

Continued process verification methods in cleaning validation

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ABSTRACT: An increasing interest in continued process verification has brought to the spread of on-line assay methods in cleaning processes [1]. This paper deals with two different on-line applications: conductivity sampling and the Total Organic Carbon analysis for washing machines.

KEYWORDS: moist-heat sterilization, steam sterilization of aqueous solutions, sealed containers, headspace volume, internal pressure, autoclaving, autoclave, superheated water sterilizers, steam/ air mixture sterilizers

INTRODUCTION

The U.S. FDA [1] process validation guidance document released in 2011 increased the emphasis on continued process verification: "ongoing assurance is gained during routine production that the process remains in a state of control". Until recently, in a washing system, conductivity analysis was the only on-line method used to monitor the quality of the final rinse water. Now, developments in the Total Organic Carbon (TOC) technology allow its integration into washing systems. A general description of these two assay methods is reported in the next section. In closing, the on-line application of conductivity and TOC on Fedegari washing machine will be briefly described.

CONDUCTIVITY AND TOC ON-LINE ASSAY METHODS

Cleaning effectiveness can be determined by visual inspection and analytical methods for measuring removal of manufactured product and cleaning agent [2-3]. Analytical methods must be appropriate because their results determine the efficacy of the cleaning validation cycle.

The analytical methods can be specific or non-specific. Specific methods measure a certain residue in the presence of expected interferences. Whereas, non-specific analytical methods measure a general property, such as conductivity or TOC, without discriminating the source identity. In order to understand when it is more appropriate to apply a specific assay method or a non-specific one, let us consider the following example: active proteins are commonly denatured by cleaning processes performed with hot, aqueous cleaning solutions. Usually, the protein is degraded into

smaller fragments or it is involved in the formation of new molecules. So, residues of the active protein are no longer detectable by specific analytical methods for the native protein. It follows that the cleaning validation protocol must include non-specific assay methods to measure residues of deactivated products [2].

Conductivity analysis is a non-specific method that detects dissociated ionic substances in water samples and cannot discriminate between different ions. Final rinse water conductivity is an additional requirement commonly included in the performance parameters of a cleaning process. It is often used to control automated cleaning processes measuring cleaning agent residues. Since the sample temperature has a strong influence on the conductivity reading, automated temperature compensation should be used to avoid incorrect results.

Most of the products involved in biotechnology processes, which represent the soils to be removed, are of organic nature and so they are not detectable by conductivity analysis. For this reason, Total Organic Carbon (TOC) analysis is introduced in a cleaning process validation. The TOC sensor is used for determining the total organic carbon in the control of water for pharmaceutical use (PW, WFI), for the analysis of detergents and APIs (active pharmaceutical ingredients) made of organic molecules when the identity of the analyte is not required. TOC analyzers oxidize organic carbon and measure the resultant carbon dioxide released from the oxidized organic molecule. Different TOC analyzer suppliers propose different measurement methods. Anyway, TOC final results are derived from conductivity readings and report the concentration in parts per billion (ppb) of the carbon derived from organic material in the water. It is a very sensitive technique, but it is clearly non-

specific. In fact, it is able to detect the organic residues of products degraded by cleaning processes but it is not able to identify the analytes in the sample. For this reason, all the organic carbon detected is assumed to be product: worst-case approach [2].

ON-LINE APPLICATION ON WASHING MACHINES

As an example of the on-line applications described above, we describe a case study using the Fedegari washers. In these machines, both conductivity and TOC analyzers are integrated in the piping system and connected to the Control System.

CONDUCTIVITY ANALYSIS

- The measure of the rinse water conductivity is performed during the final rinse. For this purpose, a conductivity meter is located on the drain line. Rinses are automatically repeated until the conductivity is lower than the pre-established set point, or until a maximum number of rinses have been completed. If the conductivity set point is not reached in the fixed number of rinses, then the Control System gives an alarm.

TOTAL ORGANIC CARBON (TOC) ANALYSIS

- The rinse water conductivity is first measured during the final rinse using a conductivity meter (external to the TOC sensor), located on the drain line. Rinses are automatically repeated until the conductivity is lower than a pre-determined set point that is within the operating range of the TOC analyzer (2 $\mu\text{S}/\text{cm}$).

- After this step, the TOC monitoring system is activated and a controlled amount of final rinse water is directed to the TOC sensor assembly through an isolation valve.

- The TOC sensor uses ultraviolet oxidation to determine the TOC concentrations in the final rinse water sample. Built-in conductivity sensors provide continuous conductivity measurement before and after sample oxidation; TOC final results are derived from conductivity readings.

- Once the sampling time has elapsed, the measured TOC value is transmitted to the washer Control System. The control can be programmed to repeat the rinse phase until the set point has been reached, or until a maximum number of rinses have been completed. If the TOC set point is not reached in the fixed number of rinses, then the Control System gives an alarm.

While conductivity measurement is very rapid, the introduction of on-line TOC analyzer mandates a longer cycle time. In fact, the washing system has to be 'frozen' during the stabilization time of the TOC analysis, in order to determine the necessity to perform a new rinse.

Nevertheless, drawing a comparison between off-line and on-line measurements, it is evident that conductivity and TOC online applications eliminate manual sampling, transportation of the samples to a laboratory, time delay in laboratory analysis, and the risk of cross contamination. Moreover, the online application allows for continuous monitoring and for the reporting of faults during an already validated process.

A schematic summary of the benefits/disadvantages of the conductivity and TOC online applications is reported below.

BENEFITS OF THE CONDUCTIVITY AND TOC ONLINE ASSAY METHODS

- Quick analysis results with reduced labor (avoiding manual sampling)
- Reduced risk of cross contamination
- Reduced associated costs: absence of manual laboratory analysis
- Reduced equipment downtime: no need to wait for a laboratory analysis
- Process trending and analysis ensuring robustness
- Real-time "warning system"
- Very sensitive techniques with accurate results.

DISADVANTAGES OF THE CONDUCTIVITY AND TOC ONLINE ASSAY METHODS

- Non-specific assay methods
- Just for TOC: initial cost of the instrument.

CONCLUSIONS

The use of online TOC and conductivity measurements are complementary for real-time verification of cleaning cycle performance. The conductivity meter and the TOC sensor can be fully integrated into the piping system and connected with the Control System.

These on-line applications avoid manual sampling and the risk of cross-contamination, typical of off-line measurements. Through these applications, the process remains in a state of control during routine production as suggested by U.S. FDA [1].

REFERENCES

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