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An Automated Approach to Process Optimisation, Parameter Setting, and Robustness Testing

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Abstract:

The design, development, and application of a robotic platform are described for use in organic synthesis. Two novel plant reactor mimics and peripheral modules have been designed and integrated with a Zymark XP Track Robot allowing a wide scope of chemistries. Throughput limitations of two reactors were resolved by incorporating automated self-draining/self-cleaning modules into the system to allow continuous operation. Control software was written in-house, allowing simple, high-quality, and reproducible control. The application of this instrument to process optimisation coupled with statistical experimental design (DOE) and parameter setting is illustrated with two examples.

1. Introduction

New technologies are having an ever-increasing effect on the pharmaceutical industry. The advent of combinatorial chemistry and other new techniques has dramatically changed the dynamics of drug discovery.[1,2] Whilst lowering attrition rates has partially reduced the effect on chemical development, the number of development candidates is rapidly rising. In addition, the rising costs of drug discovery and development have created a very significant drive to reduce the time to market. To meet these challenges, given the fact that resources for most chemical development facilities are limited, new techniques and tools are essential.

In early chemical development such tools have evolved to meet these requirements. The trend began with innovative chemists designing and building systems in collaboration with speciality laboratory robotic partners.[3−5] Such efforts, whilst ground-breaking were not widely adopted mainly due to their complexity, expense, and their requirement for specialist resource. In more recent years, this has changed with the introduction of "chemist-friendly" systems such as the Anachem SK233.[6,7] This system is now used extensively in the chemical development industry and covers a wide range of chemistries for rapidly scouting new routes and crudely optimising early development chemistry.[8,9]

In later development the driver for an automated system for chemical process optimisation is even greater. With the ever-demanding timelines forced on chemical development departments, many processes cannot be truly optimised by manual methods because of insufficient resource and strict time limits. There is also the cost associated with validation of the process in the pilot plant. This is a direct threat to a company's profitability, as poorly optimised, nonrobust processes can be extremely expensive both in terms of yield and failed manufacturing batches. In a model calculation, T. Laird[10] has shown that for a pharmaceutical product involving 10 synthetic steps with an average 80% yield for each step manufactured on 100 tonnes per annum and costing $1000/kg, a yield increase of only 1% per step would save $14 million per year. Despite these obvious business drivers, progress towards such a goal has not been so forthcoming. Larger-scale reactions necessary to effectively reproduce plant conditions coupled with the extremely close process control required have hindered the development of automated high-throughput systems, and to date no fully automated commercial system exists.

2. Equipment Design

As part of a strategic approach to meet the increasing demands being created by the combinatorial revolution in drug discovery, Pfizer development laboratories began looking at areas that could accelerate late development and potentially reduce costs. Two areas became immediately obvious:

- **process optimisation through automation and statistical design of experiments:** determining the levels of factors such as temperature and concentration to optimise a desired response such as yield or quality
- **automated parameter setting/robustness testing:** determination of the upper and lower limits of a process suitable for plant-scale operation

Both areas are extremely labour- and time-intensive procedures that are often repetitive and monotonic. For successful automation of these areas a higher quality and extremely flexible system was required with several key components and capabilities:

- plant reactor mimics
- self-cleaning and draining for continuous operation
- solids dispensing

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(6) SK233 is a registered trademark of Anachem Ltd.
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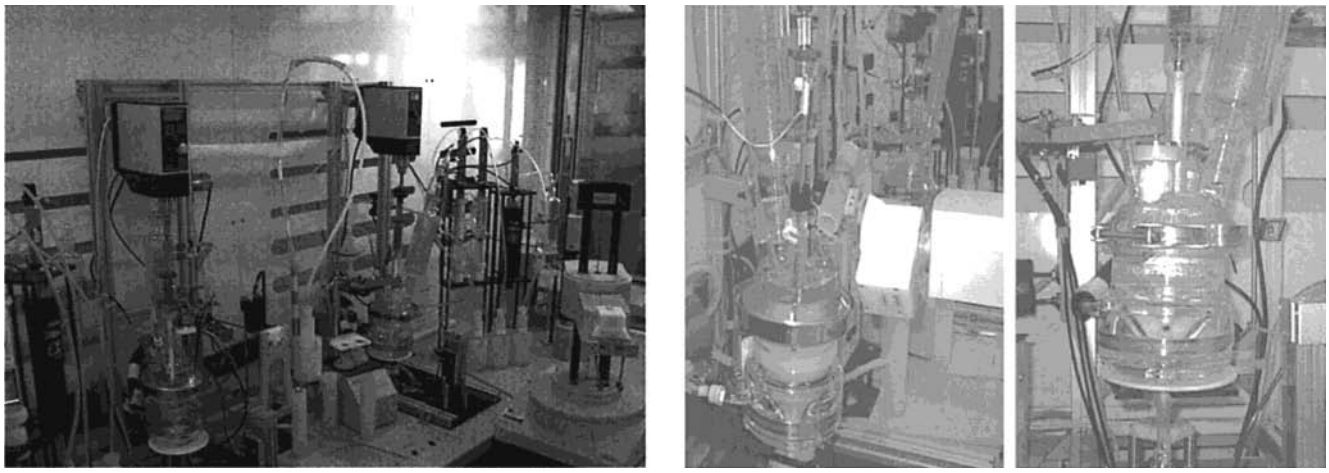


Figure 1. **System diagram.**

- accurate liquid handling
- online analysis
- flexible software

Initial literature searches and equipment evaluations showed that no commercial equipment met these criteria, and whilst computer-controlled single lab reactor systems were available, the functionality and throughput fell short of that required. A decision was reached to design and then commission a robotics company to build a solution to meet our requirements. Zymark[11,12] had prior experience in adapting mature robotics technology to chemical synthesis and were commissioned to build a bespoke system to meet our requirements, utilising the PRINCE project management protocol.[4,5,13] The system was built around a Zymark XP Track Robot as shown in Figure 1. The key features of the system included:

- **Two Plant Reactor Mimics.** Cone-bottomed glass reactors were the cornerstone of the design with 50−400 mL capacity. A five-port flange lid incorporated an automated addition port, over-head stirring, a double-coiled vacuum-jacketed condenser, a thermocouple, and a spare port for probe technology. The triple-jacketed vessel had a temperature range of −20−150 °C, controlled inert gas flow, and automated drain valve for postreaction collection and manipulation if necessary.
- **Cleaning Module.** A novel cleaning module was added to allow automated cleaning of the vessels for continuous operation.
- **Solids Dispensing.** An automated procedure for dispensing solids at anytime during the reaction, including seeding for crystallisation studies.
- **Online Analysis.** For monitoring the progress of reactions and retrospective cleaning verification to identify cross contamination between reactions which could affect the outcome of an experimental design.

3. Equipment Installation

On completion of the factory acceptance testing (FAT) the system was installed into a purpose built BigNeat[14,15] fume-cupboard. Site acceptance testing (SAT) was then conducted involving stringent verification of individual hardware module operation.

3.1. Control Software Development. Flexible control software was key to the success of the system; as the underlying EasyLab software was not flexible enough to allow extended operation, the decision was made to develop this software internally. The Software was developed in LabView, conforming to the evolving standard of Laboratory Equipment Control Interface Specification (LECIS),[16] which aims to simplify the integration of complex laboratory automated systems. The decision to develop the software "in-house" dramatically improved the quality and functionality of the software and reduced the development period by removing any lead time in solving software bugs and functionality upgrades. The end result was control software that was extremely flexible, functional, and modular. Screen shots are shown in Figure 2.

4. Operational Qualification (OQ)

As part of the OQ procedure two experimental packages of work were conducted which are described below.

4.1. Automated Process Optimisation with Experimental Design. An experimental design on the processing step outlined in Scheme 1 was conducted. Previous experience had shown the product quality was a direct result of the crystallisation procedure used; hence, the factors affecting the product quality were granulation temperature and the concentration and ratio of the two solvents. A three-factor, three-level design was utilised in the DOE software package Modde 4.0[17,18] with two responses, product yield and purity.[19] The design software suggested 14 experiments with 3 additional centre points.

(11) Zymark, System V, and EasyLab are registered trademarks of the Zymark Corporation.
(12) Available from Zymark Ltd. 1 Wellfield, Preston Brook, Runcorn, Cheshire, WA7 3AZ, UK.
(13) Bradley, K. *PRINCE A Practical Handbook,* 4th ed.; Butterworth Heinemann: Oxford, 1992.
(14) BigNeat is a trademark of BigNeat Ltd.
(15) Available from 4 & 5 Pipers Wood Industrial Park, Waterberry Drive, Waterlooville, Hampshire, PO7 7XU, UK.
(16) American Society for Testing and Materials; Standard Specification for Laboratory Equipment Control Interface (LECIS). Designation E1989-98.
(17) Modde is a registered trademark of Umetrics.

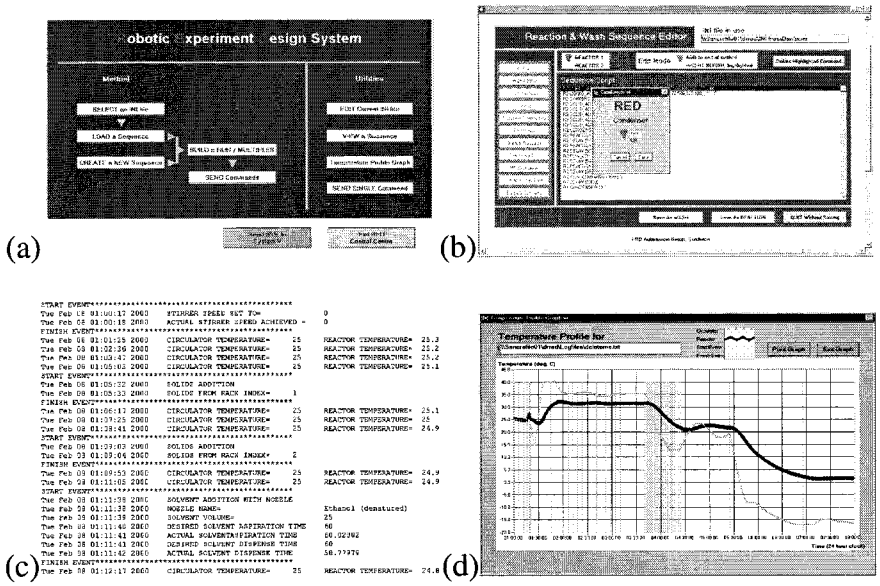


Figure 2. **Example screen shots: (a) opening menu, (b) method creation, (c) event logging, (d) temperature-profile plotting.**

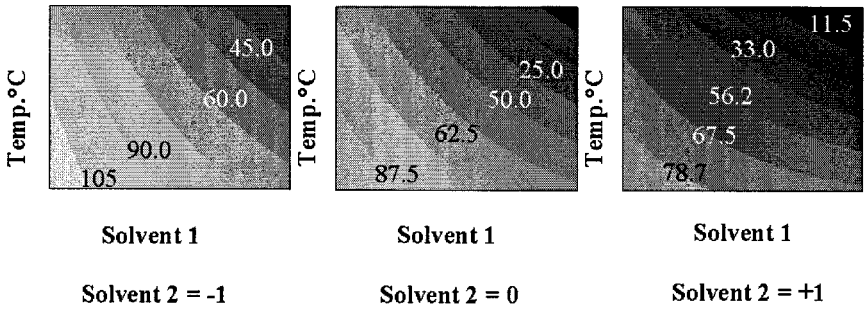
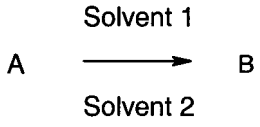
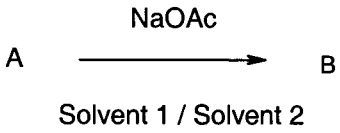


Figure 3. **Four-dimensional contour plot of yield.**

Scheme 1



Scheme 2



The reaction design was completed, and the yields and product purity were entered into the experimental design software. Using the data obtained, a 4D plot was generated to graphically represent the effect of the three factors on product yield, Figure 3. This result predicted, as expected, that both high granulation temperature and solvent levels decreased the product yield. In addition a strong interaction was detected between two of the factors, the granulation temperature and one of the solvents which also decreased the product yield. Interestingly, the generated model predicted a product yield of 105% at the very edge of the experimental region. This extremity of the experimental region had not been covered by the statistical experimentation and was an unexpected result. It was proposed that in this region the model was in fact predicting a decrease in product purity by incorporation of an impurity in the product. Further experimentation and analysis later confirmed this. The results of this package of work directed us to an experimental region that guaranteed excellent product purity whilst maintaining high product yield for this process.

4.2. Parameter Setting. This experimental package was technically more challenging for the system, involving two prolonged liquid additions and two strictly controlled cooling ramps, Scheme 2. When this process was conducted manually, it was time-consuming, tedious, and difficult to control. The decision was made to examine the factors independently at both higher and lower parameter limits. From previous work, the factors affecting the process and its parameter limits had been identified. The response for the matrix of reactions was product purity.[19] Six variables were investigated in 14 experiments, composed of 12 high and low parameter limits and 2 controls.

4.3. Results. Analysis of the reaction products showed that all material was within the required quality specification. This showed that the process was extremely robust with a large safety plateau.

(18) Modde is available from Umetrics at Box 7960, S-907 19, UMEÅ, Sweden.
(19) Reaction contents were automatically collected and stored ready for filtration. Product yield was determined by weight after drying. Product purity was determined using validated analytical methods.

5. Conclusions

A novel automated robotic system has been developed to play a valuable role in late-stage chemical development. The system can assist in process optimisations and parameter setting/robustness testing experiments covering a wide range of chemistries. The system was designed around two key reactors with extensive capabilities including novel cleaning modules, solids dispensing, and online analysis. In addition, flexible control software was developed in LabView, conforming to the evolving standard of LECIS.

The system considerably increases throughput whilst adding significant quality through close process control and monitoring, releasing chemists to do less repetitive tasks.

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