Application Note

Mitigating Risk: $NaBH_4$ Reduction

Enhanced Safety via Inline PAT

Roche

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Read the full white paper at **www.mt.com/PAT-Roche**

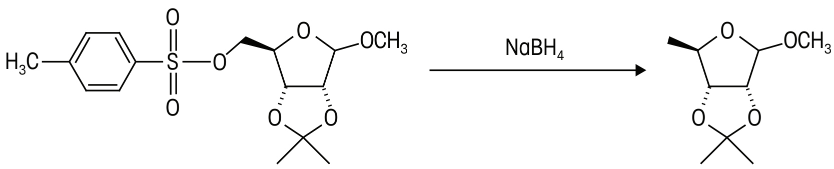
Sodium Borohydride Reduction: A Sustainable PAT System for Safe Operation

Methylfuranoside is a starting material in the synthesis of the anticancer drug Xeloda®. It is manufactured at large scale in Roche Ireland. The manufacture of methylfuranoside involves a hazardous reduction of the thermally labile tosylfuranoside with sodium borohydride reagent.

As a result of improving the chemistry for better efficiency (i.e. eliminated the original double-isolation of tosylfuranoside required prior to reduction), the original control method of measuring the heat spikes associated with each 15 Kg aliquot addition of $NaBH_4$ were no longer detectable by thermocouple. A new method of control was then required, or revert back to the less efficient double isolation method.

Figure 1. Picture of the process ReactIR 45P at the bottom of the tosylfuranoside reduction vessel (15,000 L). Mid-IR operation is continuous 24/7. Photo courtesy of Roche Clarecastle, Ireland.

Figure 1 shows the successful installation and implemention of process FTIR as the control mechanism for real-time, safe means of detecting and monitoring the progression (kinetics) of the $NaBH_4$ reduction to the desired intermediate of the API, Xeloda.



Tosylfuranoside
$C_{16}H_{22}O_7S$; MW 358.14

Methylfuranoside
$C_9H_{16}O_4S$; MW 188.22

METTLER TOLEDO

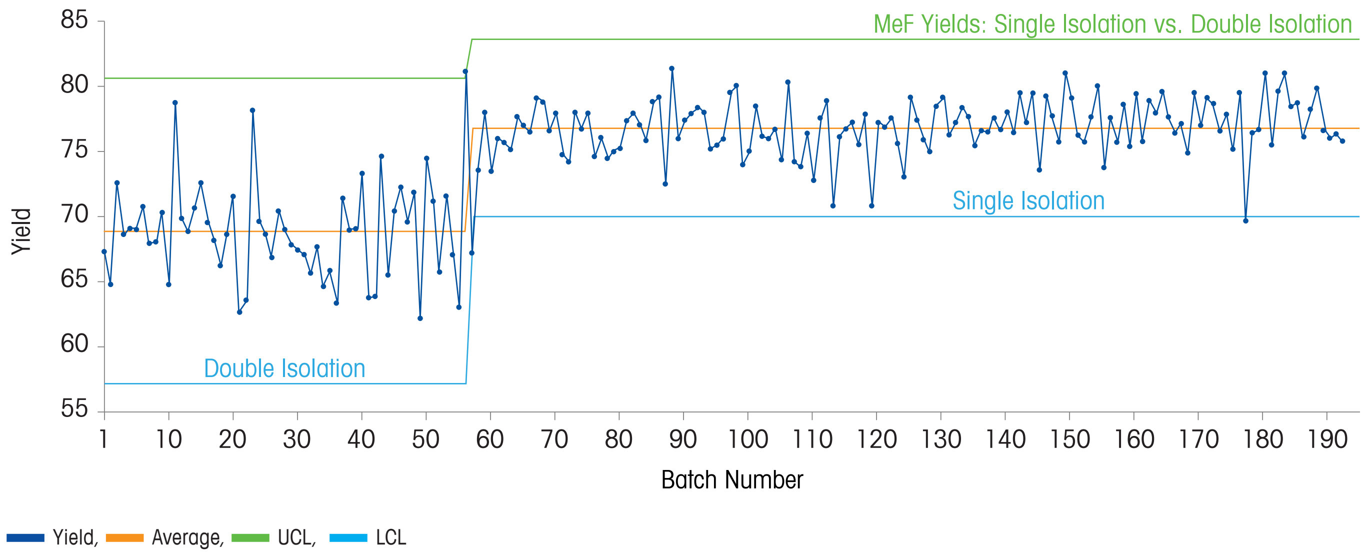


Figure 2. Process improvement (% yield/batch number) before and after implementation of in-line FTIR control.

Results

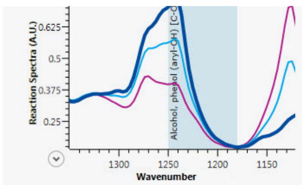
The reaction completion and downstream processing proved problematic in the initial batches from the single isolation process. In this new process the *in situ* Mid-IR showed an unexpectedly large decrease in accumulated $NaBH_4$ during the reaction age, resulting in gas evolution and foaming. Further, Mid-IR studies showed that the IPA solvent from the undried tosylfuranoside reacts further with the unreacted borohydride and the borohydride-triethylamine complex during the high temperature age, liberating hydrogen and triethylamine. The loss of accumulated sodium borohydride as evidenced by the Mid-IR was key to understanding the root cause of these process problems.

Conclusions

The in-process Mid-IR system was key in providing a solution to the process problems. The goals for throughput, plant usage and manpower were achieved within a few weeks resulting in yield improvement (Figure 2), zero batch failures, decrease from eight person operation to a six person operation, reduction in manual handling (safety), and an annual profit impact.

ReactIR: Real-Time Reaction Mechanisms

In Situ Reaction Monitoring
Monitor chemistry as it takes place to achieve optimal reaction mechanics for a safer and more efficient process.



Comprehensive Reaction Information in Real Time
Detect and monitor instantaneous changes (initiation, endpoint, process deviation) that are otherwise difficult or impossible to detect via offline methods.

Reaction Kinetics, Pathway and Mechanism
In-depth understanding of reaction mechanism for process efficiency, robustness and safety.

Applications of ReactIR include:

- Reaction Kinetics
- Flow Chemistry
- High Pressure Reactions
- Polymer Synthesis
- Energetic Reactions

www.mt.com/ReactIR
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