Chemical Development

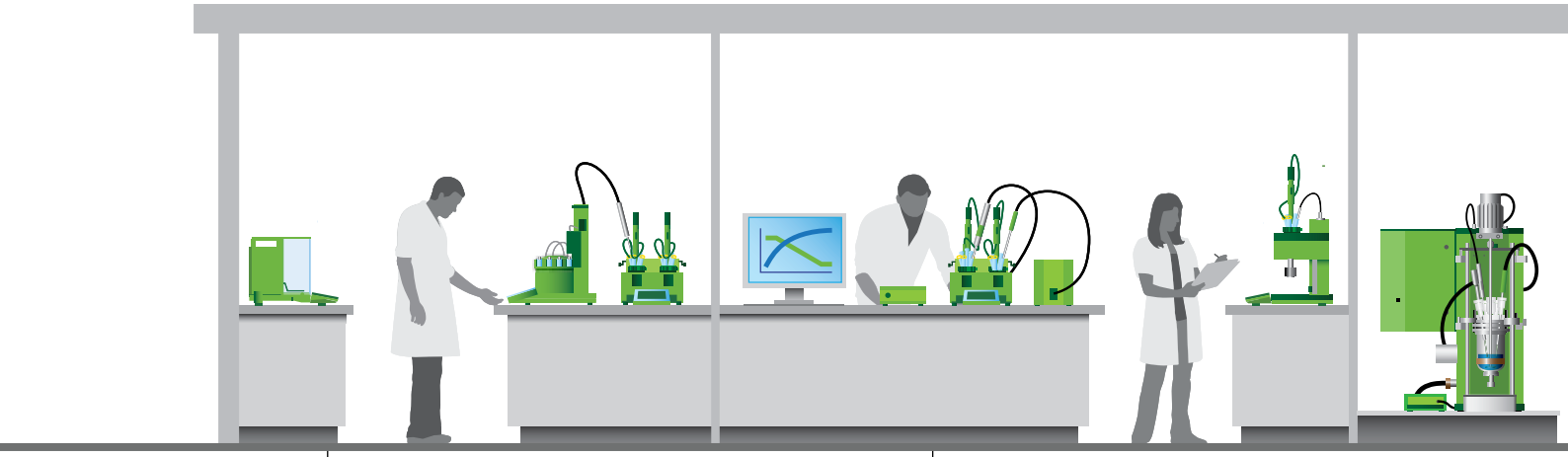
Automated Synthesis & Inline Analysis

From Molecule to Manufacturing

METTLER TOLEDO

Innovative Development
From Molecule to Manufacturing

Challenges occur across all stages of development. Innovative research and development involves finding solutions throughout each stage while keeping cost and quality in mind.



Invent the Molecule

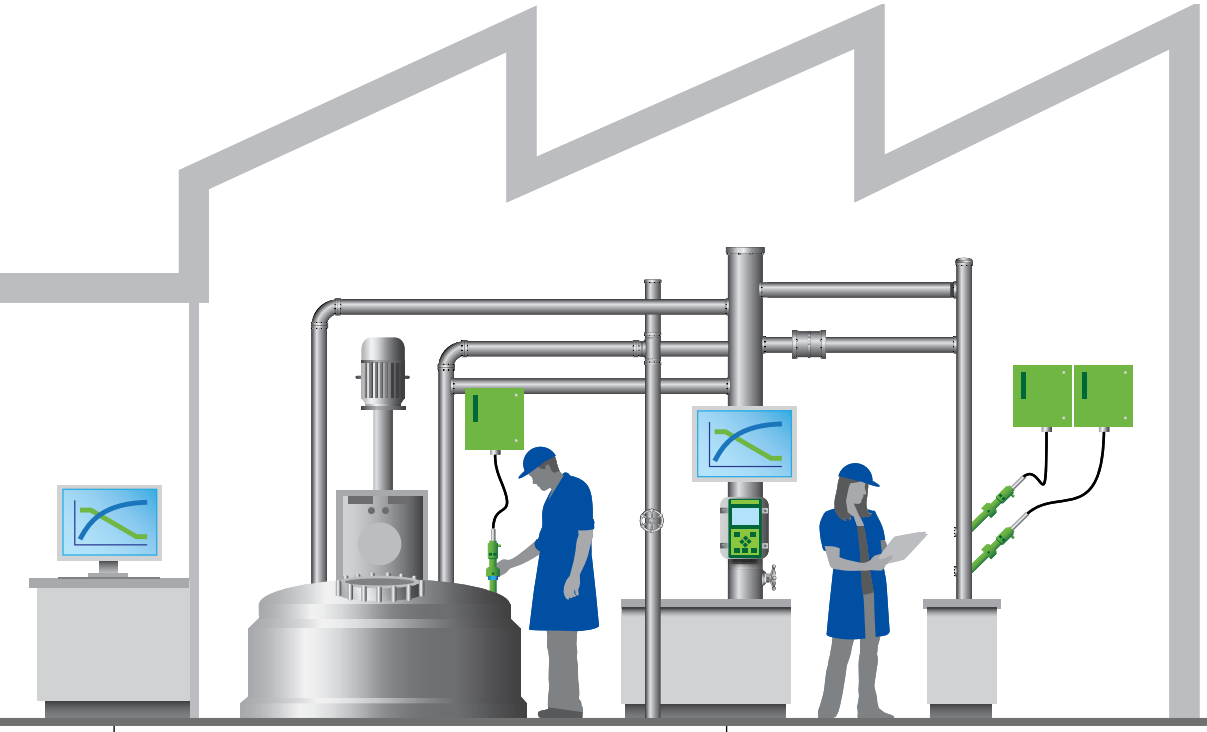
Researchers are looking to create effective compounds. Scientists explore new experimental conditions to identify new compounds.

- Does the molecule work for this specific application?
- How can we invent new compounds?
- Can personal safety be improved?

Develop the Reaction

Reactions are developed to provide robust and sustainable routes to synthesize molecules. They are then optimized for purity and yield.

- Is the reaction safe and profitable?
- Can the route be simplified?
- Can we identify the optimal reaction conditions?



Development from R&D to Manufacturing
Understanding and addressing challenges for each stage of the development process means scientists address key questions and make better, more informed decisions.

Create the Process

Each process must be created and optimized for safety, yield, and robustness.

- Is the process scalable?
- Are hazardous events under control?
- Can we make it according to our plant capabilities?

Manufacture the Material

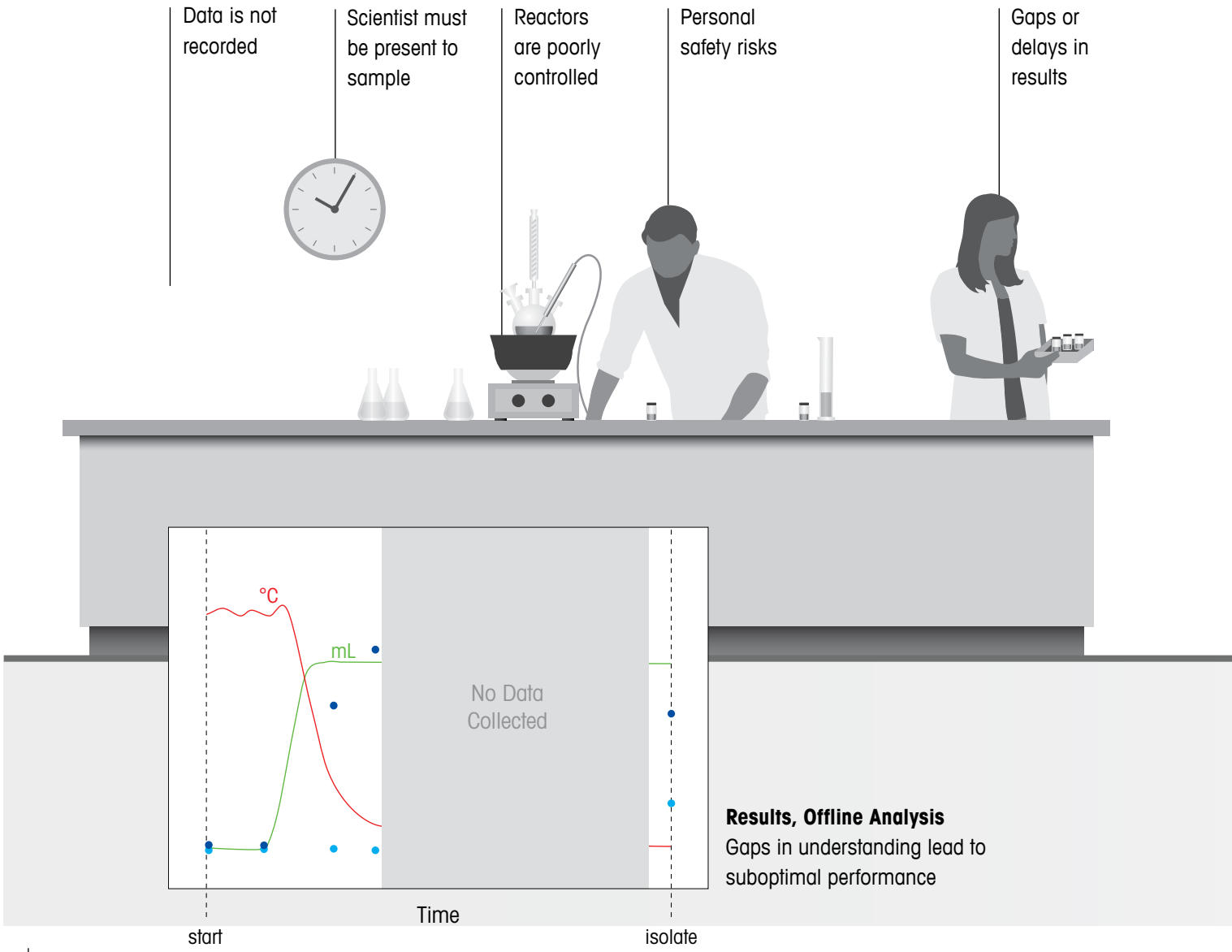
When transferring a process to manufacturing, failures are eliminated, continuous processes are controlled, and cycle time is reduced.

- Is the process repeatable?
- Can it be improved at scale?
- Can profitability be increased?

The Evolution of the Modern Laboratory

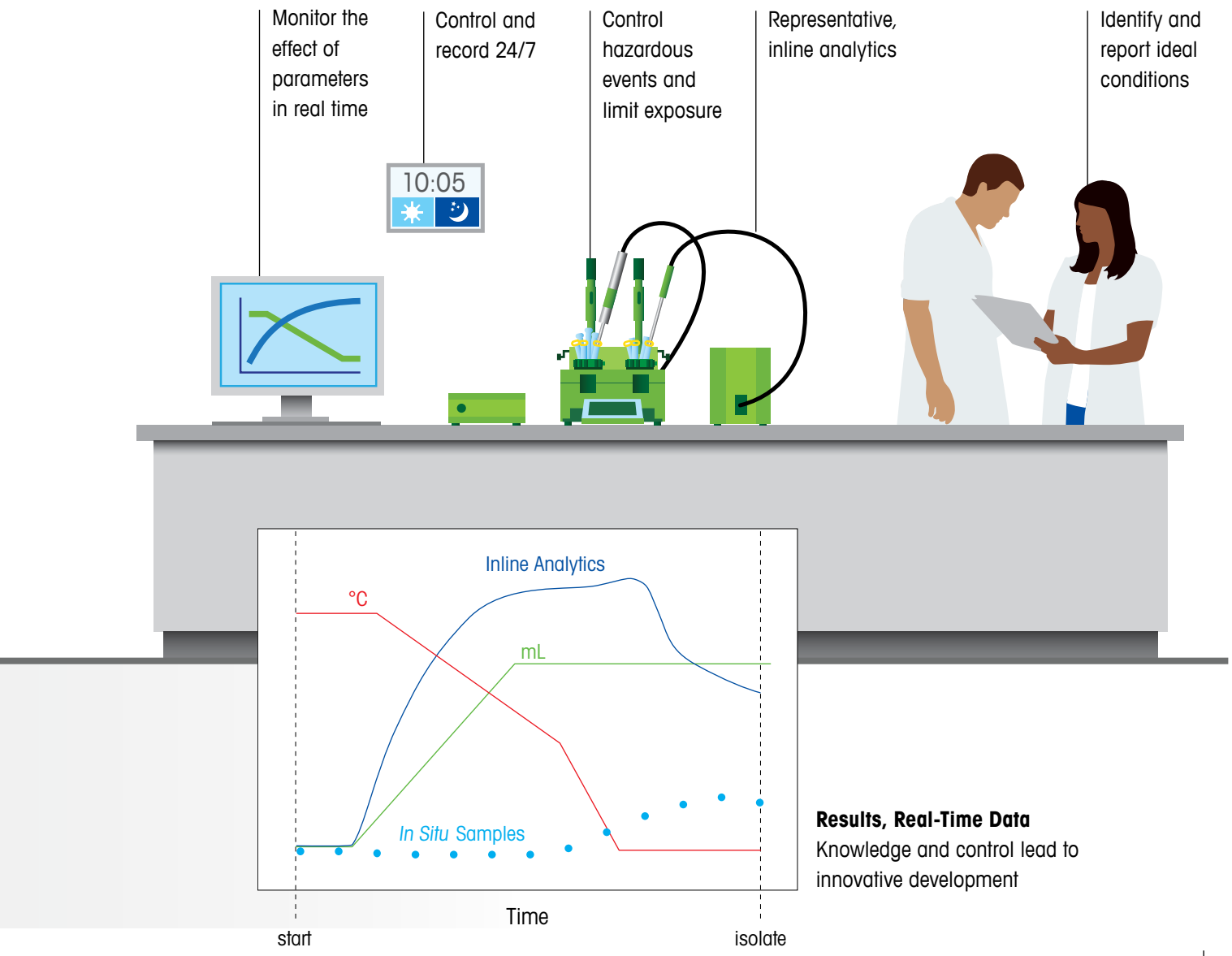
With safe and unattended experiments 24 hours a day, precise controls, and continuous measurements, researchers quickly understand the effect of changing parameters and make better, more informed decisions. Knowledge and control in the modern lab lead to innovative development.

Traditional Lab Techniques



Results, Offline Analysis
Gaps in understanding lead to suboptimal performance

The Modern Lab



Results, Real-Time Data
Knowledge and control lead to innovative development

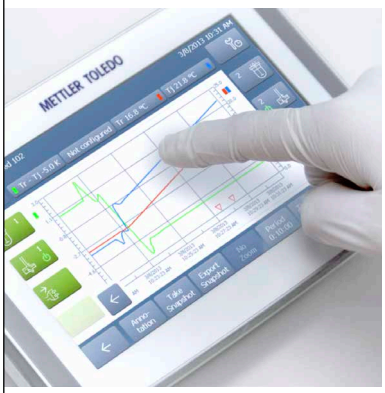
Modernize Synthesis
Automated Reactor Platforms

Automated synthesis reactors replace traditional round bottom flasks and jacketed lab reactors. These tools allow synthetic organic chemists and engineers to explore new reaction conditions while automatically and seamlessly recording all experiment data. An intuitive touchscreen for all reactors, stirrers, and thermostats reduces training needs and provides a single, standardized interface.

Flexible Configuration

Automated reactors allow chemists to run reactions and explore a wide range of operating temperatures without an ice bath, oil bath, heating mantle or cryostat. Interchangeable reactors provide flexibility to synthesize, optimize, and characterize chemistry from 0.5 mL to several liters.

Unattended Control

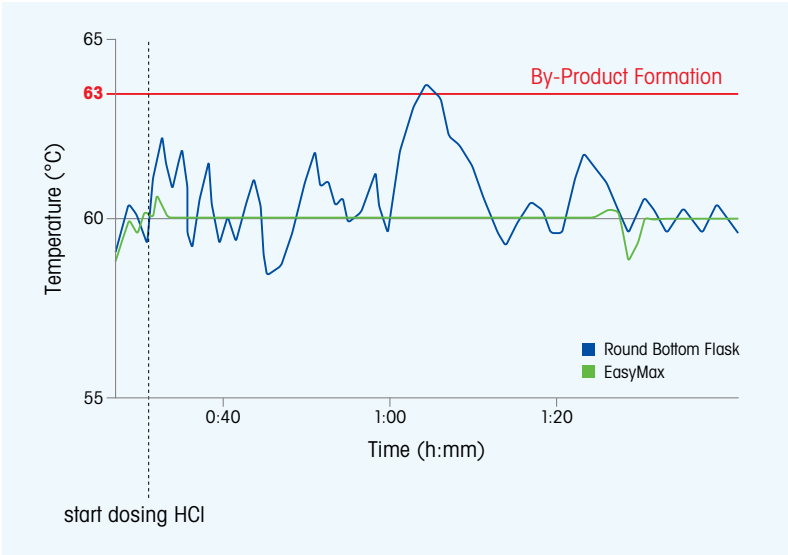


The intuitive and consistent touchscreen lowers training requirements for greater usage and increased time for investigations. Scientists screen reaction conditions while safely controlling and recording parameters during 24 hour operation. More successful experiments per researcher increases productivity.

Seamless Integration

Incorporating real-time, *in situ* instruments into synthesis workstations allows scientists to gain in-depth process understanding. By analyzing process analytical trends and controlling temperature, mixing, dosing and pH, process events are quickly identified and corrected.

EasyMax™ 102 | EasyMax™ 402 | OptiMax™ | RX-10™



Synthesis Beyond the Round Bottom Flask

With EasyMax, OptiMax, and RX-10, experiments are easy to execute and deliver highly precise and repeatable data over a wide temperature range. Scientists are able to measure the impact that process variables have on the reaction.

In this figure, the temperature trend for the manual system shows the erratic control, which raises the potential for inconsistency such as by-product formation. EasyMax provides extremely stable temperature control, reducing the need for repetition, improving comparisons between experiments, improving the ability to detect exothermic events, and lowering the risk of by-product formation.

Learn how chemists speed Design of Experiment
www.mt.com/video-DoE

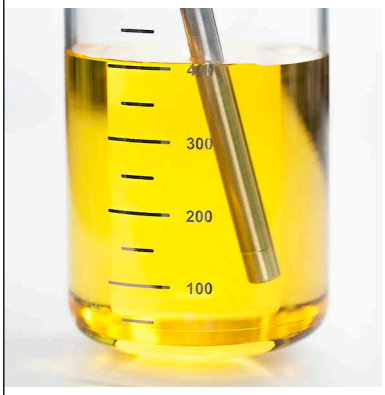
Complete Reaction Understanding
In Situ FTIR Analysis

In situ reaction analysis with Attenuated Total Reflection (ATR) Fourier Transform Infrared (FTIR) spectroscopy provides continuous monitoring of key reaction species. By following reaction progression, initiation, conversion, intermediate formation, and endpoints, researchers make informed decisions to optimize process design and quality.

Reaction Understanding

In situ reaction monitoring tracks key reactive and transient species to understand mechanism pathway, determine kinetics, and detect reaction events. Real-time monitoring provides information to control and optimize reactions where offline sampling and analysis is too slow or difficult.

Improve R&D

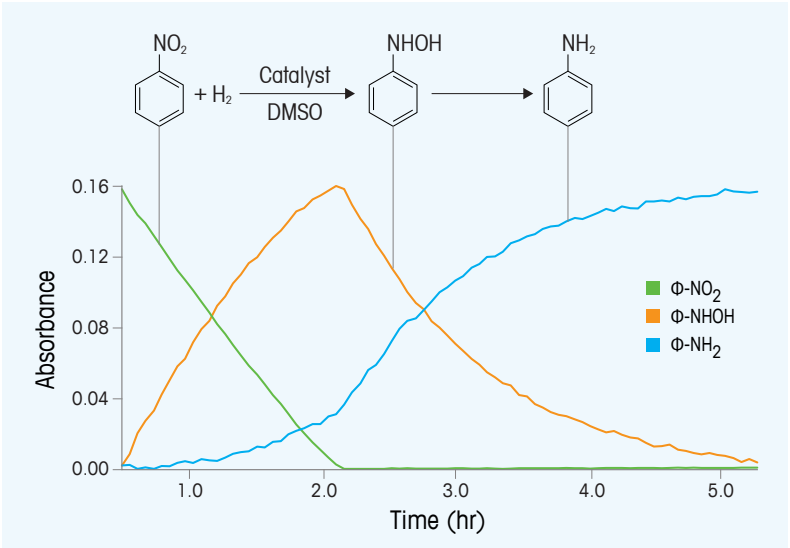


ReactIR enables chemists to develop safe, robust processes. Probe-based technology ensures easier setup and reproducible results, leading to faster process development and safer scale-up. Application examples include: flow chemistry, polymerization, high-pressure chemistry, kinetics, and many more.

Avoid Offline Sampling

Suitable for a wide range of reaction conditions (including toxic or corrosive solvents and extreme temperature or pressure), ReactIR provides real-time, *in situ* monitoring of key information for comprehensive understanding and control of reactions.

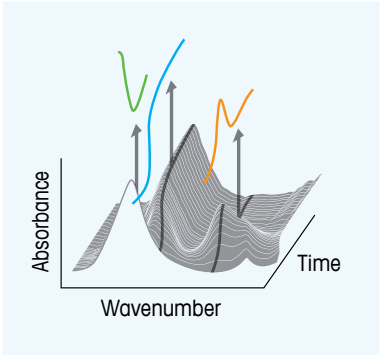
ReactIR™ 15 **ReactIR™ 45m** **ReactIR™ 45P**



Reaction Kinetics and Mechanisms

Using ReactIR, chemists avoid time delays that are associated with offline measurements. By measuring the reaction in real time, researchers gain immediate insight of the chemistry so they can make faster, more informed decisions.

In this example, ReactIR continuously takes spectra over time. Peaks are profiled as the reaction is proceeding indicating reaction initiation, endpoint, intermediates, and kinetics. This information enables scientists to fingerprint this reaction and modify the conditions to improve yield and profitability.



Researchers look to understand the impact that solvent type, catalyst, temperature, and pressure have on selectivity and reactivity.

For more watch "Introduction to ReactIR Spectroscopy"

www.mt.com/video-ReactIR

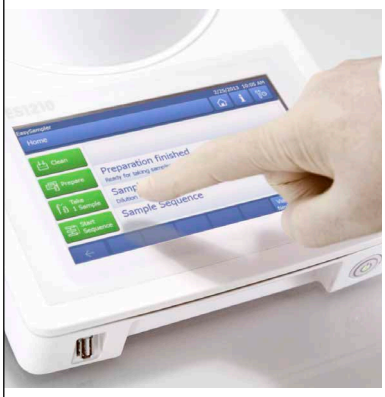
Data-Rich Experiments with Unattended, Representative Sampling

By collecting highly repeatable analytical data at regular intervals throughout each experiment, chemists get the best understanding and complete investigations in less time. Obtaining accurate and frequent samples from chemical reactions reveals fundamental insights and leads to quick, well informed decisions.

Difficult to Sample Chemistry

Gain a better understanding of chemistry from reactions where it is labor-intensive or impossible to sample, such as reactions that are air- or moisture-sensitive, highly toxic, at elevated pressure, or sub-ambient temperature.

Unattended 24/7

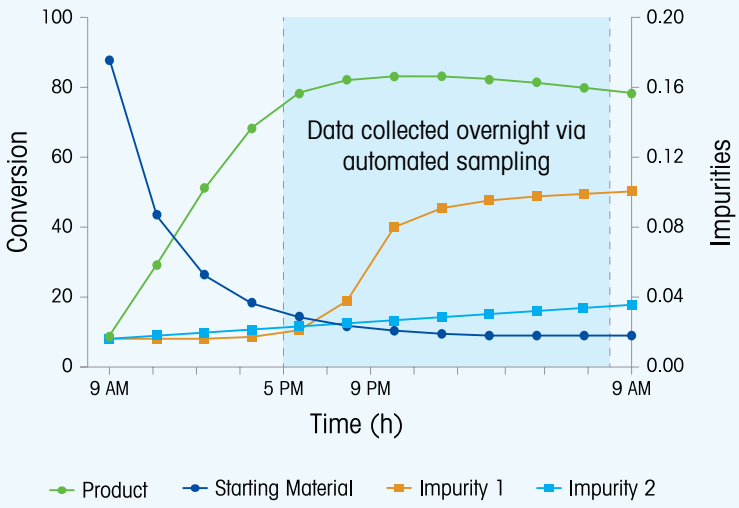


EasySampler can be easily programmed with a sequence for continued sampling operations 24 hours a day for a complete reaction profile.

Gain Fundamental Understanding

Improve yield and product quality through a comprehensive understanding of impurity profiles. Link process conditions with the points at which impurities form.

EasySampler™



Address Problems with Insightful Data

Understanding reaction kinetics and the mechanism of products, by-products, and impurities over the course of a reaction is needed in chemical development. A major hurdle in reaction progress analysis is the lack of data from reactions that must run unattended overnight.

The use of EasySampler solves the issue of information gaps and enables researchers with the ability to automatically collect, quench, and prepare HPLC-ready samples from chemical reactions 24/7.

Learn how Novartis Identified the Root Cause of By-Product Formation in a Hydrogenation Reaction

www.mt.com/wp-EasySampler

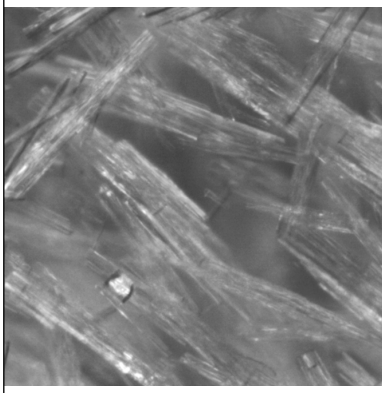
Take Control of Particle Size
Inline Particle Size, Shape, & Count

Inline particle analysis tracks the rate and degree of change to particles as they naturally exist in-process. Measure particle or droplet size, shape, and count at full process concentrations without dilution. By understanding changes to particles in real time, scientists can detect endpoints, ensure batch-to-batch consistency, and optimize downstream throughput and product quality.

Particle Size, Shape, and Count

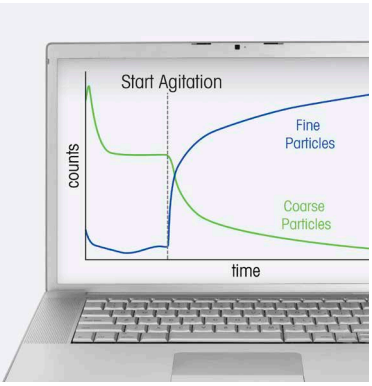
Particles directly impact performance in multiphase processes such as crystallization or emulsification. By monitoring particles in real time, scientists can confidently understand, optimize, and scale-up processes.

Understand without Sampling



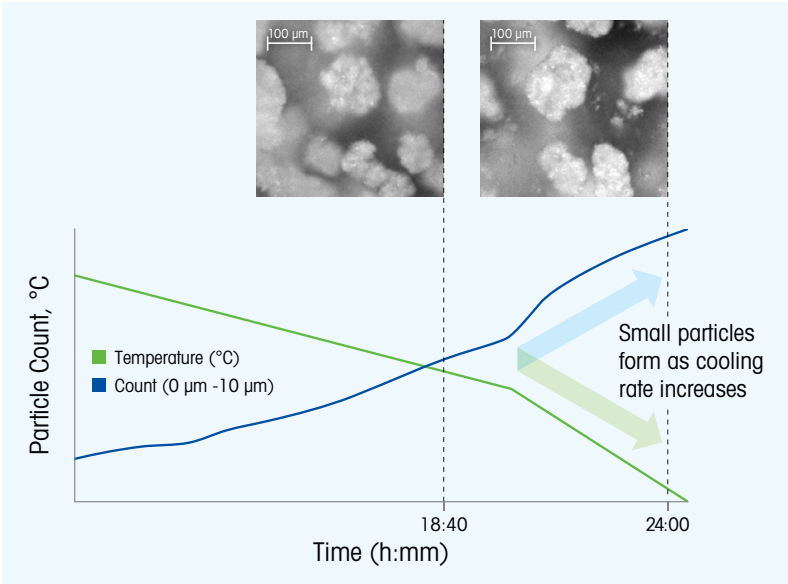
Particles can change when sampled and prepared for offline analysis. By tracking changes to size and count, as particles naturally exist in process, scientists obtain process understanding safely and with no time delay – even at extreme temperature and pressure.

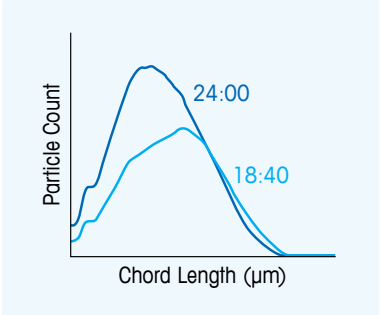
Deliver Optimized Processes



By monitoring particles continuously, as experimental parameters or raw materials vary, it is possible to conclusively determine optimized operating conditions. Evidence obtained in the laboratory and the plant, can be used to ensure fit-for-purpose particles are delivered through high-quality processes.

ParticleView™ V19 **ParticleTrack™ G400** **ParticleTrack™ G600**





Distributions for batch-to-batch can be plotted over time to compare the effects of process parameters on the particle or droplet system.

Crystallization Understanding and Control

With ParticleTrack and ParticleView, scientists routinely determine how process parameters influence particle systems. The impact of process parameters on mechanisms such as growth, agglomeration, breakage, and shape change can be identified, allowing processes to be optimized and improved using evidence-based methods.

In this example, ParticleTrack continuously measures changes to the particle size distribution and trends these changes over time. When the cooling rate increases the number of fine particles (0-10 µm) also increases. ParticleView captures real-time microscope images providing a rapid understanding of the particle size and shape. This data is used to fingerprint the process and easily identify batch deviations. By controlling fine particle formation, researchers optimize downstream isolation steps and improve product quality.

To learn more download the paper "Particle Size Analysis for Process Optimization"

www.mt.com/wp-PSA

Process Safety by Design
through Reaction Calorimetry

By establishing a culture of safety throughout all stages of development, chemists eliminate the need for frequent contact with chemicals. Risk of accidents can be minimized by automatically controlling exothermic events. Confidence in scale-up is ensured by identifying the conditions that lead to heat release and altering them to create the safest possible process.

Increase Personal Safety

Remote control over parameters such as temperature, dosing, and mixing, plus non-contact measurements with *in situ* analytics, dramatically reduces the need for researchers to come in contact with hazardous or highly exothermic reactions.

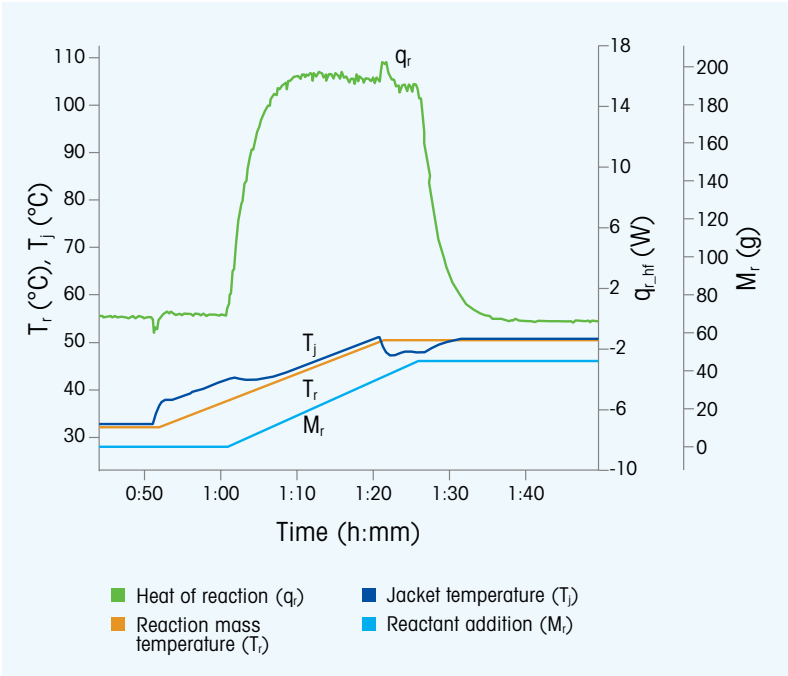
Identify Non-Scalable Events

Accurate calorimetry data is measured under all process conditions with a high level of reproducibility. Thermodynamic information, such as heat transfer, specific heat, heat flow, or enthalpy are collected ensuring even small effects are understood with confidence.

Minimize Risk and Gain Confidence in Scale-up

Predict impact of worst-case scenarios to make equipment selection at scale. Critical information (such as induction time, start/end of reaction, and max. heat release paired with enthalpy, accumulated energy, and adiabatic temperature rise) ensures potential safety issues are quickly identified.

EasyMax HFCal™ **OptiMax HFCal™** **RC1mx™**



Safety by Design

Reaction calorimeters provide early detection of unsafe processes by measuring exothermic reactions with every experiment. Even under challenging conditions, researchers gain confidence that each process is safe and scalable.

In the semi-batch reaction to the left, the reactant is added during a temperature ramp. The overlapping effects (temperature ramp, reactant addition, and the reaction itself) require an accurate determination of the heat flow across the reactor wall, the heat accumulation, and the energy needed to adjust the temperature of the added reactant. This places high demands on the measuring system accuracy and data evaluation.

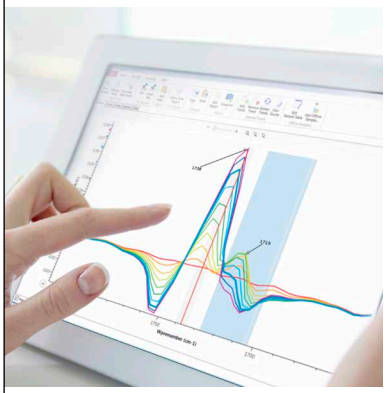
To learn more, download the guide "Risks From Rising Temperature, Safe Chemical Development Practice"

www.mt.com/wp-RisingTemp

Integrated Software
from Experiment to Decision

By overlaying and synchronizing operating conditions with inline measurements in one common interface, researchers gain an interconnected picture from each experiment. Intelligent algorithms apply big data principals to simplify the workflow from experiment to decision. This allows researchers to turn data into information, auto-generate reports, and share knowledge across an organization.

Intuitive and Intelligent

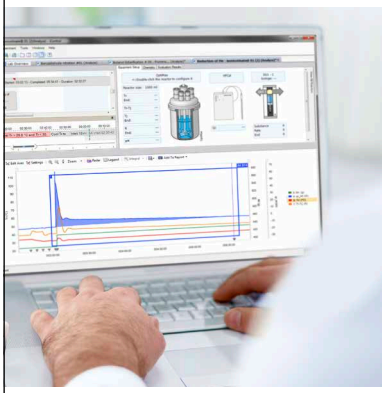


Simple yet powerful software allows consistent control and measurement of reactions and processes. This reduces human errors and training cost, and guarantees that important information will not be lost.

One Click Analytics™

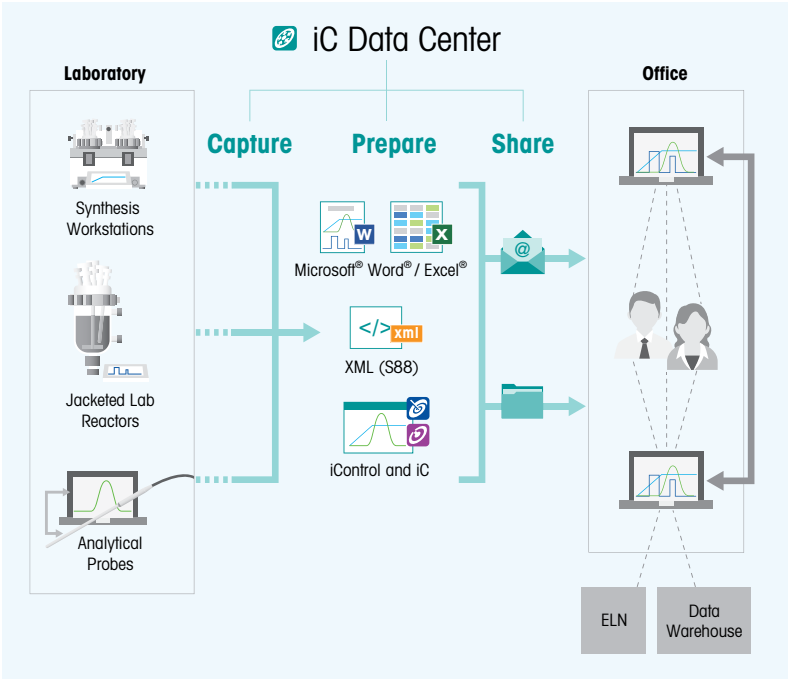
Easy-to-use analysis, reporting, and data management tools allow graphics, videos, and presentations to be created with the click of a button. Critical process knowledge can be shared easily, allowing project teams to justify decisions and reach a consensus quickly.

Application Specific Workflow



Built to analyze applications such as chemical reactions, crystallization, or calorimetry, iC software guides users through the optimal data interpretation process. Analysis specific tools means faster data analysis, enabling more time to be spent on the next experiment.

Expert Analysis for All. Integrated software enables researchers to easily extract key findings by capturing the data from all technologies in a simple and powerful platform for visualization, interpretation, and comparison.



Knowledge Management Solutions with iC Data Ceneter™

An estimated 85 % of lab data is lost because it is not transferred from lab instruments or is not recorded at all.

iC Data Center software enables knowledge management across each organization and improves regulatory compliance by ensuring all experiment data is automatically captured from the local instruments, prepared into useful formats, and shared on an electronic lab notebook (ELN) or data management system.

With an easy-to-use web-based interface for configuration, iC Data Center means users spend more time on chemistry and less time moving files or converting data into other formats.

To learn more, download the white paper "Turning 85% of Experimental Data Loss Into 100% Data Capture"

www.mt.com/wp-iCDC

Supporting Research and Analysis with a Wide Range of Technologies

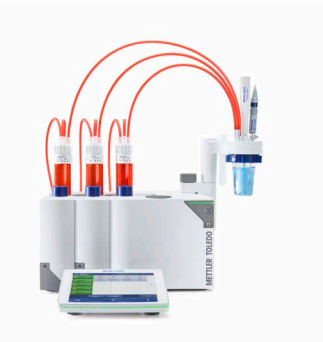
METTLER TOLEDO's comprehensive product range provides users with flexibility and precision in every application plus outstanding quality and functionality.

Weighing
METTLER TOLEDO is constantly changing the world of balances. The Quantos™ automated dosing and sample preparation solution and innovations such as StatusLight, StaticDetect and SmartGrid provide complete weighing security. Our comprehensive portfolio of lab balances offers maximum user protection, unparalleled measurement performance, full data security and seamless traceability.

Titration
The new generation of titration solutions focuses on ease of use and flexibility: Its unique OneClick™ user interface keeps training times to a minimum and speeds up workflows. The completely automatic recognition of connected sensors, burettes and other accessories saves time while also enhancing operational safety. The modular design ensures perfect adaption to any titration application.

pH Measurement
From basic handhelds to flexible two-channel meters, METTLER TOLEDO offers a full spectrum of premium quality pH and ion instruments. SevenExcellence™ meters, for example, stand for easy-to-understand operation, high measurement accuracy and outstanding flexibility. Depending on the module attached, various parameters such as pH, conductivity etc. can be measured.

Thermal Analysis
METTLER TOLEDO is the technology leader in thermal analysis instrumentation. The innovative product range includes DSC™, TGA™, TMA™ and DMA™, as well as an unmatched, very powerful common software platform. Recent innovations such as Flash DSC, the TOPEM® modulation technique and the HSS7 DSC sensor guarantee better results at higher sensitivities.



Physical Values
METTLER TOLEDO's digital instruments determine the refractive index and density simply, accurately, and, depending on the instrument, even simultaneously. Additionally, METTLER TOLEDO offers a comprehensive array of easy-to-use instruments, to quickly and reliably determine thermal data. Using optical and calorimetric methods, the instruments measure materials' physical properties and phase changes.

Pipetting
RAININ pipettes enhance lab performance and help reduce time-to-market by guaranteeing optimum accuracy and repeatability. Innovative ergonomic designs, including the patented LTS LiteTouch™ System, minimize fatigue and injuries, thus helping to reduce operator errors and inaccuracies. RAININ's calibration and maintenance services are built on METTLER TOLEDO's high-precision balances and expertise.

UV/VIS Spectroscopy
FastTrack™ UV/VIS technology and OneClick™ operation comprise the basis for sustainable, trustworthy performance for the fast and simple operation of the UV/VIS Excellence line. The PC Software LabX® fosters fast spectral data management and seamless integration into a METTLER TOLEDO based instrument network.

Automated Chemistry
METTLER TOLEDO provides the enabling technology, software and people that can help build a seamless workflow to transform bench scale chemistry into a commercial process. Our enabling tools and services have been a strategic resource providing critical information to thousands of development scientists and engineers for more than 20 years.

Learn More

METTLER TOLEDO is the world leader for automated synthesis and inline analytics. Obtain specific information about scientific applications and industry trends through peer-reviewed scientific papers, white papers, seminars, and case studies.

Application Literature
Comprehensive application examples are available in a wide range of topics including impurity profiling, reaction kinetics, flow chemistry, crystallization, reaction calorimetry, mixing and mass transfer, heat transfer, and scale-up.

▸ **www.mt.com/ac-library**

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