



Malvern | Material relationships

DRUG DEVELOPMENT

ACCELERATING TIME TO MARKET

PHARMACEUTICAL DEVELOPMENT

Discovering and developing drugs is becoming a progressively expensive, high-risk venture and pharmaceutical development has less resource from which increased productivity is expected. However, the supply of novel pharmaceuticals should know no limits; the molecular and formulation permutations are infinite. It is these endless possibilities that drive Malvern to provide the tools to accelerate development and formulation of the most demanding molecules into successful medicines.



Accelerating Drug Development

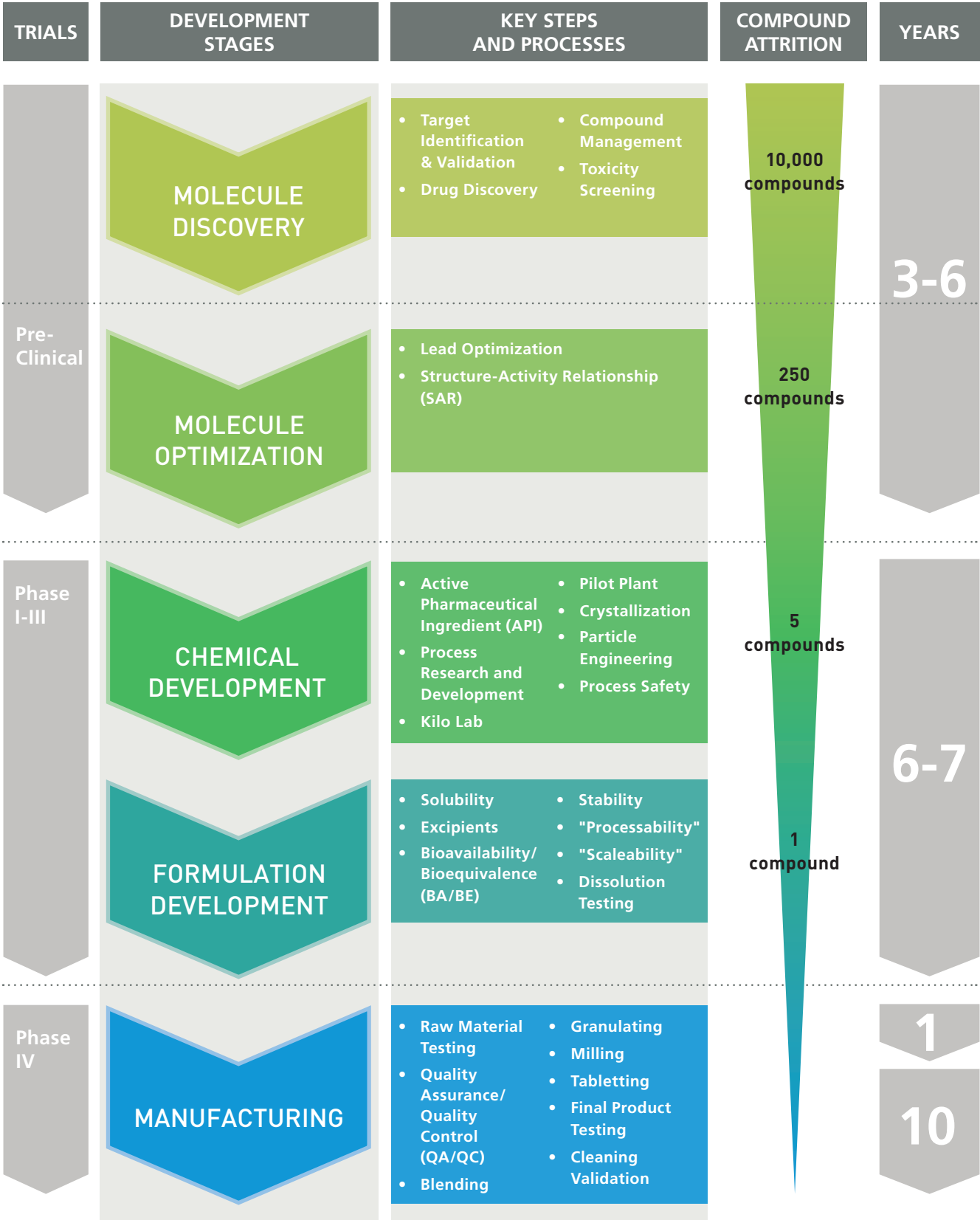
Malvern's value is in the breadth of characterization technologies that can be used to help make the development process faster. From tools that can run reliably and unattended, to systems that provide information on several key attributes in one analysis, such as particle size, shape, and chemical identity or molecular weight, size and concentration.

Malvern's instruments are deployed across the pharmaceutical discovery, development and manufacturing enterprise. Work-flow efficiencies may be achieved when these

tools are used in conjunction with each other. When characterizing the particle size and suspension stability of a highly insoluble new chemical entity, morphological and rheological attributes can be gained much more efficiently when common platform technologies are utilized. Our understanding of the interoperability of complimentary techniques, such as particle size, shape, Near Infrared (NIR) and Raman Spectroscopy, enables this.



THE CHALLENGE: TO DEVELOP MORE DIFFERENTIATED DRUG PRODUCTS, FASTER




ACCELERATING DRUG DEVELOPMENT: THE MALVERN TOOLBOX

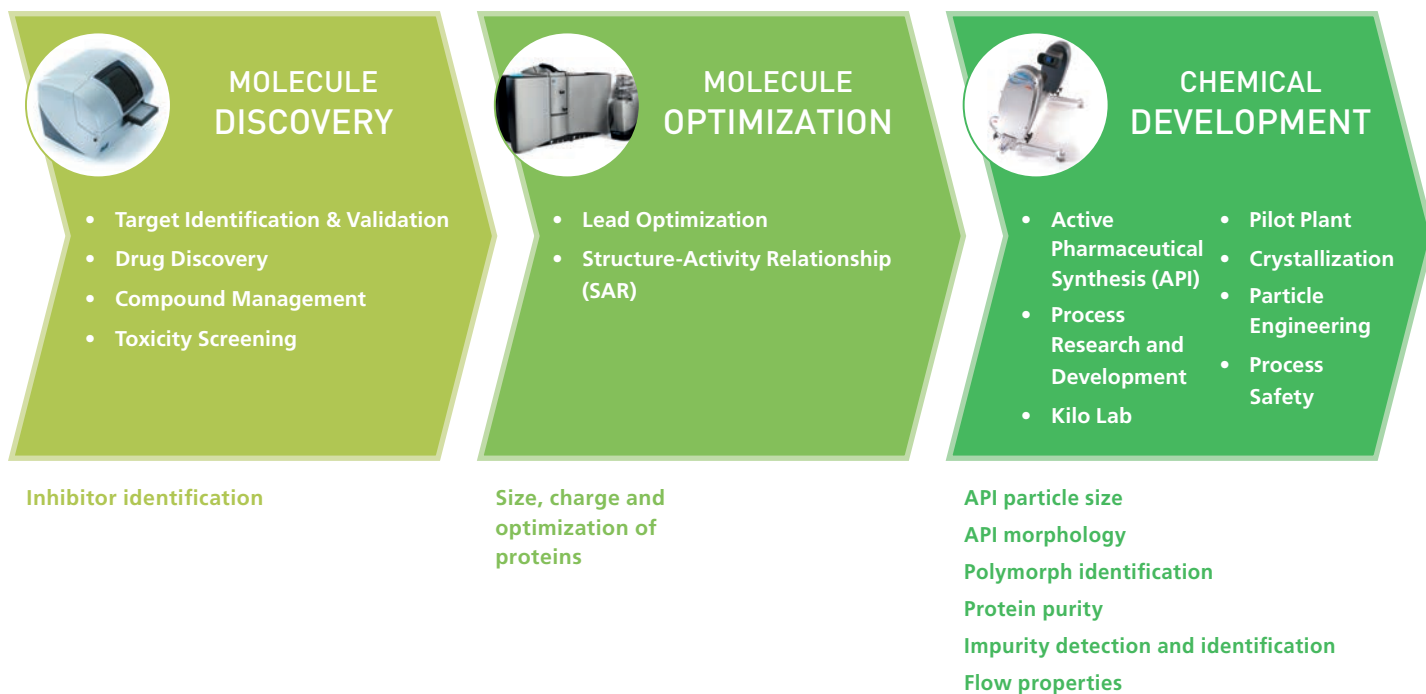
The particle size distribution of active ingredients, excipients, granules and droplets is an important physical characteristic of the materials used to create pharmaceutical products that have the right Quality Target Product Profile. It can affect product performance, manufacturing scale up, processability and stability of the final drug formulation.

Key performance parameters such as dissolution, absorption rates and content uniformity can all be affected by the particle size distribution of various components of a drug product. For example, reducing particle size can speed up pre-formulation and formulation of New Chemical Entities (NCEs) with poor water solubility; thus getting a drug into pre-clinical or clinical trials quicker.

Understanding morphological attributes of pharmaceutical products in conjunction with their chemical structure is also of great value. The morphology of drug particles, granules, topical and Orally Inhaled Nasal Drug Products (OINDP) formulations provides information about the bioavailability (BA) or bioequivalence (BE). Measurement of particle size and shape of the correct particle must be achieved and techniques such as Raman spectroscopy, in tandem with image analysis, can provide an accurate, objective and automated means to do this.

-  MOLECULAR WEIGHT
-  MOLECULAR SIZE
-  MOLECULAR STRUCTURE
-  PARTICLE SHAPE
-  PARTICLE SIZE
-  SOLUTION VISCOSITY
-  RHEOLOGICAL PROPERTIES
-  ZETA POTENTIAL - PROTEIN CHARGE
-  CHEMICAL IDENTIFICATION


WHERE MALVERN TECHNOLOGIES SPEED DISCOVERY, DEVELOPMENT, MANUFACTURING



Particle properties – such as size, size distribution, zeta potential and shape - influence the bulk rheological properties of a variety of formulated products. Characterizing the rheological properties of materials plays a crucial role in drug product performance - from the stability of suspensions containing Active Pharmaceutical Ingredients (APIs), to the delivery and application characteristics of creams and ointments for product efficacy, to the optimized properties of high performance excipients for tablet coatings.

When particulate matter is small then other light scattering techniques may be deployed. For example, when small extraneous materials affect drug efficacy in compound screening, these might be detected using Dynamic Light Scattering. The same technique may be used to optimize the size of drug carrier entities such as liposomes during formulation development.


The characteristics of excipient materials require characterization, especially when they alter drug delivery. The molecular weight distribution of polymer excipients is a key attribute when designing depot or enteric formulations.

FORMULATION DEVELOPMENT

- Solubility
- Excipients
- Bioavailability/Bioequivalence (BA/BE)
- Stability
- "Processability"
- "Scaleability"
- Dissolution Testing

Bioavailability
Bioequivalence measurement
Flow properties
Granule size, shape
Drug stability
Excipient characterization



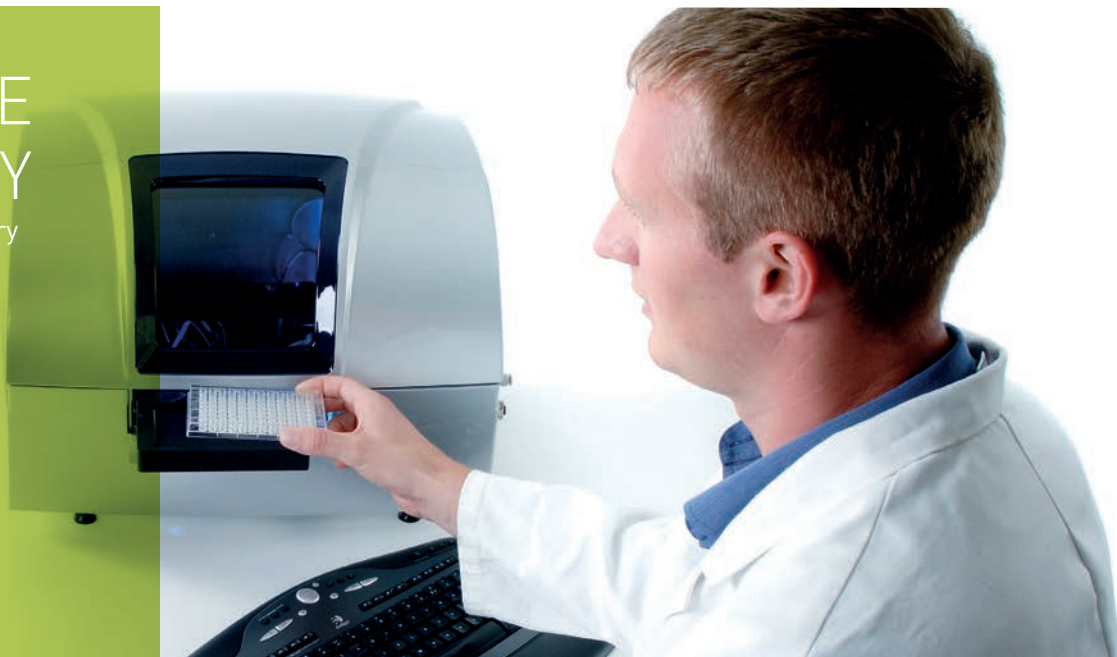
MANUFACTURING

- Raw Material Testing
- QA/QC
- Blending
- Granulating
- Milling
- Tableting
- Final Product Testing
- Cleaning Validation

API and excipient particle size
High shear wet granulation
Fluid bed granulation endpoint
Process control

MOLECULE DISCOVERY

Effective Compound Library Management: Rapid and accurate screening



Screening chemical compounds for activity

High throughput screening of large libraries of chemical compounds is the dominant technique used in early stage drug discovery. However, when screening lead compounds for activity, the true potential of new leads can become masked by the presence of non-specific or 'promiscuous' inhibitors. Often, the mechanism of inhibition is through aggregation of compound molecules and is concentration dependent.

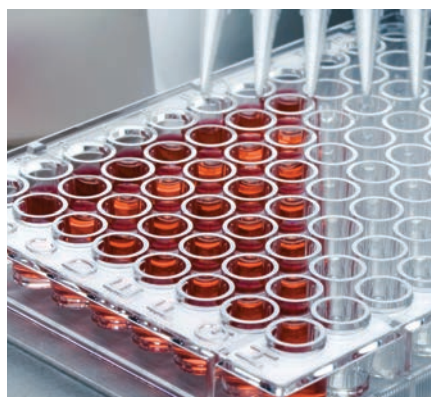
The challenge is to detect even minimal aggregation, leading to promiscuous inhibition, which in turn may deliver negative

screening results for an otherwise successful compound.

Dynamic Light Scattering (DLS) is the perfect tool. Being able to measure very small (0.2nm) particle size at low concentrations it is ideally suited as a screening tool for identifying even small levels of aggregation and thus potential inhibition.

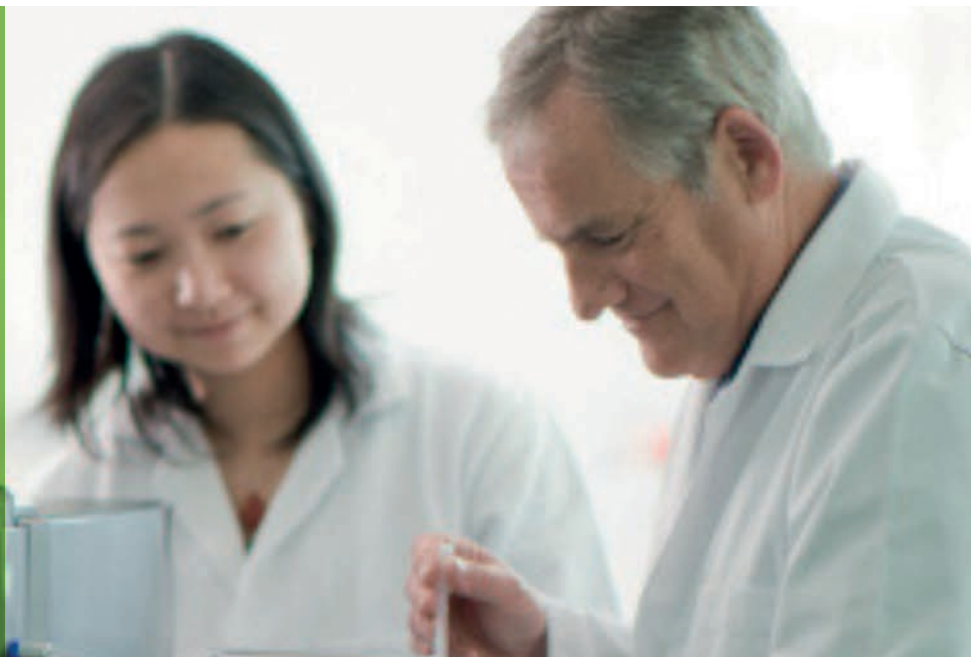
The Malvern solution can:

- Work with small sample volumes (20µL)
- Return sample post analysis
- Facilitate measurement on a wide range of concentrations
- Enable single or multiple sample automation
- Provide rapid throughput.



MOLECULE OPTIMIZATION

Getting NCEs to pre-clinical trials faster



Optimization of new chemical entities

Approximately 90% of new chemical entities (NCEs) discovered today are poorly soluble, which creates a major challenge for efficient drug development. In order to rapidly evaluate such compounds at the preclinical stage, the drug candidate is often dosed orally as an aqueous-based suspension.

In order to monitor efficacy of the suspension accurately, administering trial drug candidates in this form requires accurate, repeatable and validatable control of the active ingredient's particle size, often on limited sample volumes.

Laser Diffraction is the best tool to meet these pre-formulation requirements. This technique provides particle size distribution of nano-scale material while also having a wide dynamic range (10nm to 3.5mm). A well-designed system for this application should meet all relevant ISO and USP requirements and be able to work with milligram quantities of active compound in milliliters of suspending liquid.

The Malvern solution can:

- Meet and exceeds all industry qualification guidelines such as ISO 13320:2009, USP <429>, USP <1058>
- Allow for easy creation, execution of Standard Operating Procedures
- Provide for data integrity through 21 CFR Part 11 compliance
- Validation Documentation.



CHEMICAL DEVELOPMENT

Automate bioavailability and bioequivalence studies



Optimization and bioequivalence

When characterizing bioavailability or bioequivalence of nasally administered drugs, in support of (New Drug Application) NDAs or (Abbreviated New Drug Application) ANDAs, for nasal aerosols and sprays, the United States Food and Drug Administration (FDA) recommends several tests. In cases where the active component or components are suspensions, one important attribute is the drug particle size distribution.

The challenges of this particular test are in determining drug particle size in the presence of suspending agents and validating the analytical method. Automated combined morphological and spectroscopic analysis provides the answers by:

- Removing operator variability
- Ensuring that Test and Reference products are measured under the same conditions
- Eliminating the occurrence of apparent drug particles (false positives) due to excipient.

Droplet size of aerosols and sprays also influences BA/BE. The US FDA recommends “thorough characterization” of the delivery device in conjunction with the formulation.

A laser diffraction system fit for this purpose must be able to rapidly measure obscuration (optical concentration) in addition to changes in droplet size distribution and span, in real-time over the life of a single actuation from the drug delivery device.



Malvern’s solution can enable:

- Measurement times in the order of 100µs over the “beginning”, “fully developed” and “end” phases of the actuation
- Accurate and repeatable setting of measurement distance from actuator orifice
- Ability to automate reliable and repeatable actuation of device.



FORMULATION DEVELOPMENT

Controlling liposome formulation drug delivery



Controlling liposome formulation

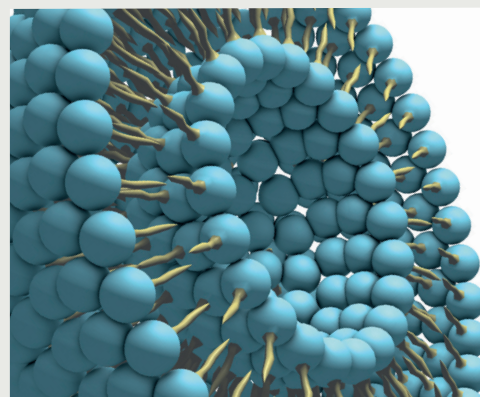
The size of a liposomal vesicle plays a pivotal role in the pharmacokinetic and pharmacodynamic attributes of chemotherapeutic drugs, whereby the liposome acts as a carrier of the drug to the site of action.

The challenge is accurate and rapid measurement of the size of liposomes, on very limited amounts of sample, at the formulation concentration and under physiological conditions. This is necessary to ensure effective drug delivery systems that do not aggregate, allowing the best vesicle to be chosen for its intended use.

Dynamic Light scattering facilitates these types of studies.

The Malvern solution can provide for:

- Control of pH and temperature of sample
- Measurement of small sample volumes down to 12 μ L
- A wide range of sample concentrations to be studied
- Transferable Standard Operating Procedures.



FORMULATION DEVELOPMENT

Getting the depot and enteric formulation right first time



Formulation Development

Polymer excipients are widely used in parenteral and oral solid dosage forms. The degree of polymerization (DP) determines the polymer's performance for a given action.

Whether it is used to protect, sustain the release of, or make site specific, the active ingredients, the challenge is accurate determination of the number average molecular weight, weight average molecular weight and the polydispersity.

Triple-Detection Size Exclusion Chromatography (TD-SEC) can accurately characterize polymer excipient molecular size and weight and avoid incorrect determination due to conformation differences between the analyte in solution and that of the calibration standard used in conventional calibration methods.

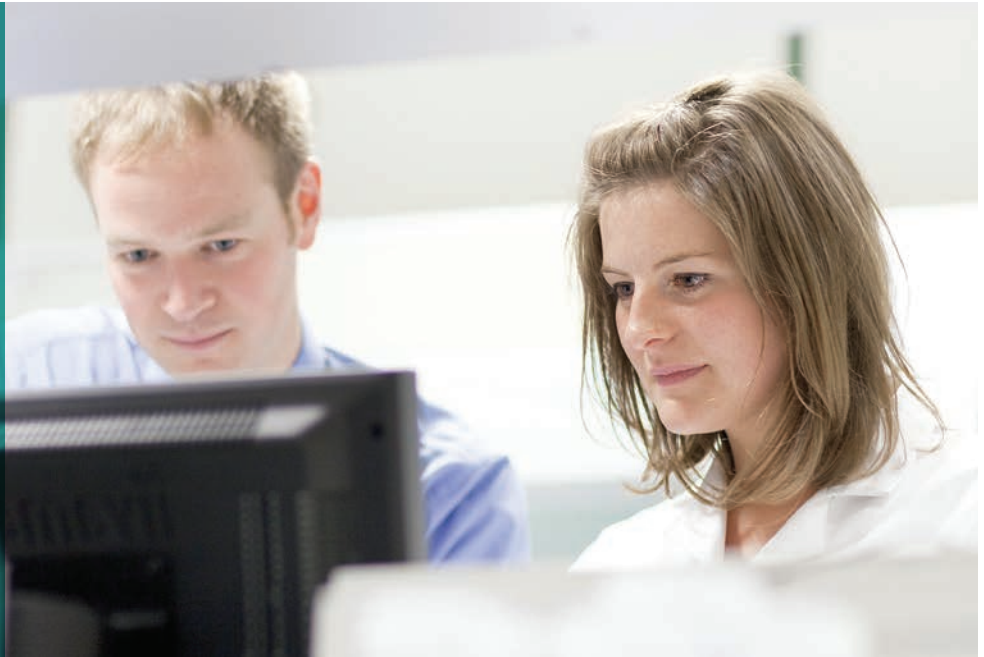
The Malvern TD-SEC system:

- Complete turnkey system or add-on to existing HPLC
- Direct molecular weight measurement by light scattering
- Methods for polymers, proteins and conjugates
- Meets USP <621> recommendations
- Allows 21 CFR part 11 compliance.



FORMULATION DEVELOPMENT

Optimizing tablet coating processes



Optimizing tablet coatings

The uniformity with which a tablet coating is applied to a core is highly dependent on the rheological characteristics of the film coating itself. The liquid spray coating has a finite time from landing on the tablet surface, to level and join the rest of the coating before it dries. The time-dependent rheological response, or thixotropy of the coating material, after passing through a spray nozzle onto an Oral Solid Dose (OSD) such as tablet, is a key element in process understanding.

The conditions of a tablet coating process can be simulated using a rotational rheometer system. The viscosity of the liquid coating is measured initially under low stress conditions to quantify its full structure, then at high shear rates to simulate spraying, and again at low stress conditions to assess the viscosity rebuild with time. A change in coating formulation – from thickener type to solids content in a suspension – can change thixotropic properties, and therefore the uniformity, and ultimately the efficacy of the final coating.

The Malvern rheometer can:

- Simulate the conditions of processes such as spray coating on the laboratory bench
- Solve material process problems and be used to optimize new coating formulations
- Run rheology tests tailored to your needs as Standard Operating Procedures (SOPs) that include appropriate analysis steps to report the key data.



FORMULATION DEVELOPMENT

Improving the stability of low solubility APIs



Stabilizing low solubility APIs

When developing suspensions of micron-sized, insoluble particles of Active Pharmaceutical Ingredient (API) at high solids concentration, it is important to have an understanding of the system's rheology, to ensure the formulation is stable over the lifetime of the product. Engineering the rheological properties of the formulation enables control of the degree of sedimentation and the ease of redispersion, the optimization of packaging and product delivery, and subsequently the correct administration of its contents.

The challenges include being able to understand the interplay between particle size, zeta potential and rheology, and how manipulation of these properties can provide mechanisms for suspension stabilization. The ability to make high quality rheological measurements easily and reliably, under appropriate conditions of shear rate, shear stress, strain and time is essential to both benchmark and improve material performance characteristics.



Malvern's rheology measurement technology meets these challenges by:

- Providing a Toolkit of standard rheology tests preconfigured with intelligent defaults to ensure robust data – from viscosity to complex viscoelasticity
- Enabling Standard Operating Procedure (SOP)-driven rheology testing to drive robust methodology and reduce operator-to-operator variability
- Supporting a wide variety of measurement geometries optimized for rheological characterization of dispersed multi-phase systems, including large particle suspensions compatible with large particle suspensions.



FORMULATION DEVELOPMENT

Storage of active pharmaceutical ingredients in accordance with Good Manufacturing Practice (cGMP) guidelines.



Stabilizing compounds for storage

The shelf life of active pharmaceutical ingredient is often cited as a critical quality attribute (CQA) of a drug product. Different polymorphs and solvates can have a dramatic effect on the drug product performance attributes such as dissolution and bioavailability.

The challenge comes in quantifying any changes of active pharmaceutical ingredient, particularly in solid-solid transformations, during storage, in a manner which is not operator intensive and follows the cGMP guidelines whereby every lot of material is required to be tested with a validated analytical method or by a method which is set forth in the United States Pharmacopeia National Formulary.

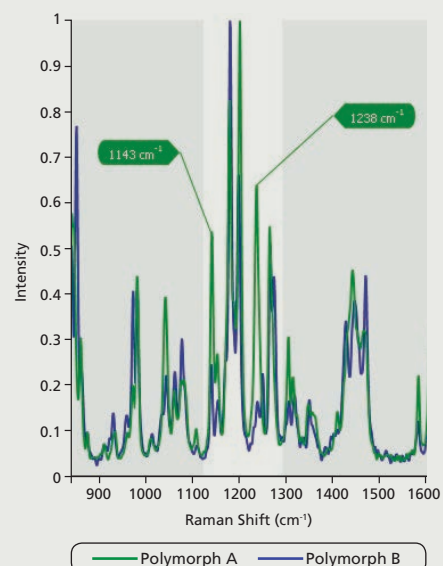
Malvern's automated morphological analysis combined with spectroscopic confirmation is the right tool for this requirement.

- Rapid and repeatable morphological investigation of any transformations
- Transferable SOPs used in the DMF or NDA/ANDA from development to QC
- Chemical confirmation of polymorph changes with built in Raman spectroscopy.

Polymorph A Close-up



Polymorph B Close-up



MANUFACTURING

Producing consistent granules prior to blending or compression



Optimizing granulation

High shear, wet granulation is a widespread unit operation within the pharmaceutical industry. Granulation can improve the ease of handling of powder blends and prevents the segregation of fine constituents, improving consistency in subsequent process steps, principally tableting.

However inconsistencies often occur during granulation development and scale up due to changing API, raw materials, or changing process dynamics such as segregation, agglomeration, or breakage, making end point hard to determine.

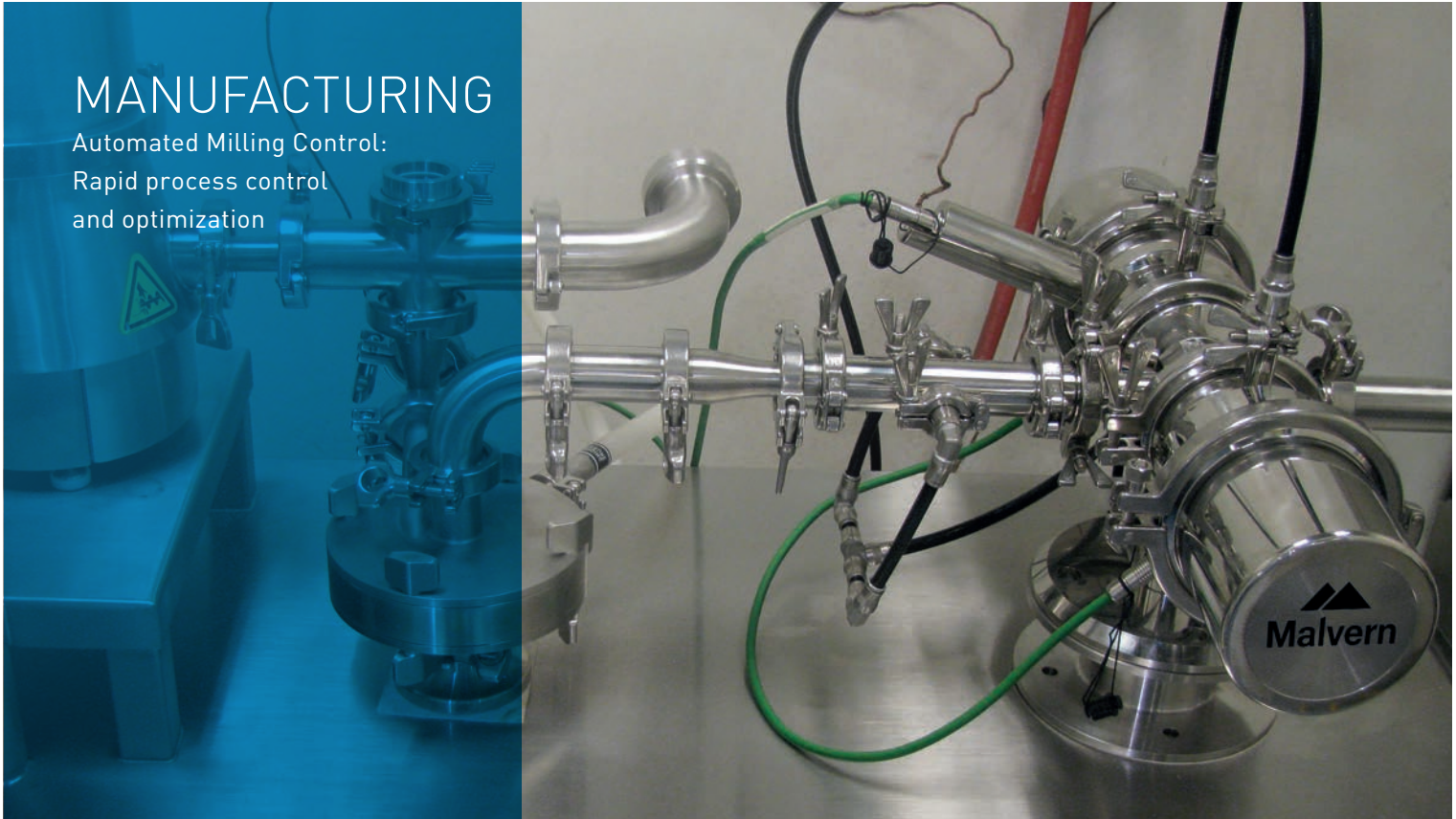
Malvern's Process Analytical Technology can meet these challenges.

- *In-situ* real time measurement of granule particle size
- Scalable technology that can be implemented from small to large granulators
- ATEX certified for installation in hazardous environments
- Granulation end-point determination.



MANUFACTURING

Automated Milling Control:
Rapid process control
and optimization



Automated milling control

Batch milling is widely used during API manufacture to reduce particle size to an acceptable range in order to meet the defined specification. With only off-line analysis in place, controlling the API particle size within an acceptable range is an iterative process. This is time consuming and wastes material. Equally important, the particle size of the milled powder can be quite variable.

To improve the efficiency of the milling operation, and to deliver more consistent milled particle sizes, on-line particle-size analysis is a solution for continuous milling monitoring and control. In addition, measurements made by the on-line analyzer can control the process through a closed loop with the mill's programmable logic controller (PLC).

Malvern's in-line particle size distribution analysis has been implemented in this way.

- Robust, clean in place (CIP) hardware designed for on-line implementation
- Fully integrated with mill to enable process control
- cGMP and 21 CFR Part 11 compliant.



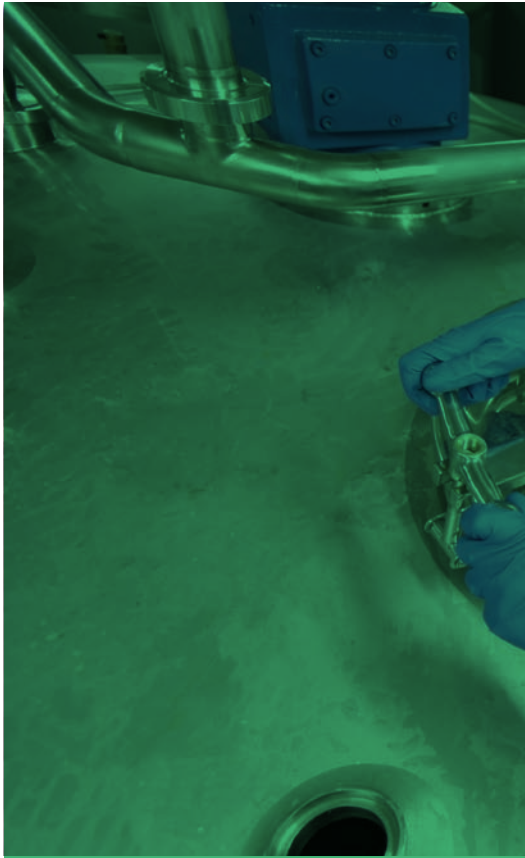
GLOBAL SUPPORT WHERE AND WHEN YOU NEED IT

When you purchase a Malvern product we understand that this is only the first stage of a collaborative relationship that lasts for the lifetime of the instrument and we want you to achieve the maximum return from your investment. At Malvern we are committed to providing the highest quality support, from simply answering occasional questions and supplying software updates through to delivering a comprehensive support package with priority call out and fixed costs of ownership.

Within our organization we not only have scientists who are leaders in their chosen fields, but also the accumulated knowledge and experience of more than 45 years in materials characterization across a very broad range of industries. Our customers can access this global technical and applications expertise through a variety of convenient channels and in formats structured to ensure the widest possible availability, anywhere in the world. Dedicated Helpdesk teams provide telephone and email support, ensuring you get a complete answer to any questions.

Our specialists deliver training via convenient online e-learning, classroom participation at a Malvern facility or on-site in your workplace. We help with validation documentation, provide expert applications support and offer a range of service contracts appropriate to individual needs.





For the wider community, ensuring access to learning has always been a defining part of Malvern's offering. A pioneer in delivering web seminars more than a decade ago, today we run one of the industry's most active webinar programs with events freely available to customers and non-customers alike. We actively encourage interaction with our teams via the 'Materials Talks' blog (www.materials-talks.com) and our comprehensive library of application notes, technical information, articles, case studies and on-demand multi-media presentations are all universally and freely available to read or download.

Making material relationships work better.



ACCELERATING DRUG DEVELOPMENT

Malvern's comprehensive range of products delivers particle, rheological and chemical characterization data on a wide variety of materials encountered in the development of pharmaceutical products. Malvern's systems open the way to improved raw material, drug product and process understanding and can bring measurement know how to the following:



Material	Relevant Critical Quality Attribute (CQA)	Malvern Product Range
API	Particle Size Distribution	Mastersizer 3000 Zetasizer Nano Parsum Insitec
API	Crystal form	Morphologi G3
Excipient	Particle size	Mastersizer 3000 Zetasizer Nano Parsum Insitec
Excipient	Particle size and shape / structure	Morphologi G3 FPIA 3000
Droplets (nasal spray, nebulisers)	Particle size	Spraytec Morphologi G3-ID
Liposomes	Particle size	Zetasizer Nano ZSP
Proteins	Size / hydrodynamic radius	Zetasizer Nano ZSP
Proteins	Form (dimer / trimer etc)	Zetasizer μ v

Material	Relevant Critical Quality Attribute (CQA)	Malvern Product Range
Powders and granules	Particle Shape	Morphologi G3  Morphologi G3-ID  FPIA 3000 
Topicals	Rheological properties	Kinexus 
Suspensions	Rheological properties	Kinexus 
Polymer excipients	Rheological properties	Kinexus 
Polymer excipients	Zeta Potential	Zetasizer ZSP 
Polymers	Molecular Weight Distribution	Viscotek  Zetasizer ZSP  Zetasizer μ v 
Bio-polymers	Molecular Weight Distribution	Viscotek  Zetasizer ZSP  Zetasizer μ v 
Proteins	Size/hydrodynamic radius	Viscotek  Zetasizer ZSP  Zetasizer μ v 
Polymer	Size/hydrodynamic radius	Viscotek  Zetasizer ZSP  Zetasizer μ v 
Bio-Polymer	Size/hydrodynamic radius	Viscotek  Zetasizer ZSP  Zetasizer μ v 
Polymers, biopolymers	Molecular Structure	Viscotek  Morphologi G3-ID 
Granules, API, Excipients, Creams and Ointments	Chemical Characterization	Morphologi G3-ID 



Malvern Instruments Limited
Groewood Road, Malvern,
Worcestershire, UK, WR14 1XZ

Tel +44 1684 892456
Fax +44 1684 892789

www.malvern.com

Malvern Instruments is part of Spectris plc, the Precision Instrumentation and Controls Company.

Spectris and the Spectris logo are Trade Marks of Spectris plc.

spectris

All information supplied within is correct at time of publication.

Malvern Instruments pursues a policy of continual improvement due to technical development. We therefore reserve the right to deviate from information, descriptions, and specifications in this publication without notice. Malvern Instruments shall not be liable for errors contained herein or for incidental or consequential damages in connection with the furnishing, performance or use of this material.

Malvern and the 'hills' logo, Insitex, Kinexus, Mastersizer, Morphologi, Spraytec, Sysmex, Parsum, Viscotek and Zetasizer, are International Trade Marks owned by Malvern Instruments Ltd.

MRK1864-01

Technology that is instrumental to your success - distributor details

Distributore per l'Italia:



Contattaci:
alfatest@alfatest.it

alfatest.it
alfatestbio.it
alfatestlab.com

