Abstraction

This paper describes a method for automating CIP validation analysis of both conductivity and TOC. This is achieved by integrating a reagentless direct conductivity online TOC analyzer with a modern mobile Cleaning-in-Place module for real-time cleaning verification. The ANATEL A643a online TOC analyzer provides both real-time conductivity and real-time TOC results for the CIP unit, providing rapid approval of cleaning processes and subsequent release of the production equipment for manufacturing. The potential cost savings described include material costs, labor costs and reduction in downtime. By integrating online TOC into the CIP system, the pharmaceutical vessel being cleaned can be returned to production more rapidly and efficiently and with greater reliability.

Introduction

The use of online total organic carbon (TOC) analysis for real-time cleaning verification represents one of the first major technological advances in Cleaning-In-Place (CIP) processes and CIP equipment designs within the pharmaceutical industry in many years. Previously, the pharmaceutical industry relied on industry guidelines that specified processes and CIP equipment designs that were conceived within the dairy industry in the 1950’s and used essentially without modification. Outdated traditional CIP designs are based upon the “clean-until-clean” approach, using static spray balls, single stage centrifugal pumps, large buffer vessels dedicated for chemicals and rinse water, and remote CIP return pumps with large diameter CIP supply and return lines. These traditional CIP designs relied exclusively on increasing chemical concentration and time/volume of water (rinse until clean). This has led to ineffective, inconsistent and wasteful CIP processes. However, new CIP technologies are based upon a decentralized batch concept that provides the highest degree of process control and flexibility. The advent of new, modern mobile CIP skids equipped with real-time process instrumentation such as online conductivity and online TOC analysis allows for designs that provide a system with improved cleaning consistency, higher cleaning quality, substantial resource savings (water, electricity and time), and require much less manual labor.

Although laboratory TOC analyzers are ubiquitous in the pharmaceutical industry, many companies are now realizing the advantages of online TOC measurements for pharmaceutical water production. Online TOC has the principal advantage of providing nearly instantaneous results, while eliminating sampling errors common with the laboratory practice. However, until recently it has been difficult to apply online, reagentless TOC...
Analyzers to CIP applications owing to the wide dynamic range of TOC values present. Most reagentless TOC analyzers are unable to measure TOC values greater than 2000 – 2500 ppb without overloading the system. This presents a significant challenge in the CIP application since initial TOC values can be much higher at the onset of cleaning. In this paper we describe a process that avoids the overloading problem, and allows a simple, low-cost reagent-free online TOC analyzer to be used in CIP applications.

PROCEDURE

Currently, a typical standard operating procedure (SOP) for checking the success of a cleaning process is to rinse the vessel for a period of time sufficient to reach a predetermined conductivity level as determined during the validation process. Next, grab samples are taken in vials and sent to an in-house or off site testing laboratory to verify the cleaning process. Historically, a combination of conductivity and either TOC or HPLC has been the most common method of verifying (and approving) that the cleaning process was performed correctly. Typically, the maximum allowable conductivity value is established during the pharmaceutical site’s cleaning validation program and is supported by other samples and analyses, such as swabs and rinse water samples that are analyzed in the laboratory using HPLC or TOC. This process is labor intensive, material intensive and slow, as it requires a large number of vials and swabs to be collected and analyzed. Often, delayed laboratory results mandate quarantining the vessel being cleaned until the process can be fully verified. As a result, valuable manufacturing time may be lost.

Moving to on-line TOC and conductivity measurements reduces labor and material costs and increases productivity by providing instantaneous data on the vessel’s hygiene. This allows faster turnover. Accuracy and precision are increased versus laboratory analyzers, as the samples are neither exposed to a bottle, nor the atmosphere, nor other sampling errors because sample handling is eliminated. Furthermore, the on-line TOC analyzer does not require any reagents and will yield calibrated TOC and conductivity results simultaneously using a single analyzer.

In order to protect the on-line TOC analyzer from being overloaded by the high TOC concentration found in initial CIP solutions, flow is passed through an in-line conductivity sensor. As soon as the system reaches a conductivity level close to the established required cleanliness, a signal is sent from the conductivity analyzer to the CIP control system, which in turn sends a signal to both a diverter valve and the TOC analyzer. A sample of rinse water then flows to the TOC analyzer which then automatically measures the TOC value. Since conductivity measurements will establish that the TOC levels are already within instrument tolerance, low TOC concentrations are quickly and accurately measured and cleanliness can be verified by both conductivity and TOC.

The schematic below illustrates the process mechanical setup. The additional hardware consists of the on-line TOC analyzer (ANATEL A643a), heat exchanger to cool down the waste water to < 65°C, and automated valves. All of these components are extremely robust and reduce the likelihood of a system failure compared to performing the TOC analysis in the laboratory.
RESULTS

In order to determine a threshold conductivity level for TOC measurements to begin, isopropanol was added to a 250-gallon test vessel to simulate organic residues from a bio reactor. RO water was added in steps, while the conductivity level was monitored and documented.

The conductivity value was linked to TOC values, and it was established that conductivity values higher than ~ 0.80 µS led to long TOC analysis times due to high TOC levels. Table 1 below shows the results of 5 consecutive TOC measurements along with the conductivity results.

<table>
<thead>
<tr>
<th>Solvent test</th>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Sample 3</th>
<th>Sample 4</th>
<th>Sample 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conductivity, uncompensated (µS)</td>
<td>1.03</td>
<td>0.95</td>
<td>0.85</td>
<td>0.69</td>
<td>0.70</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>18.5</td>
<td>18.8</td>
<td>17.2</td>
<td>14.6</td>
<td>16.9</td>
</tr>
<tr>
<td>TOC (pbb)</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>655</td>
<td>140</td>
</tr>
</tbody>
</table>

Table 1: Resulting TOC measurements and conductivity results
Next, a CIP recipe was established that covers all sequences typically applied to clean-in-place (CIP) a fermentor / bio reactor. These steps include:

- **Pre-rinse 1 & 2**
  - The two (2) pre-rinse cycles were performed with relative low- or ambient-temperature water in order to avoid denaturizing protein based residues.
  - The pre-rinse cycles were performed in once-through and aimed at removing the majority of the product residues directly to drain.

- **Wash 1**
  - The wash cycle applied a formulated detergent based on sodium hydroxide that was re-circulated in order to allow the caustic detergent to clean the vessel surfaces effectively.
  - The temperature was increased in order to boost the formulated detergent’s effectiveness.

- **Post rinse 1**
  - The post rinse was performed in once-through (single-pass to drain) and aimed exclusively at removing caustic residues.

- **Wash 2**
  - The wash cycle applied a formulated detergent based on citric acid that was re-circulated in order to remove any caustic residues.
  - The acidic detergent has a positive effect, as it restores the stainless steel surfaces of the production vessel.
  - The temperature was increased in order to boost the effectiveness of the formulated detergent.

- **Post rinse 2**
  - The post rinse was performed in once-through (single-pass to drain) and aimed exclusively at removing acidic residues.
  - The post rinse was performed at highly elevated temperatures.

- **Final rinse**
  - The final rinse was performed in once-through (single-pass to drain).
  - The final rinse was, in this case, run at ambient temperature in order to facilitate accurate TOC measurement (typically, final rinse cycles are performed at elevated temperatures).
  - The final rinse was monitored by conductivity and TOC.
Table 2 below shows the final batch report created by the system following the completed verification. Note the final conductivity value 0.72 S/cm and final TOC value 73 ppb following the final rinse.

### DISCUSSION

For pharmaceutical manufacturers, improving batch cycle time can significantly impact profitability. A reduction in downtime between production runs (batches) is a continuous issue and focal point. With the integration of on-board, on-line TOC analysis to a decentralized CIP system this downtime can be reduced significantly. Verification using direct conductometric reagentless online TOC offers material and labor savings versus laboratory analysis. These saving include:

**Materials cost**
- Sample vials for both TOC and conductivity
- TOC and conductivity testing instrumentation in the laboratory
- Reagents and standards for laboratory instrumentation
Labor Cost

- Laboratory technician prepares vials and collects samples on the production floor
- Time required to return samples to the lab or send out to outside lab
- Time to set up laboratory instrumentation and testing

Downtime Cost

- 6 to 48 hours to get results from in-house laboratory
- Three to Five days to get results from an outside laboratory

While material and labor cost can be significant, the greatest impact to a company’s bottom line is “Downtime Cost”. This is the cost of having the manufacturing floor idle.

The solution is on-board, on-line TOC and Conductivity testing integrated into the CIP system. These results are available within minutes of the final rinse cycle. As described in this paper, the need to wait for hours or days can be eliminated, the return on investment is quick and the potential for continued savings is huge.

CONCLUSIONS

The addition of on-line TOC will not only reduce cost and simplify the CIP process, but also will propel its adopter further towards the FDA’s 21st Century Initiatives on PAT and Continuous Process Improvements. For the first time, reagentless online TOC measurements may be applied during final rinse operations on CIP applications and used as one of the Cleaning Verification (CV) acceptance criteria. This allows fully automated operations with on-line monitoring of critical cleaning parameters, which are captured and documented in an automated batch report after completion of the cleaning process. By performing the final TOC verification at the CIP skid, the production equipment can be released immediately for manufacturing without waiting for laboratory results. As a result, equipment cycle times are reduced, efficiency is improved and manufacturing costs are lowered.