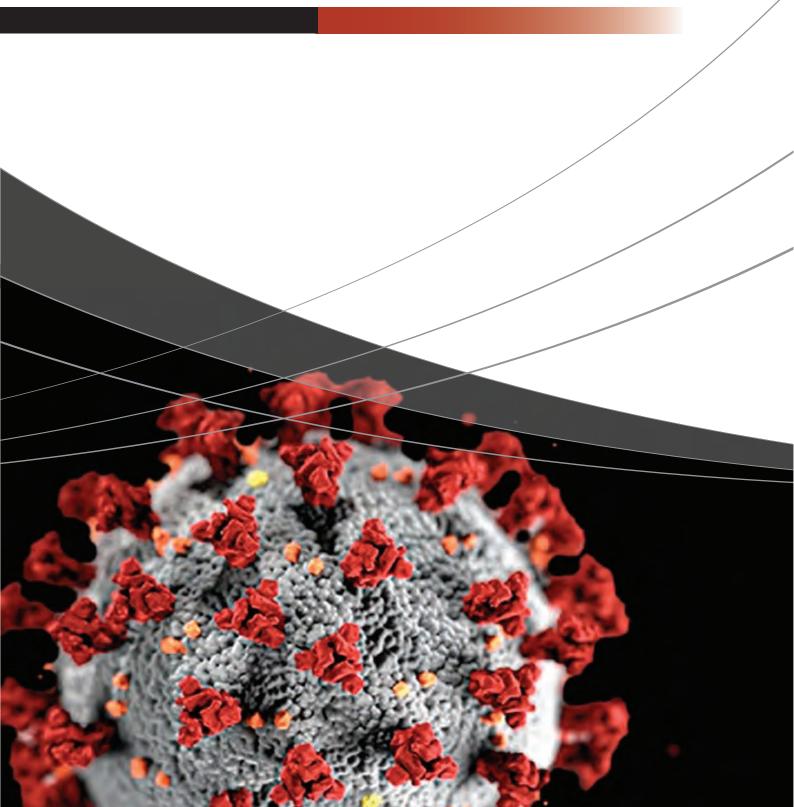


Analytical Technologies for COVID-19 Challenge

Our role in helping customers respond to the pandemic



Analytical Technologies for COVID-19 Crisis

The COVID-19 pandemic has brought unprecedented challenges for the communities and economies worldwide, causing a profound effect on the lives of billions of people. While government and communities are trying to contain the spread, researchers are aggressively focusing their efforts towards finding a treatment and/or vaccine.

Science is more important now than ever before. Shimadzu is the longest serving analytical and medical instrument manufacturer in the world, since 1875. We are committed to contribute to society — to overcome and eventually recover from this global pandemic through science and technology.

To the ones who are fighting for us in the frontlines, we are truly humbled by the immense sacrifices, invaluable dedication, commitment and unwavering efforts that you have given during this battle against COVID-19. We cannot thank you enough for your noble contributions and sacrifices.

We have compiled this application brochure which features the current analytical technologies and solutions that Shimadzu is committed to provide – such as analytical techniques for drug testing and vaccine research, production and testing of sanitizers and personal protective equipment and analysis of medical sewage waste. These comprehensive and effective solutions aid in the fight against this novel coronavirus.

Science will get us through this pandemic.



Drug Repurposing

- Analytical Technologies for Drug Research
- Quality Analysis of Hydroxychloroquine Sulfate using LC Nexera Series
- Quantitation of Hydroxychloroquine in Human Plasma by LC-MS/MS
- Simultaneous Analysis of Remdesivir and its Metabolites
- Material Characterization Instruments for Drug and Vaccine Discovery

Vaccine Analysis

- Vaccine Production and Testing
- Cell Culture and Supernatant Analysis
- Testing for Active Ingredients and Other Substances
- Total Nitrogen (TN) for Protein Estimation in Vaccines

Nucleic Acid Detection and Research

- Comprehensive Spectroscopy Solutions for Nucleic Acid Analysis
- Desktop MALDI-TOF MS for Peptide Nucleic Acid (PNA) Analysis

Research for Alternative Detection Methods

• Novel Development of Microarray Chip MALDI-TOF Assay

Hand Sanitizers & Personal Protective Equipment (PPE)

Quality Assessment of Hand Sanitizers

• Composition Analysis and Quality Assessment of Hand Sanitizers

Production and Testing of PPE

- Testing for Safety and Quality Assurance for Masks
- PPE Material Testing Based on Tensile Strength
- Microfocus X-ray CT Observation of Respirator Mask



Testing of Medical Wastewater and Waste

- Analysis of Dioxins (PCDD/Fs) in Incinerated Medicated Waste
- Nitrosamine in Wastewater
- Spectrophotometric Determination of Residual Cl with N,N-diethyl-p-phenylenediamine
- Analysis of PPCPs in Wastes and the Environment using LC-MS/MS
- PFAS Analysis in Drinking Water and Environmental Matrices



Research and Development

Develop new drugs, ensure quality and achieve laboratory productivity during this COVID-19 period with Shimadzu's wide range of instruments and innovative technologies.

Drug Repurposing

Analytical Technologies for Drug Research

Medical researchers are racing against time to develop new drugs and treatments for COVID-19 and also investigate the possibility of repurposing available medicines. Some of these drug candidates include hydroxychloroquine, ivermectin etc.

Apart from the study of the efficacy of these drugs towards COVID-19, the quality of drugs is as crucial. Quality control and reliable operation and productivity during this period can be achieved through Shimadzu analytical instruments and informatics solutions.



i-Series Plus

Most robust platform to meet high pressing quality needs of assay and related impurity methods as per pharmacopoeia

innovative Advanced interactive design

Easy operation

htuitive

intelligent Smart features for high productivity

Nexis GC-2030

Together with headspace HS-20, this simple setup is the optimal platform for residual solvent analysis based on USP-467

- Low helium gas consumption ensures long unattended operations for maximum throughput
- Minimal carryover with super short headspace transfer line





Informatics Solutions | Enabling Remote Operations

Wide range of informatics solutions to address your laboratory challenges

- Fast and easy analysis setup with remote access
- Safe and secure data management
- Efficient workflows and consolidated reporting

ALSA

Total support for regulatory compliance

ALSACHIM

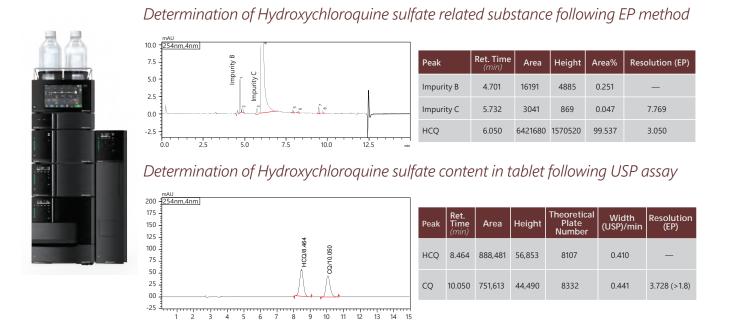
Shimadzu and Alsachim are supporting these drug development and clinical trials by providing internal standards for MS analysis of anti COVID-19 drug candidates.

a Shimadzu Group Download the app data sheet and learn more about the various stable isotope- labeled standard references and the LC-MS/MS method for multiple drug analysi



Quality Analysis of Hydroxychloroquine Sulfate using LC Nexera Series

Comprehensive monitoring and evaluation on the quality of hydroxychloroquine sulfate tablets is essential for drug development and analysis. Using Nexera Series, the desired peak separation and reproducibility of hydroxychloroquine sulfate analysis described in the pharmacopoeia were achieved.

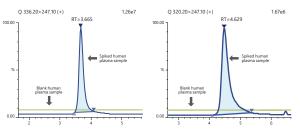


Quantitation of Hydroxychloroquine in Human Plasma by LC-MS/MS

After simple protein precipitation, hydroxychloroquine can be accurately quantitated in human plasma within 10 minutes using Shimadzu UHPLC-MS/MS (LCMS-8050). The developed method demonstrated good linearity, repeatability and high sensitivity.

ompound	Concentration (ng/mL)	Precision (RSD, %)	Accuracy (%)	100.00
CQ Sulfate	0.5	8.33	106.02	
	20	5.19	101.83	%
	400	1.57	97.91	0.00





Chromatograms of (a) HCQ and (b) CQ in blank and spiked human plasma samples

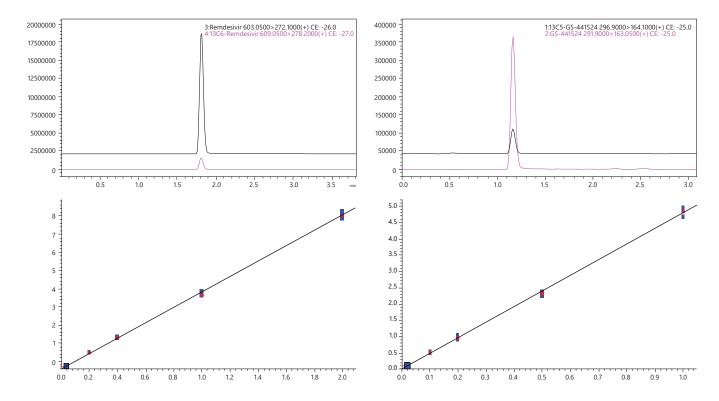
LCMS-8050 can easily and quickly analyze drug candidates such as hydroxychloroquine for the efficient development and accurate drug validation.

Co

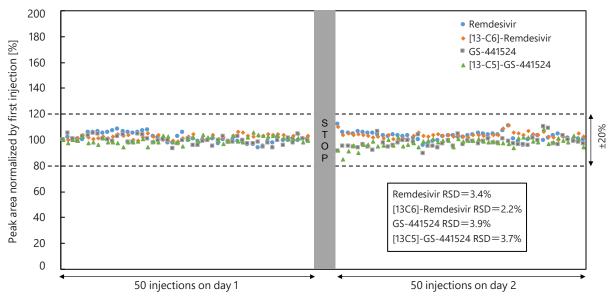
HC

Simultaneous Analysis of Remdesivir and its Metabolites

The analysis of another drug, remdesivir and its metabolites are demonstrated with Shim-pack Scepter C18 column and LCMS-8060. The results showed high sensitivity and repeatability, with good robustness and recovery rate with minimal carryover and no significant matrix effects.



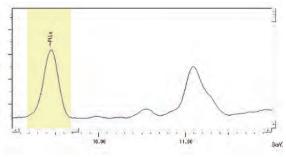
Robustness was evaluated using peak area normalized by first injection Sample: Medium QC sample (Remdesivir: 1,000 ng/mL, GS-441524: 50 ng/mL in plasma)



Material Characterization Instruments for Drug and Vaccine Discovery

Energy Dispersive X-ray Fluorescence (EDX): USP-Approved Screening Method for Impurity Control in Drug Development

Shimadzu EDX-7000 can easily verify and evaluate inorganic impurities in pharmaceutical products, excipients and Active Pharmaceutical Ingredients (API). With no chemical pre-treatment, this nondestructive analysis technique costs lower and requires less time, materials and labour than other chemical analysis methods.

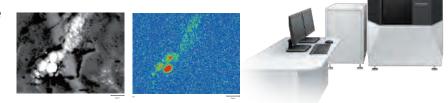


EDX Spectrum of Sample with Platinum and Arsenic Mixed in Cellulose Powder

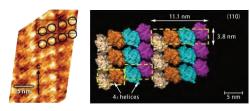
Electron Probe Microanalyzer (EPMA): Analysis of Metallic Elements in Biological Tissues

For the observation of metallic elements, Shimadzu EPMA can provide unprecedented spatial resolution under a beam current conditions from SEM observation conditions

up to 1µA order. It can visualize the presence of metallic elements (e.g. Pt) in biological tissues, and also clearly indicate how the drug is delivered.



Scanning Probe Microscope (SPM): Determination of Molecular Structure of Proteins



With high resolution and improved usability, Shimadzu SPM-8100FM (High-Resolution SPM) is capable of imaging and observation of the molecular structure of proteins. An example of an egg-white lysozyme in a saturated aqueous solution is illustrated.

With such capabilities in high-resolution imaging and observations, protein structures and the potential drug candidate could be better understood and aid in the drug development for the virus pandemic.

Vaccine Analysis

Vaccine Production and Testing



The final way for recovery from the current pandemic is discovery of appropriate vaccine and its mass production for global population. Vaccine research, production and testing require use of different analytical technologies at various stages. The quality, safety, efficacy and reliability of the vaccines can be tested using LCMS, MALDI-TOF and biomedical aggregate analysis.

Cell Culture and Supernatant Analysis

Culture media and processes for linear amplification of products need to be optimized so that vaccine quality and yield can be monitored in real time during vaccine production. To optimize culture media and processes, it is necessary to correlate changes in the contents of cell culture supernatants with favorable outcome, such as high yield.



We developed a cell culture analysis package to rapidly and

comprehensively analyze components of cell culture supernatants, and to detect and analyze basic carbon sources, nitrogen sources, nucleotides, vitamins, and other major metabolites so that biological processes can be described in detail. Using LC-MS/MS technology platform, relative changes in quantities of 125 nutrients and metabolites in cell culture supernatants were monitored and analyzed simultaneously in less than 20 min. The present cell culture analysis package can be used with the Shimadzu Nexera UHPLC with LCMS-8050 triple quadrupole mass spectrometer.

Testing for Active Ingredients and Other Substances

Apart from active ingredients, there are also other added substances present in vaccines such as antibiotics, adjuvants, stabilizers, emulsifiers, and even trace amounts of substances used during manufacturing. The determination of these ingredients in vaccine is essential and necessary for the safety and efficacy of the vaccines.

The amount of saccharides in vaccines is a key quality control criterion, one such example is the pneumococcal polysaccharide vaccine (PPSV). The detection can be conducted using LC coupled with various detectors (e.g. UV spectrophotometry or differential refraction detectors) or LC-MS/MS.

Proteins can be commonly found in vaccines and the contents of the protein subunits are an important quality criterion of vaccine formulation. MALDI-TOF MS is an established technique suitable for quick analysis of proteins and other macromolecules in vaccines.

Aluminum can be present in vaccine as an adjuvant, despite the known health risks. The quantity of aluminum allowed needs to be determined. In this case, ICP-OES and ICP-MS can be used to rapidly determine these contents in the vaccines.

Aggregate formation is typically monitored in pharmaceutical products for safety assurance as aggregates can stimulate severe immunological side effects. Shimadzu Aggregates Sizer instrument can be used to monitor the vaccine production process and at the same time evaluate its efficacy and safety.



- Cover a wide particle diameter of vaccine aggregates in a single measurement (even sub visible particles, usually between 0.20 - 10µm)
- Real time quantitative measurement even when stress or temperature is applied
- Samples can be recovered after measurement

Total Nitrogen (TN) for Protein Estimation in Vaccines

In pharmaceutical vaccine production, all viral vaccines or bacterial vaccines are tested for the quantity of respective attenuated or inactivated viruses or bacteria. Since these antigens typically consist of proteins, analytical quantification of total nitrogen content of protein becomes crucial. Total Nitrogen (TN) analysis is

fast and efficient way to monitor nitrogen loading using Shimadzu Total Organic Carbon (TOC) analyser coupled with Total Nitrogen Module (TNM). TN analysis uses hightemperature combustion coupled with chemiluminescence detection technique for the estimation of organic and inorganic nitrogen.

A comparative study of TN measurement of the DPT vaccine was done using TNM and conventional Kjeldahl method. Both the methods showed comparable result and percentage recovery was found to be within 100±10%. The TOC analyzer with TNM offers a time saving and safe method for protein estimation.



Batch	TOC/TN Nitrogen content (mg/L)	Kjeldahl Nitrogen content (mg/L)
Batch 1	1.481	1.537
Batch 2	1.523	1.559
Batch 3	1.544	1.587

Nucleic Acid Detection and Research

Comprehensive Spectroscopy Solutions for Nucleic Acid Analysis

Nucleic acids are a key structural component of a virus. Diversified spectroscopy solutions from Shimadzu can provide answers to quantitative measurement and structural information of these compounds, giving better understanding of the virus.



Biospec-nano

Dedicated high throughput spectrophotometer for DNA and RNA measurement

- Micro volume of sample is required (ranging from 1-2 uL)
- Automatic functions and easy to use operating software
- Fast and accurate nucleic acid quantitation

UV-1900i

High performance UV-Vis spectrophotometer to meet diverse needs

- Built-in measurement modes such as Kinetic and Biomethods (DNA or proteins)
- High precision double beam optics and low stray light for sensitive analysis
- Advanced regulatory compliance





TMSPC-8

- Excellent accuracy and reliability for thermal stability evaluation
- Equipped with 8-series micro multi-cells for simultaneous analysis of up to 8 samples, operated between 0-100°C
- Ideal for structure prediction and determination of duplex, triplex, antisense and siRNA based on the thermodynamic parameters (Δ G, Δ H, Δ S), supported by high precision temperature control

Desktop MALDI-TOF MS for Peptide Nucleic Acid (PNA) Analysis

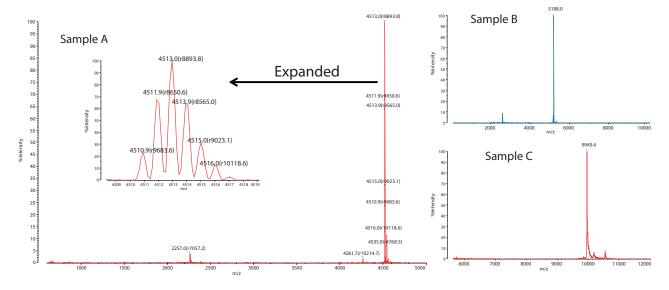


Due to its high sequence selectivity and biological stability, PNA is widely applied in the field of molecular diagnostics and research. Notably, PNA are used as molecular probes that can distinguish single base mutations of related genetic diseases, and for the treatment of human immunodeficiency virus. The MALDI-TOF MS used is an effective technique for quality control and research in synthesis of peptide nucleic acid (PNA) oligomers and confirmation of end products with some clear advantages:

• Simple sample pretreatment

• Accurate molecular weight results

Three samples of PNA analysis using benchtop MALDI-TOF MS are illustrated.



Sample A:

- Mono-isotope peak was measured to be m/z 4510.9
- Excellent isotope peak separation observed
- Mass resolution is sufficiently satisfactory (> 8000 FWHM), even when measured in linear mode

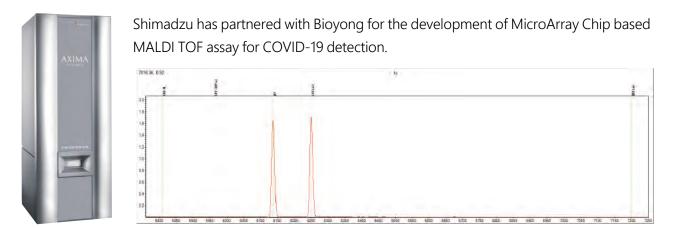
Sample B and C:

- Detection of large PNA molecules (5.5 pmol/7.5 pmol)
- The analysis results annotated in average molecular mass

Research for Alternative Detection Methods

Globally, research teams are investigating on different approaches and methodologies for the development of alternate test methods. Checking viral proteins and nucleic acid, or the immune response of human body are a few of such approaches. This diverse range of approaches indicate the use of different analytical technologies. MALDI is one such mass spectrometry-based technology used to evaluate new detection methods.

Novel Development of Microarray Chip MALDI-TOF Assay



This platform has recently passed the National COVID-19 test External Quality Assessment (EQA) organized by the Chinese National Centre for Clinical Laboratories (NCCL).

This microarray chip MALDI TOF assay (Research Use Only. Only available in China) can:

- Provide high throughput analysis of 1600 samples per day
- Detect 18 different pathogen in each sample with virus detection limit at 10 copies/ μ L

How it works?

Coronaviruses express their replication and transcription complex from a single, large open reading frame referred to as ORF1ab. The coronavirus structural proteins includes the envelope (E), nucleocapsid (N), and spike (S) proteins. The ORF1ab and N genes are two of the most frequently used targets for SARS-CoV-2 detection. The PCR – TOF MS method kit can be used to qualitatively detect ORF1ab, N genes nucleic acid of COVID-19 virus in throat swab, sputum sample with MALDI-TOF instrument.



Hand Sanitizers & Personal Protective Equipment (PPE)

Human safety and health are of utmost importance during this difficult period of COVID-19. Quality testing and safety inspection of sanitizers, disinfectants and PPE can ensure and protect our health and well-being.

Quality Assessment of Hand Sanitizers

Composition Analysis and Quality Assessment of Hand Sanitizers

World Health Organization (WHO) recommends the practice of good hand hygiene as one of the basic protective measures against COVID-19. This includes washing hands with soap and water or using an alcohol-based hand sanitizer. U.S. CDC have recommended sanitizers with 60–95% alcohol as the most effective composition of sanitizers.

Additionally, with concerns over product fraud or fake substances used in the manufacturing of sanitizers, the analysis of key active ingredients, such as alcohol, in sanitizers is crucial. Shimadzu FTIR IRSpiritTM and GC Nexis-2030 provide ready to use simple methodology for the measurement of ethanol and isopropyl alcohol (IPA) in hand sanitizers.

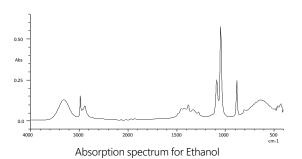


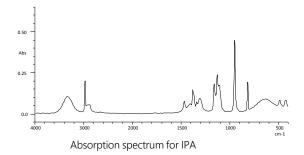
Download the app note on the quick and easy analysis of alcohol content in hand sanitizer by FTIR Spectroscopy.

IRSpirit with QATR[™] –S

Provides a simple methodology Drop and Click workflow for the quantitation of ethanol or IPA in sanitizers The Drop and Click workflow enables:

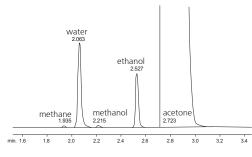
- Fast results, under 1 min analysis time
- No or minimal sample preparation required
- Excellent data quality and reproducibility
- Low running cost and minimal instrument maintenance





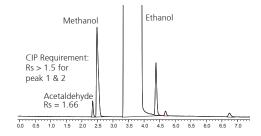
Gas Chromatograph GC-2030

- Ideal for the analysis of volatile compounds
- Determination of purity of ethanol in sanitizers based on the Chinese National standards "Hygienic standard for alcohol disinfectants" (GB/T 26373-2010) to fulfil the Chinese Pharmacopoeia (CIP 2010 version 2)



Measurement of ethanol content in hand sanitizers





Determination of maximum allowable impurities in ethanol

Production and Testing of PPE

Testing for Safety and Quality Assurance for Masks

Masks can prevent spread of viruses (e.g. respiratory infections) and minimise exposure to airborne particles. However, there are various types of face masks and the quality of masks generally depends on the materials used. Additionally, masks have to be sterile and the disinfection process may involve the use of toxic chemicals. To curb the spread of COVID-19 virus successfully, there is a crucial need to ensure the safety and quality of masks used by medical professionals and the general public.

Measurement of Ethylene Oxide (a sterilant) Using Headspace Gas Chromatography (HS-GC)

Medical equipment and surgical masks are commonly sterilized with ethylene oxide at room temperature. However being a toxic carcinogen, there are strict requirements on residue indicators for single use medical device products.

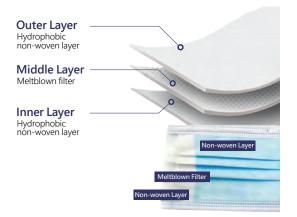
Shimadzu HS-GC are ideal for the measurement of residual ethylene oxide in masks and can detect the specified range of maximum allowable residual amount in standards such as:

- National standards Biological Evaluation of Medical Devices Part VII: Ethylene Oxide Sterilization Residues (GB / T16886.7-2015)
- International standard ISO 10993.7-2008 (Biological Evaluation of Medical Devices)



Identification and Verification of Fake and Inferior Masks Using FTIR (IRSpirit™)

Quality and relevance of a mask is heavily determined by the multiple layers of material or fabric which function as differential successive filters.

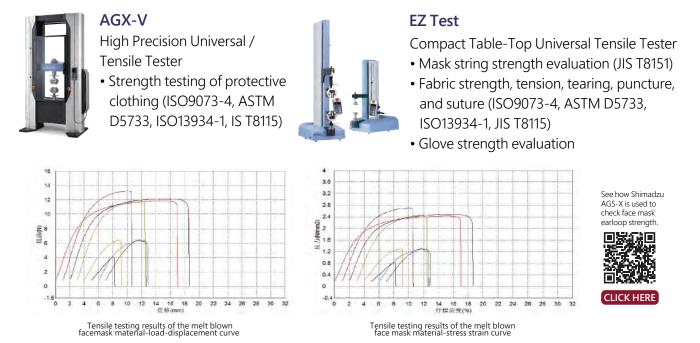


IRSpiritTM (FTIR) is a quick and easy technique to examine and confirm the identity of the layers in a mask based on their characteristic infra-red (IR) spectrum. Even for masks with blended fabrics, the IRSpirit with LabSolutions IR delivers highly precise search results equipped with:

- 4 high-performance search methods (spectral search, peak search, text search and combination search)
- Libraries containing approximately 12,000 spectra

PPE Material Testing Based on Tensile Strength

Apart from measurements using GC and FTIR, the quality and durability of mask can be evaluated based on the tensile strength measurement. There are several guidelines available for these measurements. Shimadzu has a range of precise universal tensile testers for all your material testing applications.



Microfocus X-ray CT Observation of Respirator Mask

Respirators are designed to filter and block harmful gases and particles in the air that we breathe. However, these respirators may often have manufacturing and quality defects. It is essential to check the quality of the respirator plate as well as the pores and inclusions. Similarly, these checks are required in the R&D workflow to verify its proof-of-concept and prototype.

For this purpose, a dedicated industrial microfocus X-ray computed tomography (CT) system is required. Shimadzu's inspeXio SMX- 225CT FPD HR microfocus X-ray CT system not only allows the scanning of the entire mask but also the viewing and examining of the internal structure of the mask respirator. The image of the mask respirator can be magnified to view the detailed structure and identify defects. With the Point Master Reverse Engineering Software, the respirator can provide additional insights on the design, wall thickness and porosity/inclusions. The same system and data analysis functions are also applicable to many applications such as aluminum die-casting analysis and resin analysis.

- High-resolution (up to 14-megapixel input resolution) and highcontrast CT image
- Easy and fast CT scan (intuitive and automated)
- Equipped with unique functions and features (extended filament lifetime, acquisition mode switching function and more)





Due to the COVID-19 pandemic, there is an increase in the generation of medical sewage. Comprehensive analysis is crucial for the necessary treatment and safe disposal of these medical wastes.

Testing of Medical Wastewater and Waste

Analysis of Dioxins (PCDD/Fs) in Incinerated Medicated Waste

Effective treatment and quantity reduction of medical wastes are the last line of defense in controlling the sources of infection and cutting the transmission routes in epidemic areas. Currently, high temperature incineration of medical waste is considered as general practice for the final treatment and disposal of medical waste.

Due to the complexity of wastes, it is inevitable that toxic and harmful components such as dioxins are generated in the incineration processes. For safety and understanding of the toxic components, Shimadzu

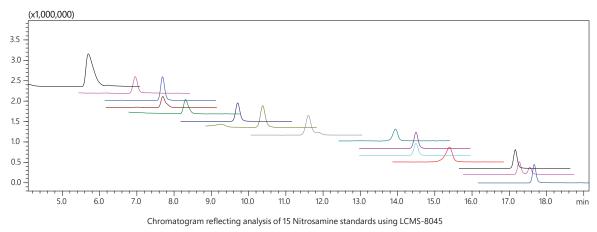
GCMS-TQ8050 NX with Smart MRM function provides easy to use and reliable methodologies. The analysis of real samples adopting this method were in good agreement with those obtained by high resolution gas chromatography/high resolution mass spectrometry (HRGC/HRMS).



Nitrosamine in Wastewater

Wastewater treatment plants can generate potential carcinogens during disinfection and chlorination processes. Nitrosamines are one such major class of contaminants or disinfection by-products. The presence of nitrosamines in treated wastewater or sludge could be detrimental, especially if these compounds could find their way and leach into our groundwater and drinking water sources.

The investigation of nitrosamines and the fate and concentration of these compounds in wastewater treatment plants and our environment are very crucial in the possible removal and prevention of these compounds. Here, Shimadzu LC-MS/MS (LCMS-8045) demonstrated the ultra-fast and high-sensitivity measurement of 15 of such nitrosamines.

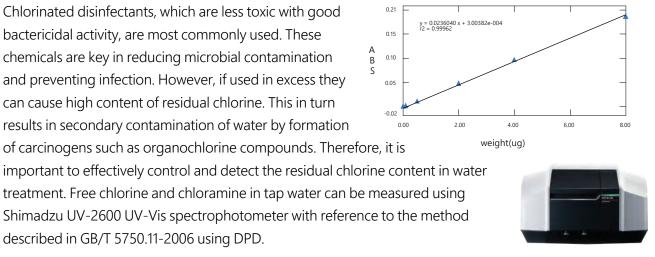


- 1. N-Nitrosodimethylamine
- 2. N-Nitrosodiethylamine
- 3. N-Nitrosoisopropylethylamine
- 4. N-Nitroso-N-methyl-4-aminobutyric Acid (NMBA)
- 5. N-Nitrosodiisopropylamine

- 6. N- Nitrosodibutylamine
- 7. N-Nitrosopiperidine
- 8. N-Nitroso-n- ethyl n-propylamine
- 9. N-nitrosopyrrolidine
- 10. N-nitrosodibenzylamine
- 11. N-nitrosomorpholine
- 12. N-nitroso di n propyl amine
- 13. N-nitroso methylethylamine
- 14. N-nitroso diphenylamine
- 15. N-nitroso-n-methyl n-phenyl amine

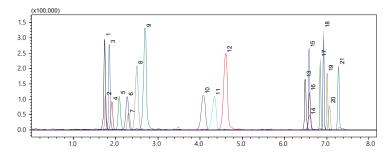
Spectrophotometric Determination of Residual Chlorine in Water with N,N-diethyl-p-phenylenediamine (DPD)

Medical and domestic wastewater generated during the epidemic are not allowed to be discharged directly to sewage treatment plants for normal treatment. It must undergo more stringent sterilization and disinfection.



Analysis of PPCPs in Wastes and the Environment using LC-MS/MS

The presence of Pharmaceutical and Personal Care Products (PPCPs) in the environment is a growing public concern due to their continuous input and persistence nature. This group of compounds includes many drugs from medicines, and chemicals from daily personal care products such as soaps, detergents, toothpastes and cosmetics. Many PPCPs act as endocrine disruptors and thus alter the normal functions of hormones resulting in reproductive defects and health issues.





The main sources of PPCPs are wastewaters from industries and domestic sewages (e.g. medical wastes, sewage plants and natural disposal). It has been reported that the levels of PPCPs in sewage treatment plants are in the range of low ng/L to µg/L. These compounds can further contaminate our environment e.g. rivers, aquifers, and soils.

Regulations and practices are set in place to control and manage PPCPs in the environment. To determine these PPCPs at low ppt level, Shimadzu LC-MS/MS is a powerful instrument capable of analysing PPCPs in drinking water, environmental samples and waste matrices.

PFAS Analysis in Drinking Water and Environmental Matrices

With the world focusing on containing the new pandemic, the presence of persistent organic pollutants and emerging contaminants in our environment should not be overlooked as it could still have significant consequences.

Perfluoroalkyl substances (PFAS) are a group of harmful contaminants that should not be disregarded. During this period, with the increased in production of PPEs and waterproof coatings (potentially containing PFAS) and possibly industrial emissions and discharges of PFAS into the environment, the environmental contamination of PFAS can be even more significant and widespread.



The analysis of PFAS in our drinking water and environmental waters can be performed using Shimadzu LC-MS/MS. Refer to our comprehensive compilation of PFAS analysis in drinking water and environmental matrices for more details.

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