Organic Process Research & Development **2009,** *13,* 1059–1067

Concept Articles

An Efficient Laboratory Automation Concept for Process Chemistry

Christian Bernlind* and Csaba Urbaniczky

Global Process R&D, Process Chemistry, AstraZeneca, SE-151 85 Södertälje, SWEDEN

Abstract:

This concept article presents and outlines a successful strategy to roll out an automation concept on a broad basis to AstraZeneca Process R&D laboratories. Examples of hardware and software are presented as well as a couple of examples related to process safety.

Introduction

Today, automated equipment plays an important role in almost every process chemistry laboratory. The use of, for example, HPLC autosamplers and diode-array detectors, NMR spectroscopy, literature search tools and, to some extent, also electronic lab notebooks have revolutionised planning, analysis and documentation of chemical experiments in the pharmaceutical industry.[1] Automation has also replaced some of the manual work that is carried out in Process R&D laboratories. Automatic weighing stations and liquid dispensers have the potential to carry out tedious and repetitive work, leaving the chemists free to perform more creative activities. Simple reaction blocks in combination with stirring bars and test tubes are reliable workhorses in the study of reactions, solubility and stability.

Automatic synthesizers and workstations for combinatorial chemistry and high-throughput screening are today widely used within medicinal chemistry departments to find new candidate drugs.[2] Automated systems for Process R&D work have also been available on the market for many years,[3,4] but since the systems generally are very expensive and require dedicated expert users, only a limited number of them are likely to have found their way into the average Process R&D laboratory. Hence, in order to provide lab automation to every single Process R&D chemist, it is clear that an additional and complementary approach is needed. A wide and universal use of automation and logging of experimental data will be key to the industry to be able to smoothly pass the expected "paradigm shift" within drug development.[5]

Background

Around the start of the year 2000 the market for commercial robotized systems experienced a boost. Similarly to many companies, we walked down the aisle with a few robotized systems and automated reactor platforms for parallel reactions supplied by well-known manufacturers. The objective was to increase efficiency both in order to save time and to increase capacity to meet an increasing flow of candidate drugs from our discovery units. The systems were widely employed in a diversity of investigations during the first years. Although the benefits of these systems, such as the ability to take many samples and to perform unattended experiments remain unchallenged, the overall impact on our development work was limited. Compared to performing the same work manually, we perceived that there were no clear gains in time or efficiency when the full cycle time for an investigation was taken into account. The automated systems still required a lot of previously acquired knowledge about the chemistry and the physical properties of the starting materials and reagents, (*e.g.*, solubility, stability, dissolution times, suitable sample concentrations as well as robust and universal cleaning procedures for needles and containers). Even an expert user would have to prepare him or herself for a few wasted experiments before the equipment could deliver useful results. This proved particularly unfortunate for early screening work, where the supply of starting material was minimal, as was the tolerance towards failure. The overall conclusion was that these automated systems could very well be used for homogeneous and diluted reagent screens at moderate temperature ranges, but could generally not be recommended for screens or optimisation studies where factors such as concentration, stirring, prolonged addition times or extreme temperatures were under investigation.

In parallel to the evaluation of the commercial systems another strategy was initiated at our department in 2001 with the primary aim being to facilitate and integrate laboratory automation in the preferred ways of working. The project was

---

* Author to whom correspondence may be sent. E-mail: christian.bernlind@astrazeneca.com.

(1) Martin, V. Everything old is new again. Developing a new paradigm for process research through application of new technologies. In *Proceedings of the Siegfried Symposium*; Siegfried Symposium, Zurich, CH, October 14, 2004.

(2) (a) Coates, W. J.; Hunter, D. J.; MacLachlan, W. S. *Drug Discovery Today* **2000**, *5* (11), 521. (b) Reader, J. C. *Curr. Top. Med. Chem.* **2004**, *4* (7), 671.

(3) Rubin, A. E.; Tummala, S.; Both, D. A.; Wang, C.; Delaney, E. J. *Chem. Rev.* **2006**, *106* (7), 2794.

(4) For a comparison of three major brands see: Van Loo, M. E.; Lengowski, P. E. *Org. Process Res. Dev.* **2002**, *6* (6), 833.

(5) Federsel, H.-J. *Drug News Perspect* **2008**, *21* (4), 193.

(6) Urbaniczky, C.; Bernlind, C. *Oscar Wilde* for the common chemist. In *Proceedings of the 8th International Conference & Exhibition: Laboratory Automation. Faster Process Development - New Tools for New Challenges*; Scientific Update:Mayfield, U.K. 8th International Conference & Exhibition: Laboratory Automation. Faster Process Development - New Tools for New Challenges, London, U.K., September, 13−14, 2005.

10.1021/op900154c CCC: $40.75

Table 1. **Example of RS232-controlled laboratory equipment**

device type	model	manufacturer
data logger	Almemo 2390-5/8, 2590-2/3/4/9	Ahlborn Mess- and Regelungstechnik
overhead stirrer	IKA Power Control Visc Heidolph RZR2051	IKA Werke Heidolph Instruments
heater chiller	Julabo F, FS, FP, CF, Presto Haake Phoenix II, DC50, F6 Huber ministat, unistat	Julabo Labortechnik Thermo Fisher Scientific Peter Huber Kältemaschinenbau
syringe pump	Harvard pump 11	Harvard Apparatus
liquid dispenser	Metrohm Dosimat	Metrohm
peristaltic pump	Ismatec Reglo Digital	Ismatec SA Labortechnik
piston pump	Knauer Pump 100	Dr. Ing. Herbert Knauer
diaphragm pump	STEPDOS 03RC, 08RC	KNF Neuberger
gear pump	mzr-7255 Ismatec mcp-z	HNP Mikrosysteme Ismatec SA Labortechnik
laboratory balance	Mettler AB, AX, PB, PG, PR, SB, SR Sartorius BP, ME, Combics3	Mettler-Toledo Sartorius
heating plate	IKA RET Control Visc	IKA Werke
mass flow meter	ASF1400	Sensirion

given the name *Oscar Wilde*, an acronym for *O*rganic *S*ynthetic *C*hemist's *A*utomated *R*eactor-based *W*orkstation with *I*ntegrated *L*ogging of *D*ata from *E*xperiments. The fundamental idea was to use established, commercially available, over-the-counter laboratory equipment, with the ability to communicate via an RS232 interface, and to find a commercially available, easy-to-use software package to control the equipment. An absolute prerequisite was to incorporate only equipment that could equally well be operated manually. This would allow the users themselves to decide to which extent they would like to use automation, and also remove the risk of down-time and wasted experiments, a factor that is inherently associated with systems that solely depend upon computer control. The investment strategy was to gradually phase in new equipment as old units needed to be replaced.

Hardware

Table 1 lists some of the devices that were either purchased or were already available in-house during the progress of the *Oscar Wilde* project. The listing does not, *per se*, imply any endorsement of a particular vendor.

One of the key players in the range of *Oscar Wilde* devices turned out to be the Almemo logger from Ahlborn.[7] The device is an affordable and robust state-of-the-art data logger which can be equipped with a multitude of different sensors to measure, for example, temperature, pressure, pH, resistance, voltage, current, conductivity and humidity. All sensors have built-in EEPROM chips which make them automatically recognisable to the logger. Any calibration parameters will also be conveniently stored onto the chips and follow the sensors regardless of which logger is used. The loggers are also equipped with output channels that can be used to control external relays and even generate programmable current and voltage signals suitable for analog control of external devices. In our view, the data logger equipped with a Pt100 temperature sensor, together with a heater/chiller unit and a syringe pump, forms a powerful base when it comes to logging and controlling process parameters and being able to evaluate and understand the ways our processes evolve.

An immediate issue was to ensure that several laboratory devices could be conveniently connected to a single standard computer. Consequently, a main priority became to increase the number of serial communication ports. Most modern desktop computers only have one or possibly two serial ports, and some laptops even lack them completely. For this purpose, a range of different USB-to-serial adapters was tested and evaluated in terms of stability and robustness in order to increase the number of comm ports up to a maximum of 16. Adapters that had control chips and drivers manufactured by FTDI[8] proved to perform best at the time of testing. These chips power several commercial USB-to-serial adapters from different manufacturers. The USB-to-serial adapter was mounted inside the fume hood and all laboratory devices were plugged into this adapter. Only a single cable was then required between the fume hood and the computer. For a photograph showing an example of a typical *Oscar Wilde* arrangement for controlling and logging a single reactor see Figure 1.

The concept could as well be applied to multiple reactor systems. The picture to the left in Figure 2 shows an arrangement of three 40-mL reactors (purchased from HEL[9]) with gastight stirrer shaft connections and overhead agitation. In front of the reactors is an orbital shaker designed for 4 mL disposable vials. Three separate heater/chillers provide temperature control to each reactor and to the vial blocks in the shaker. The right picture in Figure 2 shows a permanent arrangement with four identical reactors. The availability of starting material permitting, the use of standard lab reactors in process validations, experimental design or investigation of suitable workup procedures offers excellent control over the process parameters.

Software

The quest for suitable software to control the equipment from a computer proved to be a much less straightforward task than was initially realised. Although most purchased equipment came with a functional and fit-for-purpose control software, it was not considered worthwhile to find a method to run the individual pieces of software in parallel, and still be able to collect their data using a single application.

For this purpose, less manufacturer-specific software platforms had to be evaluated. Thus, LabView (National Instruments), Camile (Argonaut Technologies), WinIso (HEL), Lara (Radleys UK), VirtualLab and LabMax (Mettler-Toledo), FlexyLab (Systag) and LabWorldSoft (IKA Werke) were assessed. The LabWorldSoft software proved to be the most suitable candidate in terms of cost, user-friendliness and

---

(7) Ahlborn Messtechnik und Regelungstechnik GmbH: Holzkirchen, Ger. http://www.ahlborn.com. Accessed May 2009.

(8) For information and download of latest drivers visit Future Technology Devices International Ltd. http://www.ftdichip.com. Accessed May 2009.

(9) HEL Ltd. http://www.helgroup.com. Accessed May 2009.

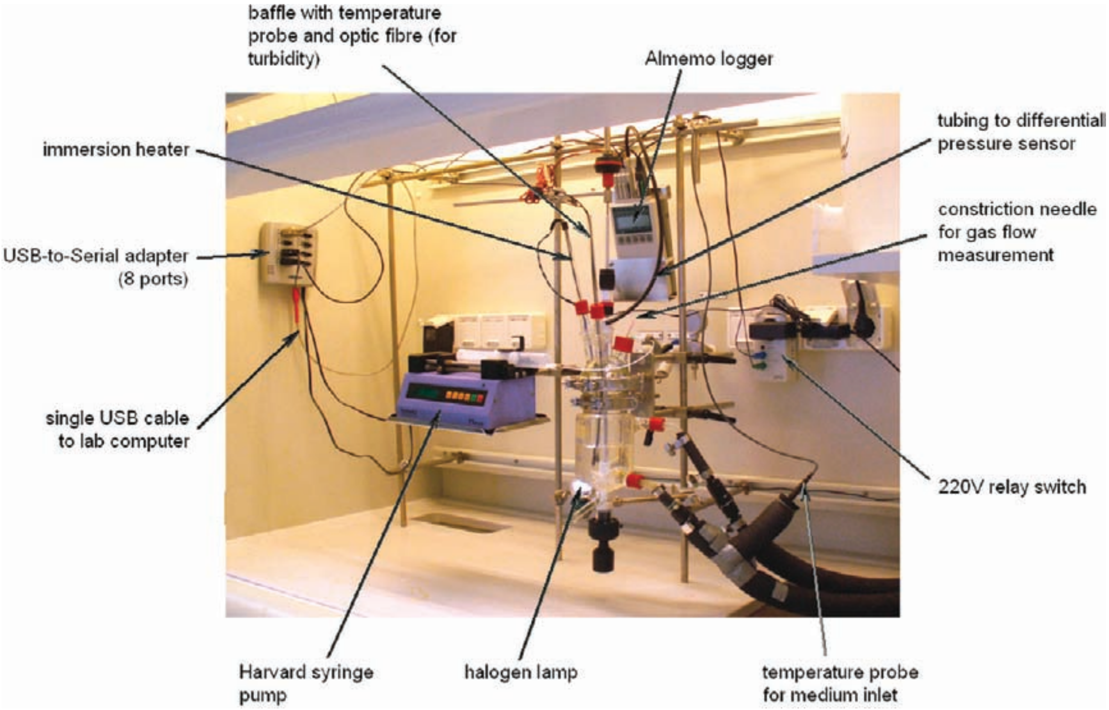


Figure 1. **Fume hood view of an *Oscar Wilde* arrangement with standard equipment to measure turbidity, energy and gas flow.**

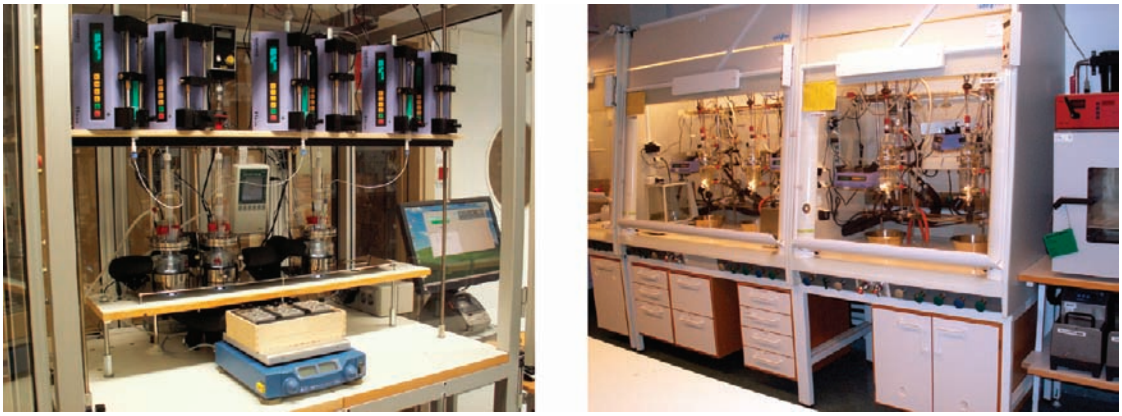


Figure 2. **Examples of two multiple-reactor arrangements.**

manufacturer's willingness to incorporate new devices and develop the software. In close collaboration with the developers, the software was modified and rolled out across the department during 2002. The uptake was low, however, mainly due to the fact that the user interface still was too demanding and time-consuming to program. During the months that followed dedicated resource was required to keep the software up and running by, for example, delivering prewritten templates and hands-on support, but unfortunately the degree of uptake did not increase accordingly.

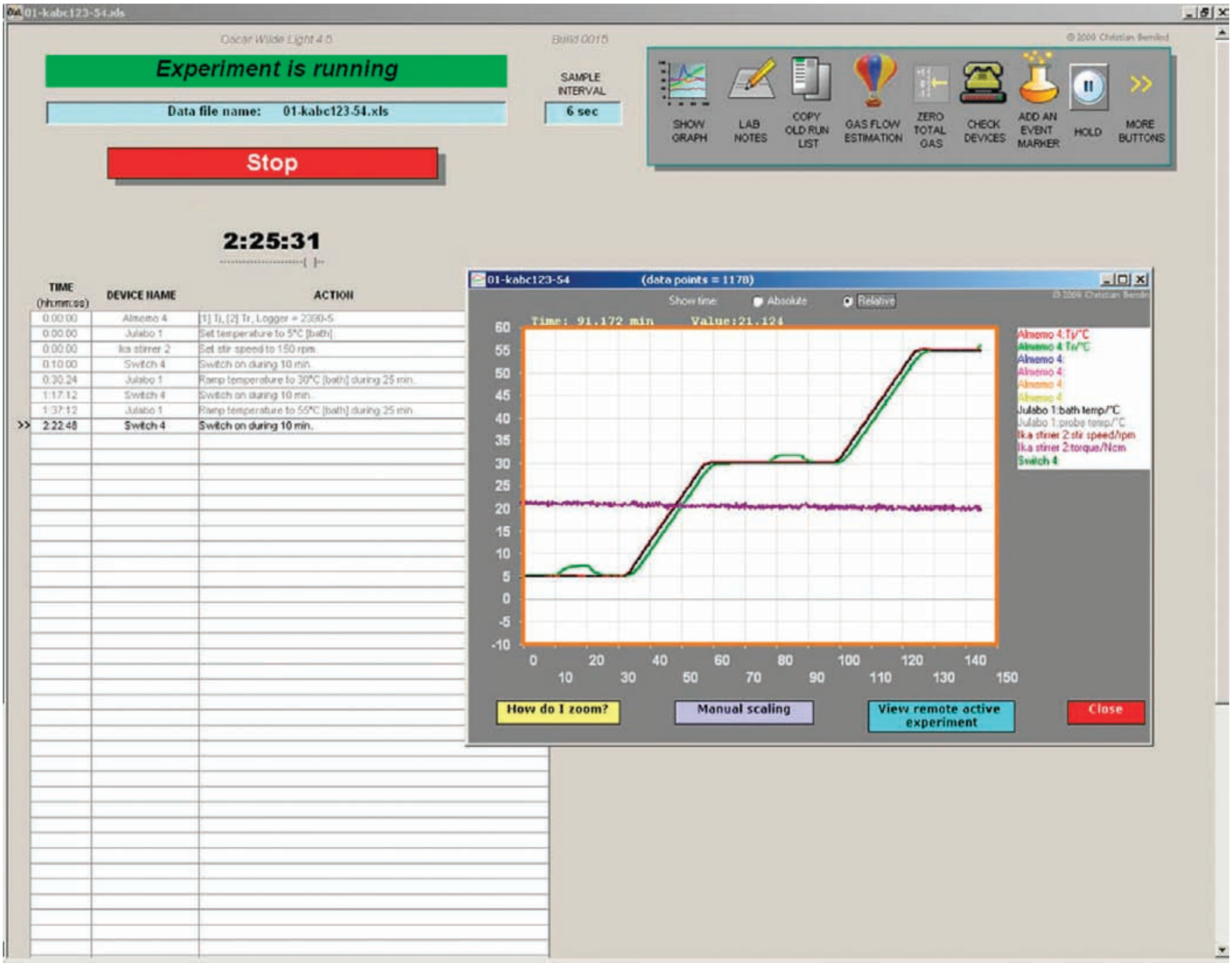
This made it necessary for us to start development of in-house software applications. Recommended strategies to do this have been presented previously by others.[3,10,11] We had the necessary knowledge of computer programming in-house and had a clear list of requirements. Among the criteria for this software were that it should

- be as easy to use as possible. The number of mouse-clicks that is required to perform a certain task should be kept to a minimum (in general this is an excellent measure of software user-friendliness);
- record and document experiments in one single data file in a universal format. For this purpose, the Microsoft Excel spreadsheet format was chosen. The file would, apart from the raw data and a chart, also contain other important information about the experiment on work-sheets within the file;
- have a robust and reliable error handling in case RS232 communication with the devices would fail;
- be retrieved from a central network disk available to every chemist. This would allow rapid distribution of new versions and bug fixes with minimal support and effort.

The first in-house developed software to be rolled out was a simple data logging application which had been developed in the powerful and, more importantly (for employees at a company with a strong and restrictive IT department), readily

---

(10) Pollard, M. *Org. Process Res. Dev.* **2001**, *5* (3), 272.
(11) Owen, M. R.; Dewitt, S. H. Laboratory Automation in Chemical Development. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; Marcel Dekker: New York, 1999; p 429.



Data file name: 01-kabc123-54.xls

SAMPLE INTERVAL: 6 sec

2:25:31

(data points = 1178)

	TIME (hh:mm:ss)	DEVICE NAME	ACTION
	0:00:00	Almemo 4	[1] Ti, [2] Tr, Logger = 2390-5
	0:00:00	Julabo 1	Set temperature to 5°C [bath]
	0:00:00	Ika stirrer 2	Set stir speed to 150 rpm.
	0:10:00	Switch 4	Switch on during 10 min.
	0:30:24	Julabo 1	Ramp temperature to 30°C [bath] during 25 min.
	1:17:12	Switch 4	Switch on during 10 min.
	1:37:12	Julabo 1	Ramp temperature to 55°C [bath] during 25 min
>>	2:22:48	Switch 4	Switch on during 10 min.

Figure 3. **Screen dump from an *Oscar Wilde Light* run.**

available Visual Basic for Applications (VBA) using Microsoft Excel as the development platform.[12] The application contained functionality allowing gas flow measurement and rough estimation of energy release.

This basic logger application was rapidly embraced by the organisation, but it was soon realised that there was also a need to be able to actively control and send set values to the devices instead of just passively logging output data. For this purpose the software *Oscar Wilde Light* was developed in-house and rolled out in late 2005. Since its deployment *Oscar Wilde Light* has been further refined in close collaboration with chemists and applied on "live" process chemistry problems. Today, the software is a pure Visual Basic application,[13] and the number of controllable laboratory devices and the level of uptake among our chemists is steadily increasing. During the year 2008 nearly 3000 software-controlled experiments were performed at our department, generating a total of 47000 h of data. A screen shot of a running *Oscar Wilde Light* experiment is shown in Figure 3. A more exhaustive description of *Oscar Wilde Light* is beyond the scope of this article, but some of the features are listed below:

- addition of a liquid reagent at such a rate as to maintain a specified exotherm or a specified effect using a PID control loop
- maintenance of a constant pH during the reaction
- ability to start equipment automatically (*e.g.*, heater/chillers) during out-of-office hours in order to decrease the impact of lag time associated with temperature stabilisation
- perform experiments that are completely controlled by the software to reduce variations of parameters
- start an addition automatically via adaptive feedback, *e.g.*, when a temperature value is stable
- copy measured values to an electronic lab notebook without the risk of transcription errors
- automatic creation of suitable cooling profiles for heater/chillers using best process understanding practice

---

(12) A fully functional version of the data logger application named *Dorian Gray* together with a manual and installation instructions are available from the authors on request. The application requires an Almemo data logger.

(13) For Visual Basic 6, see *e.g.*: Norton, P.; Groh, M. *Peter Norton's Guide to Visual Basic 6*; SAMS:: Indianapolis, IN, 1998 orWong, W. *Visual Basic 6 for Dummies*, 2nd ed.; IDG Books Worldwide Inc.: Foster City, CA, 1998. For Visual Basic 2008 see *e.g.*: Halvorson, M. *Visual Basic 2008. Step by Step*; Microsoft Press: Redmond, WA, 2008.

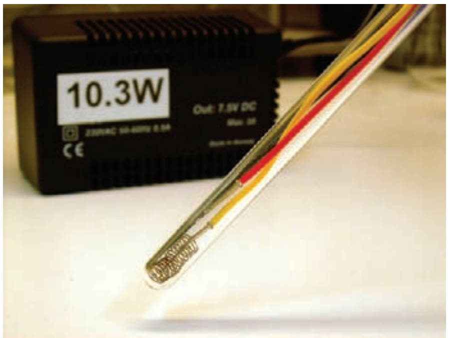


Figure 4. **Immersion heater manufactured from a glass tube and a coiled heater cable. A net adapter is shown in the background.**

- ability to freely connect and disconnect devices during an active experiment in order to maximize their use of operation
- perform *ad hoc* programming of experiments, *i.e.*, add, remove or change actions after the start of an experiment

Today, *Oscar Wilde* systems have been installed for nearly 100 chemists at AstraZeneca. In addition, the *Oscar Wilde Light* software is operating at several common resource laboratories such as those used for small- and medium-scale parallel equipment, the hydrogenation facility (<5 L), the scale-up laboratories (5−10 L) and the continuous flow reactor system. The ability to have the same automation software throughout different stages of process development greatly facilitates comparison of experimental data sets and enables "recycling" of chemical recipes.

Effect and Energy Measurements

The ability to measure effect and energy for a chemical reaction is a fundamental tool enabling rough estimation of the thermal hazards for a given reaction.[14,15] If this could be performed in the standard equipment that is normally used by process chemists, they could immediately get early information about safety issues for a specific transformation. In order to carry out such calorimetric measurements, the *Oscar Wilde* concept uses immersion heaters, an established and largely noncontroversial way to calibrate a reactor system before and/or after reaction, since they simulate instantaneous chemical reactions having known power outputs. The heater elements could be constructed from heater cable or low-ohmic carbon resistors connected to standard low-voltage net adapters as can be seen in Figure 4. After manufacture, and at regular intervals, each immersion heater should be calibrated in order to assign the accurate effect value to it.

At this point it must be clearly stressed that the immersion heater method described here does not replace a stringent calorimetric measurement. Process safety is defined by many factors of which thermal hazard assessment is only one component.[16] In any case, the estimated figures for effect and energy obtained by this method provide chemists with important information about their process, such as suitable minimum addition times for reagents and whether the reaction is accumulated. The effect trace for a given chemical reaction could point out when the end of reaction has been reached and also, under favorable circumstances, give information about the overall reaction kinetics.

During an experiment, the power to the immersion heater is either activated manually, or by software control. The automatic option is performed by means of a 220 V relay switch between the net adapter and the power plug which can be conveniently operated via the Almemo logger. The standard procedure is to first switch on the heater for a few minutes before reaction, then the reaction is carried out and the heater is started again once the reaction exotherm has declined.

In order to estimate the effect and energy for the reaction a special procedure has been developed, which is performed by an Excel macro.[17] The mathematical algorithms in this macro are based on a simplified formula for effect calculation[18] (eq 1).

$$P = UA \times (T_R - T_J) + m \times c_P \times \frac{dT_R}{dt} \qquad (1)$$

where P is the effect, UA is the heat transfer coefficient U multiplied by the wetted reactor area A, T_R is the reactor temperature, T_J the jacket temperature, m is the mass, and c_P is the specific heat for the reactor content.

The energy, Q, for a completed reaction is obtained by integration of the effect.

$$Q = \int P\, dt = UA \times \int (T_R - T_J)\, dt \qquad (2)$$

Although data for c_P are readily available for a number of pure solvents, it is not a trivial task to try to estimate c_P for complex reaction mixtures. Thus, in practice, eq 1 should be considered to contain two unknown terms, namely UA and $m \cdot c_P$.

Given the additional fact that the effect plateau during the time the immersion heater is active should equal the nominal effect value of the heater, there is also a second relationship between the UA and $m \cdot c_P$ terms which can be employed to find a solution to eq 1.

An experiment is evaluated as follows: After collection of the logged data from the experiment, the Excel macro mentioned above starts by assigning an arbitrary initial value to UA. At the same time the factor $m \cdot c_P$ is calculated from the fact that the difference between the grouped values for the upper and lower state of the effect curve should equal the effect of the immersion heater. From eq 1 a preliminary effect trace is printed out in the graph. Due to the presence of noise in the input data, mainly due to slope calculations, it is necessary for

---

(14) Zogg, A.; Stoessel, F.; Fischer, U.; Hungerbühler, K. *Thermochim. Acta* **2004**, *419*, 1.

(15) Fischer, U.; Hungerbühler, K. Calorimetric Methods of Investigating Organic Reactions. In *The Investigation of Organic Reactions and their Mechanisms*; Maskill, H., Ed.; Blackwell Publishing: Oxford, U.K., 2006; Chapter 8, p 198.

(16) Lees, F. P. *Loss Prevention in the Process Industries; Hazard Identification and Control*, 2nd ed.; Butterworth Heinemann: Woburn, MA, 1996; Vol. 1.

(17) More detailed information about the Microsoft Excel macro to calculate effect and energy is available from the authors on request.

(18) Poling, B. E.; Thomson, G. H.; Friend, D. G.; Rowley, R. L.; Wilding, W. V. *Perry's Chemical Engineers Handbook*, 8th ed.; McGraw-Hill: New York, 2008; Chapter 2, p 170.

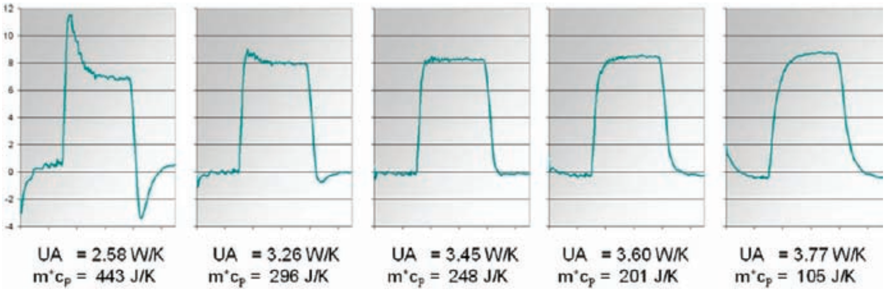


Figure 5. **Screen shot from an iteration process to find the best square shape for the effect trace. The immersion heater was active for 10 min. The effect trace was generated from the values for the reactor and jacket temperatures.**

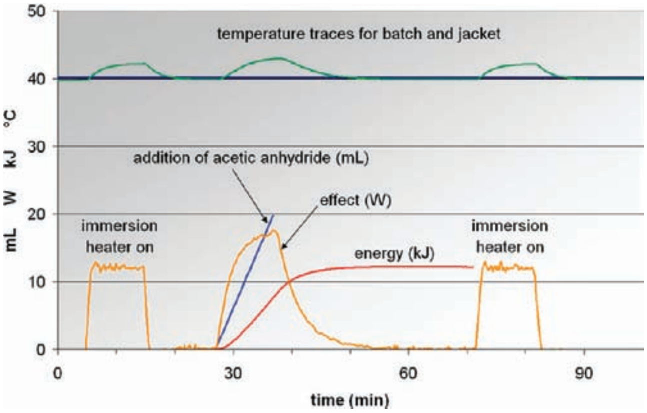
some human intervention to judge the appearance of the effect curve. Using a scroll bar in the macro interface, the user can assign new values to *UA* and then view the result of the new *UA* and calculated $m{\cdot}c_P$. An example of the iteration process is shown in Figure 5. The iteration process aims to produce an effect trace shape that resembles a square (obtained in the middle picture in Figure 5). Intuitively, this would be the expected shape of an effect trace where an immersion heater is switched on and off. Final values for *UA* and $m{\cdot}c_P$ have then been assigned and are used in the subsequent analysis of the chemical reaction.

The data in Figure 5 were obtained from a 250 mL reactor that contained 150 mL of toluene and was equipped with an 8.1 W immersion heater. The observed $m{\cdot}c_P$ value for the best square-shaped effect curve (middle) was 248 J/K. For reference, the expected c_P for toluene at 25 °C is 1.79 J/K,[18] and hence, the theoretical value for $m{\cdot}c_P$ would be 235 J/K. In practice, a slightly higher value should be expected. This could be attributed to the fact that the impeller, thermometer baffle and the immersion heater themselves also contribute with their $m{\cdot}c_P$ terms.

It is important to activate the immersion heater both before and after reaction. In cases where the jacket temperature is changed or ramped between the start and the end of the reaction this becomes especially important because the *U* term, for example, is strongly dependent on the temperature. A linearity algorithm in the Excel macro is used to balance the *UA* and $m{\cdot}c_P$ values before and after the reaction to be able to use them in the calculation. After the macro has finished the calculations, two additional data traces, effect and energy, have been added to the graph. Some additional data of interest are also shown in plain text, for example, the maximum effect during the reaction, the theoretical adiabatic temperature increase (the temperature that would be reached in a large-scale process if the cooling should fail), and the degree of accumulation (energy released after the end of charging).

No additional data other than the temperature curves and the effect value for the immersion heater are needed in order to be able to estimate effect and energy for the chemical reaction. The method works equally well for both small and large reactors as long as the effect of the immersion heater is chosen accordingly. Furthermore, the method provides excellent results when the effect and energy are calculated for reactions that take place during ramping of the jacket temperature. An important advantage is also that the measurement can be carried out in a standard lab reactor under normal experimental conditions. It is simply an "add-on" to an otherwise standard experiment where the usual process chemistry parameters are investigated. Thus, effect and energy calculations do not require an extra dedicated run, which is usually the case for other types of calorimeters.

Chart 1. **Reaction and energy profile for hydrolysis of acetic anhydride**



The hydrolysis reaction of acetic anhydride is well studied and is frequently used to show the applicability of a certain calorimetric method. When this reaction was studied using the *Oscar Wilde* concept with an immersion heater in a standard 250 mL lab reactor, the heat of reaction was shown to be 57.4 kJ/mol, a value in very close accordance with the literature value of 58 kJ/mol.[19] Chart 1 shows the temperature profile and the effect/energy traces for a reaction where 20 mL of acetic anhydride was added to 150 mL of water over 10 min at 40 °C. The acetic anhydride addition started at 27 min. The temperature increase from the 12.0 W immersion heater is seen before and after reaction.

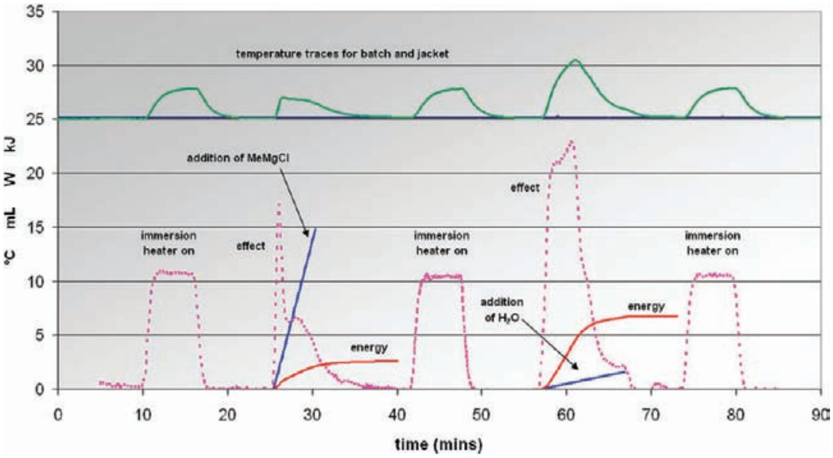
Chart 2 shows another effect and energy measurement that was carried out in order to investigate suitable conditions for an aqueous quench of methylmagnesium chloride. This example clearly demonstrates the large amount of information about a chemical process that can be extracted from a set of logged experimental data for the reactor and jacket temperatures.

A standard 250 mL reactor was charged with 150 mL THF, and the reactor inner temperature (green trace in Chart 2) was stabilized at 25 °C. Starting at 25 min, 15 mL of methylmagnesium chloride (3 M in THF) was added from a syringe pump over 5 min; to quench the Grignard reagent 1.62 mL of water was added over 10 min starting at 57 min. Before, in between, and after the additions, an immersion heater with a calibrated effect of 10.45 W was activated. The effect and energy were

---

(19) Smith, T. L. *J. Phys. Chem.* **1955**, *59* (5), 385.

Chart 2. **Effect and energy measurements for a water quench of methylmagnesium chloride**



calculated by the procedures described above, and the resulting data are included in Chart 2.

Upon addition of MeMgCl there was an initial effect spike that reached to a maximum of 17 W, which is likely to be due to residual water in the THF. It is clear that there was some accumulation of energy during the addition, apparent from the effect trace (dotted line in Chart 2), since it did not drop immediately at the end of the addition. The second charge showed much less accumulation. Since an excess of water was added (1.5 equiv), the effect dropped before the addition had finished. The effect trace showed a spike at the end of the addition, reaching to a maximum of 23 W. This additional exotherm was attributed to precipitation of MgClOH and was further corroborated by the turbidity trace (not shown in Chart 2). Some heat of mixing during the water addition was also apparent from the effect trace. Not surprisingly, the quench evolved methane gas. This is discussed in the Gas Flow Measurements section below.

Today, the *Oscar Wilde* method is used routinely, in conjunction with differential scanning calorimetry, DSC,[20] as the source of safety data required to take processes up to 100 L in the large-scale laboratories. The chemists who perform these evaluations should be trained in the methodology and equipment and should always consult experts within the process safety group whenever there seems to be any potential safety hazard with the process. For pilot-plant production (>100 L) the *Oscar Wilde* method has not replaced more established process safety assessment methods. Here, standardized equipment (e.g., the Mettler RC1 calorimeter[21] and the HEL Simular[9]) operated and evaluated by process safety engineers is still the preferred method of choice.

Gas Flow Measurements

Gas flow measurements for process chemistry can be carried out using mass flow meters, where the reaction gas is allowed to pass over a heated sensor. The degree of cooling depends on the specific capacity of the gas and the mass that passes over it per time unit.[22] Cuvette-based systems are also available, in which the evolved gas repeatedly fills a container of a known volume.[23] The *Oscar Wilde* concept uses measurement of the differential pressure drop that will build up over a constriction pipe—also known as a Poiseuille flow meter—in order to estimate gas flow rate.[24] A typical arrangement is seen in Figure 1 above.

The reactor is connected to a differential pressure probe, preferentially through a piece of silicon tubing, needle and septum or, as is the case in Figure 1, using a specially designed screw cap with a glass connector pipe outlet on the side. The pressure probe is, in turn, plugged into an Almemo data logger. A disposable needle is pushed through a septum on the reactor to act as a constriction pipe. During an experiment a small overpressure will build up inside the reactor when gas evolution occurs. The constriction needle will cause the pressure to reach a steady-state value for a given gas flow. In a typical experiment a 250 mL reactor equipped with a 1.2 × 50 mm disposable needle would experience a pressure rise of 50−200 Pa (0.0005−0.002 atm) for moderate gas flows, so the overpressure in the reactor will be negligible.

The upper pressure limit for the Almemo differential pressure probe is 1250 Pa (0.012 atm). In order to adjust the pressure that is built up inside the reactor and to fit the method to different reaction scales, the length and bore of the needle should be adjusted accordingly. For larger reactors, other types of constriction devices could be considered (see Figure 6).

The relationship between gas flow rate and the differential pressure drop over a circular constriction pipe is described by the Hagen−Poiseuille equation.[24]

$$Q = \frac{\Delta P \times \pi \times d^4}{128 \times \mu \times L} \qquad (3)$$

where Q is the volumetric flow rate, ΔP is the pressure drop, d is the pipe diameter, μ is the dynamic viscosity and L the

---

(20) O'Neill, M. J. *Anal. Chem.* **1964**, *36* (7), 1238.

(21) Mettler-Toledo Inc; http://www.mt.com. Accessed May 2009.

(22) (a) For an overview of different techniques see *e.g.*, http://en.wikipedia.org/wiki/Flow_measurement or(b) Weisenburger, G. A.; Barnhart, R. W.; Steeno, G. S. *Org. Process Res. Dev.* **2008**, *12* (6), 1299.

(23) For information about the "U" tube, visit: Intertek ASG; http://www.intertek-cb.com/asgmc/GasMeasurementApparatus.shtml. Accessed May 2009.

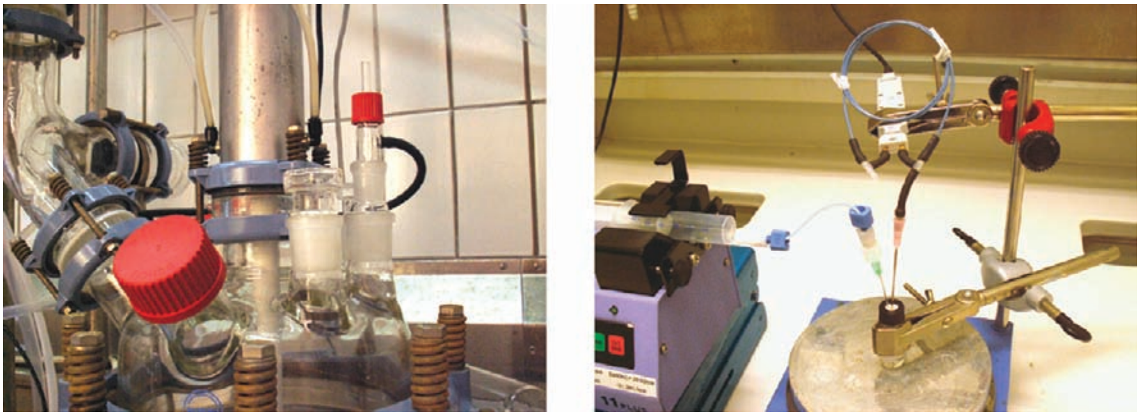
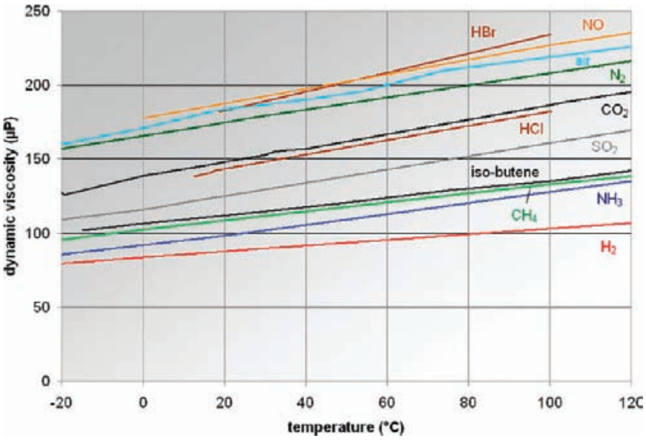


Figure 6. **Gas flow measurements on large and small scale. For the 10 L reactor (left) the constriction device was a 60 mm glass pipe, i.d. = 3.0 mm, mounted at the small red GL cap in the reactor lid. The black silicon tubing to the differential pressure probe is visible below the pipe. For the 4 mL GC vial (right) the pressure difference was measured over a 60 cm coiled PEEK tubing (inner diameter 0.25 mm).**

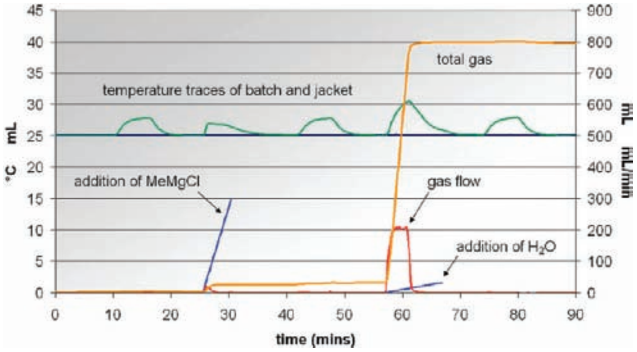
Chart 3. **Dynamic viscosities for some gases**[25,26]



length of the pipe. Chart 3 shows the dynamic viscosities for some gases familiar to process chemists. Note the conversion 1 μP (micropoises) = 0.1 μPa·s.

It is wise to take a pragmatic approach to eq 3 since it requires an otherwise hermetically gastight reactor in order for the gas to exclusively pass through a constriction needle of exact known inner diameter. Minor leaks through stirrer shaft connections, ground glass joints and through the reactor lid gaskets can never be ignored. Therefore, the recommended way to quantify the volume of gas is to calibrate the flow by an injection of a known gas volume before or after the presumed gas-producing reaction. The gas can be injected using a standard syringe, and the amount of gas should typically be 5−20% of the nominal reactor volume. The integrated area of the pressure increase during reaction can then be related to the known integrated area of the calibration volume and thus quantified. Alternatively, the gas can be injected using a syringe pump and the steady-state value be used as a conversion factor between pressure and gas flow rate. Although the *Oscar Wilde Light* software has a built-in routine which integrates the pressure in real-time so that the volume of gas is displayed on screen directly, it is considered good practice to reintegrate the pressure trace after the reaction. This would take care of any baseline drift that can occasionally be observed for experiments which stretch over several hours.

Chart 4. **Gas flow measurement for a water quench of methylmagnesium chloride**



In order to perform a successful gas flow estimation there are a few additional points that need to be made. Before the calibration the pressure in the reactor should be allowed to stabilize for a few minutes before addition of the calibration gas. It is equally important to minimize the risk of solvent vapours condensing inside the constriction needle. At elevated temperatures the needle should preferably be placed above a condenser, otherwise the needle should be positioned as far away from the reaction mixture as possible to avoid splashes. There are no imminent safety concerns about pressure building up in the reactor, should the needle become filled with solvent, but the accuracy of the measurement will be significantly reduced.

Chart 4 shows the gas flow profile for the water quench of methylmagnesium chloride discussed in Chart 2 above. The addition of methylmagnesium chloride at 25 min caused a small initial gas evolution (residual water in reactor solvent). The addition of water at 57 min caused extensive gas evolution. The gas flow dropped rapidly after about half the addition of water due to the excess of added water. In total, 0.8 L gas was

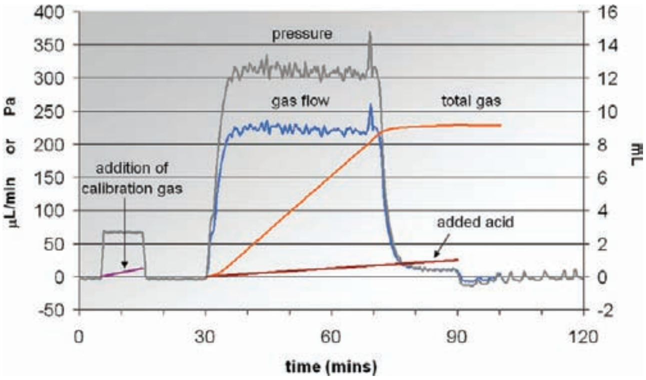
---

(24) Karger, B. L.; Snyder, L. R.; Horvath, C. *An Introduction to Separation Science*; John Wiley & Sons: New York, 1973; Chapter 3, p 88.

(25) Weast, R. C., Ed. *CRC Handbook of Chemistry & Physics*, 64th ed.; CRC Press: Roca Baton, FL, 1984; F42−F44.

(26) The viscosity values for isobutene were calculated using a Java application for gas viscosities found at LMNO Engineering, Research and Software Ltd. http://www.lmnoeng.com/Flow/GasViscosity.htm. Accessed May 2009.

Chart 5. **Gas flow calculation for addition of 0.6 M HCl (aq) to 0.2 M $NaHCO_3$ (aq) on a 4 mL scale**



released: the theoretical amount is 1.0 L (45 mmol) but some methane is expected to dissolve in the THF.

For qualitative measurements it is sufficient to use air or nitrogen as the calibration gas. If more accuracy is desired, the values in Chart 3 together with eq 3 can be used to recalculate the gas flow. When unknown gases or mixtures of gases are to be measured (*e.g.*, Boc-deprotection) the preferred alternative is to perform the gas calibration after the gas-evolving reaction. Then the atmosphere inside the reactor will consist of the gas in question and injection of a small amount of air or nitrogen will not disturb the system significantly. If desired, mathematical methods to predict gas viscosities are also available.[27]

It is worth mentioning that the steady-state pressure value for a given gas flow rate is independent of the headspace volume in the reactor. Hence, no correction other than the displacement volume from added material needs to be made for reactions where a large volume of reagent is added during the gas evolving process. Also, the gas does not physically pass through the probe, a fact that will prolong the probe lifetime substantially especially when corrosive gases are measured. Figure 6 shows two examples of gas flow measurements on 10 L and 4 mL scale, respectively, which used the same type of pressure probe and method.

The scalability of the Poiseuille flow meter is quite remarkable. Chart 5 shows the gas flow measurement from the 4 mL vial arrangement depicted in Figure 6. The vial was initially filled with 2000 μL of 0.2 M $NaHCO_3$ (aq) and was calibrated by 500 μL of CO_2 that was pumped into the vial using a syringe pump over 10 min. Then 1000 μL 0.6 M HCl (aq) was added over 60 min. The estimated volume of evolved gas (orange line) was 9.1 mL (theoretically 9.0 mL). Since an excess of acid was added, the gas flow rate (blue trace) dropped after one equivalent had been added. Most notably, the noise level during the calibration phase was less than ±2 μL/min!

Conclusions

A key to a smooth implementation of laboratory automation is to find ways to lower the threshold between manual and automated work. Easy-to-use software tools and laboratory equipment that can also be operated manually can offer an efficient and cost-effective platform to allow every chemist to enter the digital world in an incremental fashion. In parallel, efforts must be made, via appropriate channels and examples, to clearly show users that the ability to log a lot of different data from each experiment will lead to a much deeper understanding of the processes and add value to their work. For example, the sensitivity of modern temperature probes can easily measure even very small temperature changes of the order of a few hundredths of a Kelvin. This can enable monitoring of exotherms or endotherms that stem from crystallisations or from the evolution of gas. Together with a sound risk assessment, automation also enables fully or partly unattended experiments to be performed during nights and weekends. In addition, the accuracy and degree of control that computerized systems provide, as well as the possibility to reuse the chemical recipes and to perform repetitive runs, make them ideal candidates for *quality by design* (QbD) work, which is an emerging and challenging opportunity for pharma companies.[28]

Acknowledgment

We thank Peter Jaksch for sharing his technical knowledge and Jörgen Blixt, Daniel Fahlén and Patric Fransson, all in our department, for valuable input and ideas. We also thank Dr. Hans-Jürgen Federsel and Dr. Adrian Clark for constructive criticism on this manuscript.

Received for review June 16, 2009.

OP900154C

---

(27) (a) Yoon, P.; Thodos, G. *AIChE J.* **1970**, *16*, 300. (b) Reichenberg, D. *AIChE J.* **1975**, *21*, 181.

(28) (a) Pharmaceutical cGMPs for the 21st century, a risk-based approach; Department of Health and Human Services, U.S. Food and Drug Administration: Washington, DC, September 2004. Final report. Available at: http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm. Accessed Jan 2009. (b) Seibert, K. D.; Sethuraman, S.; Mitchell, J. D.; Griffiths, K.; McGarvey, B. *J. Pharm. Innovation* **2008**, *3*, 105.