PEER REVIEWED

Mitigating Risk Roche's Approach to PAT Implementation in a Sodium Borohydride Product

Roche Ireland is a manufacturer of active drug substances. Many compounds are synthesised from raw materials in multi-batch and multi-ton quantities over extended time periods. The repetitious nature of the multi-batch business has proven a rich source of opportunity for process analytical technologies (PAT) applications at Roche, for over 15 years in some cases. The key focus has been the integration of the PAT applications into the existing manufacturing systems such as automation, IT, QC, QA, maintenance and R&D, to mitigate risk and improve process efficiency. This case study specifically looks at the approach to PAT implementation on one such process with a sodium borohydride reduction.

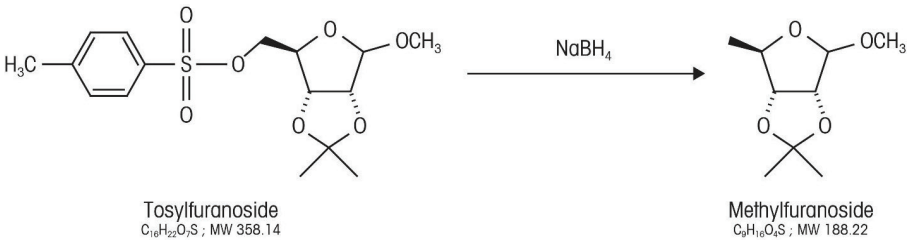

Figure 1. Reaction Scheme

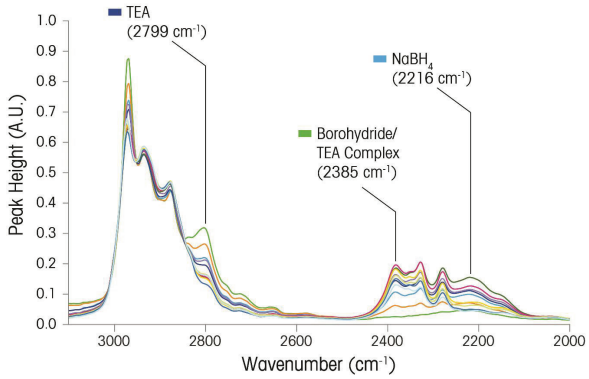

Figure 2. Mid-IR spectra observed following the aliquot additions of sodium borohydride in a laboratory reduction experiment.

The Opportunity

Methylfuranoside is a starting material in the synthesis of an anti-cancer drug, manufactured on a large scale in Ireland. The manufacturing of the methylfuranoside involves a hazardous reduction of the thermally labile tosylfuranoside with sodium borohydride reagent as shown in Figure 1.

The reaction is carried out near 80 °C with hydrogen gas evolution, foaming, and the precipitation of tosylate salts. The sodium borohydride is converted to a borohydride-triethylamine complex during the reaction, with the temperature strictly maintained at less than 90 °C due to the thermal instability of the tosylfuranoside. Unreacted sodium borohydride (up to 20 % by weight) accumulates naturally during the reaction.

Safety First

In the original process for the reduction of the tosylfuranoside to methylfuranoside, the sodium borohydride was added to the reaction in 15 kg aliquots as a safety measure to reduce the risk of excessive sodium borohydride accumulation. The reaction of the borohydride was confirmed by the heat-spike/temperature rise observed after each addition. The next aliquot of borohydride was only added when the reaction temperature had fallen to a predetermined level.

The Problem

In a new optimised process, the heat-spike which signalled the reaction initiation had been observed in the laboratory during process development, but not to the same extent as found at production scale. The lack of a reliable heat-spike in the new process is related to the levels of isopropanol solvent entering the reaction with the undried tosylfuranoside. After risk assessment, it was decided that an alternative risk mitigation solution was required before the new process could be used.

A PAT Solution

Mid-IR had been used in the laboratory to investigate the original process (during technology transfer), and in the development of the new process. The reaction of the sodium borohydride could be followed in great detail using inline Mid-IR without interference from the evolved gas, foaming, and precipitated sodium tosylate (Figure 2).

ReactIR™ was equipped in the laboratory with a silicon crystal (SiComp™) ATR probe and a K4 light-guide in order to detect the borohydride peaks which occur above 2000 cm-1, and to achieve optimum sensitivity. Each of the key reaction steps are clearly detected by the Mid-IR system. These key events include the sharp increase in the dissolved sodium borohydride peak at 2216 cm-1 after each aliquot addition, the subsequent slow decrease in the sodium borohydride peak and triethylamine peak at 2799 cm-1 as they react, leading to an increase in the borohydride-TEA complex peak at 2385 cm-1, and reduction of the tosylfuranoside peak at 1600 cm-1.

PAT Implementation

All PAT solutions start as feasibility studies; a positive outcome of a

feasibility study can lead to a business proposal. The business case decision is made with reference to all aspects of the drug substance manufacturing business including safety, return on investment (ROI), site development, regulatory impact, etc.

In-process Mid-IR was investigated for use as a possible process safety risk mitigation technology, which was proven and accepted. Extensive risk assessments, FMEA, HAZOP, LOPA, etc. were carried out to ensure the revised process would deliver the product safely. The Mid-IR system was installed in October 2012, and has been operating continuously and successfully since (Figure 3).

Figure 3. Installation of the METTLER TOLEDO ReactIR 45P system at the bottom of the Tosylfuranoside reduction vessel (15,000 L). Mid-IR operation is continuous 24/7.

Seeing the Chemistry

Mid-IR is ideally suited as a PAT tool. It provides readily interpretable spectra with peaks directly associated with specific chemical components. It is rugged and relatively immune to physical interferences caused by bubbling and particulates, which severely impact the measurements from other spectroscopic techniques. Mid-IR is almost universally applicable to all chemistries, both inorganic and organic, and provides both quantitative and qualitative information on the chemicals as they change in response to the physical processes applied to them.

All PAT Data is Useful

Figure 3 shows the installation of the in situ Mid-IR directly into the borohydride reduction vessel. The recycling of the reactor contents during the borohydride addition was not an option because of safety reasons, in particular possible line blockages.

The instrument is cooled with instrument air and the light-guide is flushed continuously with process nitrogen (cryogenic, oil free). The instrument is controlled by dedicated METTLER TOLEDO iC process control software, and integrated with the manufacturing DCS process control system. The Mid-IR process data is delivered to the site process information (PI) database, and integrated with all process data for general access. The instrument is permanently on and acquiring spectra continuously. As a general rule, the changes observed in the spectra of the Mid-IR can be correlated to the changing conditions in the reactor, such as filling and emptying at the beginning and end of the reaction, and during solvent washes and reactor cleaning. The responses of the Mid-IR to process change can be used to evaluate and confirm the operational status of the PAT system.

Match the Probe to the Process

Figure 4 shows the Mid-IR spectral data translated into changes in the relative amounts of some of the chemical components during the borohydride addition and the reaction. The rapid increase in the sodium borohydride (light blue) in the solution is always followed by a slower exponential decay in the borohydride peak as it reacts. The decrease in the borohydride peak coincides with the previously seen heat-spike. This decrease also coincides exactly with a dramatic decrease in the triethylamine peak (orange) and the tosylfuranoside peak (green). The increase in the borohydride–triethylamine complex (dark blue) is less dramatic, but follows closely the reaction of the borohydride. The reaction proceeds with the same profile as each aliquot is added, but with the accumulation of more borohydride after each addition. After the last aliquot is added, the reaction is aged.

Process Knowledge Must Lead to Process Control

In the single isolation process, the *in situ* Mid-IR showed an unexpectedly large decrease in accumulated sodium borohydride during the reaction age, which was not observed in the original process. This disappearance of the accumulated borohydride during the age was also associated with persistent gas evolution and foaming. There was little or no foaming or gas evolution observed during the aging in the original double isolation process. Further Mid-IR studies in the laboratory have shown that an isopropanol (IPA)-borohydride complex is formed during the reaction. The IPA solvent from the undried tosylfuranoside reacts further with the unreacted borohydride, and also with the borohydride-triethylamine complex during the age (higher temperature) liberating hydrogen and triethylamine. The reaction completion and downstream processing proved problematic in the initial batches from the single isolation process. The loss of accumulated sodium borohydride as evidenced by the Mid-IR was key to understanding

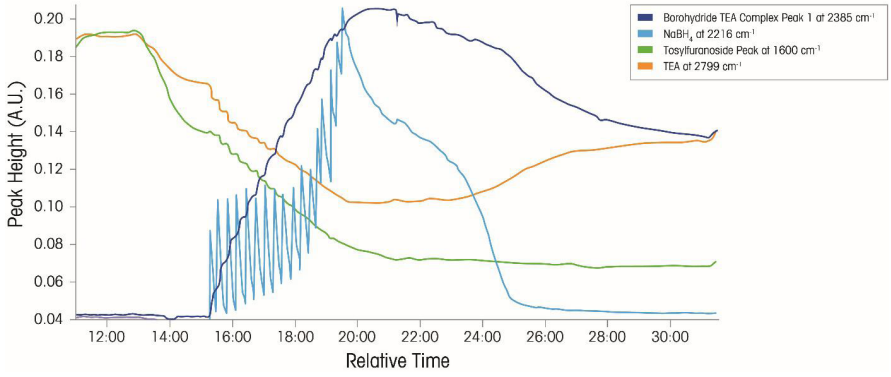

Figure 4. Mid-IR trend data for output to the process control system (PCS) and the process information (PI).

the root cause of these process problems. The in-process Mid-IR system was instrumental in providing a solution to the process problems. The goals for throughput, plant usage, and manpower were achieved within a few weeks.

Eliminate the Sample

At the end of each borohydride reduction, the batch is physically sampled to confirm reaction completion. This sampling involves the recycle of the thick reaction slurry through the reactor recycle loop (acceptable levels of tosylfuranoside at this stage). If the sample completion check fails, then the batch is heated further to effect completion. A safety sample is also taken at the start of the reduction reaction prior to borohydride addition, to ensure that sufficient triethylamine is present.

Early in the original double isolation process it was found that failed completion checks were caused by small amounts of residual tosylfuranoside left in the recycle loop after the initial safety sample. This problem was solved in the double isolation process by recycling the reaction mixture through the recycle loop toward the end of the reaction age in order to bring any unreacted tosylfuranoside into the vessel, to react it with the excess sodium borohydride still present in the reaction. However, in the new single isolation process, up to 20 % completion check failures were observed even when this recycle was carried out. The Mid-IR clearly showed that in the new process there was little or no unreacted borohydride remaining by the time the recycle operation was carried out. It was considered an unacceptable change to recycle the batch earlier in the reaction. It was decided to replace the initial physical safety sample with an in-process Mid-IR measurement of the triethylamine level in the vessel (Figure 5). This approach was successful and eliminated all completion check failures.

PAT Sustainability

Figure 6 shows the yield improvement and batch consistency since implementing the new single isolation process supported by in-process Mid-IR and QC-PAT. The average yield increased from 69 % to 77 %. The elimination of the completion check failures was a contributor to the improved yields through the elimination of prolonged age times. The single isolation process delivered the throughput increase of four batches per week, (instead of 2.5/ week) with zero failed batches (25 % failure rate before QC-PAT).

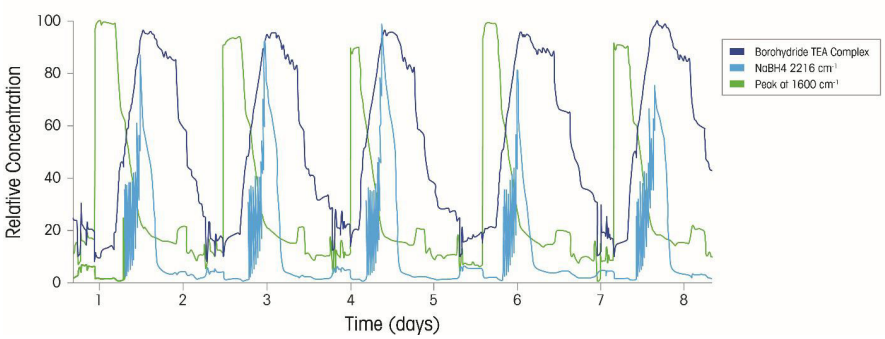

Figure 5. A typical borohydride reduction reaction Mid-IR trend over a one-week period demonstration of the rhythmical nature of the process from batch to batch.

Since the new process started, over 200 successful batches have been completed with zero failed batches since the introduction of the QC-PAT virtual sample at batch 60. The new process led to an improvement in manpower by going from an eight-person operation per shift to a six-person operation. In addition to much-improved worker safety, the implementation of the new process achieved a reduction in mass intensity (i.e. all materials used in the synthesis of the product) of 15 % (primarily from a 3000 L reduction in solvent per batch).

The Mid-IR has been used for additional MeF (methyl furanoside) campaigns over two years. The system has performed well over that time, requiring only preventative maintenance/ calibration and yearly IQ/OQ. The PAT system is fully integrated into manufacturing operations, the IT network, and QC procedures. The direct benefits from the single isolation process have been further consolidated:

- 8 % yield increase
- 15 % reduction in mass intensity factor (all materials used in the process)
- 25 % reduction in equipment
- 40 % reduction in manual handling operations
- Elimination of significant site safety risk by removal of drying step
- 14 % improvement in production reliability
- € 60,000 reduction in energy costs per campaign
- Use of PAT to:
  - Continuously monitor the reaction to ensure process

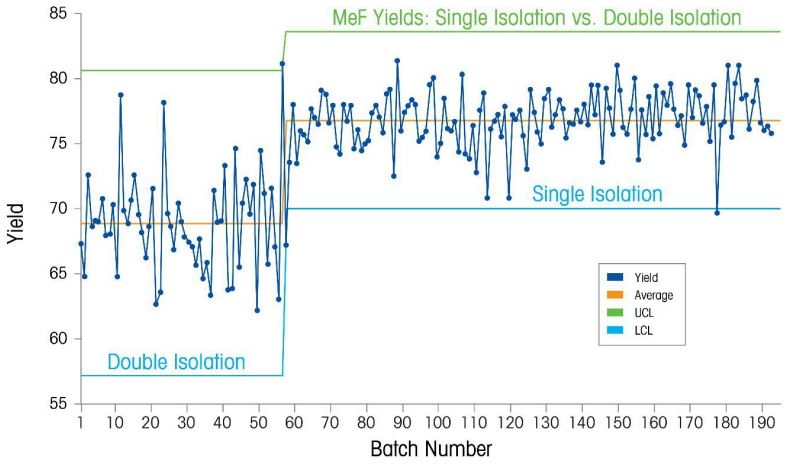

Figure 6. Benefits of new single isolation process.

safety
- Eliminate IPC failures
- Eliminate physical QC sample
- Reduce exposure risk to a hazardous material
- Implement the new process safely
- Increase process understanding

- This process change resulted in an overall favourable profit impact of € 3.8 million in one year vs. target due to yield and throughput improvements.
- The single isolation process recently received Roche global green chemistry and innovation awards.

The Future for PAT at Roche Ireland
Bridging the Gap Between QC and Real-time Process Control

QC-PAT moves the QC function closer to the manufacturing process and closer to real-time process analysis. QC-PAT provides an independent expert evaluation of PAT raw data using proven analytical methodologies. QC-PAT verifies the quality of PAT raw data, upon which process decisions may be made in real time. An interesting feature of the QC-PAT concept is the possibility that a QC-PAT virtual sample analysis required by the production site may be performed by any QC-PAT individual from any other location, no matter how remote they may be. This feature may be of interest to those sites where the availability of analytical support is limited in number or even restricted to particular times.

Toward Continuous Process Verification

The borohydride reduction described here is a striking example of the effect PAT can have on an individual chemical process, and on the systems and organisations required to carry out that process. The ability to "see" individual chemicals non-convoluted with other chemistries as they progress along a desired reaction path in a complex reaction mixture using in-process Mid-IR is a tremendous advance in PAT. This is in contrast to the traditional manufacturing approach where we infer the process path by reference to external process parameters such as temperature and pressure, and then verify the process performance much later through downstream analysis. For the process discussed here, it is planned to define the relative kinetics of the reaction and to monitor the chemical path followed by each chemical component in real-time batch reactions using the in-process Mid-IR. The adherence of the chemistry to the desired reaction path may be defined as a process quality (PQ) parameter.

It is hoped that through such continuous process verification efforts, the requirement for downstream analysis will be reduced or even eliminated, and that a given minimum acceptable value of PQ may be specified for a process. Downstream QC analysis will not be required for values above the specified PQ, only for batches where the PQ value is below the specified value.

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