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Application News

TOC-4200 On-Line TOC Analyzer

Cleaning Validation System for Biopharmaceutical Cell Culture Tanks Using On-Line TOC Analyzer

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User Benefits

- The cleaning effect can be confirmed immediately by using an on-line TOC analyzer, reducing lost time and cost in the manufacturing process.
- Because combustion type TOC is not affected by salts in the culture solution and unexpected and hard-to-analysis substances can also be measured, high measurement accuracy is possible.

■ Introduction

Biopharmaceutical products are produced by culturing and refining cells, *E. coli*, yeast, and other biomaterials. A large number of culture tanks are used in a single production line, and it is necessary to confirm that the cleanliness of each of these tanks passes regulations before proceeding to the next process. Fig. 1 shows an example of the workflow.

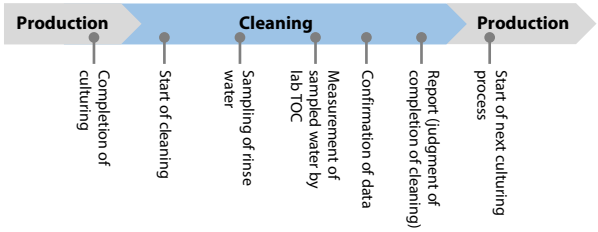

Fig. 1 Example of Workflow

Cleaning of culture tanks is an extremely important process because the homogeneity of the following culturing process cannot be guaranteed if there are variations in the condition of contamination in the tanks after cleaning. In addition, because culturing requires several weeks, culturing will not progress as assumed and all of this time will be lost if cleaning is inadequate.

This article introduces an example of cleaning validation of biopharmaceutical culture tanks using a Shimadzu on-line total organic carbon (TOC) analyzer. It is possible to minimize retention time and work between processes by using an on-line TOC analyzer. In particular, cleaning validation work can be substantially reduced by utilizing an on-line system because the culture tank rinse water is automatically sampled and measured periodically, and the acquired data are transferred successively to the upper level system. Use of this system in continuous production is also expected.

■ Overview of On-Line System

If a laboratory TOC analyzer is used in cleaning checks, the analyst must sample the water used to rinse the culture tanks and other equipment and take to samples to the laboratory for measurement with the TOC analyzer. When the measurement is completed, the analyst checks the data, and if TOC is lower than the predetermined threshold value, reports completion of cleaning to the superiors and other departments. Only then can production proceed to the next process. Since each of these tasks requires human intervention, this process is expensive and time-consuming.

In contrast, if the TOC-4200 on-line analyzer is used, ① sampling is conducted automatically, ② the samples are measured automatically, and ③ the measurement results are transferred automatically to the upper level system. The most recent information on the culture tanks can be monitored with a measurement cycle as short as 4 minutes. As a result, the upper level system can immediately make a judgment to proceed to the next process, reducing lost time between processes. In addition, human error is also significantly reduced because all the sampling, measurement, and data evaluation work that had been done manually until now are carried out automatically.

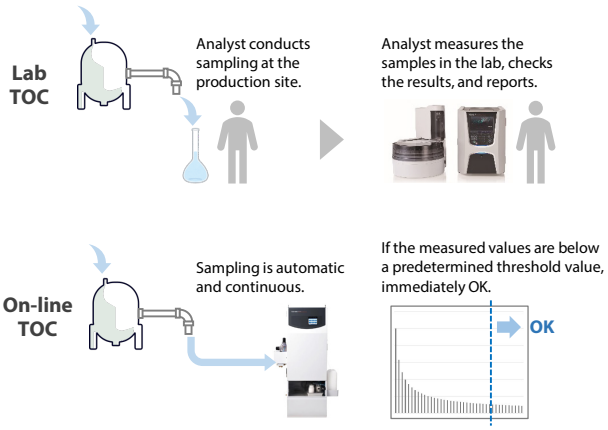

Fig. 2 Comparison of Workflows

With on-line TOC, ① Automatic sampling, ② Automatic measurement, and ③ Automatic data transfer to the upper level system are possible. This eliminates the need for human intervention, leading to reduced labor costs and shorter production time.

■ Advantages of Combustion Type TOC Analyzer

Shimadzu TOC-4200 is a combustion catalytic oxidation TOC analyzer. Higher measurement accuracy is possible than with the wet chemical type, as the combustion type is not affected by interference by salts contained in samples. In evaluations by liquid chromatography (LC), salts appear as impurities in the measurement results in some cases, but salts do not affect combustion type TOC analyzers.

Moreover, because the sample is subjected to combustion oxidation at high temperature, reliable detection is possible regardless of the residue composition, and the risk of equipment contamination is minimal.

Fig. 3 TOC-4200 On-Line TOC Analyzer

■ Measurement Sample

The measurement in this experiment was conducted using a 700 mL stainless steel container, as shown in Fig. 4, which is similar to a culture tank. After an RPMI culture solution was introduced into the tank, cleaning was carried out by the following procedure, and the rinse water was sampled after each rinse. A cleaning evaluation was conducted by monitoring the decrease in the organic content of the rinse water by measuring TOC.

Fig. 4 Stainless Steel Container

<Cleaning procedure>

① An RPMI culture solution was introduced into the container and deposited on the entire inner surface, after which the solution was discarded.

② Purified water was introduced into the container, stirred, and then removed from the container. This rinse water was called 1st rinse water.

③ Cleaning was repeated several times in the same manner as in ②, and the rinse water was denoted 2nd rinse, 3rd rinse, and so on.

■ Measurement Conditions

The rinse water samples prepared by the above-mentioned procedure were measured with an on-line TOC analyzer. Table 1 shows the measurement conditions.

Table 1 Measurement Conditions

Instrument	: TOC-4200 on-line TOC analyzer
Measurement principle	: 680 ˚C combustion catalytic oxidation-NDIR detection method
Catalyst	: Standard catalysts
Calibration	: Two-point calibration curve prepared using 0 to 5 mgC/L potassium hydrogen phthalate (aq.)
Measurement item	: NPOC (non-purgeable organic carbon; TOC by acidification and sparging treatment)
Culture solution	: RPMI-1640 cell culture solution (FUJIFILM Wako Pure Chemical Corporation)

■ Measurement Results

Fig. 5 shows a graph of the number of cleaning cycles and the TOC concentration of the rinse water. The history of the decrease in the TOC concentration with repeated cleaning can be confirmed.

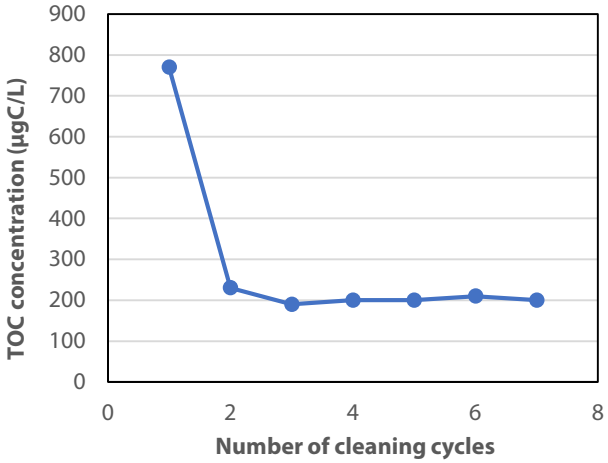

Fig. 5 Change of TOC Concentration of Rinse Water

■ Conclusion

Immediate monitoring of the effect of culture tank cleaning is possible by using an on-line TOC analyzer, which enables quick and automatic confirmation of cleaning. As a result, the time and cost required in the process can be reduced and human work error can be prevented, realizing high-level quality control in the manufacture of pharmaceutical products.

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