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Automated Workstations for Parallel Synthesis

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Abstract:

One of the main objectives in current chemical process development is increasing laboratory efficiency by high throughput experimentation (HTE) for screening of reaction and process parameters and by high speed experimentation (HSE) for optimisation of process parameters. An important tool in reaching this second goal is the use of parallel automated reactor systems. This report describes the tests, requirements, and evaluation scheme we used in our laboratories for testing three commercially available systems.

Introduction

The development of chemical routes in the pharmaceutical industry has to be faster and cheaper.[1] This can be realised by high throughput experimentation (HTE).[2] At Diosynth we started HTE with the introduction of the Anachem SK233[3] and the use of experimental design. This strategy works very well for the investigation of the reactions themselves: screening and some optimisation can be performed on relatively small scale (approximately 10 mL). However, in the case where the product should be isolated, for example to determine isolated yields or to investigate the workup and purification procedures, the volumes used in the SK233 are too small. Furthermore, for optimisation experiments it would be useful to measure process parameters such as temperature. Therefore, we were interested in automated parallel reactor systems in which larger volumes can be used to isolate products. In these systems fewer experiments per run (than for example in the SK233) can be performed, but they enable the measurement of several parameters so that more information is gathered. This kind of automation is called high speed experimentation (HSE).

Requirements for the System. On the basis of the experiences with the Anachem SK233 we set up the following requirements for a new system:

(1) The operation of experiments should be similar to that in pilot-plant processes. Agitation should be mechanical to obtain a controllable degree of mixing and to avoid the scratching of a magnetic stirring bar, for example, in crystallisations. The temperature should be regulated preferably via the jacket. The temperature ranges should be in the same range as those obtainable in the (pilot) plant. Heating and cooling as well as addition rates should be adjustable and comparable to those in the (pilot) plant. Furthermore, the step order should be equivalent to that in the production processes.

(2) The equipment should be able to perform the following functions: (a) optimisation of reactions by variation of critical parameters such as temperature (profiles), dosing rates, pH, and agitation, (b) initial scale-up experiments, that is, gathering information such as reaction kinetics, which can be helpful during further scale-up, (c) robustness tests, (d) preparation of reaction mixtures which can be used in the investigation of workup, such as crystallisation and extraction behaviour.

(3) The system should be used by every lab worker, and thus it should have a low barrier to work with. This requires an easy-to-use and robust hardware configuration. This includes the interchangeability of glassware, agitators, and syringes. The configuration should be multipurpose to be utilised in different projects. The reactors must be easy to clean. The software must be user-friendly; after a short instruction a lab worker must be able to perform simple experiments himself. One supervisor will be in charge for difficult problems and trouble-shooting. The supervisor will give the training and support to the lab workers.

(4) The system should generate much more information with respect to traditional methods. This includes continuous recording of reactor temperature, jacket temperature, dosing rates, pH, and stirring speed. In addition to the accurate recording of these parameters, the system should control these parameters very well. Due to this superior recording and control, an indication of reaction and crystallisation heats should be obtained. An additional advantage will be the gathering of safety information such as identification of significant heat effects.

(5) The use of an automated system will provide the use of recipes; reactions can be performed 24 h a day, generating more results in shorter times. Automation improves the reproducibility of the experiments.

Available Systems

At the moment three systems are commercially available which meet most of the requirements: Automate (HEL),[4] Multimax (Mettler Toledo),[5] and Flexylab (Systag)[6] (See

(1) See the Special Feature Section: Laboratory Automation in Process R&D. *Org. Process Res. Dev.* **2001**, *3*, 272−339.
(2) For a complete review of all kinds of labautomates, see: Harre, M.; Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **1999**, *3*, 304−318.
(3) Available from Anachem, Anachem House, Charles Street, Luton, Bedfordshire, LU2 0EB, U.K., http://www.reactarray.com.
(4) Available from Hazard Evaluation Laboratories Limited (HEL), 50 Moxon Street, Barnet, Herts. EN5 5TS, England, http://www.helgroup.co.uk.
(5) Available from Mettler Toledo, Sonnenbergstrasse 74, CH-8603 Schwerzenbach, Switzerland, http://www.mt.autochem.com.
(6) Available from Systag, System Technik AG, Bahnhofstrasse 76, CH-8803 Ruschlikon, Switzerland, http://www.systag.ch.

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Table 1. **Comparison of HEL-Automate, MT-Multimax, and Flexylab**

	Automate	Multimax	Flexylab
		Reactors	
number	4 (max 16)	4 (max 16)	4−6 (max 20)
size	50/100 mL	65 mL	250 mL
reaction volume	20−35/85 mL	20−50 mL	40−200 mL
material	standard: glass; metal, Hastelloy, PTFE possible	standard: glass; metal, Hastelloy possible	standard: glass
fixation	clamp	magnetic ring or clamp	clamp
visibility	good, below 0 °C restricted due to ice formation	poor, with clamp better, use flashlight	poor, difficult to raise reactor
		Temperature	
max	+350 °C (depends on cryostat)	+180 °C	+300 °C
min	−80 °C (depends on cryostat)	−50 °C (depends on cryostat)	−100 °C (depends on cryostat)
difference	50 °C, in practice 20 °C	150 °C highest/lowest	200 °C highest/lowest
gradient	per reactor settable not independent (!)	per reactor settable independent	per reactor settable independent
heating	electric internal heater[a] and cryostat	jacket	jacket
measurement	T_r, T_c, power	T_r, T_j, $T_r - T_j$, T_c	T_r, T_j, T_c
control via	T_r, T_c, power	T_r, T_j, $T_r - T_j$, T_{reflux}, $T_{cryst.}$	T_r, T_j, $T_r - T_j$
		Agitation	
magnetic	settable (not tested)	0, 150−1000 rpm	no
independent	yes (not tested)	yes	no
mechanical	yes, different types	yes, different types	yes, different types
independent	yes	yes	yes
baffles	no	no	no
torque measurement	yes (not tested)	no	yes (not tested)
		Dosing	
via	syringe or pump/balance	dispenser box	peristaltic pump/balance
simultaneous	yes	yes	yes
independent	yes	yes	yes
number	min one dose unit per reactor	min 1 dose unit per four reactors (four-way valve)	2 dose units per reactor already installed
dosing rate	settable	0−50 mL/min	settable
amount	0−25 mL (depends on max syringe volume) volume measured	0-unrestricted volume measured	250 mL mass measured
suspensions	yes	yes	yes
solids	yes	no	no
		Sampling	
possible	yes	not yet	no
on-line HPLC	coming soon	no	no

[a] An external electrical heater (28−30 W) is now available.

Figure 1). In Table 1 the features of the systems are described. All three instruments were tested in our laboratories for at least 5 days. The Automate demonstration apparatus had two reactors, which could be equipped with either 50- or 100-mL reactors. The Multimax reactor box contained four 65-mL reactors.[7] The Flexylab was demonstrated using two reactor blocks each containing one 250-mL reactor. The main difference between the Automate and the other two is the temperature regulation. In the Automate, the temperature in the reactor is mainly controlled by the cryostat temperature; this should be set 5−15 °C below the desired reactor temperature. An internal electrical heater heats the reactor contents to its desired value. Small changes in reactor temperature are corrected by power compensation of the heater. The temperatures in the Multimax and the Flexylab are jacket-controlled. They both use individual electrical jackets to heat the reactor contents. This jacket is cooled by a cryostat at a constant low temperature (more than 15 °C lower than lowest temperature required). In Figure 2, a schematic overview of the heating systems of HEL-Automate, MT-Multimax, and Flexylab is given.

To be able to compare the performance of the systems, similar reactions were performed.

Experiments

Acetic Anhydride Hydrolysis. This standard reaction was performed to test the dosing, the temperature stability, and the evolution of the reaction heat. In the HEL Automate 5 mL of acetic anhydride was added linearly in a 10-min period to 30 mL of water; in the MT Multimax a 30-min period was used. The results are shown in Figure 3a−c.

Automate. Figure 3a shows that the heater needed about 12 W to stabilise the temperature. After 16 min the temperature rose because the first acetic anhydride came into the solution. This heat generation was compensated by decreasing the power of the heater. After completion of the acetic anhydride addition, more heat was needed to keep the

(7) The test apparatus was a prototype: the stirrers were placed out of the center. In the commercial version the stirrers are placed in the center.

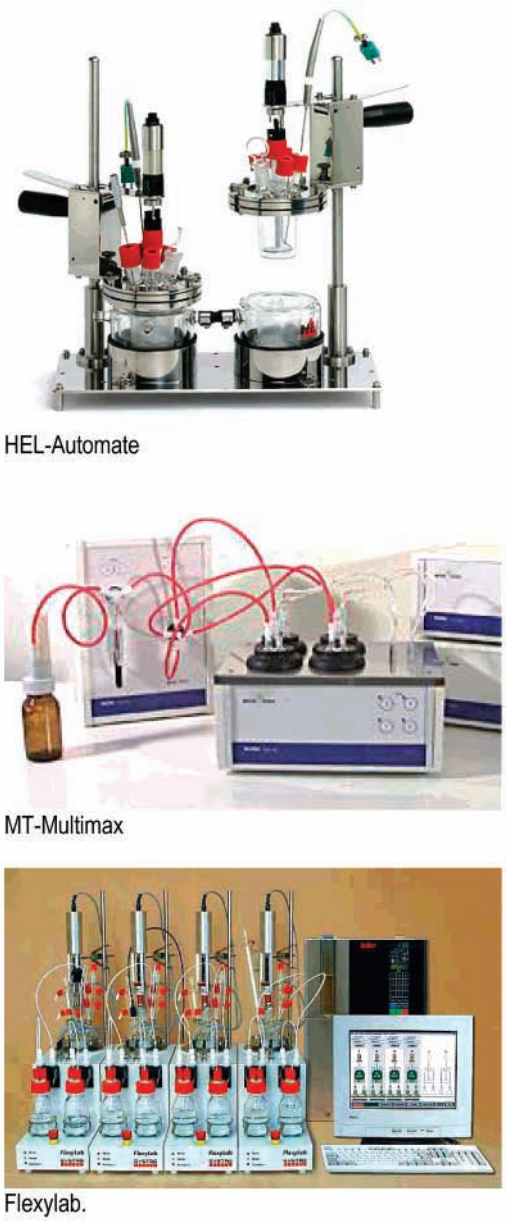

Figure 1. **Photographs of the three discussed systems.**

temperature at 30 °C, and the power was increased to 11 W. From the power curve the reaction heat can be easily calculated. Compared to the theoretical value (58 kJ/mol), the calculated heat, 60 kJ/mol, is a good estimation of the real heat. In Figure 3a, the pH decrease due to the formation of acetic acid is also shown.

Multimax. In reactor 1 (Figure 3b) the reaction was performed at 20 °C. The temperature rose after the first acetic anhydride came into the solution ($t = 800$ s). A decrease in the jacket temperature, and thus an increase in the $T_r - T_j$, compensated this heat generation. The reaction heat was compensated very fast: only a 0.2 °C rise in the reactor temperature was observed. After completion of the acetic anhydride dosage, the temperature of the jacket rose again to maintain the temperature at 20 °C. In reactor 3 (Figure 3c), the reaction was performed at 30 °C. The $T_r - T_j$ is higher and the $T_r - T_j$ curve is steeper than for the reaction at 20 °C.

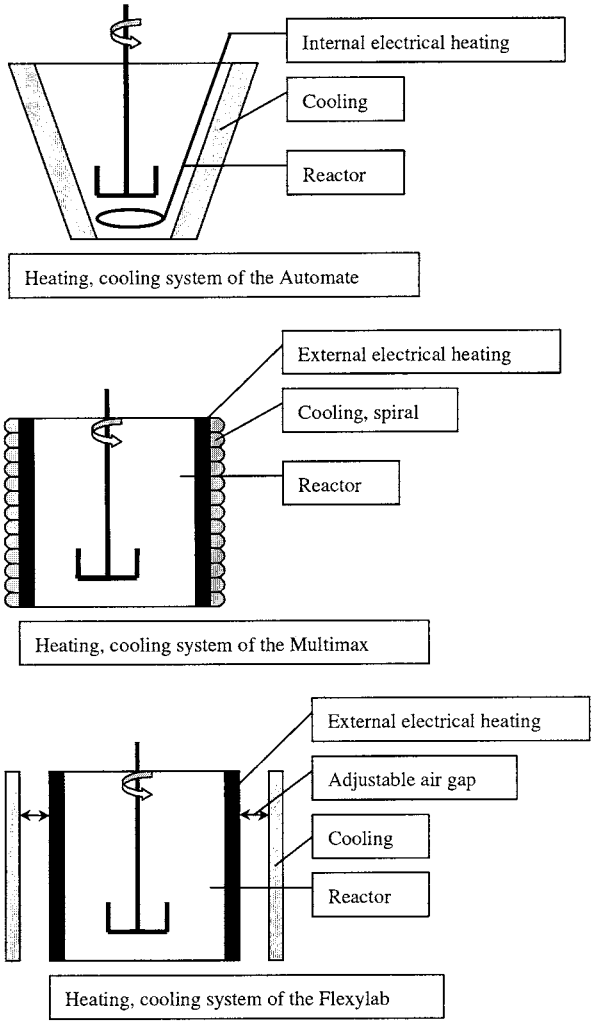

Figure 2. **Schematic overview of the heating system of HEL Automate, MT-Multimax, and Flexylab.**

The $T_r - T_j$ curve gives an indication of the heat evolution during the reaction. To calculate the reaction heat, the heat capacities of the reactor (U) and of the reaction mixture (c_p) should be known. These can be determined at the begin and at the end of the reaction using a calibration heater, which was not present at that time. From the $T_r - T_j$ curve it is clear that at 30 °C, because of the faster reaction, less heat accumulation occurs than at 20 °C.

Flexylab. The same experiment was performed in the Flexylab. The results were not as good as in the Multimax and the Automate. The problems were due to the large gap between the condenser circuit and the electric heating jacket (see Figure 1c) and to insensitive PID-regulation. Systag has reported that these problems have been solved. Systag repeated the acetic anhydride hydrolysis experiment, and they obtained rather good results.

Enolether Preparation. The objective of this experiment was to test the stirring capacity of the systems with a suspension and to observe the effect of the internal heater in the Automate.

The enolether synthesis performed in the three systems gives a dense suspension during the reaction. At low temperature a catalytic amount of *p*-toluene sulphonic acid is added to the reactors.

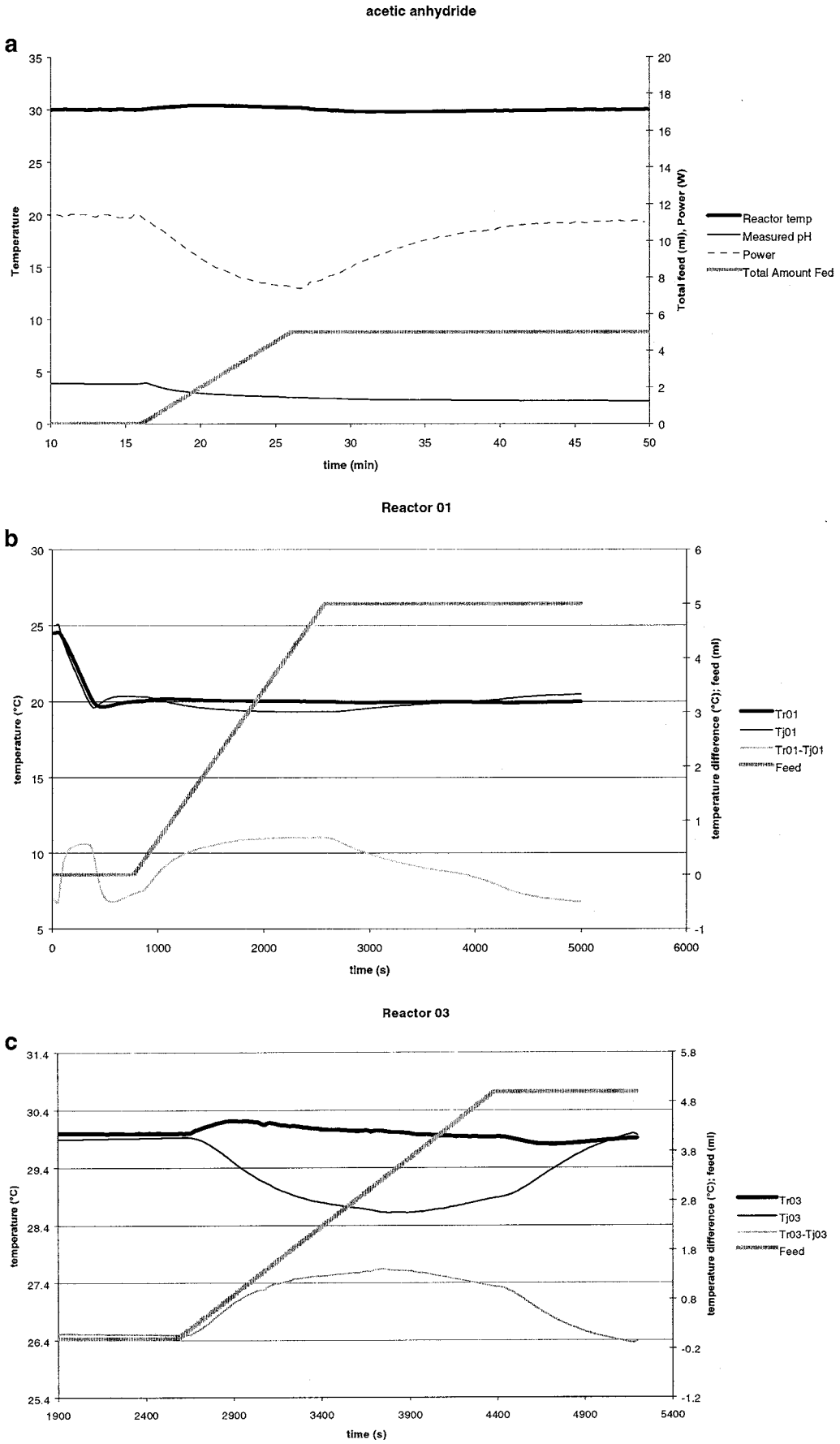

Figure 3. **(a) Acetic anhydride hydrolysis in Automate at 30 °C. (b) Acetic anhydride hydrolyses in Multimax at 20 °C. (c) Acetic anhydride hydrolyses in Multimax at 30 °C.**

During the reaction the mixture becomes thicker and thicker. As the degree of mixing and the reaction temperature determine the quality and the yield of the product, if the mixing is not sufficient, a larger amount of dienolether will be formed.

Automate. One experiment was carried out using a flat-blade stirrer, and the other was carried out using an anchor stirrer. The circulator temperature was set 10 °C lower than the reactor temperature to investigate the influence of the internal heater on the quality of the product. The reaction, in which the flat-blade stirrer was used, was not stirred properly: the upper layer of the suspension remained unstirred. During reflux of the reaction mixture a homogeneous mixture was obtained. The quality of the resulting product, less than that of the reference reaction, was determined with TLC (more dienolether had been formed). This was due to the poor mixing conditions. The reaction was repeated with an anchor stirrer. During this reaction, proper stirring was achieved. The product from this reaction was nearly equal to the standard; however, a small amount of byproduct had been formed. It is unclear whether this byproduct was formed because of the internal heater or because of oxidation by air (because of poor inert conditions).

Multimax. Reactor 1 was equipped with magnetic stirring, reactors 3 and 4 were mechanically stirred. Reactor 3 was equipped with a turbine, reactor 4 with a flat-blade agitator. The reaction with the magnetic stirring gave poor mixing which resulted in a large amount of the undesired dienolether. The mechanically stirred reactions gave less dienolether; however, both experiments were worse than the standard reaction. This might be caused by the position of the mechanical stirrers in the test apparatus: not in the centre of the reactors but more to the side. The agitator itself was powerful enough to stir the suspension. In the commercial version of the Multimax, the agitator is centered.

Flexylab. The reactor was equipped with an anchor. This provided very good stirring: even at the end of the reaction the thick suspension remained in motion. Due to the problems with the temperature regulation (software problem), the enolether synthesis could not be performed identically to the experiments in the Automate and Multimax, and thus a comparison between Flexylab and the other apparatuses was not possible. The agitation during the reaction was very good: despite the thick suspension the whole reaction mixture kept moving.

Oxidation with Potassium Permanganate. A steroid is oxidised to its dihydroxy analogue by reaction with potassium permanganate. In this reaction, the dosing ramp of the potassium permanganate solution was thought to be critical for the conversion of the oxidation. Normally the potassium permanganate solution is added linearly. Now the following procedure was tested: 75% was dosed in the first 2 h and 25% in the last 2 h.

Automate. The dosing performed well. The yield of the reaction was considerably lower than generally obtained in production. Performance of the reaction in standard laboratory equipment (although the dosing cannot be performed as accurately as with the Automate) gives results identical with those on production scale. An attempt to verify the results of the Automate in laboratory glassware, using two different dosing rates, gave better results, however, comparable with those of the standard reaction. The lower yield obtained in the Automate procedure cannot be explained.

Multimax. The dosing was performed both linearly and in two steps. The switch to the other rate was performed well. The yields of both reactions were considerably lower than the ones performed on production scale. Also, in this case it is not clear why the yields are lower than in standard laboratory glassware or in production.

This reaction was not performed in the Flexylab.

Crystallisation of a Steroid. In these experiments a solution of a steroid in heptane is cooled from ca. 70 to 20 °C, resulting in crystallisation of the steroid.

Automate. The crystallisation was carried out using different cooling slopes, 0.5 and 0.1 °C/min, in two runs. At 0.1 °C/min no specific crystallisation point could be determined on the reaction temperature chart or in the power compensation curve. However, at the slope of 0.5 °C/min, it is clearly visible that crystallisation occurred at approximately 45°C (see Figure 4a). The crystallisation point is even more visible in the power compensation curve. This is an advantage of this system: even small temperature effects can be clearly observed due to the response of the power.

Multimax. The steroid was dissolved in heptane at 75°C, and the solution was subsequently cooled simultaneously at different ramps (0.25, 0.5, 1, and 2°/min). From the experiments it can be concluded that the cooling ramp has a profound effect on the crystallisation point. The independent temperature control of the reactors allowed a parallel performance of the reactions (see Figure 4b).

Remarks. Both the crystallisation in the Automate and in the Multimax were proven to be reproducible. The difference in melting point is due to the purity of the steroid: in the case of the Multimax experiments a higher quality was available.

The crystallisation was not performed in the Flexylab because the cooling capacity of the test apparatus was not fast enough at lower temperatures for these experiments.

Evaluation

General. All three systems are developed for the same purpose: optimisation of chemical reactions. Reactions can be performed rather easily in all systems, although the workup has to be done separately.

HEL Automate. The reactors and jackets are glass and allowed good visibility of the reaction mixture at temperature above 0 °C. The systems is equipped normally with 50-mL reactors, but it is also possible to use 100-mL reactors. The 100-mL reactors are higher, and the area above the jacket needs to be insulated when low temperatures are required.

MT Multimax. The system is very compact and clean. A disadvantage of the system is that the reactors are not visible. The magnetic ring that was originally used to fix the cap on the reactor has been replaced by a clamp. This enables the

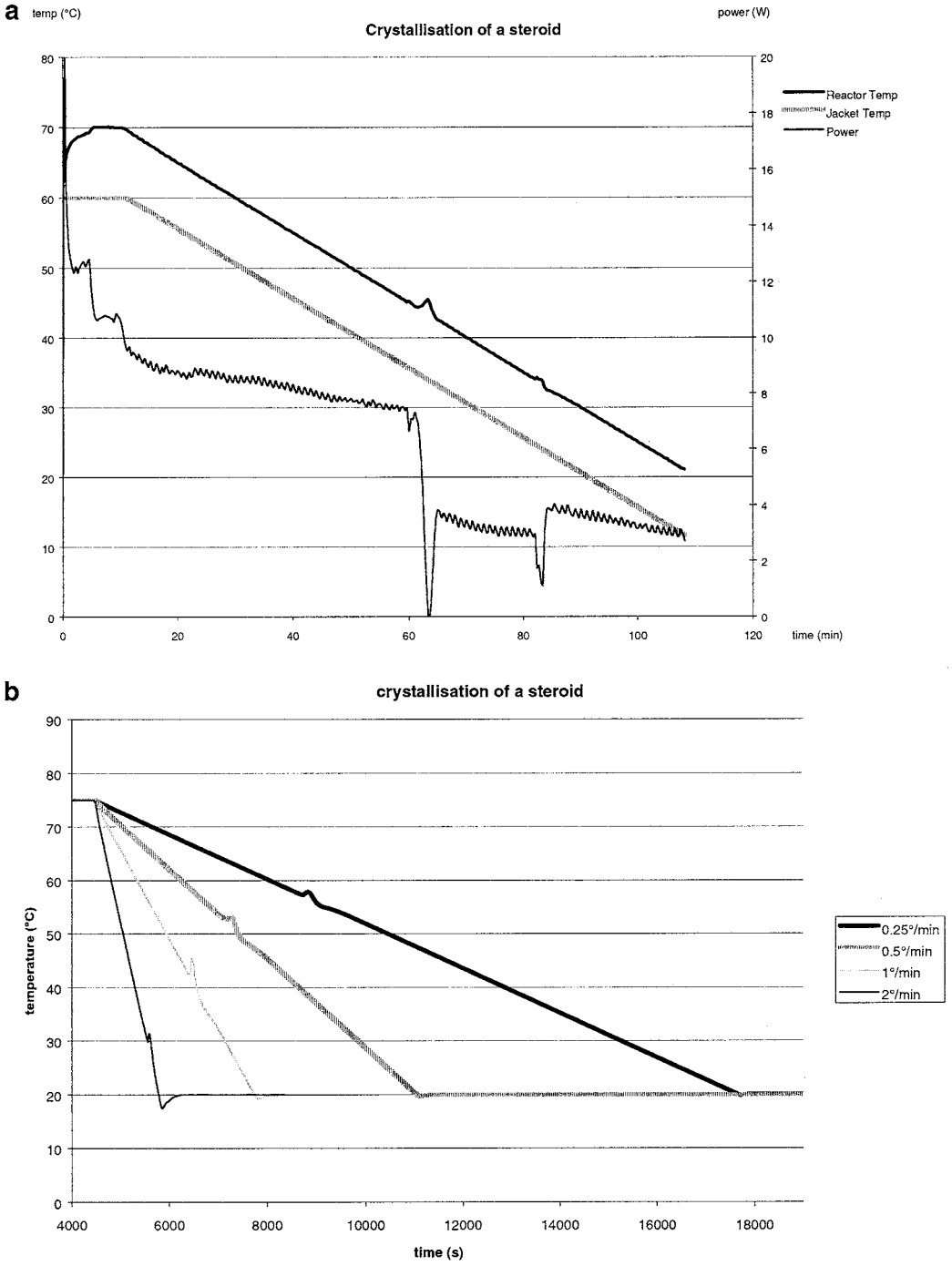

Figure 4. **(a) Crystallisation of a steroid in the Automate. (b) Crystallisation of a steroid in the Multimax.**

user to have a better look in the reactor; furthermore, the reactor can now be removed easily from the reactor box to observe the contents.

Flexylab. The system looks very compact; however, the hood will be full with four reaction blocks. The control unit is also very large, but this control unit can be placed up to 15 m from the reaction blocks. The 250 mL-reactors are large enough for the (semi-) quantitative isolation of crystals. Their size also enables the use of regular laboratory glassware. The visibility of the reaction mixture is rather poor because of the position of the vessel in the back of the platform and the design with the electric jacket. It is difficult to remove the reactors from the reaction block. Also positioning into the block is not easy. The bottom of the reactors is not flat: rings should be supplied to place the reactors outside the reaction block, for example, for filling or at the end of the reaction. The emergency button is placed in front of the reagent bottles and can easily be pushed accidentally. Pushing this button results in switching off the system: not only the heating but also the agitation stops.

Software. *HEL Automate*. The software program is very user-friendly: after a short introduction the average lab assistant is able to make a recipe and run an experiment. The time needed to program the Automate is very short. The end-criteria for each reaction step are easily adjustable and clear. The data can be shown in real time interactive graphs.

During the runtime the recipe can be changed. This is absolutely the best software in this field.

MT Multimax. The software tested was not independent per reactor and therefore not so user-friendly in our test period (April, 2001). Mettler Toledo now delivers a new version, which is comparable with the RC-1 and Labmax software and which is independent per reactor and more user-friendly. The new software is easier to work with so that after a short instruction a laboratory worker should be able to work with the Multimax. Safety settings for the temperatures were included. In case of run-aways or other problems with a reaction, one reactor can be set to its safety settings while the other reactions continue. A simulation mode has been added. The evaluation of the data is comparable with that for the new RC-1 software; it is very simple, and it generates clear graphs during measurement.

Flexylab. Reactions can be performed in the Flexylab using manual or recipe control. The software is independent for all the reactors. The recipe editor is based on Microsoft Excel. It is more difficult to program than with the other two systems. Programming is done by copy−paste basic operation blocks in the reaction phases. It is easy to introduce errors in the operation blocks, control blocks can be missed, and the function of the blocks is not always clear. Therefore, a more specialised person would be needed to control the software. The "hold" option in the software is very good: the recipe waits until the desired action is performed, and the operator continues the recipe manually. Also during a recipe, the "hold" function can be used. The graphic editor is less intuitive. The software needs some more development for our applications.

Temperature. *HEL Automate*. A single cryostat is used for all the reactors, and four different reaction temperatures are achieved by using four internal electrical heaters. However, as the reaction temperatures are thus not fully independent, this allows only small temperature differences between the reactors. Larger temperature differences might be achieved by insulation of the reactors, although this is not an elegant solution. Another solution would be the use of multiple cryostats. The electrical heater adjusts the temperature to the temperature set point. The heater has a maximal power of 20 W. In cases where the stirring is good or the reaction mixture is fully dissolved, the heater seems to have no negative effect on the reaction. In the case of a very thick suspension and poor agitation, byproducts can be formed due to the higher local temperature of the heater.

MT Multimax. The temperature control is independent for all four reactors. The reactor box is cooled by a cryostat, whereas the jacket is heated electrically. The temperatures in the reactor, in the jacket, and of the cryostat liquid are measured. The independent control allows reactions at different temperatures and different temperature slopes (e.g., in crystallisations). Next to T_r and T_j control, it is possible to use a reflux and a crystallisation mode.

Flexylab. The temperature control is independent for all the reactors. The jacket regulates the temperature in the reaction. An electric jacket is cooled by a second jacket, which is cooled by a cryostat. The gap between the condenser circuit and the electrical jacket can be adjusted by Systag, allowing different temperature ranges. In the demonstration system the gap between the two jackets was too large, however. The temperature could therefore not be regulated very well: cooling was too slow (1.5 h to lower the temperature from 20 to −5 °C), and warming from −5 to +5 °C gave an enormous overshoot in the temperature (10 °C). A different setup of the PIDs might solve this problem. The results of a properly installed system at Systag, in which the PID was adjusted, are available and are certainly much better than the results obtained by us. The temperature of the cryostat has to be 40−50 °C lower than the lowest temperature. It is possible to regulate the system in a $T_r - T_j$ mode for reflux or crystallisation; however, it is not standard and requires more experience to use.

Calorimetry. *HEL Automate*. The power generated by the heater is a measure for the process heat (power compensation). This makes it very easy and fast to obtain calorimetric data. The measured values in the case of the acetic anhydride hydrolysis are remarkably good in comparison with literature data (see acetic anhydride hydrolysis). Even small heat effects can be observed as a result of the power compensation. The accuracy of small heat effects is of course less than in a calorimeter, but the power compensation is highly useful for screening work. Due to the need for extra insulation on the larger reactors, the measurements are only reliable in the case of the 50-mL reactors. Another limitation is that the measurement does not work at reflux.

MT Multimax. The difference between T_r and T_j can be used as a measure for the reaction heat. At the moment, this is qualitative, but a calibration heater is in development. However, heat flow measurements on such small scale should be mainly used for the indication of significant heat effects and the gathering of additional information for scale-up experiments.

Flexylab. Calorimetry will be available in the future. As a measure for reaction heats the difference between T_r and T_j can be used.

Agitation. *HEL Automate*. The glass stirrers are very fragile; stainless steel or Hastelloy would be preferable (and are available). Different stirrer shapes are available. Effectiveness of agitation depends on both power and stirrer shape.

MT Multimax. Magnetic stirring is not preferred, although it works rather well for solutions. However, in the case of suspensions, the magnetic stirring fails.

The mechanic stirring works rather well. The agitators are now placed in the centre of the reactors, instead of eccentric, which gives much better agitation. Different types of agitators will be available in the future.

Flexylab. The mechanic stirrer works very well: the motor has enough power to stir very thick suspensions. The glass stirrers are available in different shapes.

Dosing. *HEL Automate*. The dosing is performed by syringe pumps. The syringes must be filled manually; for reactive reagents this is not very desirable. The dosing is well-controlled and accurate. It is also possible to use peristaltic pumps (not tested).

MT Multimax. The dispenser box works very well. It should be mentioned that sufficient reagent should be present to fill the whole syringe. This will be altered in the new software. In addition to the 10-mL syringe, a 1-mL syringe is also available.

Flexylab. The gravimetric dosing might, for example in case of gas bubbles in reagent, be more accurate than volumetric dosing. The range in flow rate of a single peristaltic pump is restricted (standard tube:1−10 g/min) and tubes with different sizes should therefore be used to adjust the flow rates. This means that the tubes have to be changed frequently. Again, this requires the operation by a more specialised person. It will be possible to use other ways of dosing.

pH Measurement and Control. *HEL Automate*. The pH could be measured well in aqueous solutions. The probes used in the demonstration system were not suited for measurement in organic solvents: the measured pH did not represent the trend observed with manual measurement using pH-indicator paper. The pH control worked very well, although rather slowly. This might be adjusted in the software. The pH control can be very easily programmed in the software.

MT Multimax. The demonstration system was not provided with pH measurement. At the time of testing only pH measurement was possible. In the newest software version a pH control loop can be easily inserted in the recipe.

Flexylab. In the demonstration system it was not possible to calibrate the pH probes properly. Therefore, the measurement and control of the pH were not tested. In the equipment and the software, options to measure and control the pH by addition of acid/base are available.

Newest Developments. All three systems are developing very fast. In this section the most remarkable improvements will be mentioned, but the list is certainly not complete.

HEL Automate. Hazard Evaluation Laboratories Limited (HEL) launched a parallel synthesis workstation incorporating the Chemscan (small-scale reactions, ∼10 mL) for screening and the Automate for process development. The system has robotic sampling. and the samples can be directly injected on HPLC. Next to the 50/100 mL Automate reactors, a 250/500 mL reactor system was developed. The temperature can now also be controlled by external electrical heaters, especially designed for heat-sensitive materials and crystallisation studies. The external heaters are built in the bottom of the reactors. Unfortunately, no data of the performance were received.

MT Multimax. The software was redesigned to be independent per reactor. Additional possibilities such as pH control and choice of termination conditions are incorporated. Next to the 2 × 2 reactor box, a four-in-line reactor box will be available for the 50-mL reactors. This new box is placed on a docking station and can then be easily interchanged with the new 2 × 250-mL reactor box or the 16 × 10-mL reactor box. MT also developed a robot platform which enables automatic sampling of the reactors. The samples can be diluted and injected directly on HPLC.

*Flexylab***.** Systag developed a fast-tracking system in addition to the current system. The system has been improved significantly, according to communication with Akzo Nobel Chemical Research Arnhem.

Conclusions

Three automated workstations are commercially available for parallel synthesis: HEL Automate, MT Multimax, and Systag Flexylab. All three systems can be used to develop and optimise chemical processes. In general normal manual laboratory equipment is used for the development and optimisation of chemical processes. However, the automated workstations provide a lot more information because process parameters such as reaction temperatures and pH can be easily measured and recorded during the reaction. Furthermore, the process parameters can be controlled precisely due to the automation. Development times can be reduced because four reactions (in the normal setup) can be run at the same time, and as a consequence of the use of recipes, reactions can be performed 24 h a day. A second advantage of the use of recipes is the reproducibility of the experiments.

The three automated workstation were tested in our laboratories. Each of the systems has its strong features; depending on the kind of chemistry, one of the systems is preferable.

The main advantages of the HEL Automate are the very user-friendly software, the visibility of the reaction mixture, and the fast calorimetric data. The nonfully independent temperature control and the use of the internal electrical heater are, however, not favourable in all kinds of chemistry.

The Multimax has a completely independent and very accurate temperature control. Dosing by the dispenser box to all four reactors is also an advantage. At the time of testing, some features still had to be developed in the software, such as pH- and temperature-controlled dosing.

The Flexylab requires more specialised operators but has more degrees of freedom in creating chemistry-dependent recipes. The larger size of the reactors enables the quantitative isolation of crystals. Both the hardware and software need some more optimisation, but the system has large possibilities.

The developments in these systems are going very fast. Much of the points of criticism written here may have been overcome at the time of publishing. An important lesson for us was that working with a system gives far more information than just looking at it.

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