Some of the world’s foremost medications have been developed by AstraZeneca, which holds a leading position in the global market within the therapeutic areas oncology, cardiovascular, gastrointestinal, neuroscience, respiratory, and inflammation. The Group has 60,000 employees and sales that totaled USD 18.8 billion in 2003.

One of three Swedish sites within AstraZeneca R&D is located in Södertälje, south of Stockholm. Of its many employees, around 350 people work here in preclinical research developing new drugs that will ensure the future of the company. One of them is Dirk Weigelt, who is responsible for a team in Compound Collection Enhancement within Discovery Chemistry.

“Our reality is constantly changing,” says Dirk Weigelt. “For example, we clearly feel the growing demands for efficiency, especially over the past two years. In reality this means that we have to step up the pace of development, in part by using better and faster equipment.”

Dirk’s group works on developing new active substances that can then be developed into active medications. Similar substances are collected in libraries, which often consist of 480 substances that are synthesized simultaneously. The production phase for each library can take from a couple of days up to two weeks.
Large MiniBlock shaking station for maximum six reactor blocks. The reactor blocks are connected by the insulated hoses to a recirculator for temperature control of the reactions.

Organic chemists Andreas Petersson and Magnus Waldman, preparing a library synthesis with six 48-position MiniBlock reactors on a large shaking station. In total 288 compounds can be synthesized in one run.

As part of its efforts to increase efficiency, in 2000 AstraZeneca R&D in Södertälje bought its first six MiniBlocks, equipment for chemical synthesis from Mettler-Toledo. MiniBlock is the only compact equipment for parallel synthesis in which synthesis via solid phase or liquid phase and purification can take place on the same platform. The results were quickly measurable and today the Group uses 64 MiniBlocks, often up to ten simultaneously.

“MiniBlock enables us to run much larger volumes than previously, when we used ordinary 96-well microtiter plates”, says Dirk. “The equipment also allows us to filter, and to both heat and cool the reaction solutions. It’s also good that it’s easy to use and that the benefit is so clear for users, since the increased productivity is so obvious.”

So what are the numbers that describe AstraZeneca’s increased productivity? Understandably, Dirk Weigelt chooses his words cautiously; much information is not released for business-critical reasons. “But it’s no secret that in 2003 each chemist handled six times as many syntheses as in 2002 and that in 2004 we doubled our efficiency. Both quantity and quality have improved and it is clear that MiniBlock played an important role in this achievement.”

Dirk’s group was the first to use MiniBlock at AstraZeneca in Sweden. Today many others have followed suit.

“Being the first with new technology at a company means you have to deal with some growing pains, related to both the equipment and the internal procedures,” says Dirk. “In the beginning, for example, we had a problem with leakage, but we solved it together with Mettler-Toledo. In response to our feedback they came back with improved products and this is indeed a development that benefits both parties,” he says.

MiniBlock XT and XT-Plus

In AutoChem News No 1 2004, new reaction block MiniBlock XT was more closely introduced. MiniBlock XT has now been further developed and provided with new appliances.

**The XT-Plus** is a unique reaction block with built-in liquid circulation allowing temperature control using a standard heating and cooling recirculator.

The XT-Plus allows:
- Heating and cooling of reaction vessels in one step, with a single connection.
- Allows precise temperature control, while taking advantage of temperature ramp up, and other recirculator features.
- Small Footprint, which makes the XT-Plus the most compact and space efficient reaction block in its class.

**MiniBlock, XT, XT-Plus**

The Purge / Evap Manifold is a cost effective solution for evaporating solvents using MiniBlocks and XT Reaction Blocks. The Purge / Evap Manifold allows you to:
- Evaporate off solvents right in your fume hood, without changing any parts, moving reaction vessels or moving racks.
- Efficiently removes solvents with heating while using moderate air or nitrogen flow rates.
- Perform reactions under inert conditions for chemistries involving ultra-sensitive air and moisture reagents and reactants.

Compact design requires no additional fume hood space. The manifold enables reactions to be maintained under inert conditions, and provides efficient evaporation capability. Robust design maximizes gas flow, enables efficient purging, and provides superior inerting capability. Internal and external components are designed to withstand aggressive solvents and reagents.
LabMax – a single reactor system for automation of lab syntheses

LabMax is a computer-controlled, automatic lab reactor – a complete single reactor system for 24-hour operation in chemical research, kilogram, scale-up and product development labs. A modern graphical user interface allows experimental instructions and parameters to be entered and the current reaction to be continuously monitored.

Advantages
- Improves the development process
- Increases lab capacity through automatic, unattended operation
- Outstanding reproducibility
- Efficient and precise process optimization
- Mimics conditions close to those in production
- Improves safety at the workplace
- Experiment is comprehensively and clearly documented

Direct communication from ALR to real-time analytics
By using WinRC for LabMax v 7.3 it is possible to directly connect the Automatic Laboratory Reactor system to an associated analytical tool such as FBRM, Raman or ReactIR and exchange online data between the two instruments for control and evaluation. This is managed via the TCP/IP network interface, which allows up to 30 curves to be transmitted to the reactor software.

By defining the analytics as a series of additional measured values of the reactor, the analytical data may be displayed directly on screen along with the ALR data, and in addition be used to fulfill terminating conditions that control the execution of the ALR experiment.

LabMax 2 litre reactor.

Real-time melamine formaldehyde reaction monitoring

Melamine formaldehyde resins are widely used in commercial applications such as impregnation resins for decorative laminates. The characteristics of these resins such as storage stability and impregnation behaviour are related to their chemical structure. Typical analytical tools such as HPLC and 13C NMR require sample removal and introduce time delays of up to two hours. In-situ analysis of the reactions in real time and under actual reaction conditions is now possible with the development of the ReactIR™ reaction analysis system. ReactIR™ offers high sensitivity and allows monitoring of key reaction species, kinetics and reaction endpoints without calibration.

This Note presents results using the ReactIR™ in-situ FTIR system using a DiComp™ diamond probe to monitor the key melamine for-maldehyde functional groups in real-time and has been executed with cooperation between DSM Melamine and ASI Applied Systems Inc.

Primary methylolation
\[ M - \text{NH}_2 + F \rightarrow M - \text{NH} - \text{CH}_2\text{OH} + \text{H}_2\text{O} \]

Secondary methylolation
\[ M - \text{NRH} + F \rightarrow M - \text{NR} - \text{CH}_2\text{OH} + \text{H}_2\text{O} \]

Methylene bridge formation
\[ M - \text{NRH} + M - \text{NR}^1 - \text{CH}_2\text{OH} \rightarrow M - \text{NR} - \text{CH}_2 - \text{NR}^1 - M + \text{H}_2\text{O} \]

Methylene-ether bridge formation
\[ M - \text{NR} - \text{CH}_2\text{OH} + M - \text{NR}^1 - \text{CH}_2\text{OH} \rightarrow M - \text{NR} - \text{CH}_2\text{O} - \text{CH}_2 - \text{NR}^1 - M + \text{H}_2\text{O} \]

MF chemistry
Melamine formaldehyde (MF) chemistry starts with the dissolution of melamine in formalin, a process that is driven by the methylolation reaction, in which both primary and secondary methylols are formed. For melamine nine different methylolmelamines can be formed and the final mixture of methylolmelamines formed is determined by the formalin to melamine ratio. In the second stage of the resin synthesis the (methylol) melamines condense into methylene and methylene-ether bridges. The type and amount of bridges that form, depend on the reaction conditions, eg, F/M ratio, solid content, initial pH of the formalin, temperature, etc.

Real time MF reaction monitoring
The reactions were carried out in the METTLER TOLEDO LabMax™ automated laboratory reactor which provides full, precise and accurate control of the reaction conditions (temperature, pH dosing,
stirring, torque monitoring etc). The reactions were analysed using a ReactIR™ equipped with a DiComp™ ATR insertion probe which offers unrivalled physical and chemical robustness. The full laboratory set up is shown in Figure 1.

In the study, various MF resins were made with different F/M ratios and initial pH. In all cases, melamine was added to formalin in the vessel followed by a temperature ramp to 90°C at 1.5°C/min. The reaction exotherm can be seen in Figure 2. The ReactIR studies the C-O stretching vibrations of the methylolyl groups being formed at 1200 cm⁻¹ (Figure 3).

Variations in the melamine/ formalin ratio affect the relative concentrations of primary and secondary methylol groups and these can be determined by analysis of the ReactIR spectral data.

In highly complex or overlapped spectra, either 2nd derivative or ConcIRT (Concentration-in-real-time) can be applied. ConcIRT uses sophisticated factor analysis to automatically extract spectral and relative concentration data without any calibration. Figure 3 shows the highly complex nature of the spectral data.

Figure 4 shows the second derivative spectra during the resin synthesis prepared from F/M 1.7 and an initial formalin pH of 9.5. The changes around 1200 cm⁻¹ are assigned to different C-O groups: primary methylol groups, secondary methylol groups and methylene-ether bridges. The band at 1340 cm⁻¹ is attributed to the twisting vibration of the methylene groups in the methylene bridges.

For this reaction, ConcIRT® yielded 5 component spectra, which were assigned to species with primary methylol groups, secondary methylol groups, methylene bridges, methylene ether bridges and formaline. The corresponding generated infrared profiles for these compounds shown in Figure 5 are in line with the fundamental kinetics of these resin systems. (VD)

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