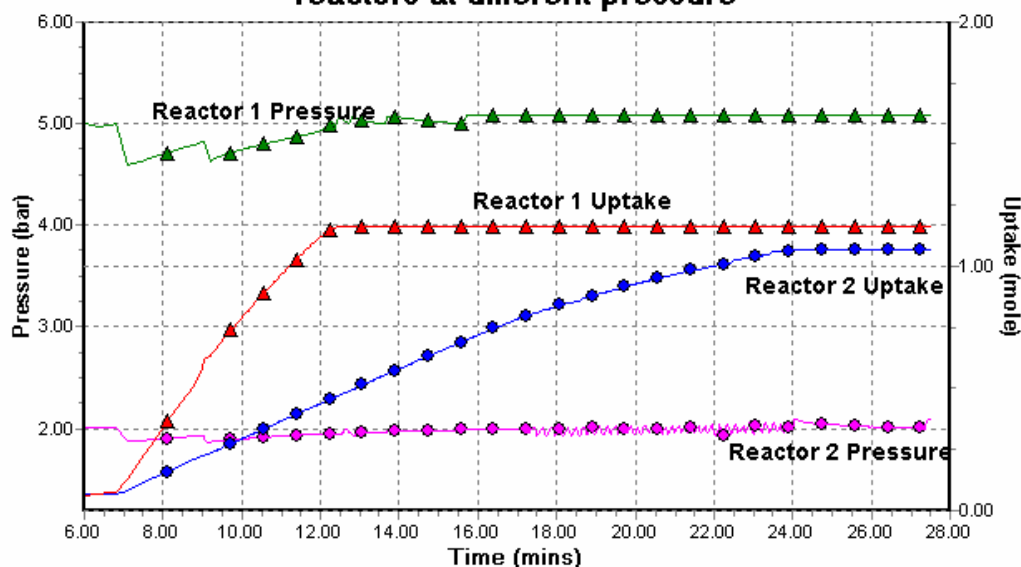
It is not the job of the research chemist to do a detailed evaluation of hazard but even just ranking the heat output to some reference reaction – low, medium or high hazard – is sufficient and takes no extra effort. The reference reaction may be as simple as an acid-base neutralisation or it could be an important reaction performed by the company.

6 Hydrogenation with the auto-MATE

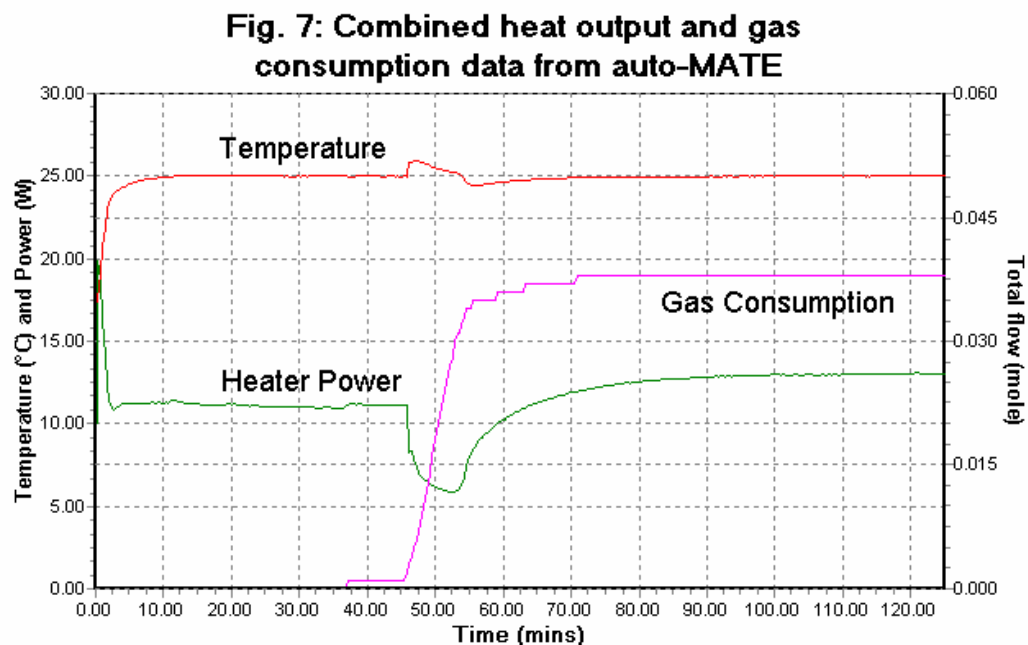
Once reactions have been successfully screened – for example the most promising catalysts have been reduced to one or two - it is then necessary to develop the operating conditions for a process built around the catalyst selected and under those conditions, confirm important details such as selectivity and yield.

The results of a hydrogenation at pressures of 2 and 5 bar in two separate reactor at constant temperature, is shown in figure 6. Plotted is the pressure and gas consumption (ie integration of the rate of gas uptake). Clearly, the rate of reaction is significantly different at the selected pressures but, as expected, the total consumption is almost the same. The reaction was performed in hastelloy reactors using hollow shaft aspirating stirrers at 1000 rpm.

Fig. 6: Hydrogenation in 2 auto-MATE reactors at different pressure



A different hydrogenation is illustrated in figure 7, where the heat output was also monitored. In this case, gas consumption and reaction heat output are plotted as reaction proceeds. To a large extent these two parameters mirror each other – which is reassuring – but the thermal data is extremely useful in scaling up. It is possible to evaluate the effect of different catalyst loadings, different temperatures, stirrer speeds and operating pressures to arrive at the optimal solution.



The ability to control and monitor these variables makes it easy to perform optimisation studies using statistical experimental design procedures.

7 Conclusions

Rapid screening of high pressure reactions and subsequent parallel process development is extremely difficult, especially where heterogeneous gas/liquid reactions. Two systems that represent a possible solution have been presented in this paper.

The Chem-SCAN allows a wide range of pressures and temperatures to be tested simultaneously in eight, 10 ml reactors, with semi-quantitative information about gas uptake. High pressure liquid additions are also possible.

For more accurate control of all process variables, including availability of heat output data, the auto-MATE offers an excellent option. With a reactor volume range of 50 to 100ml, reliable data for scale-up can be generated. This is now a well tested design with widespread industry acceptance.