

CQS Innovation, Inc.

Automatic Titration for Pharmaceutical Intermediates

- Eliminates product rework and rejection
- Improves cycle time
- Reduces process variability
- Frees operators from tedious work



Automation of common tasks saves time, effort and avoids process upsets.

BACKGROUND

A pharmaceutical manufacturer was experiencing yield and quality problems related to a processing step that neutralizes acidic solutions. The existing process control system was not able to meter caustic solution with enough precision to reliably hit a pH target. The consequence was rework and rejection of many small product batches.

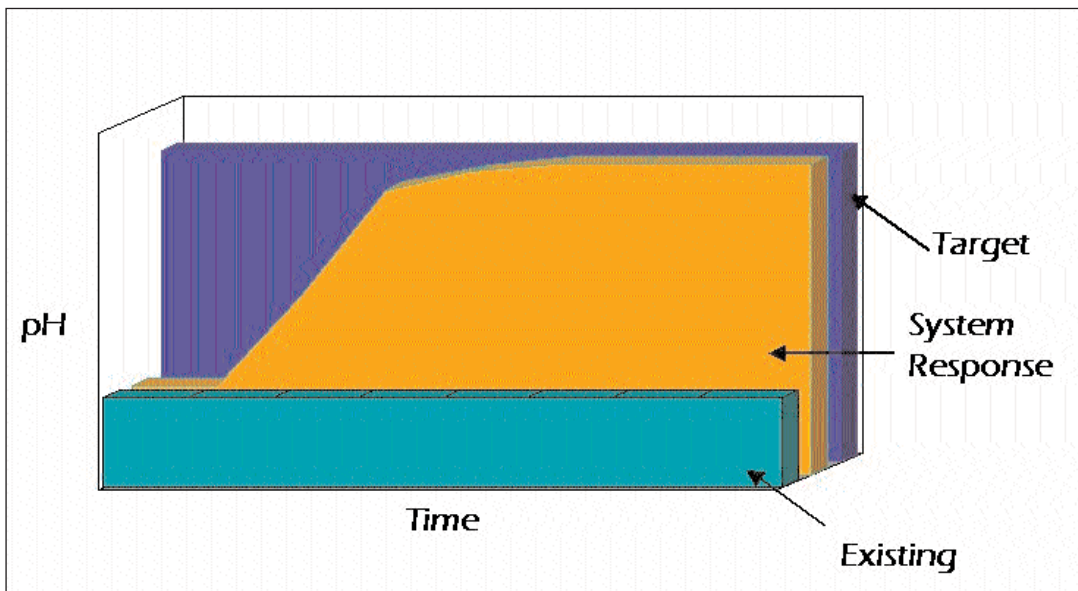
The manufacturing process for pharmaceutical injectables begins with mixing pre-weighed solids and ultra-pure water in a portable tank. The resulting solution is usually quite acidic and must be neutralized by addition of a caustic agent. This titration step was jeopardized by deficiencies in the existing process controller. Controller overshoot and locally high concentrations of caustic compromised the product solution quality.

CQSI engineers investigated the situation, determined the causes of failure, and helped identify an appropriate solution. A CQSI project team was engaged to specify, design, build, and deliver a mobile system. They also participated in system qualification based on the detailed document set produced during system development.

CHALLENGE

Small batches of product are easily damaged by excess caustic. This can result from adding too much neutralizing agent or from introducing neutralizing agent so quickly that locally high concentrations of caustic are produced. Poor mixing can compound the problem by introducing pH measurement time lags and "noise".

One obvious solution is to slow the caustic addition rate. Unfortunately, imposing an addition rate that prevents overshoot in very small batches would dramatically increase the cycle time of every batch. A variable titration rate, based on the batch size, the pH adjustment rate, and the pH offset from target, is needed to reduce cycle time while positively preventing product damage.



Automatic titration improves control of the process.

SOLUTION

CQSI developed an automatic titration system to reliably add caustic neutralizing agents to any mixing tank. The system executes a special control algorithm that introduces the solution at an optimized variable rate. The product intermediate quickly reaches the target pH value without any overshoot.

To use the new system, the operator simply moves the titration system cart to the product tank, connects the adjustment solution delivery hose, inserts the pH probe, and supplies power. The system prompts the operator to enter the batch size and target pH. Once these parameters are entered and the titration sequence is initiated, the operator can step away and let the system complete the titration automatically.

A peristaltic pump, located on the system cart, meters the neutralizing agent from a scale-mounted container into the product mixing tank. Based on the batch size value entered by the operator, the titration system controller limits the addition rate to prevent locally high pH concentrations. As the target pH value is approached, the controller gradually reduces the addition rate to prevent pH overshoot.

Once the product solution pH is above the lower control limit, the titration sequence completes. The system returns to a manual addition mode that permits the operator to jog the metering pump, if necessary.

RESULTS

The new automatic titration system is easy to use, accurate, and maintainable. Significant time and money savings have been realized both in initial manufacturing labor and in the reporting, investigation, and correction of processing errors.

- Product damage resulting from caustic overdosing is eliminated by the system's advanced control algorithm.
- Locally high concentrations of caustic are controlled by batch size compensation.
- The titration system can operate unattended, freeing the operator for other activities.
- Qualification was accelerated by complete and accurate documentation of a well-designed system.
- The CQSI system is constructed of configurable, off-the-shelf components to ensure maintainability.
- Batch rework and lot rejection are greatly reduced.

Making your manufacturing world-class

From plant-wide systems to customized solutions for specific needs, CQS Innovation, Inc. has the experience in automation systems to meet your project's goals.

For more information on how our integration of computer systems, controllers, networks and software systems can improve your manufacturing site's product quality, production flexibility and quality-control tracking, call (800)860-1968, ext. 385.



CQS Innovation, Inc.
 2390 Pipestone Road
 Benton Harbor, MI 49022
 Tel: (269)926-2148 FAX: (269)926-6854
 Website: www.cqsinnovation.com