Pharmaceutical analysis

Quality control of pharmaceuticals

Metrohm

Metrohm ...

- is the global market leader in titration
- offers a complete portfolio for NIR and Raman analysis, in addition to all of the methods of ion analysis – titration, voltammetry, and ion chromatography
- is a Swiss company and manufactures exclusively in Switzerland
- grants a 3-year instrument warranty and a 10-year warranty on chemical suppressors for anion chromatography
- provides you with unparalleled application expertise
- offers you more than 1800 applications free of charge
- supports you with dependable on-site service worldwide
- is not listed on the stock exchange, but is owned by a foundation
- takes a sustainable approach to corporate management, putting the interests of customers and employees ahead of maximizing profit

Metrohm – customized analysis for the pharmaceutical industry

The high standards of approval authorities

Authorities around the globe hold the pharmaceutical industry to very high standards of drug quality and safety. The standards are documented in official collections of recognized pharmaceutical rules in pharmacopoeias. They provide a legal consumer protection framework for ensuring that drugs are used safely. Measurement and testing procedures used in the context of drug testing identify drugs and determine whether they can be released.

Reliable instruments and methods are required to guarantee these strict quality and safety standards.

You can count on our support

As a leading manufacturer of instruments for chemical analysis, we are well aware of the challenges you face. For this reason, Metrohm offers you not only the most advanced instruments, but also complete solutions for analytical studies. Your partners at Metrohm are competent specialists who develop customized applications and offer competent support in every aspect of regulatory compliance.

Discover the solutions Metrohm offers the pharmaceutical industry and you in particular for ensuring the quality and safety of your products.

Chemical pharmaceutical analysis

04

The history of pharmacology

The search for medicines is nearly as old as humanity itself. Documentary evidence exists to show that active pharmaceutical ingredients from plant, mineral, and animal sources were already being used for medicinal purposes by the earliest advanced civilizations (China, India, Mesopotamia and Egypt). Systematic descriptions of medicines have been handed down to us from Greek antiquity (Hippocrates, Theophrastus) and from the Roman Empire (Dioscorides, Galen). This knowledge was adopted and further developed by Arab scholars (e.g., Avicenna). This body of knowledge served for a long time as an important basis for pharmacology. It was not until the 16th century that the science began its departure from the models passed down from antiquity. A typical representative of the new direction was Paracelsus, who – in 1537 – coined the famous phrase: «The dose makes the poison» («dosis sola facit venenum»).

The path to organic synthetic drugs

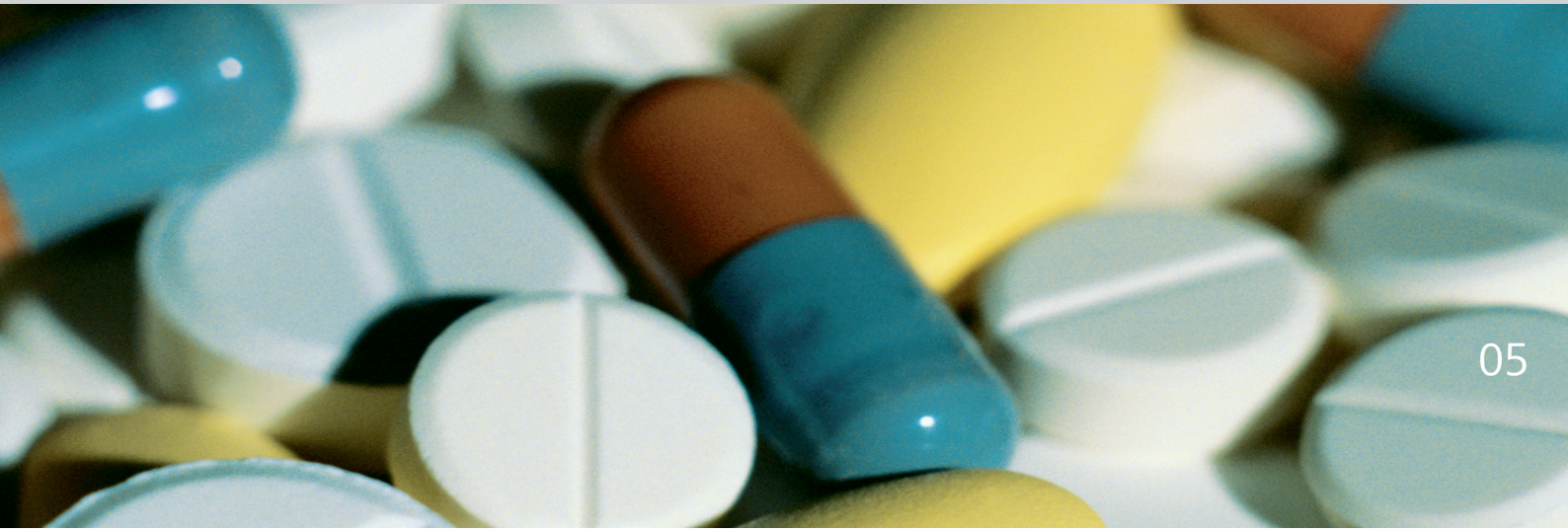
The significance of the advances that came with the emergence of organic chemistry at the dawn of the 19th century cannot be overstated. Although drug therapies up to that point had been limited to naturally occurring substances and inorganic chemicals, this changed with the targeted production of organic synthetic drugs based on substances isolated from medicinal plants. Within a very short period, an unprecedented advance in pharmaceutical synthesis led to a vast number of synthesized active pharmaceutical ingredients. Researchers had finally come to understand the relationship between the action of these substances and their chemical structures.

Determination of active ingredients, excipients, and impurities

Pharmaceutical analysis provides information on the identity, purity, content and stability of starting materials, excipients, and active pharmaceutical ingredients (API). A distinction is made between analysis of the pure active pharmaceutical ingredients used to cure, alleviate, prevent, or identify illnesses and diseases (active ingredient analysis) and analysis of drug products (drug product analysis). Drug products come in various forms (ointments, tinctures, pills, lotions, suppositories, infusions, drops, etc.) and consist of the pharmaceutically active substance and at least one pharmaceutical excipient. Impurities are mainly introduced during the synthesis of the active ingredient, and are usually monitored according to both the directives of the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) and the pharmacopoeias.

Pharmacopoeias and drug safety

According to the World Health Organization (WHO), specifications and test methods for commonly used active ingredients and excipients are outlined in detail in monographs contained in the national pharmacopoeias of more than 38 countries. These include the United States Pharmacopeia (USP), the European Pharmacopoeia (Ph.Eur.), derived from a harmonization of the regulations of a number of individual states, and the Japanese Pharmacopoeia (JP), to name just a few examples. The pharmacopoeias are official compendia containing statutory requirements pertaining to identity, content, quality, purity, packaging, storage, and labeling of active pharmaceutical ingredients and other products used for therapeutic purposes. They are essential for anyone seeking to produce, test, or market medicinal products.



Test methods, tests, and USP-NF monographs

Applications in accordance with pharmacopoeias

Metrohm is your qualified partner for all chemical-pharmaceutical analysis issues and for analytical methods validation. In addition to their compliance with official directives, Metrohm instruments and applications comply with many of the quality control and product approval test methods cited in pharmacopoeias.

Harmonization efforts

Based on the harmonization efforts of the Pharmacopoeial Discussion Group (PDG), this brochure relates primarily to selected test methods and monographs of the USP as representative of the pharmacopoias not mentioned here. The National Formulary (NF) is the official compendium of standards for excipients and plant-based drugs.

Structure of the USP-NF

Four chapters form the backbone of the USP-NF. One chapter provides the analytical tools of the pharmacopoeia with a detailed description of test methods and tests. Test methods numbered from <1> to <1000> are mandatory, whereas the procedures with numbers above <1000> are recommended.

The most comprehensive chapter of the USP-NF contains a list of the USP monographs, listed alphabetically according to active pharmaceutical ingredient, which provide detailed descriptions of test methods, tests, requirements, and storage conditions. The scope of the NF monographs is an order of magnitude smaller and is contained in a separate chapter. Another chapter defines the reagents, indicators, and solutions to use.

Test methods referenced in USP-NF monographs

Application/parameters	USP monograph	Citation frequency of the test method	Test methods	Page
pH value	USP<791>	In approx. 1400 USP monographs In approx. 250 NF monographs	pH value measurement	6
Conductivity	USP<645>	Ultrapure water (pharma)	Conductivity measurement	6
Various APIs Various excipients	USP<541>	In approx. 250 USP monographs In approx. 130 NF monographs	Titration	7–11
Water content	USP<921> Method I	In approx. 630 USP monographs In approx. 110 NF monographs	Karl Fischer titration	12–13
Various APIs Various excipients Amino acids	USP<621> USP<1065> USP<1052>, Method I	In approx. 58 USP and 13 NF monographs In 3 NF monographs In 5 USP monographs	Ion chromatography	18–21
Various APIs Thiomersal Heavy metals	USP<801> USP<341> USP<232>, <233>	In 8 USP monographs Various antimicrobial agent determinations In approx. 780 USP and 230 NF monographs	Polarography	22–23 23
Various parameters	USP<1119>	Various	Near-infrared spectroscopy	26–28
Various process parameters	Process-dependent	Various	Process analysis	29–33

In addition to the above-mentioned methods, this brochure contains chapters on automated sample preparation (pages 14–15), determination of oxidation stability in ointments and creams (pages 16–17), and analysis of electroactive pharmaceuticals using electrochemistry (page 24). The brochure concludes with a final chapter on the comprehensive services provided by Metrohm Quality Service on pages 34 and 35.

Water for pharmaceutical use (water for injection)

pH value

The 867 pH Module provides everything you need to measure the pH value according to USP<791>: it meets the requirements of FDA Regulation 21 CFR Part 11 thanks to either 900 Touch Control or ***tiamo*** full software. An electrode test can be performed in conjunction with ***tiamo*** or 900 Touch Control. Conductivity and pH value can be measured in the same vessel when the 856 Conductivity Module is combined with the 867 pH Module.

Conductivity

Particularly strict regulations apply to the measurement of the conductivity of water for pharmaceutical use (water for injection) in accordance with USP<645>. In addition to the highest level of precision, the test must fulfill all of the requirements of U.S. FDA Regulation 21 CFR Part 11. Compliance is assured using the 856 Conductivity Module in combination with the 900 Touch Control or ***tiamo*** full.

Conductivity measuring cell with Pt1000

This measuring cell was developed especially for measurements in water with very low conductivity. The robust stainless steel construction is easy to clean and ideal suited for conductivity values < 300 µS/cm, and thus for measuring waters for pharmaceutical use.

Application know-how from the experts

Because of their simplicity and accuracy, titration methods are used for a large proportion of the content determinations described in the monographs, for example in accordance with USP<541>. Taking into account the latest methodological findings, Metrohm has developed hundreds of titration methods with Metrosensors based on the U.S. Pharmacopeia (USP) and European Pharmacopoeia (Ph. Eur.).

Some older USP methods are still based on high sample weights with a titrant consumption of up to 50 mL. Based on Ph. Eur., Metrohm has reduced the sample weights considerably, reducing titrant consumption to at most 10 mL.

All the methods were developed to enable you to adopt them as SOPs (Standard Operating Procedures) in your titration laboratory.

Aqueous acid-base titrations	Titrations with bases or acids Indirect titration (back titration) Determination of enzyme activity (lipase, trypsin, etc.)
Nonaqueous acid-base titrations	**Alkaline titrants** In ethanol with the addition of HCl In dimethylformamide (DMF) In acetone In pyridine In ethanol or methanol In special solvents **Acidic titrants** In glacial acetic acid, with $HClO_4$ In glacial acetic acid/acetic anhydride, with $HClO_4$ In glacial acetic acid plus mercury acetate, with $HClO_4$ In glacial acetic acid/methyl ethyl ketone, with $HClO_4$ In formic acid/glacial acetic acid or acetic anhydride with $HClO_4$ In other solvents or solvent mixtures
Redox titrations	Iodine/thiosulfate (iodometry) Iodine/arsenite (iodometry) Diazotization with $NaNO_2$ Cer(IV) (cerimetry) $KBrO_3$ (bromatometry) $KMnO_4$ (permanganometry) KIO_3 Reducing sugars
Precipitation titrations	$AgNO_3$ (argentometry) Surfactant titrations
Photometric titrations	Photometric EDTA titrations (chelatometry/complexometry)
Characteristic fat and oil values	Acid number and free fatty acids (FFA) Hydroxyl number Iodine value Peroxide value Saponification number

Titrando – the smart titrator with comprehensive security

Thanks to its modular design, the Titrando System can be optimally adapted to any application. Both as a stand-alone titrator and in combination with the 900 Touch Control or ***tiamo***, it is in compliance with FDA Regulation 21 CFR Part 11.

Certified and smart dosing elements

Metrohm dosing elements set new standards in reliability. An inconspicuous data chip contains all the data that the Titrando needs to perform titrations, i.e., serial number, cylinder number, type of reagent, titer, last titer determination, shelf-life data, and much more. But that's not all – the Titrando compares the data it has obtained with that of the selected method and issues an error message if they do not agree.

iTrodes – intelligent electrodes

The electrode is the most important part of any titration system. The Titrando with iConnect and iTrodes guarantees complete traceability of the analytic result to every participating component in the analysis. The chip integrated in the electrode head enables the storage of important sensor data such as article number, serial number, calibration data, calibration history, and calibration interval. All of the sensor data is uploaded automatically when the sensor is connected to the Titrando. This provides added security because the user is informed if the electrode type does not match the type specified in the method.

STAT titration with tandem dosing

The determination of enzyme activity (lipase, trypsin, etc.) or the release of active ingredients from antacid tablets requires a titrator that rapidly adjusts to a preset pH value and keeps it constant over a long period. Tandem dosing prevents dosing interruptions when burets are refilled during titration – a second burette immediately takes over dosing. This means that rapid and consumption-intensive reactions can be monitored in real time.

Flexibility – from individual instruments to fully automated systems

Increasing numbers of samples, time-consuming sample preparation, and unattended overnight operation are all good reasons for using sample changers. When combined with the 814 USB Sample Processor, the 815 Robotic USB Sample Processor XL, and the 898 XYZ Sample Changer, the Titrando offers a high degree of automation at a low investment cost. The 855 Robotic Sample Processor combines a first-rate Robotic Sample Processor with a Titrando and takes up minimal space.

Sample preparation at the press of a button

Metrohm instruments not only handle analysis itself, but as demonstrated by the 815 Robotic SoliPrep (see pages 14 and 15), also perform the most frequent sample preparation steps.

- **Homogenization**
  The Polytron PT 1300 D made by Kinematica ensures reproducible particle size reduction and homogenization of all samples.
- **Filtration**
  Commercially available syringe filters with standard Luer connectors can be used directly with the Robotic Soliprep.
- **Liquid Handling**
  From dilution series to sample filling in sealed vessels, there are no limits to Liquid Handling with Metrohm.

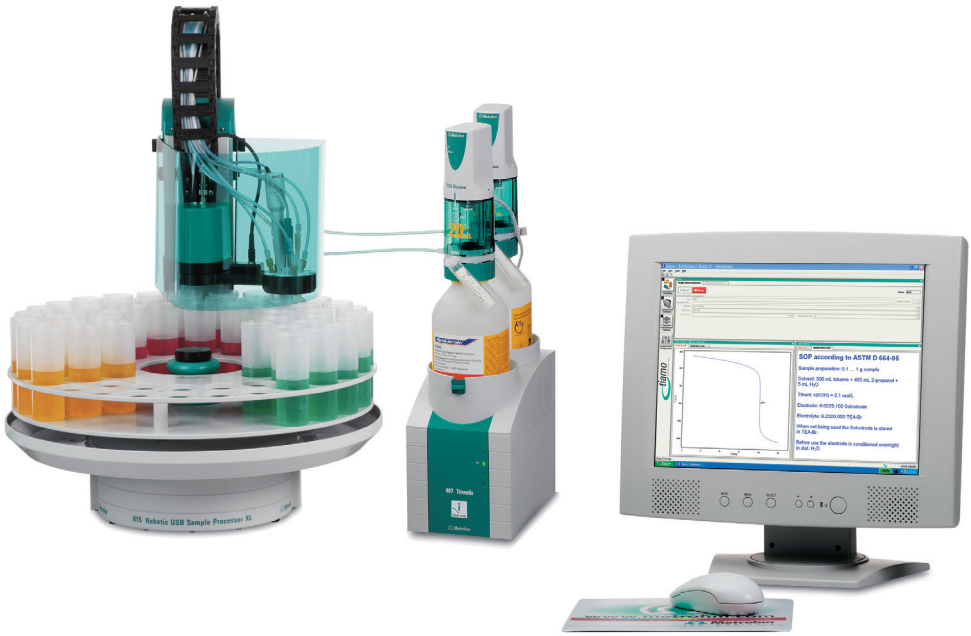
tiamo – titration and more

tiamo is the leader in control and database software, not only for titrators and dosing devices, but also for total laboratory automation that includes the client/server system. The name ***tiamo*** stands for "titration and more" – ***tiamo*** can do more than just titrate. ***tiamo*** is a titration network (NTDS = Networked Titration Data System).

- ***tiamo* guarantees data security**
  Whether you need to satisfy GMP or GLP rules, regulations regarding the security of electronic data, or traceability requirement for results in accordance with the FDA's Regulation 21 CFR Part 11, ***tiamo*** has been developed from the ground up to comply with all of these requirements and is setting new standards.
- **Signatures**
  You can add digital signatures to determinations. ***tiamo*** offers two levels of signatures. The data becomes write-protected as soon as the determination is assigned a level 2 signature.
- **User administration**
  Assign the access rights of each user according to your company's in-house security policy. ***tiamo*** sets no limits and impresses with its unique flexibility.
- **Complete audit trail**
  Every user-performed action is automatically stored in the audit trail. Audit data is available at the press of a button.
- **Traceability**
  Play it safe and entrust your titration work only to the traceability of Metrohm software and hardware. Every data record contains all the raw data necessary to ensure traceability.
- **Data export**
  tiamo offers you a wide selection of export formats, including XML. Your data are available to all conceivable Office applications, databases, and long-term archiving programs.
- **Reprocessing a determination**
  Incorrect sample size? No problem. With the reprocessing function you do not have to worry about your documentation. ***tiamo*** automatically records all changes, thus providing a comprehensive overview.
- **Report generator**
  The report generator gives you full control over the design of your analytical reports. Modify one of the many report templates to suit your needs, and conveniently send the report by e-mail.
- **Data security**
  tiamo helps you ensure data security. When you activate the automatic backup function, ***tiamo*** will then automatically make complete copies of all determinations and configurations.
- **Client/server functionality**
  In the simplest case you install the databases on your local measurement computer. ***tiamo*** grows along with your requirements. You can configure ***tiamo*** later as a client/server whenever data security and central data management make this a requirement.
- **Plug and play**
  Our modern USB devices ensure that all connected devices appear in the devices window. Monitoring options rule out the use of system components that are wrong or have expired.
- **Parallel titration**
  tiamo and Titrando make a powerful team. Parallel titrations – if necessary, carried out by different users – increase efficiency.

Automatic nonaqueous titration with the MATi 03

Enormous time savings and results that are more accurate and precise are the crucial benefits of automation. The MATi 03 (Metrohm Automated Titration) is specially designed for nonaqueous titrations in the pharmaceutical industry – both potentiometric and photometric. Series of up to 59 samples can be accommodated on the 815 Robotic USB Sample Processor XL. ***tiamo*** is responsible for all of the controls. The system is noteworthy for its high resistance to organic solvents.



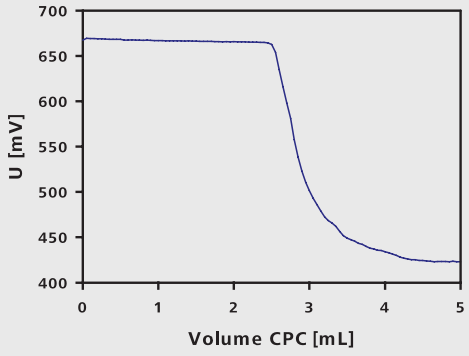
The MATi 03 with 815 Robotic USB Sample Processor XL (left) and 907 Titrando (center)

Photometric titrations with the Optrode

Maximum precision

Titrations using color indicators are still widely used in pharmacopoeias (chelatometry/complexometry), but when performed manually, the results depend, quite literally, on the eye of the beholder. The new Optrode makes it possible to replace this subjective determination of the equivalence point with an objective process that is completely independent of the human eye. Its eight wavelengths, ranging from 470 to 660 nm, cover a broad spectrum of color indicators. The great advantage of this is that the chemistry does not change – that is, the standard operation procedure generally does not have to be adapted. In addition to the determination of chondroitin sulfate (T-083) described below, bismuth nitrate (T-088), manganese sulfate (T-089), and zinc sulfate (T-090) can also be determined in accordance with Ph. Eur. and USP.

The Optrode – highest measurement precision in photometric titration



In accordance with Ph. Eur. and USP: photometric determination of chondroitin sulfate using the Optrode (660 nm) and with 1-hexadecylpyridinium chloride (also called cetylpyridinium chloride, CPC) as titrant

More information and more than 1800 other applications can be downloaded free of charge at:
www.metrohm.com/applications/

Water determination according to Karl Fischer

The quality, effectiveness, and shelf life of pharmaceutical products depends to a very great extent on their water content, which is why a great deal of importance is attached to water determination in pharmaceutical analysis. Thanks to its specific and selective reaction with water, Karl Fischer titration (KFT) is one of the most accurate and reproducible water determination methods, which is why numerous pharmacopoeias have prescribed it for years as a standard method for fast, automation-ready water determination.

If the test substance is completely soluble in the Karl Fischer reagent and if it does not enter into any side reactions with the solvent, the sample can be added directly into the titration cell. The water content can then be determined directly using volumetry or coulometry.

Not all substances dissolve completely in methanol, but that is an important prerequisite for correct determination of a sample's water content. Some techniques for improving the solubility of samples are listed below. These techniques can also be combined with one another.

Solubility promoters

Solubility promoters can be added, depending on the test substance. For samples containing fat or oil, such as ointments or creams, chloroform is added to the KF reagent to ensure that the sample dissolves completely.

High-frequency homogenizers

Tablets must be pulverized before titration. This can either be done manually with a mortar or, more conveniently and above all more reproducibly, using a high-frequency homogenizer directly in the closed titration cell. The latter method prevents any changes to the water content of the sample during preparation. In some cases, it can also eliminate the need for toxic solubility promoters.

Higher temperatures in the titration cell

Another option is titration of the water at a higher temperature (e.g., at 50 °C).

901 Titrando with 900 Touch Control

The 852 Titrando for volumetric and coulometric water determination

860 KF Thermoprep with 901 Titrando, 803 Ti Stand, and 900 Touch Control

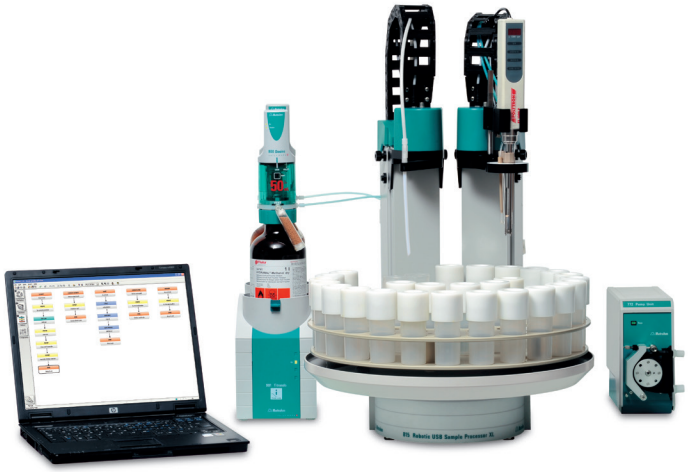
Thermostatically controlled titration cell

Karl Fischer oven method

Many substances release their water only very slowly or only at high temperatures. Some react with KF reagents to form water or consume iodine, thus resulting in an erroneous determination of water content. Such samples are unsuitable for direct Karl Fischer titration. Both the U.S. Pharmacopeia and the European Pharmacopoeia require determination of the drying loss in a drying oven or desiccator for such substances. The drawback of this method, however, is that it determines not only the water content, but also that of other volatile constituents contained in the sample.

In the KF oven method, the test substance is heated in a tightly sealed vessel in an oven. The water driven off from the sample is transferred with a stream of dry carrier gas into the titration cell, where it is determined as a rule with coulometric Karl Fischer titration. The possibility of side reactions and matrix effects can be excluded because the sample itself remains in the vessel and only water enters the titration cell.

The 874 Oven Sample Processor with 852 Titrando



MATi 11 – fully automatic Karl Fischer titration including sample preparation

Sample preparation

The complete range of automatic sample preparation from a single source

Normally, accurate pipetting and dilution of the sample is enough to determine the liquid forms of drugs (tinctures, infusions, drops, etc.). Metrohm offers you a wide range of products for automated, precise, and time-saving preparation of liquid samples.

Sample preparation becomes more demanding, however, when solid or semisolid samples are involved, i.e., tablets, suppositories, and ointments. As a specialist in the field of laboratory automation, we also offer you a wide range of solutions for the preparation of solid samples – customized to your needs upon request.

Automation: time savings and more accurate results

In addition to direct titration, chromatographic methods such as IC, HPLC, and GC are of primary use in pharmaceuticals analysis. These techniques require that the sample is available as a filtered liquid before it is injected on to the column. When carried out manually, as is often the case, sample preparation steps such as

- pulverization and homogenization
- filtration
- pipetting and dilution

are tedious and time-consuming. Furthermore, manual sample preparation involves the risk of inaccurate results. Consistent sample preparation quality can hardly be guaranteed, particularly in cases of high sample throughput and when several people are involved.

Fully automated sample preparation and analysis of tablets: following the addition of a solvent, the Polytron high-frequency homogenizer pulverizes the tablets directly in the sample beaker. Every sample gets the same treatment.

The 815 Robotic Filtration Soliprep

Fully automated filtration: The 815 Robotic Filtration Soliprep filters out residual solid matter from the homogenized sample. What remains is a clear filtrate that can be either injected directly into an analyzer or subjected to further dilution.

Robotic Soliprep – automatic sample preparation tailored to your needs

With the instruments of the Robotic Soliprep family, neither deviation in results nor time-consuming manual routines are an issue any longer. The solid substance is simply weighed out and placed on the sample rack – everything else is completely automated. Depending on the version selected, different steps can be combined – including the direct connection to a chromatograph or the titration of the homogenized sample.

	Robotic Titration Soliprep	Robotic Filtration Soliprep	Robotic Flexible Soliprep	Robotic Soliprep for LC
Homogenization	+	+	+	+
Titration	+			
Filtration		+	+	+
HPLC/GC vial filling			+	
Connection to an LC instrument				+

Oxidation stability

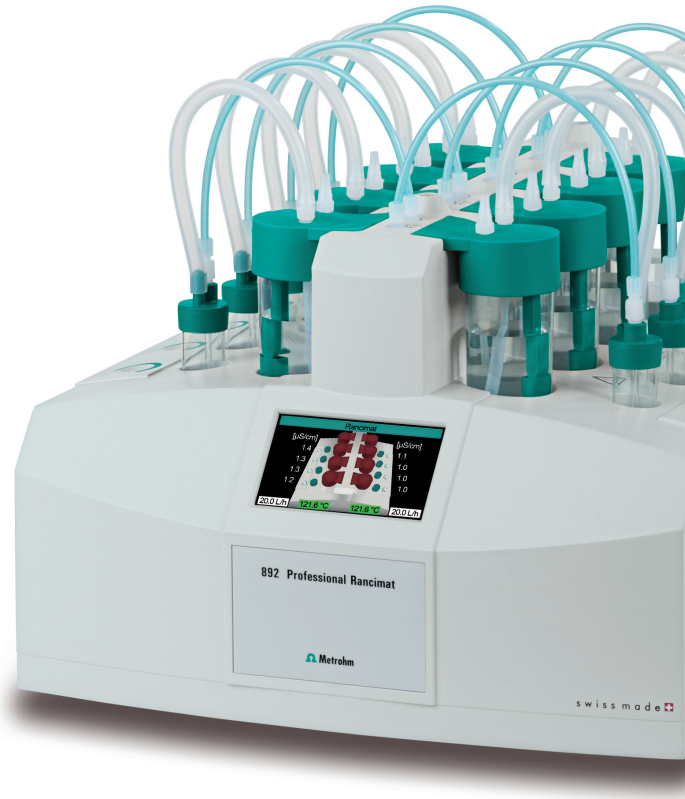
Ointments, lotions, and cosmetics

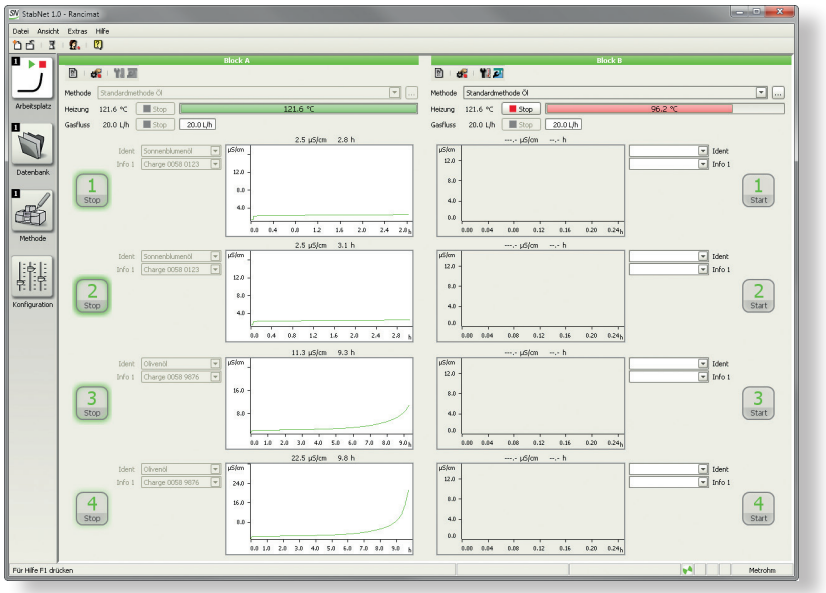
Natural fats and oils have limited storage stability because they are slowly oxidized by atmospheric oxygen. The oxidation stability of fats and oils has been a default parameter in quality assurance for many years. To determine oxidation stability with the Rancimat method, air is passed through the test sample at a high temperature to cause artificial aging. During this process, the fatty acids are oxidized by oxygen, forming volatile organic compounds and other products. These are driven off by the air flow and absorbed in water, where they are detected with conductivity measurement. The time it takes for these decomposition products to form is known as the induction time and characterizes the resistance of the sample to oxidative aging processes, i.e., its oxidation stability.

The method is used to monitor natural fats and oils that are used in the manufacture of aliphatic pharmaceutical products such as ointments, creams, and lotions. In many cases, however, it is also possible to investigate the oxidation stability of the finished formulations. For this to work properly, the proportion of fat in the sample must be significantly higher than the proportion of water.

892 Professional Rancimat and StabNet software

The 892 Professional Rancimat enables simple and reliable determination of oxidation stability in natural fats and oils for up to eight samples. The instrument is controlled by a PC using StabNet software to plot measurement curves, evaluate them automatically, and calculate the result.





Rancimat control with StabNet software: Up to eight samples can be analyzed simultaneously for oxidation stability – and all in conformance with FDA and GLP requirements.

Ion chromatography

Ion chromatography (IC) is the method of choice for determining active pharmaceutical ingredients, excipients, traces of impurities, and metabolites in the form of organic and inorganic ions or polar substances – not only in a broad range of pharmaceuticals and pharmaceutical solutions, but also in bodily fluids. Ion chromatography can determine chemically similar substances in a very short time in just a single analysis. The concentration range of the analytes can extend from ng/L up to the percentage range. Another advantage is the large selection of separation columns and elution systems available. Interfering matrix effects can be avoided by using a suitable inline sample preparation method or through the choice of detection method:

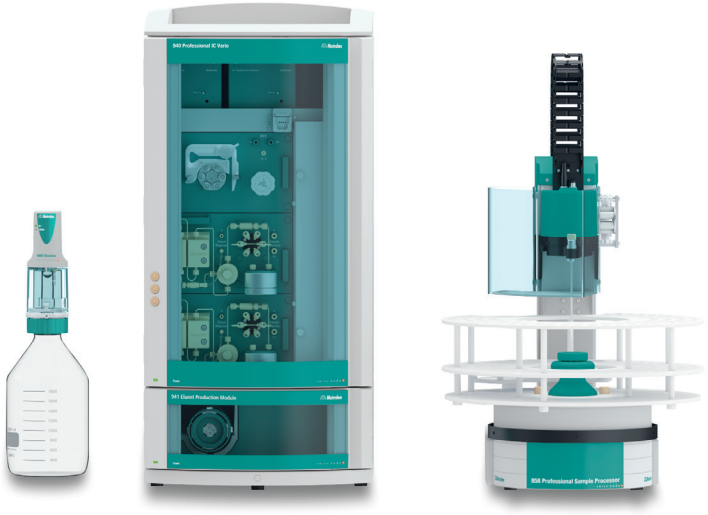
- Conductivity detection with or without chemical suppression
- Amperometric detection
- Spectrophotometric detection – direct or with post-column derivatization (UV/VIS)
- Coupled detection methods such as IC-MS and IC-ICP/MS

The intelligent ion chromatographs with their automation devices and peripheral equipment are controlled by the user-friendly MagIC Net software. Complete documentation on the status of the analytical instruments and user activities enables complete traceability of the analytical results. MagIC Net supports FDA Regulation 21 CFR Part 11, and offers numerous tools for compliance with GLP guidelines.

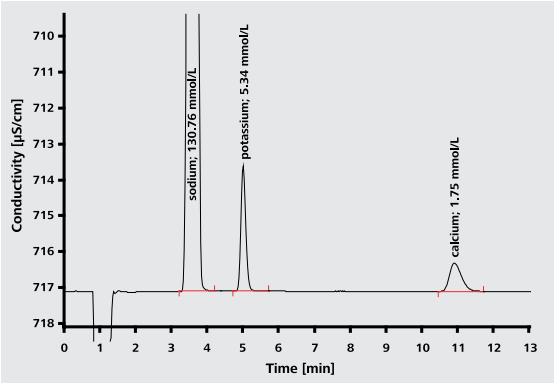
Metrohm ion chromatographs can also be operated with Empower™ software from Waters. In a certified environment, uniform software minimizes training requirements and reduces expenses associated with GLP compliance.

Pharmaceutical solutions

The term «pharmaceutical solutions» denotes isotonic solutions, hemodialysis solutions, or infusion solutions. They contain anions, cations, carbohydrates, and organic acids, the concentrations of which frequently differ from one another by several orders of magnitude. In the context of production monitoring and final quality control, these ingredients need to be determined easily, quickly, and with a high degree of precision. Ion chromatography is well up to this task with its intelligent analysis technique and automatic inline sample preparation.



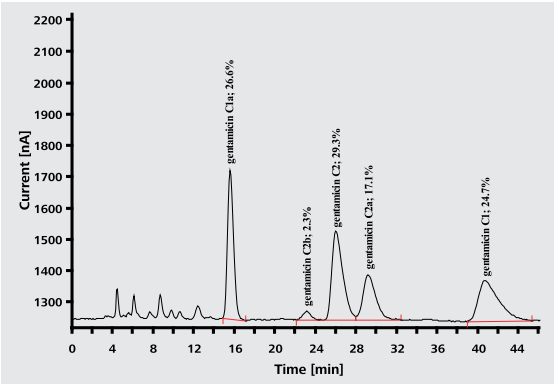
940 Professional IC Vario with 941 Eluent Production Module and 858 Professional Sample Processor: an intelligent ion chromatography system for parallel determination of anions and cations in pharmaceutical products



Cation analysis of a solution of Ringer's lactate. Column: Metrosep C 4 - 100/4.0; Eluent: 1.7 mmol/L HNO_3, 0.7 mmol/L dipicolinic acid, 0.9 mL/min; sample volume: 10 µL; 1:20 (v/v) Inline Dilution

Active pharmaceutical ingredients

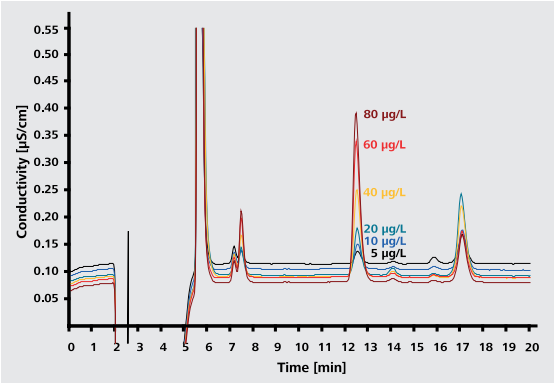
Active pharmaceutical ingredients in tablets such as gentamicin, neomycin, cefadroxil, or bethanechol chloride can be determined by ion chromatography in accordance with the regulations of the U.S. Pharmacopeia and European Pharmacopoeia. Requirements with regard to precision, separation, and recovery of the analytes are described in detail in the pharmacopoeias.



IC determination of the antibiotic gentamicin with pulsed amperometric detection. Column: Polymer Laboratories RP-S; eluent: 60 g/L Na_2SO_4, 1.75 g/L sodium octane sulfonate, 1.34 g/L NaH_2PO_4, 8 mL/L THF (pH = 3, H_3PO_4), 1.0 mL/min; column temperature: 55 °C; sample volume: 20 µL; post-column addition: 300 mmol/L NaOH (0.4 mL/min)

Impurities in pharmaceuticals

In addition to active pharmaceutical ingredient analysis, ion chromatography can also be used to determine impurities in pharmaceutical products. Even small concentrations of an impurity can cause significant side effects. The azide used in the synthesis of the antihypertensive Irbesartan can be detected in trace amounts as an impurity in the product. The U.S. Pharmacopeia recommends ion chromatographic azide determination after direct injection in accordance with USP<621>. The azide determination is more selective, more sensitive, and most importantly – faster – when using Inline Matrix Elimination, whereby the interfering pharmaceutical matrix is already separated from the target analyte during the sample preparation step.



Irbesartan sample spiked with 5–80 µg/L azide; Column: Metrosep A Supp 10 - 250/4.0; eluent: 5 mmol/L Na_2CO_3, 5 mol/L $NaHCO_3$, 1.0 mL/min; column temperature: 60 °C; sample volume: 1000 µL; Inline Matrix Elimination with 70:30 (v/v) methanol/water

Precision and recovery of the azide

	Peak area		
	Mean value [µS/cm]	RSD [%]	Recovery [%]
5 µg/L spike	0.4223	1.96	101.71
30 µg/L spike	2.5754	0.14	103.38

n = 3 measurements

Radiopharmaceuticals in nuclear medicine

Radiopharmaceuticals are radioactive substances used in diagnostic procedures such as positron emission tomography (PET). They consist of an inert or biologically active molecule bonded with a radioactive isotope, a so-called radionuclide. Radiopharmaceuticals participate in metabolic processes, which is why they are critical for gaining an understanding of biochemical and physiological processes in oncology, cardiology, and neurology.

Useful annihilation radiation

PET is based on the fact that every time a nuclide decays, a positron is emitted that annihilates with its antiparticle, the electron. In doing so, the masses of each of these elementary particles are converted directly into energy, thereby emitting two gamma rays in opposite directions. This so-called annihilation radiation can be detected with high-sensitivity detectors aligned in a ring surrounding the patient.

Positron emission tomography

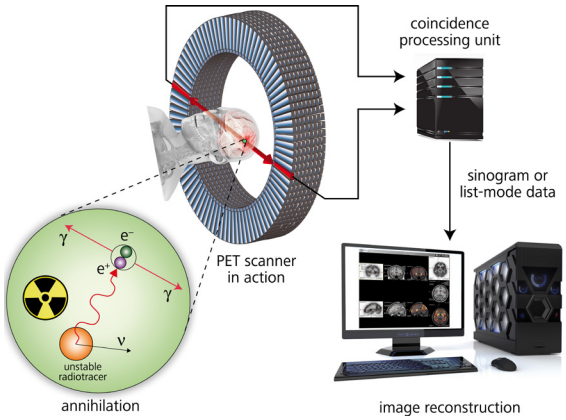
Computers use the PET data to calculate the origin of the gamma rays and thus the location where the radiopharmaceutical decayed. A selection of available radiopharmaceuticals and sophisticated detector systems make it possible to create three-dimensional images of a wide variety of tissues. This provides a unique picture of physiological, biochemical, and pharmacological processes taking place in the body, even at the molecular level.

[^{18}F]Fluorodeoxyglucose ([^{18}F]FDG)

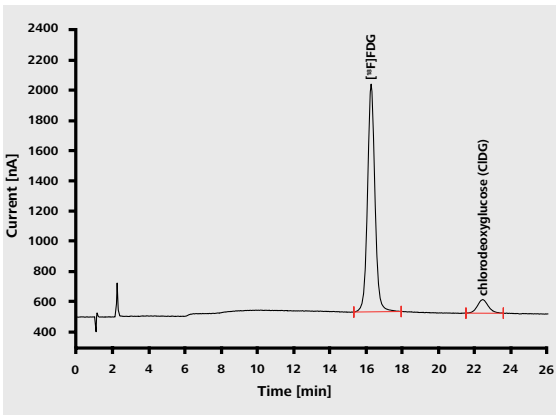
[^{18}F]Fluorodeoxyglucose is a glucose analog in which the ^{18}F nuclide is substituted for the hydroxyl group at the 2' position. FDG, which makes possible the determination of regional glucose consumption, is the most commonly used radiopharmaceutical.

Sophisticated quality control

Quality control in radiopharmaceuticals is demanding, not least due to the strict time requirements, the safety regulations, and the concentrations in the nanomolar range. Metrohm's ion chromatographs fulfill these requirements and the regulations contained in many pharmacopoeias. A single multichannel radio ion chromatograph is capable of performing quality control on different production lines. In addition to the highest analysis quality, ion chromatography provides users with safety, low maintenance costs, and extreme robustness.



Principle of positron emission tomography (PET): Disintegration of the radionuclide releases two photons that can be sensitively registered by coincident detection. By tracking the photons, powerful computers generate three-dimensional images of the photon source.



The IC-PAD chromatogram shows the peaks of the radio tracer [^{18}F]FDG and the impurity chlorodeoxyglucose. [^{18}F]FDG is used to trace organism's glucose metabolism. In case of diseases, this metabolism shows irregularities that emerge in the PET scan.
Column: Metrosep Carb 2 - 150/4.0; Eluent: 0.1 mol/L NaOH, 1 mL/min; column temperature: 30 °C; sample volume: 20 µL; pulsed amperometric detection

Numerous other applications

Ion chromatography from Metrohm has much more to offer. The following table presents a selection of additional key determinations relevant to pharmaceutical quality control. If you do not see your application, please contact your local Metrohm representative.

Pharmaceutical or excipient	Analyte
Acamprosate calcium	Acetate
Acifluorfen, sodium	Acetate
Adrenaline	Adrenaline
Amisulpride	Dimethyl and diethyl sulfate
Anticoagulation solution	Phosphate, citrate
Arsenic trioxide	Arsenate, arsenite
Atovaquone	Acetate
Atorvastatin calcium salt	Cyanide, tetrabutylammonium
Sulfobutylether-ß-cyclodextrin	ß-cyclodextrin
Bethanechol chloride	Bethanechol, sodium, calcium, decomposition product (HPTA)
Bromide salt	Chloride
Busulfan	Methanesulfonic acid
Calcium gluconate	Oxalate
Calcium salt	Borate
Camphorsulfonic acid	Camphorsulfonic acid
Carbamazepine	Chloride, bromide
Carbidopa	EDTA, hydrazine, sodium disulfite
Cefadroxil	Cefadroxil
Cefdinir	Iron, EDTA
Cefepime hydrochloride	N-methyl-pyrrolidinium
Ceftazidime sodium	Sodium
Clopidogrel besylate	Anions, carbonate, cations
Colesevelam	Quaternary alkylamines
Copovidone EP	Acetate, formate
Dasatinib	Ethylenediamine
Dextromethorphan HBr	Formic acid
(2,3-Dichlorophenyl) oxoacetonitrile	Cyanide, tetrabutylammonium
Diclofenac sodium	Sodium, potassium
Dicyclopropylmethylamine	Dicyclopropylmethylamine
Doxazosin, methanesulfonic acid	Bromide
Drospirenone	Propargyl alcohol
Enoxaparin sodium	Sulfate
Esomeprazole magnesium	Tartrate
Febuxostat	Hydroxylamine
Felodipine	Silicate, sodium
Fenofibrate	Sodium lauryl sulfate (SLS)
Ferumoxide (contrast enhancer)	Citrate
Fluorouracil (also fluoruracil)	Fluoride
Gabapentin	Chloride
Gadopentetate dimeglumine	Gadolinium
Gentamicin sulfate (see page 17)	Gentamicin

Pharmaceutical or excipient	Analyte
Glycine carbonate, sodium salt	Carbonate
Glimepiride	Trans-4-methylcyclohexylamine
Guaifenesin	Epichlorhydrine
Heparin sodium	Glucosamine and galactosamine
Ibandronic acid sodium	Ibandronate, phosphite, phosphate
Indinavir sulfate	Ethyl sulfate
Indomethacin sodium	2-ethylhexane acid
Irbesartan	Cyanide, azide
Ibuprofen	Ibuprofen, valerophenone
Lamotrigine	Cyanide
Lanthanum carbonate	Nitrate
Levetiracetam	Tetrabutylammonium
Levofloxacin	Fluoride
Linezolid	Morpholine
Losartan potassium	Azide
Meropenem	EDTA, dimethylamine
Metformin hydrochloride	Dimethylamine
(Mono)sulfiram (temosol)	Cyanide
Montelukast sodium	Methanesulfonic acid, acetate
Multivitamin tablets	Cations, Vitamin C
Mycophenolate mofetil	Morpholine
Nebivolol hydrochloride	Monomethylamine
Neomycin sulfate	Neomycin
Oxaliplatin	Chloride
Pioglitazone hydrochloride	Piperidine
Piperacillin	Chloride
Piperazine	Piperazine, N-methylpiperazine
RA-Thermoseal toothpaste	Potassium, zinc
Ribitol	Ribitol (adonitol)
S-Adenosyl methionine	Sulfate
Sevelamer	Binding capacity of phosphate
Suxamethonium chloride	Choline chloride
Tadalafil	Methanolic methylamine
Terbinafine hydrochloride	Monomethylamine, tetrabutyl-ammonium
Topiramate	Carbohydrates, sulfate and sulfamate
Triclosan	Potassium
Timolol maleate	Chlorite
Varenicline tartrate salt	Trifluormethanesulfonic acid
Voriconazole	Camphorsulfonic acid
Zingisol	Potassium and zinc
Zoledronic acid	Phosphite, phosphate

Detection method: conductivity detection with suppression; direct conductivity detection; conductivity detection with and without suppression; amperometric detection; spectrophotometric detection

Voltammetry

Voltammetric trace analysis determines electrochemically active substances. In many cases, these are traces of heavy metals. Voltammetry is frequently employed to complement and validate spectroscopic methods. It features modest equipment requirements, relatively low investment and operating costs, simple sample preparation, short analysis times, and high accuracy and sensitivity. In addition, unlike spectroscopic methods, voltammetry can distinguish between different oxidation states of metal ions as well as between free and bound metal ions. This is referred to as speciation analysis. Voltammetric results provide important information regarding the bioavailability and toxicity of heavy metals.

Detection limits (1 ppt = 1 ng/kg)

Element		Detection limit [ppt]
Antimony	Sb^{III}/Sb^{V}	200
Arsenic	As^{III}/As^{V}	100
Bismuth	Bi	500
Lead	Pb	50
Cadmium	Cd	50
Chromium	Cr^{III}/Cr^{VI}	25
Cobalt	Co	50
Iron	Fe^{II}/Fe^{III}	50
Copper	Cu	50

Element		Detection limit [ppt]
Molybdenum	Mo	50
Nickel	Ni	50
Platinum	Pt	0.1
Rhodium	Rh	0.1
Mercury	Hg	100
Selenium	Se^{IV}/Se^{VI}	300
Thallium	Tl	50
Uranium	U	25
Tungsten	W	200
Zinc	Zn	50

Voltammetry also enables organic compounds to be determined with a high degree of sensitivity. This makes it possible to analyze many active pharmaceutical ingredients in accordance with USP<801>.

Voltammetry is particularly well-suited to laboratories in which only a few parameters need to be monitored in combination with a moderate sample throughput. It is frequently used for special applications which cannot be performed using other techniques or only with a great deal of effort

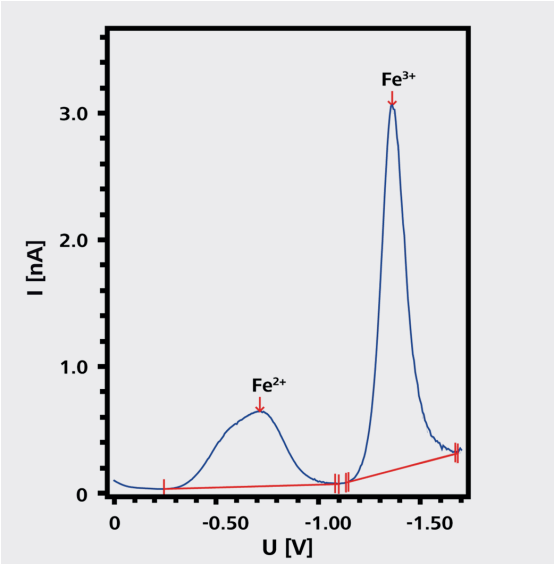
884 Professional VA

The 884 Professional VA is a flexible measuring instrument for accurate and sensitive polarographic voltammetric analyses. The accompanying viva software enables individual optimization of methods, for example, the automatic calculation of results according to special formulas prescribed by the USP.

Application examples

Fe(II) in iron sucrose injection solution in accordance with USP-NF

Polarography makes it possible to determine, directly and selectively, the proportion of iron(II) within the total concentration of iron in a preparation. No prior sample preparation and chemical separation of the iron species is required. The separated signals of the iron(II) and iron(III) complex are measured during determination. The iron(II) content is derived from the ratio of the signals.



Polarographic determination of iron(II) content

Thimerosal in accordance with USP-NF

Mercury-containing thimerosal (or thiomersal) is used as a preservative for pharmaceuticals and cosmetics to protect them from microbial contamination. Examples of the use of thimerosal are: cleaning and storage solutions for contact lenses; eye, nose, and ear drops; and tattoo inks. Injectable medicinal products – for example, immunoglobulins and many vaccines (flu, hepatitis B, etc.) – can also be preserved with thimerosal. Direct determination in the finished preparation is possible in many cases.

Heavy metal impurities

For more than a century now, international pharmacopoeias have relied on sulfide precipitation for a semiquantitative determination of the heavy metal content in pharmaceutical products. As of 2018, this is no longer the case: USP regulations USP<232> and USP<233> then require individual determinations of selected heavy metals in place of sum parameters. The USP leaves it up to the user to select the analysis method, requiring only its validation. Stripping voltammetry is particularly suitable here, and a simple sample digestion is sufficient for sample preparation.

Other active pharmaceutical ingredients that can be determined by polarography in accordance with USP-NF

Electrochemically active pharmaceutical ingredients, such as azathioprine, cefamandole, cysteine hydrochloride, diclofenamide, iodine, or procarbazine, can be determined directly with polarography in accordance with USP<801>.

Electrochemistry for electroactive pharmaceuticals

Electrochemistry in pharmaceuticals

Many of the active pharmaceutical ingredients are electroactive, which makes them easy to determine using electrochemical methods. Electrochemistry is both highly sensitive and selective, and also has an outstanding dynamic range with very rapid response times. Furthermore, there are numerous possibilities for recording signals. Potentiometric, amperometric, impedimetric, and electrogravimetric analyses are numbered among these.

Real-time blood sugar monitoring

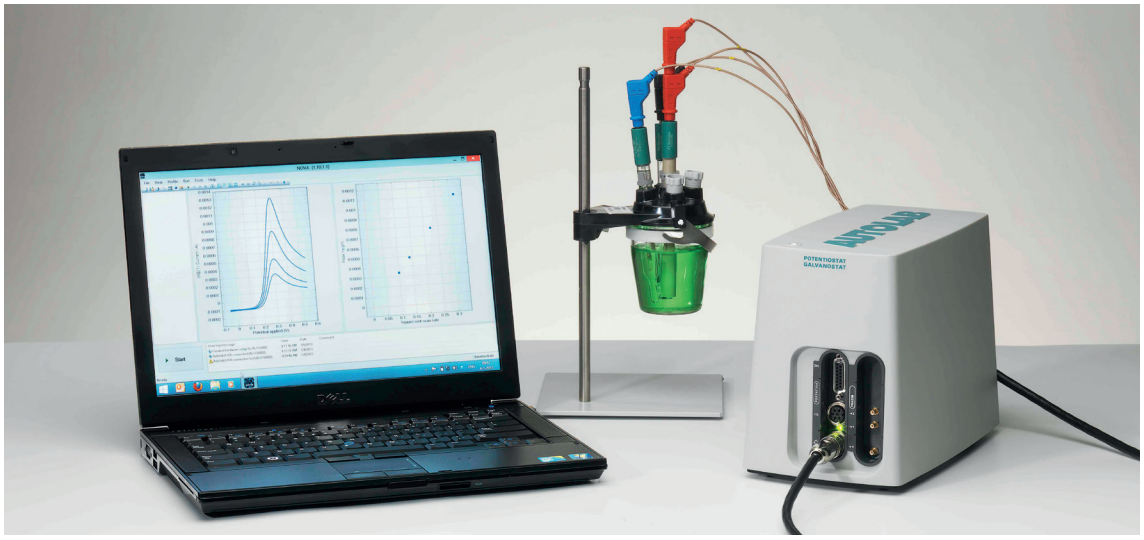
With the development of amperometric glucose sensors – at the heart of every blood glucose meter – electrochemistry has significantly improved the quality of life of diabetes patients. Basic research efforts are constantly being directed towards further improvements of these types of sensors. The goal is to develop an implantable sensor for real-time monitoring.

Research and development

Electrochemical methods help to develop and characterize new materials for use in biosensors and electroanalysis. In combination with proven electroanalytical methods, these new, specially designed composite materials – mostly based on metal nanoparticles, carbon nanotubes, or graphene – improve the sensitivity, specificity, and detection limits of measurements.

High-end instruments from Metrohm Autolab

Metrohm Autolab offers a range of high-end instruments for electrochemical research. A broad array of modules enables individual adaptation of the instruments to every desired application. Electrochemical impedance spectroscopy measurements can be performed with the FRA32M, and the EQCM enables electrochemical quartz crystal microbalance measurements.



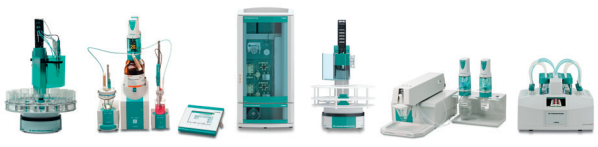
For sensitive electrochemical impedance measurements in pharmacy: the Autolab PGSTAT204 with the FRA32M module

Metrohm Autolab B.V.

www.metrohm-autolab.com

«Why did I choose Metrohm? I have been working with Metrohm for 25 years. When a new lab was to be built here in Montpellier, we naturally chose Metrohm.»

Sandrine Caristan, Sanofi-aventis



Sandrine Caristan and her team provide analytical support at Sanofi-aventis' R&D center in Montpellier, France. Determination of the water content by Karl Fischer titration is one of their most frequent analyses. A Metrohm USB Oven Sample Processor is their solution of choice for higher throughput and reliable results. And thanks to the client-server version of Metrohm's ***tiamo*** software, Sandrine doesn't have to leave her office to manage data from workplaces all over the site.

Metrohm. People you can trust.

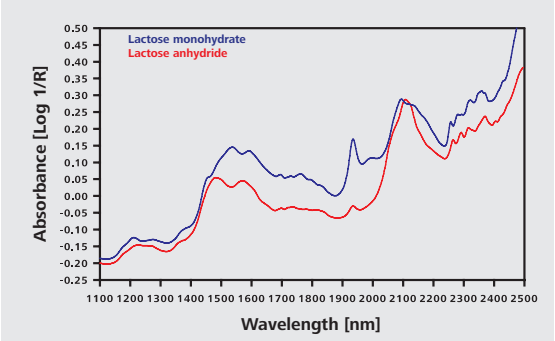
testimonials.metrohm.com

Metrohm

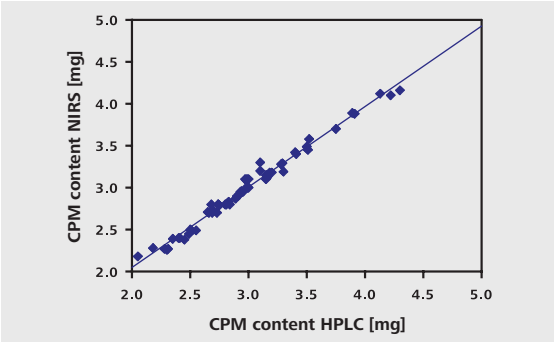
Near-infrared spectroscopy

NIRS – interaction of light and physical matter

Near-infrared spectroscopy (NIRS) is an analytical technique based on the absorption of radiation by matter. Molecular vibrations are induced in the near-infrared region of the magnetic spectrum (800–2500 nm) – i.e., from the end of the visible to the mid-infrared (MIR) range. The main absorption bands of the functional groups of chemical substances are located in the MIR range and are very strong. The absorption bands of the harmonics, however, and the combination of the fundamental molecular vibrations are in the NIR spectral region. They are significantly weaker and enable direct measurement without sample preparation, while at the same time offering deep insights into the chemical and physical properties of the sample. The strongest overtone absorptions in the NIR range are displayed by compounds with OH, CH, NH, and SH bonds. Because the NIR spectrum represents the result of numerous overlapping absorption bands, it is normally evaluated with multivariate chemometric methods.



NIR spectra of lactose monohydrate and lactose anhydride for identifying excipients



Calibration model for the quantitative determination of the active ingredient content of tablets; in this case, chlorpheniramine maleate (CPM). NIR analysis establishes a connection between the target value of a determination – in this case, CPM content – and the measured data in the spectrum.

Many parameters in a single analysis

NIRS offers numerous advantages over many wet-chemical analytical methods. A diverse range of parameters can be determined simultaneously with just one analysis. NIRS is economical and fast, enabling qualitative and quantitative analyses that are noninvasive and nondestructive.

NIRS is an indispensable analysis technique that can be used along the entire production chain – from incoming materials to processing to the quality control of finished products. NIRS meets the requirements of numerous international pharmacopoeias, e.g., USP, Ph. Eur., and JP.

How

Atline/offline
- **Warehouse**
- **QC laboratory**

Inline/online
- **Production**

Atline/offline
- **Process control (IPC) laboratory**

Atline/offline
- **IPC laboratory**
- **QC laboratory**

Offline
- **QA/QC laboratory**

NIRS – the fast solution for every sample matrix

Near-infrared spectroscopy requires no sample preparation and can handle any sample matrix, no matter if it is:

- powders or granulates
- tablets or capsules
- creams or gels
- solutions or suspensions
- polymer films
- freeze-dried samples.

NIRS – screening through packaged materials

NIRS can even perform determinations on contents sealed in transparent packaging such as glass and films. This is particularly appealing for incoming goods inspections and packaged end products. Handling could not be easier; in fact, it is so easy that NIRS can be used directly in pharmacies and customs offices.

Where	What
Incoming materials	**Incoming goods inspection of raw materials starting from step one** • Identity tests directly in the warehouse for active pharmaceutical ingredients, excipients, and packaging • Quality control (purity, chemical and physical properties)
Drying	**Real-time monitoring, optimizing the drying process** • Inline determination of water and solvents in powders and granulates (page 33) • Determination of the endpoint of drying processes • Determination of residual water content in freeze-dried products
Blending and granulation	**Monitoring blending processes** • Determination of blend homogeneity • Setting required granulation time by tracking blend quality
Tablet pressing and capsule filling	**Faster analytical results and minimization of rejected products** • Content uniformity test in solid dosage forms (tablets and capsules) • Determination of tablet characteristics (hardness, stability, etc.) • Identification of tablets and products before they are packaged
Final product control and packaging	**Less expended effort compared to reference methods (e.g., HPLC)** • Content determination in finished products (creams, gels, solutions, tablets, capsules) • Final product inspection

Nondestructive analysis technique

NIRS has long been one of the most important and versatile analytical techniques in the pharmaceutical industry – and not just because everybody in the pharma industry is talking about PAT and QbD. The decisive benefit of NIRS is the possibility of obtaining reliable analysis results in just seconds without any sample preparation or reagents whatsoever.

PAT and QbD – with NIRS in search of the best of all methods

Drug manufacturing is undergoing a transformation. The FDA's stated goal is to cut development time for new drugs while at the same time significantly improving quality. This requirement can only be fulfilled with analytical techniques which monitor the entire process – from incoming raw materials to the final inspection. To achieve that, perfect PAT sensors are needed that enable "live" tracking of the manufacturing process. NIRS is the technique that makes this possible. An inline sensor monitors product quality in real time (see also pages 32 and 33). This prevents charges related to rejected products and reduces overall costs.

In accordance with international pharmacopoeias

As a secondary test method, NIRS is recommended in all of the key pharmacopoeias – from the European (Ph. Eur. 2.2.40) to the American (USP<1119>) to the Japanese pharmacopoeia. All of Metrohm's NIRSystems instruments meet the standards for wavelength precision, reproducibility, and photometric noise. Numerous reference standards and user-friendly software make it easy to check the instrument requirements specified in the pharmacopoeias. The pharmaceutical version of the Vision software is fully validated and compliant with 21 CFR Part 11.

Metrohm NIRSystems also offers complete IQ/OQ documentation and instrument performance certification (IPC). Documented parameters guarantee that the instrument performs properly.

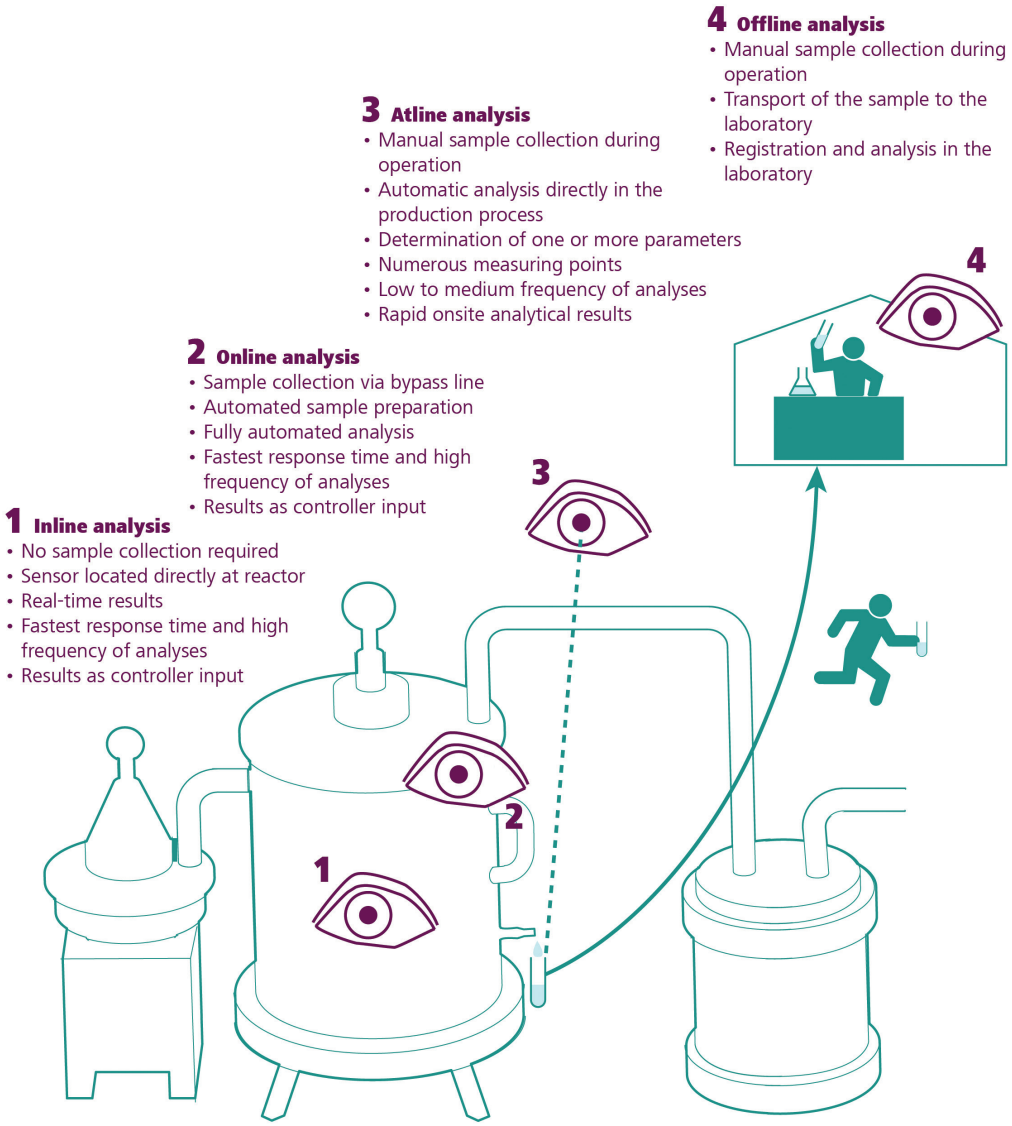
Atline, online, and inline analysis systems from Metrohm Process Analytics

Atline, online, and inline analysis systems from Metrohm Process Analytics are the preferred solution for process monitoring in a wide range of industries. Reliable analysis results are determined directly in-process with the latest methods of ion analysis and spectroscopy: Measurement of pH value, conductivity, and redox potential, as well as titration, Karl Fischer titration, photometry, ion-selective electrode measurement (dynamic standard addition), ion chromatography, voltammetry, and near-infrared spectroscopy.

Metrohm Applikon, with the brand name Metrohm Process Analytics, is an inline, online, and atline analysis specialist with more than 40 years' experience in the field. We offer a broad program of process analyzers and sample preparation systems for a large array of applications in a wide number of industries.

Metrohm Applikon – globally present

Metrohm Applikon is part of the Metrohm Group supporting you globally with offices in 45 countries. Our specialists offer you advice during the planning and development of your own custom-designed analysis system, commission the system, and provide professional maintenance and service during routine operations.



Atline process analysis

More efficient production with PAT and QbD

Drugs are manufactured in accordance with very strict directives and must meet high standards with respect to quality, effectiveness, and safety. Every process step is thoroughly monitored during the manufacture of various active ingredients and excipients. Added to that are exhaustive approval analyses at the end of the manufacturing process: pharmaceutical producers often spend more time on final checks than on the production itself. Stringent regulatory requirements also make it more difficult to optimize pharmaceutical manufacturing processes. With its Process Analytical Technology (PAT) initiative and the principle of Quality-by-Design (QbD), the FDA is striving to increase the efficiency of drug production. The approach involves a departure from final inspections toward real-time process analysis and checks.

Rapid process monitoring

Metrohm Process Analytics offers a robust analysis system that is easy to operate and can be set up directly on the production floor. The sample is brought to the ProcessLab and the analysis started at the push of a single button. ProcessLab is based on the proven Titrando system, which in combination with ***tiamo*** software meets the requirements of the FDA Regulation 21 CFR Part 11. ProcessLab features a modular design and is configured to meet specific analytical requirements. It can be optimally integrated into process communications through inputs and outputs (typically 4–20 mA). Sample identification is further simplified through the use of a barcode reader. Just minutes after the sample is collected, the relevant process information is available to a LIMS or the master display.

Atline analyzer ADI 2045PL ProcessLab

The ADI 2045PL ProcessLab atline analyzer is ideally suited to rapid and independent process monitoring in the production environment. A ProcessLab analysis system consists of a TFT touch screen operating unit and an analysis module that is tailored to the specific application. Thanks to its splashproof housing (housing protection class IP66/NEMA 4), ProcessLab is ideally suited to harsh production environments. The pharmaceutical industry is held to high standards of hygiene, which is why most equipment is made with a stainless steel housing.

ADI 2045PL ProcessLab: each system is configured with the relevant modules according to user preferences.

Analysis of acidic and basic components

Numerous pharmaceutical intermediates and end products contain acidic and basic components. These are determined with a suitable acid-base titration method. Depending on the sample matrix, either aqueous or non-aqueous titrations are carried out. The latter are done with a titrant and solvent suitable for the particular application – for example, with perchloric acid in glacial acetic acid or with tetrabutylammonium hydroxide (TBAH) in 2-propanol or acetone.

Determination of redox-sensitive components

Oxidizable and reducible components and active ingredients are determined with redox titrations. Methods frequently used include iodometry, cerimetry, bromatometry, and/or permanganometry. The modular structure of ProcessLab enables easy adaptation to the specific requirements of the application. Because of its proximity to the process, the relevant analytical values are available within just a few minutes.

Metrohm
Process Analytics

Online and inline process analysis

Customized online process control

Production processes in the pharmaceuticals industry must be continuously monitored. Online and inline analyzers from Metrohm Process Analytics optimally fulfill this requirement. Engineered for continuous operation, these instruments enable fully automatic checks of production processes – around the clock, seven days a week. Moreover, it does not make a difference whether a single parameter is to be determined in a single sample stream or several different parameters are to be determined simultaneously in complex, multiple sample streams – Metrohm Process Analytics provides you with a suitable system for all applications.

Proven wet chemistry methods

Metrohm Process Analytics online analyzers are based on wet chemistry processes such as titration, colorimetry, and measurements with ion-selective electrodes; near-infrared spectroscopy is used for inline monitoring. Sampling and sample preparation are at least as important as the analysis itself. Metrohm Process Analytics has great expertise in this field and configures the sampling system to fit your application precisely, including features such as filtration, the removal of samples from pressurized containers, and degassing.

Straightforward network integration

All Metrohm Process Analytics online and inline analyzers are equipped with digital and analog data outputs. Results can be transmitted via analog 4–20 mA signals and alarms can be triggered by digital outputs. Digital inputs can be employed for remote start/stop commands.

Robust design in stainless steel

Metrohm Process Analytics analyzers are constructed for the demands of the harsh production environment. The housings meet NEMA 4 and protection class IP66 specifications. In environments that demand the highest standards of hygiene and durability, Metrohm Process Analytics offers its ADI 2045TI and ADI 201Y Process Analyzers equipped with stainless steel housings.

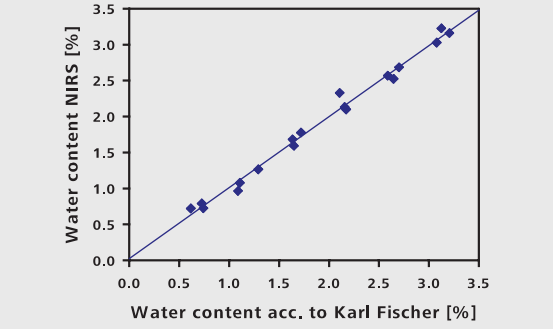
Inline process analysis with NIRS

The goal of the FDA's PAT/QbD approach is process optimization through improved process controls. Instead of time-consuming final inspections, PAT calls for monitoring product quality in real time. Near-infrared spectroscopy offers meaningful help toward achieving this objective: NIR always has the process in view, it is not destructive, requires no sample preparation, and delivers precise results in just seconds. The software uses multivariate data analysis to extract the data required for the analysis at hand from the comprehensive NIR data. Physical parameters, such as density and particle size distribution, in addition to water or solvent content, can also be conveniently determined.

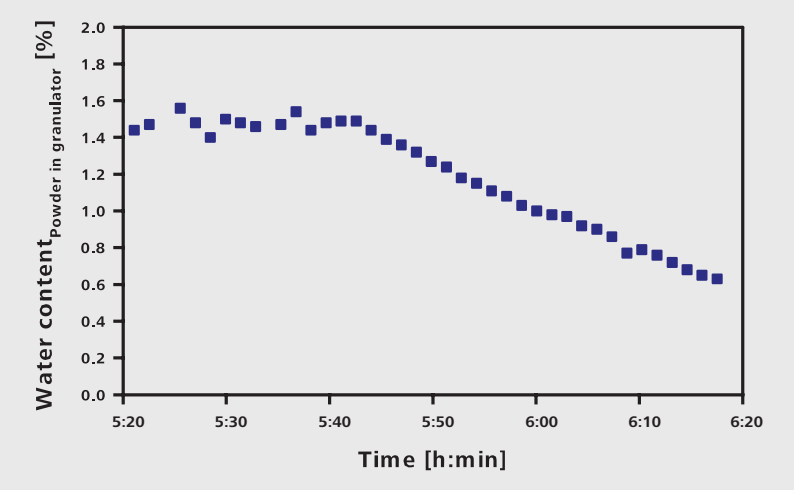
The robust NIRS Analyzer PRO for inline analysis with interfaces for reflection or transmission technology.

Eye on the process: granulation and drying

A key manufacturing process in the pharmaceutical industry is the granulation and drying process for powders that precedes tablet manufacturing and makes it possible to press powders into tablets in the first place. NIRS is the method of choice for determining the reaction endpoint when pressability is at the optimal point. Probes in the drier or granulator make it possible to track the process in real time. That reduces the process duration and thus increases the drying and granulation capacity of the system. At the same time, it minimizes the deviation from the required setpoint values.



Calibration model for quantitative determination of water content in powders. Karl Fischer titration is the reference method for the determination of the water content.



Reduction of water content in a pharmaceutical powder over time. Rapid and nondestructive NIR analysis makes it possible to determine the optimal moment for further processing in real time. The sensor is installed directly in the granulator.

Metrohm Quality Service – Service you can rely on

Reliable results – for the lifetime of the analyzer

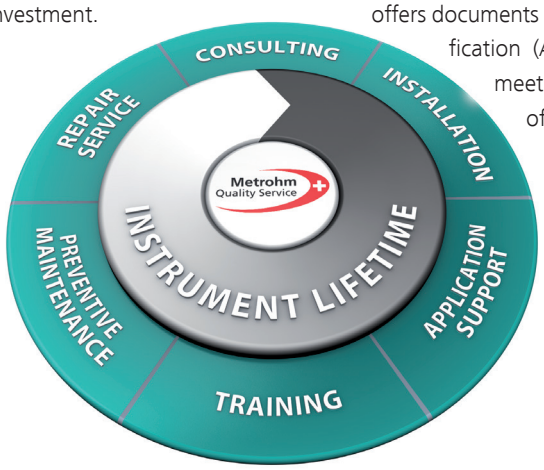
Particularly in the pharmaceutical industry, measurement errors can have serious consequences and must therefore be avoided at all cost. The name Metrohm stands throughout the world for high-quality laboratory analyzers for ion analysis. They are designed to deliver exceptionally precise results. Leading international pharmaceutical companies also value Metrohm for our comprehensive service, which ensures that the users can rely on their results for the entire lifetime of their instruments.

With Metrohm Quality Service you are on the safe side from day one. From installation and start-up, to regular maintenance and fast repair – if problems arise – we guarantee that you can rely on your instrument and gain maximum uptime from your investment.

Metrohm Compliance Service

You can trust Metrohm Compliance Service when it is time for the professional qualification of your analyzers. The wide range of different laboratory instruments and analyzers makes it very complicated for pharmaceutical companies to keep in step with legal requirements. As an experienced and reliable partner, Metrohm provides its customers with technical advice and expertise, with respect not only to instruments and applications, but also to the latest regulatory requirements.

Analyzers used in laboratories must satisfy the latest requirements of FDA regulations, GLP/GMP standards, and the GAMP directives. This is achieved through instrument qualification and system validation. Metrohm offers documents for analytical instrument qualification (AIQ) as well as services that meet or exceed the requirements of the FDA and other regulatory authorities.



Metrohm Quality Service

Metrohm's global Quality Service, and regularly scheduled preventive maintenance in particular, extends your instrument's lifetime and ensures trouble-free operation. Maintenance work is carried out by qualified and certified service engineers. You have the option of selecting different types of service contracts depending on your particular need. With a Total Care Contract, for example, you can rely on the optimum performance of your Metrohm instruments at all times, incurring no additional costs whatsoever and benefit from complete and compliant documentation.

Metrohm Quality Service	Customer benefits
Metrohm Care Contracts	• Minimizes downtime through preventive maintenance • Cost control and savings through free or discounted replacement materials and consumables • Guaranteed reaction times and rapid on-site repair • Documented instrument certification as an ideal preparation for audits
Metrohm Software Care	• High data security and maximum system performance through regular, professional software maintenance
Metrohm Compliance Service	• Customized services and documentation for analytical instrument qualification (AIQ) • Professional start-up (IQ/OQ or Certified Installation) and requalification or recertification by specifically trained employees
Metrohm Remote Support	• Quick resolution of software and application issues directly at the workplace
Metrohm Dosing Test	• Calibration of burettes (e.g., dosing and exchange units) with certification • Accurate measurement results • Verification documentation for compliance with regulations and efficient audits
Metrohm Repair Service	• Rapid availability of repaired instruments thanks to decentralized repair workshops around the world and a central workshop at the manufacturer site • Highly qualified service technicians ensure sustainable repair success • Rapid resolution of problems and minimized downtimes through on-site emergency services and express repairs
Metrohm Spare Parts	• Original spare parts, made in Switzerland and available worldwide • Short delivery times through warehousing from local distributors • Investment security through ten-year spare parts guarantee after discontinuation
Metrohm Application Support	• Free access to the Metrohm Application Finder (**www.metrohm.com/en/applications/**) with more than 1800 applications (Application Bulletins, Application Notes, monographs, technical posters, and technical articles) • Rapid and professional resolution of any application issues through personal consultations with our specialists by e-mail, telephone, or remote support • Support for the solution of complex analytical problems, as well as method optimization on-site or at our application laboratories
Metrohm Training Programs	• Basic and advanced training with local representatives, at the Metrohm Academy or directly on-site • Efficient and proper use of all analytical methods, as well as results reliability through competently trained users • Training documentation and certificates for trouble-free audits

Metrohm
Quality Service

Ordering information

pH value and conductivity measurement

pH value measurement

2.867.0110	867 pH Module with Touch Control
2.867.0210	867 pH Module with ***tiamo*** light

Conductivity measurement

2.856.0120	856 Conductivity Module with Touch Control and stainless steel measuring cell
2.856.0220	856 Conductivity Module with ***tiamo*** light and stainless steel measuring cell
6.0916.040	Conductivity measuring cell made of stainless steel, c = 0.1 cm^{-1}, with Pt1000

Titration

2.907.1020	Pharm Titrando
2.902.0010	902 Stat Titrando
6.6056.2X2	***tiamo*** 2.X full

Water determination according to Karl Fischer

Coulometric KF Titration

2.756.0010	756 KF Coulometer with generator electrode with diaphragm
2.756.0110*	756 KF Coulometer with generator electrode without diaphragm
2.831.0010	831 KF Coulometer with generator electrode with diaphragm
2.831.0110*	831 KF Coulometer with generator electrode without diaphragm

2.851.0010	851 Titrando with generator electrode with diaphragm
2.851.0110*	851 Titrando with generator electrode without diaphragm
2.852.0050	852 Titrando with generator electrode with diaphragm and volumetric titration cell
2.852.0150*	852 Titrando with generator electrode without diaphragm and volumetric titration cell

* The magnetic stirrer has to be ordered separately.

Volumetric KF Titration

2.890.0110	890 Titrando with Touch Control
2.890.0210	890 Titrando with ***tiamo*** light
2.901.0010	901 Titrando including titration cell
MATi 11	Automated volumetric Karl Fischer titration including sample preparation

KF oven

2.860.0010	860 KF Thermoprep
2.874.0010	874 Oven Sample Processor

Automation

MATi 03	Automatic titration system for nonaqueous titrations in the pharmaceutical industry in series of up to 59 samples
2.815.1110	815 Robotic Titration Soliprep
2.815.2110	815 Robotic Flexible Soliprep
2.815.3110	815 Robotic Filtration Soliprep
2.815.4110	815 Robotic Soliprep for LC

Oxidation stability

2.892.0010	892 Professional Rancimat including accessories, without StabNet software
6.6068.102	StabNet 1.0 Full
6.6068.103	StabNet 1.0 Multi

Ion chromatography

2.940.2500	940 Professional IC Vario TWO/SeS/PP for anion and cation determination
2.940.1520	940 Professional IC Vario ONE/SeS/PP/Prep2
2.850.9010	IC Conductivity Detector
2.850.9110	IC Amperometric Detector
2.858.0020	858 Professional Sample Processor for the automation of determinations
6.5337.010	IC Equipment Wall-Jet cell for carbohydrate determination
6.1090.420	Metrosep Carb 2 - 150/4.0 for carbohydrate determination
6.1050.410	Metrosep C 4 - 100/4.0 for cation determination
6.1020.030	Metrosep A Supp 10 - 250/4.0 for anion determination

Voltammetry

2.884.0110	884 Professional VA manual for Multi-Mode Electrode (MME)
2.884.1110	884 Professional VA semiautomated for MME consisting of 884 Professional VA, measuring head for MME and two 800 Dosinos.
MVA-22	Fully automated Professional VA system consisting of 884 Professional VA, measuring head for MME, 919 IC Autosampler plus for VA and two 800 Dosinos for automatic addition of auxiliary solutions. Allows the automatic processing of up to 28 samples. This system is the optimum solution for automatic analysis of small sample series.
	Required Accessories
6.5339.030	VA-Elektrodenkit with Multi-Mode Electrode
6.6065.202	viva 2.0 Full

Near-infrared spectroscopy – laboratory, atline

2.922.0010	NIRS DS2500 Analyzer
2.921.1110	NIRS XDS RapidContent Analyzer
2.921.1120	NIRS XDS RapidContent Analyzer – Solids
2.921.1210	NIRS XDS MultiVial Analyzer
2.921.1310	NIRS XDS MasterLab Analyzer
2.921.1410	NIRS XDS RapidLiquid Analyzer
2.921.1510	NIRS XDS Interactance Optiprobe Analyzer
2.921.1520	NIRS XDS Transmission Optiprobe Analyzer
2.291.1530	NIRS XDS Transmission Optiprobe Analyzer – Heated Vials
2.291.1610	NIRS XDS SmartProbe Analyzer – 2 m fiber
2.291.1620	NIRS XDS SmartProbe Analyzer – 3 m fiber

Process analysis

We offer online and atline Analyzers that meet any requirement in the process industry, from single-parameter to the most advanced multiparameter analyzers. Every analyzer is custom-tailored to the specific task at hand.

Wet chemistry

ADI 2045PL	ProcessLab system for atline determination of various parameters using titration, colorimetry, and ISE
ADI 201Y Series	Single method Process Analyzers, available with titration, colorimetry, or ISE
ADI 204Y Series	Multifunctional Process Analyzers, available with titration, ISE, colorimetry, and voltammetry
2035 Series	Analyzer family designed in 3 configurations: potentiometric, photometric, and thermometric titration

Furthermore, we offer the Plug and Analyze Series – ICON and Alert for single method, single component water analysis.

Near-infrared spectroscopy

2.928.0210	NIRS XDS Process Analyzer – SingleFiber SinglePoint
2.928.0220	NIRS XDS Process Analyzer – SingleFiber 4 Channels
2.928.0230	NIRS XDS Process Analyzer – SingleFiber 9 Channels
2.928.0110	NIRS XDS Process Analyzer – Microbundle SinglePoint
2.928.0120	NIRS XDS Process Analyzer – Microbundle 4 Channels
2.928.0130	NIRS XDS Process Analyzer – Microbundle 9 Channels
2.928.0310	NIRS XDS Process Analyzer – DirectLight/NonContact
2.928.1110	NIRS Analyzer PRO – ContactReflection
2.928.1120	NIRS Analyzer PRO – FiberSystem
2.928.1130	NIRS Analyzer PRO – DirectLight/NonContact

Please contact your Metrohm supplier for further information. Please also consult **www.metrohm.com**

pharma.metrohm.com

Subject to modifications
Layout by Ecknauer+Schoch ASW; printed by Metrohm AG, CH-9100 Herisau, Switzerland
8.000.5139EN – 2015-09

Metrohm