



S O L U T I O N S



PHARMACEUTICALS PAT

ON-LINE PARTICLE SIZING SOLUTIONS

APPLICATIONS

Spray Drying
Milling
Classification
Granulators
Fluidized Beds

ANALYZER SYSTEMS

Insítec T
Insítec X
Parsum

"Each gram saved is a real gain and we can now perform much better in a sector where high quality is crucial."

Hubert Müller, Process Engineer,
Siemens Axiva GmbH & Co KG

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WHY RUN BLIND?

THE CUTTING EDGE OF PROCESS ANALYTICAL TECHNOLOGY

The pharmaceutical industry is characterized by high value products and relatively small tonnage batch processes. Reliable and consistent product quality is essential. Historically process efficiency in this sector has been low, relative to other industries, and the adoption of new process technologies slow as a result of process validation requirements. The FDA's Process Analytical Technologies (PAT) initiative is designed to encourage manufacturers to make more use of on- and at-line analysis techniques to increase process efficiency, improve batch-to-batch consistency and reduce risk. As many pharmaceutical processes involve particulate handling, on-line particle size analysis is key. Malvern's extensive knowledge of the pharmaceutical industry has led to the development of analytical solutions which meet the specific requirements of both active and excipient manufacturers. The widespread use and acceptance of Malvern's Insitac technology is testament to its industrial robustness, relevance and usefulness.



Pharmaceutical milling at Siemens Axiva GmbH & Co. KG, Frankfurt, Germany

Particle Size in the Pharmaceutical Industry

- Around 70 % of pharmaceutical drugs are consumed in solid oral dosage form; efficacy is influenced by the particle size properties of both active pharmaceutical ingredients and excipients
- In general larger particles are easier to handle during manufacturing but smaller particles have better adsorption and dissolution characteristics
- In the past particle size analysis has been carried out off-line but this approach is associated with time delays and inaccuracies
- Exposure to product is a particular issue for the pharmaceutical industry. Stringent safety precautions are necessary during sampling



design. Pharmaceutical options address issues such as 21 CFR part 11 compliance, materials traceability and software validation. Hygienic fittings allow cleaning of the entire sample path between campaigns; SIP and CIP options are available. An intrinsically safe version, Insitac X, is also available, especially useful when using flammable volatile solvents in the process.

Malvern Insitac

An integrated solution meeting industry standards

Particulate systems can be monitored and controlled using a range of Malvern solutions (see table below).

The Insitac system has been specifically developed for industrial use. It employs the industry standard ensemble laser light scattering technique diffraction to rapidly generate complete volume-based particle size distribution data (at rate of up to 4 distributions per second), and requires no calibration. System reliability is extremely high and maintenance requirements are minimal.

Units specifically for pharmaceutical use in a GAMP4 environment are available, as is an intrinsically safe

Malvern's solutions-based approach extends to the provision of proven, automated sampling systems. The Jetstream eductor and Gulfstream eductor allow representative sampling from medium to high concentration dry and wet process flows respectively. For dilute streams the Insitac can be used in-line - a process analyzer needs to be flexible in the range of concentrations measured for direct measurement a patented multiple scattering correction algorithm is used which allows the analyzer to work at higher concentrations than laboratory units. The range of Insitac process interfaces ensures that the technology is suitable for both pilot-scale and full-scale operation.

Process stream	Particle size range	Analyzer	Process interface
Dry powders	0.5 - 1000 μm	Insitac	Jetstream eductor
Wet suspension	0.5 - 1000 μm	Insitac	Gulfstream multistage diluter
Dry powders	50 - 3500 μm	Parsum	In-line probe



Two software packages Malvern Link and RTSizer allow the data measured by the analyzer to be effectively used in the manufacturing environment. These packages generate data in the required form, control sampling/analysis, and integrate the system with existing process control platforms, thereby facilitating automated process control.

Each element of the Malvern system is tailored to the specific requirements of not only the industry but also the individual user, process stream and plant control system.

Malvern Parsum

This technique is based on spatial filter velocimetry, a counting technique which is used to characterize process streams containing coarse particles. This analyzer has the advantage of a very simple installation, as it is an in-line probe requiring minimal installation work. The probe delivers a chord-length distribution useful in monitoring feeds to mills, and measuring the final grade products from spray driers and agglomerators. Parsum has a range of measurement zone interfaces which allow it to be tailored to the requirements of the process stream, and an intrinsically safe version is also available. Real-time data transfer to the process control system is possible using 4 - 20 mA current loops.

The Benefits of On-Line Analysis

Meeting the challenges facing pharmaceutical manufacturers

The rich flow of particle size data which results from the installation of an Insitec system can be used to significantly improve the efficiency of particulate unit operations such as spray drying, atomization, granulation, and most commonly milling. On-line analysis allows the effects of any process changes to be instantaneously observed, thereby improving the quality of manual control and increasing process knowledge. Additionally, on-line analysis opens up a route to automated control, facilitating further optimization and eliminating the need for manual intervention. For pharmaceutical manufacturers an Insitec installation typically leads to the following benefits:

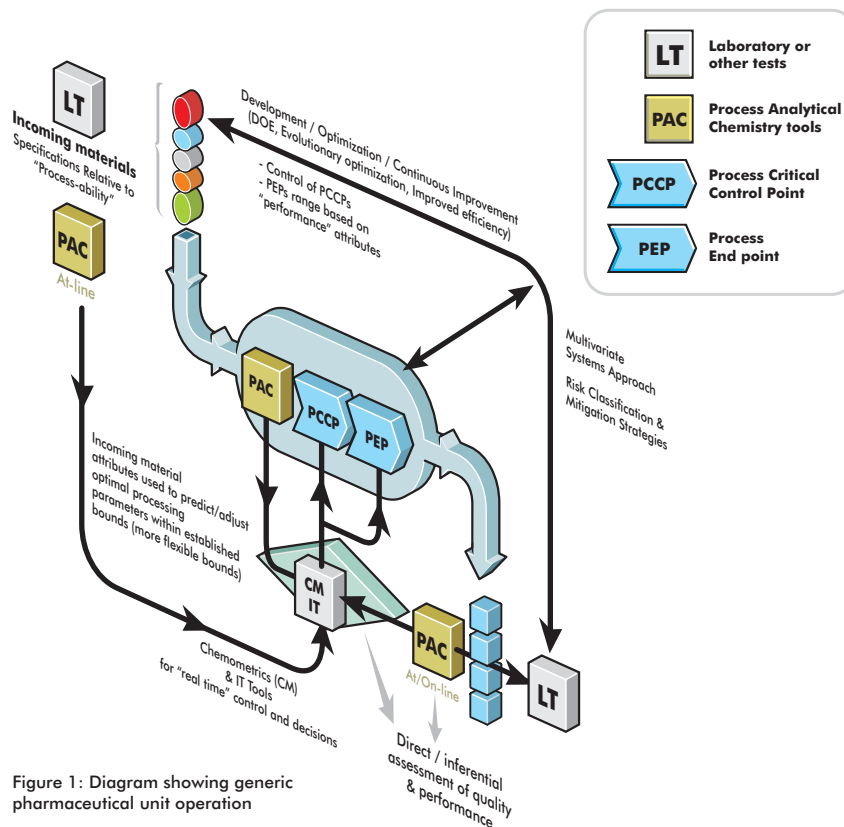


Figure 1: Diagram showing generic pharmaceutical unit operation

- Reduced time to market
- Improved process reliability
- More efficient transient operation with improved start-up/shut-down
- Reduction in risk of operator exposure to product

These benefits translate directly into reduced wastage and lower energy consumption. Batch-to-batch consistency can be improved as a result of

monitoring all of each batch (as opposed to a small sample), and batch rejection rate is typically reduced as a result of improved process understanding. Rapid process optimization becomes feasible. The following examples illustrate the achievements made by pharmaceutical manufacturers currently using the Insitec system.





Improved Process Knowledge

Reducing mill overloading

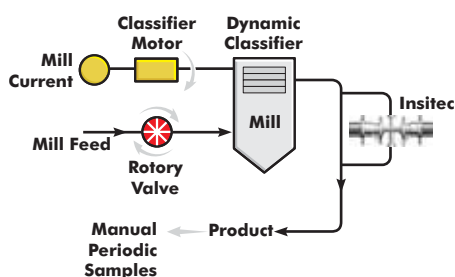


Figure 2: Off-line and on-line particle size analysis of milled product

The product from a pharmaceutical mill was found to be of variable quality. Regular off-line analysis showed particle size to be consistently close to set point but on-line data showed something completely different (See figure 3). On-line data showed that at regular intervals Dv50 and mill current increased significantly. Transmission, a parameter measured by the Insitac, indicative of the concentration of particles in the process stream, simultaneously decreased. It was concluded that material was being forced through the mill at too high a rate leading to 'short-circuiting' of the classifier. In order to improve mill control, transmission was subsequently used to drive feed rate. Figure 4 shows the improved operation which was achieved. The change resulted in enhanced product quality and yield, smoother mill operation, reduced waste and a reduction in manpower requirements.

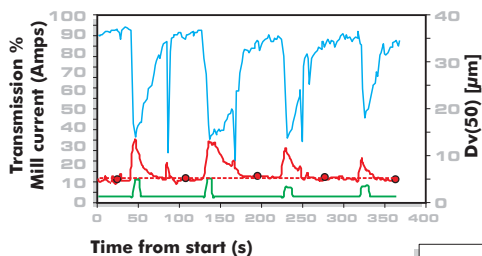
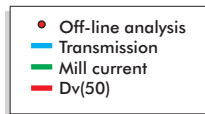


Figure 3: Periodic fluctuations due to overloading mill, shown using on-line particle size analysis.



Process Optimization

Ensuring optimal milling during pilot drug trials

A pharmaceutical manufacturer carrying out pilot drug trials found mill optimization using off-line analysis a time-consuming, wasteful process. For each new product the optimization procedure took around 1 week. The typical cost of the products being processed was US \$0.5 - \$1 M/kg; waste was excessive and costly. There was a poor understanding of the effects of air flow rate, air pressure, feed flow rate and mill speed on particle size. Optimization was therefore carried out by stepping systematically through the variables to find optimal values. The process was laborious and mill shutdown frequent.

An in-line Insitac analyzer was installed at the mill exit. The analyzer was used to characterize the whole batch, as it passed through the mill, rather than small samples (3 - 5 g) at periodic intervals. The impact of mill adjustments could be immediately seen allowing changes to be carried out much more rapidly without stopping and starting the mill.

A more complete optimization study is now possible in only 4 hours, a saving of 4.5 days for each product. In addition, the amount of wastage has been dramatically reduced; yields of around 98 - 99% are now commonplace. The product can be milled to a specific endpoint, in terms of particle size, rather than for a specific period of time.

Automated mill control is being considered and an investigation of the effects of parameters previously thought too difficult to study is being carried out. Lot size is being increased. Manpower requirements have been significantly reduced.

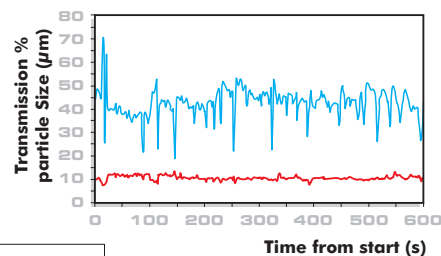


Figure 4: Improved control as a result of on-line analysis.



Malvern Instruments Limited
Enigma Business Park
Groveswood Road, Malvern, Worcs
WR14 1XZ
UK
Tel: +44 (0)1684 892456
Fax: +44 (0)1684 892789

Malvern Instruments Inc
10 Southville Road, Southborough
MA 01772
USA
Tel: +1 (508) 480 0200
Fax: +1 (508) 460 9692

Malvern Instruments Japan
South Bldg, 459 Kobe International Business Center
5-5-2 Minatojimaminami-machi
Chuo-ku, Kobe-shi Hyogo Prefecture 650-0047
Japan
Tel: +81 (0) 78 306 3806
Fax: +81 (0) 78 306 3807

Malvern Instruments GmbH
Rigipsstraße 19
71083 Herrenberg
Germany
Tel: +49 (0) 7032 97770
Fax: +49 (0) 7032 77854

Malvern Instruments S.A.
Parc Club de L'Université
30, Rue Jean Rostand
91893 Orsay Cedex
France
Tél: +33 (1) 69 35 18 00
Fax: +33 (1) 60 19 13 26

Malvern Instruments Nordic AB
Box 15045, Vallongatan 1
750 15 UPPSALA
Sweden
Tel: +46 (0) 18 55 24 55
Fax: +46 (0) 18 55 11 14

Malvern Instruments China
Room 04 8th Floor
699 Nanjing Road, Shanghai 200041
China
Tel: +86 21 5211 0072
Tel: +86 21 5211 0079



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