

Application News

No. 060

Total Organic Carbon Analysis

Cleaning Validation by TOC Analyzer with Easy Wiper

In the pharmaceutical industry, "cleaning validation" where residues on manufacturing equipment are quantitated to verify whether the amount is within tolerance, has been a valuable criterion for quality control and safety. To perform cleaning validation by Shimadzu TOC analyzer, the following three methods are available depending on selected sampling and analysis methods.

- Swab Sampling - Direct Combustion Method
- Swab Sampling - Water Extraction-TOC Analysis Method
- Rinse Sampling - TOC Analysis Method

For sampling methods, there are the swab method and the rinse method, and the swab method is suitable for accurately evaluating the amount of residues. For analysis method, the direct combustion method can achieve an effective, rapid, and easy-to-perform analysis since it does not require any pretreatment process, such as sample extraction from swab materials. With these reasons, the swab sampling-direct combustion method using Shimadzu TOC analyzer is significantly effective as a method for cleaning validation.

In past Application News which introduced the swab sampling – direct combustion method, a piece of quartz glass filter paper was used as the swab sampling material. When using this material, however, the method sometimes required re-cleaning of the equipment since fragments of the filter paper were left on surfaces. To avoid this difficulty, the method here uses Easy wiper, made of quartz glass fibers which leaves no fragments on swabbed surfaces.

Here, we introduce the method using Easy wiper as the swab sampling material in the analysis of residual pharmaceutical products and their constituent substances.

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Fig. 1 Easy Wiper

■ Preparation of Residue Sample

In order to evaluate the recovery rate in the cleaning validation with Easy wiper, residue analysis samples were created by allowing various pharmaceutical products and their constituents to adhere to a stainless plate. Water-soluble substances and water-insoluble substances were used for the sample (see Table 1).

The water-soluble substances and water-insoluble substances were dissolved with water and organic solvents listed in Table 1, respectively, and the solution concentrations were adjusted to 2000 mgC/L (=carbon concentration of 2000 mg/L). Then 100 µL of each solution was applied to a 5 cm × 5 cm square area, and the solvent was dried to produce residue analysis samples. Here, the carbon amount of each sample should be 200 µg.

Note that Rinderon ointment and Vaseline were prepared by previously obtaining the carbon amount on Shimadzu Total Organic Analyzer with Solid Sample Combustion Unit.

Table 1 Sample Type

Substance Name	Solubility in Water	Solvent Used for Solution Preparation
Tranexamic acid	Soluble	Water
Anhydrous caffeine	Soluble	Water
Isopropylantipyrene	Insoluble	Ethanol
Nifedipine	Insoluble	Acetone
Rinderon ointment	Insoluble	Acetone
Vaseline	Insoluble	Diethyl ether

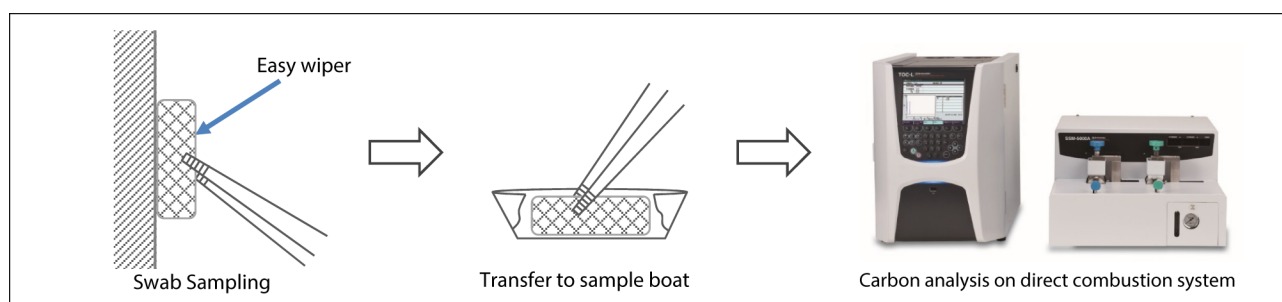


Fig. 2 Swab Sampling – Direct Combustion Method with Easy Wiper

Swab Sampling – Direct Combustion Method

In the swab sampling – direct combustion method, the internal surface of manufacturing equipment is swabbed with Easy wiper made of inorganic quartz glass fibers, and the swab is analyzed on the direct combustion system. See Fig. 2. The Easy wiper with which the residual substances are adhered is placed in the sample boat, and directly analyzed on the direct combustion system combining the Solid Sample Combustion Unit SSM-5000A and TOC analyzer.

In order to evaluate the recovery rate of various substances in this method, the stainless plate where the sample was adhered was swabbed with Easy wiper, and the swab was placed in a sample boat on SSM-5000A to perform TC analysis. A part of the analysis data is shown in Fig. 3.

Since the carbon amount of the residue analysis sample is 200 µg, the TC value when the whole sample is swabbed should be 200 µg. Note that in order to evaluate a blank sample, a stainless plate with no substance adhered was swabbed and the swab was also analyzed in the same way. The blank value was then subtracted from each TC value, and the obtained value was compared with the theoretical value 200 µg to obtain the recovery rate. The results are shown in Table 3. High recovery rates of almost 100 % were obtained for all substances, whether they were water-soluble or water-insoluble.

Table 2 Measurement Condition

Analyzer	: Shimadzu Total Organic Carbon Analyzer TOC-L _{CPH} +Solid Sample Combustion Unit SSM-5000A (IC circuit bypath using system with cell switching valve set)
Cell Length	: Short cell
SSM carrier gas	: 400 mL/min oxygen gas
Analyzed item	: TC (Total Carbon)
Calibration curve	: 1-point calibration curve using 30 µL of 1 %C aqueous glucose solution
Swab Material	: "Easy wiper made of quartz glass fiber (Heated at 600 °C for 15 minutes)"
Swabbing Method	: Add 200 µL of pure water to Easy wiper, and hold it with tweezers to swab the surface.

Table 3 Measurement Results of Swab Sampling – Direct Combustion Method with Easy Wiper

Substance Name	TC Concentration [µgC]	Recovery Rate [(TOC Conc.-Blank)/Theoretical Conc.]
Blank	0	–
Tranexamic acid	207	104 %
Anhydrous caffeine	207	104 %
Isopropylantipyrene	201	101 %
Nifedipine	208	104 %
Rinderon ointment	193	96.7 %
Vaseline	207	104 %

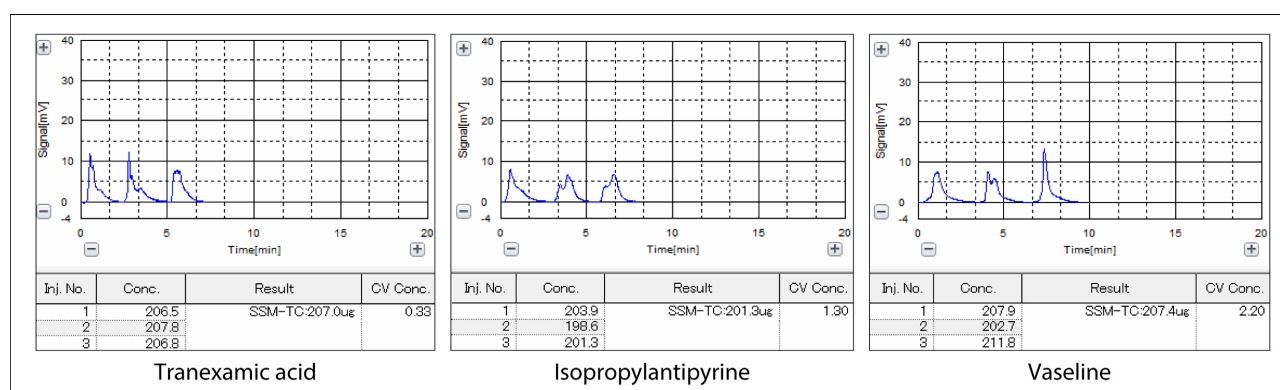


Fig. 3 Measurement Data of Swab Sampling – Direct Combustion Method by with Easy Wiper