THE IMPORTANCE OF PARTICLE SIZE ANALYSIS

Particle size is one of the decisive quality parameters of pharmaceuticals and intermediate products. Flowability and dissolution, resorption and bioavailability are determined by the particle size distribution.

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After almost 30 years of rapid development, the laser diffraction method for particle size analysis not only gained a leading position in the laboratory, but also gained the potential to face new challenges directly in the process. While off-line application is suitable for laboratories with different products, in-line application integrates representative sampling and supplies the particle size information immediately for continuous monitoring and automated process control. GMP requirements are fulfilled with modern quality management and validation procedures.

Setting up a laser diffraction system

In the classical Fourier set-up, dispersed primary particles interact with the laser light in the parallel laser beam (see Figure 1). The diffraction patterns are collected on a highly sensitive semicircular, multi-element detector. With this input information, the particle size distribution is deconvoluted using the Fraunhofer or Mie theory.

What is the advantage of using Fraunhofer? Although ISO 13320 states that 'for particles smaller than about 50 microns, the Mie theory offers the best general solution', a clear warning is given (in the same paragraph) not to use Mie if the preconditions are not fulfilled. These preconditions are challenging: no mixtures, spherical, non-isotropic particles with smooth surfaces and the knowledge of the complex refractive index with both the real part refractive index and the absorption as its imaginary part.

Fraunhofer in comparison is parameter free and model independent. Mie, however, is applicable and useful if the necessary information is available. Different dispersing modules are employed to optimise the dispersion. In general, a dry sample should be dispersed dry and a wet one in suspension because of secondary effects like dissolution or surface reactions. Instruments that use the reverse Fourier set-up, with a convergent laser beam, suffer from a blurred diffraction pattern on the detector and therefore significantly lower sensitivity and precision. Nevertheless, in any case these instruments cannot

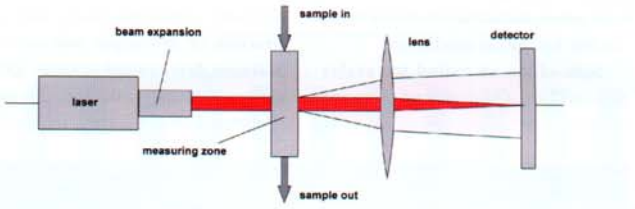


Figure 1. Optical set-up for the generation of diffraction patterns.

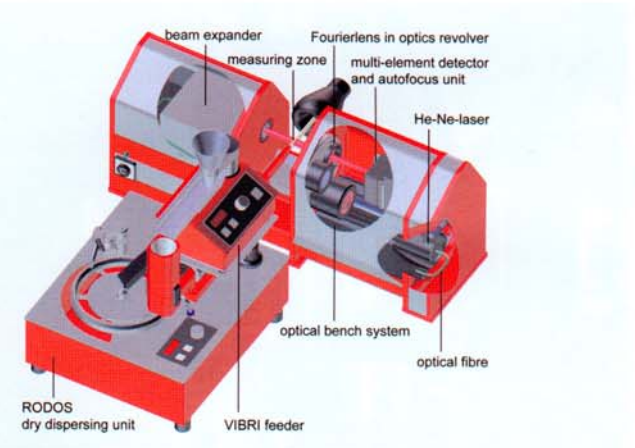


Figure 2. HELOS and RODOS as an example of a particle size analyser.

cope with challenging dry or spray applications at all, because an extremely thin measuring zone is required.[1]

Instrumentation

The quality of particle size analysis depends on different aspects: sampling, sample handling, dispersion, detection, evaluation and representation of results. A modular laser diffraction system has the advantage of being able to apply different dispersing modules with the same diffraction sensor (see Figure 2).

For dry and wet dispersion, as well as for the analysis of sprays, controlled dispersion conditions are necessary. Proper dry dispersion, for example, uses a controlled combination of shear forces, particle-particle and particle-wall collisions and is able to cope with samples from below 0.1 micron up to the millimetre range.[2] For spray applications, adapted dispersing modules with automated actuation ensure reproducible measuring conditions.

State-of-the-art control and evaluation software is built around a versatile database and offers operation using standard operating procedures (SOP) which can be recalled by pressing a single button. In addition, it provides powerful tools for data evaluation, statistics and graphical presentation. Typically the cycle time for a particle size analysis is less than a minute including feeding, dispersion, measurement, evaluation and automatic rinsing.

Validation

Production of systems according to the validation rules (GMP and FDA standards) requires the highest standards of quality assurance. Sympatec began in 1994 with its own QA system for particle size analysis, meanwhile strengthened by a large number of international applications. The high educational standard of the employees is the basis of its three levels.

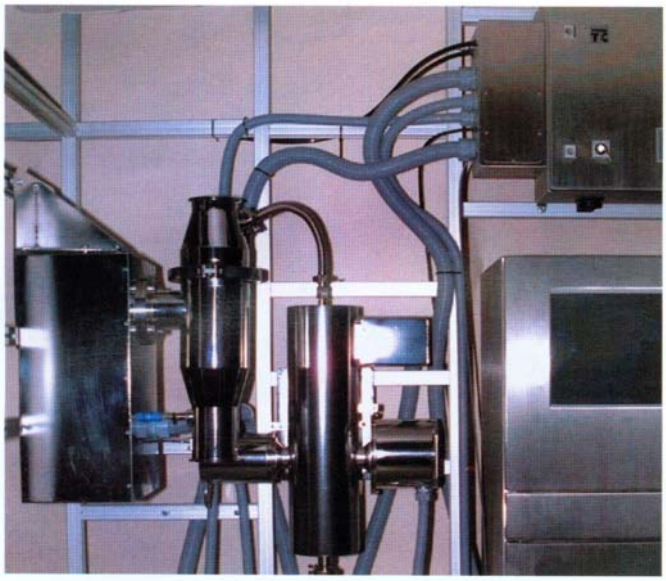
First, the development of measuring systems in the different divisions consists of particle technology, mechanics, hardware, firmware, basics and construction of prototypes and software. Software development is under special guidance because the design rules, continuous error tracking, testing documentation and effective back-up strategy are supervised. Individual responsibility is proven by signature. External certifications of testing laboratories, such as for CE conformity, are integrated.

Second, documentation of all the production steps of each instrument in the production binder follows the common differentiation in IQ, OQ and PQ. For installation qualification the components must be marked individually and installed correctly. For operational qualification the function of each single component is checked. Finally, the performance qualification after system integration tests all components as completely assembled system.

Third, for certification, not only electrical and optical properties are tested for compliance with the specifications, but series of measurements with reference materials (up to 300 measurements per system) have to prove that all requirements are fulfilled. Only in this case is the system permitted to be shipped to a customer.

All necessary documents for the validation procedure are provided in a comprehensive validation binder. With the reference materials a re-certification can be executed after installation and repeated at the customer's site whenever requested.

With this extended quality management, Sympatec guarantees extremely high accuracy and system-to-system comparability for its particle size analysers. Hence the standard deviation of results from different systems of the same type is typically less than 1 per cent. The limits defined by ISO 13320 of a maximum 3 to 5 per cent have been clearly bettered since the introduction of the Sympatec QA-system.



In-line system MYTOS and TWISTER in GMP design.

In-line particle size analysis

For reliable in-line particle size analysis (PSA), not only must controlled dispersion, sensitive measurement and powerful data evaluation be representative and reliable, but sampling and sample handling must be too. Therefore, Sympatec has developed a new PSA system with integrated repre-

sentative sampling. TWISTER is the first link in this innovative chain. From its shielded parking position at the side of the pipe, the sampling finger starts its spiral track into the centre and out again to the side, drawing a representative sample while doing so. The system can cope with a wide range of process conditions, for example, pressure up to 10 bar, temperature up to 100°C.[3]

MYTOS is composed of adapted components of the established HELOS and RODOS technology, thus also ensuring complete comparability of results to off-line analysis. The Sympatec WINDOX software, which records all measurements in a database, can be set up to show just the key features of the distribution as a trend plot against time, thus allowing effective control of important process parameters without losing any detail information. Automated control is provided by using a PLC.

Requirements for a GMP conform system for particle size analysis

A special GMP conform version of MYTOS and TWISTER is available. The starting point is the idea that the valuable pharmaceutical product is neither to be contaminated, nor to be carried to the next charge when changing batches.

All parts in contact with the product are made of polished stainless steel for simple cleaning and sterilisation. Components with no contact with the product can easily be swung aside and the components in contact can be cleaned or exchanged. Of course, validation and re-certification of MYTOS and TWISTER follow the high standards of the Sympatec QA strategy.

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Author

After working on projects with international companies and the German Ministry of Research and Technology, dealing with dry sorting technologies, Stephan Röthele became an associated founder of Sympatec GmbH in 1984. The company came under his control through a management buy-out when he became the managing director. He has received technology transfer awards for dry dispersion and on-line particle size analysis and is the owner of several patents in the fields of sampling, dispersion and particle size analysis.