In- and on-line Particle Size Analysis with Representative Sampling for Pharmaceutical Applications (GMP)

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ABSTRACT

The combination of laser diffraction with representative sampling and dry dispersion as a powerful and reliable in-line particle size analysing equipment has been introduced on PARTEC 1998 [1] and successfully extended over the last few years. Sampler diameters of the process pipes from 50 up to 660 mm, measuring ranges from 0.25 µm to 8,750 µm and mass flows from some kg/h to 400 t/h, even at temperatures up to 150°, air flows of up to 60,000 m3/h, and in hazardous areas have been reported [2].

The increasing quality requirements in the pharmaceutical industry create a growing demand for in-line and on-line particle size analysis under **G**ood **M**anufacturing **P**ractice (GMP) conditions – often combined with the requirements of hazardous areas (covered e.g. by ATEX 95). The requirements are displayed for typical applications. A flexible solution including representative sampling has been developed, comprising a representative sampler, dry dispersion, particle size analysis by laser diffraction and a transporting and mounting support unit. It allows for simple and quick connection to various points of use. GMP, ATEX 95 and CFR 21 rule 11 requirements are supported. Special heatable GMP-versions are available for direct control of e.g. spray dryers.

The possibilities are explained.

1 INTRODUCTION

An already nearly unmanageable, but still increasing jungle of laws and regulations often brings the user, suddenly facing this, to despair on his duty. This article gives an overview how to handle both GMP and ATEX regulations and shows how this challenge results in highly reliable instruments for in- and on-line particle size analysers (PSA).

2 OVERVIEW OF RULES

2.1 What is GMP all about?

A very good consumption is given at the GMP portal of gempex ltd. [3]:

The term GMP has been introduced in 1962 by the US **F**ood and **D**rug **A**dministration (FDA). The term is synonymous for a collection of behaviour measures and instructions that have to be taken into consideration during the production and handling of certain products (e.g. pharmaceuticals, food products, cosmetic products and veterinary medicines etc.) with the main goal that these products be reproducible and reliable in the desired quality.

The obligation to follow the GMP guidelines comes from various laws (e.g. the German Medicines Act) or through intergovernmental agreements (e.g. **PIC** = **P**harmaceutical **I**nspection **C**onvention = agreement between former EFTA members).

In the European guide for pharmaceutical products, III/2244/87, Rev. 3, Jan. 1989, valid since 1992 Good Manufacturing Practice, GMP, is defined as:

"… that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation or product specification."

Two major difficulties arise in the application of GMP guidelines:

I. There is not one GMP rule, but rather numerous GMP rules plus additional and supplementary guidelines and literature.

   Only if the user faced to that answers a lot of questions he should be able to choose the correct GMP guidelines.

II. GMP guidelines say what has to be done or complied with, but not how.

One of the most frequent requirements of GMP is that something should be designed, constructed and erected in a way that any kind of cross-contamination with other products is avoided under all circumstances. How this aim is achieved depends on the experience of the individual project management. Exactly this point led to a great deal of discussion in the past because it often led to the relevant activities being carried out excessively.

In conclusion: GMP guidelines must be chosen, interpreted and implemented with the necessary experience on a case-by-case basis.

2.2 The ATEX regulations

The ATEX directives are much more rigid and exact than the GMP guidelines. ATEX is a harmonised EU standard that has been established in July 2003. The biggest advantage is the removal of barriers to free trade in Europe. But it also stands for an increased safety level of equipment and therewith for better

health protection of employees. As shown in Table 1, both, manufacturer and operator have to do their duty.

EU Directives on Explosion Protection	
To be observed by operator of plant	To be observed by manufacturer
ATEX 137 *1999/92/EC*	ATEX 95 *94/9/EC*
➢ explosion protection document ➢ safety of employees ➢ declaration of zones ➢ maintenance rate	➢ declaration of conformity ➢ safety of equipment ➢ equipment categories ➢ user manual

Table 1: ATEX Directives

Based on frequency and duration of occurrence of potentially explosive atmosphere different zones are defined. Due to the required degree of protection apparatuses are classified in equipment categories. To guarantee safety, the zone and the category have to fit together.

3 THE PARTICULAR REQUIREMENTS FOR GMP PSA SYSTEMS

In order to operate the equipment under hygienic conditions several aspects have to be taken into account. Surfaces should be smooth (e. g. electro polished, Ra = 0.8 µm) and without gaps and dead spaces. Easily dismountable parts support the cleaning procedure. For pipe work there are special sanitary flange systems available.

Often the equipment has to withstand a strong chemical and thermal aggression due to product and process properties. **C**leaning **I**n **P**lace (CIP) or **S**terilization **I**n **P**lace (SIP) procedures also may stress the material by solvents as alcohols and ketones or higher temperatures (e. g. 150 °C).

Metallic parts are usually made of austenitic stainless steel (e. g. SS316L, SS316Ti). The material specifications are documented by inspection certificates according to EN 10204-3.1B for each piece of raw material. In combination with test procedures for welded parts a so called “Welding & Material Certificate” is generated.

Similarly, plastic and rubber parts have to pass their own qualification. Every contractor has to prepare a declaration of conformity in terms of FDA 21 CFR 177.2600 or 177.1550 and a test report in accordance with EN 10204-2.2.

4 REALISATION OF GMP-SYSTEMS AND RESULTS

Due to different process conditions and different company rules there is nearly no standard system, that means every system has it’s special features.

4.1 Samplers used in GMP systems

The well known basis for good particle sizing is the representative sampling as performed with a spiral trajectory sampler TWISTER as introduced 1998 [1]. These systems, now available for tube diameters of 35mm to 660mm [4], have been transformed to GMP versions as shown in Figure 1. The importance of representative sampling cannot be overestimated.

Figure 1: Representative samplers TWISTER for tube diameters of 50mm and 150mm as GMP versions.

Only if there is not enough room for a spiral trajectory sampler one sometimes has to use a probe as shown in Figure 2. The pivoting L-probe is used in a trickling tube and turns downwards during idle time, because the frequently used back blowing into the process to keep the sample tube open is not allowed due to GMP reasons.

Figure 2: Pivoting L-probe as an example for non-representative sampling.

4.2 PSA devices used in GMP systems

4.2.1 Used measuring principles

For dry particle size analysis the laser diffraction (LD) technique is the dominating measuring principle [1]. Together with a successful dry disperser the combination with the before mentioned samplers has become a kind of standard method. Strong dispersion forces highly needed for fine particles are not suitable for fragile agglomerates. For this purpose a new system has been developed that integrates the very smooth dispersing of a fallshaft with integrated baffles, called gravity disperser, into the well proven on-line system.

For the characterisation of the shape of particles dynamic image analysis (DIA) is becoming the dominating technique [5,6]. Here are also two variations of dispersing available: The high energy injector dispersion for fine and sticky particles and low energy gravity dispersion for fragile particles.

Two new systems for LD (MYTIS) and for DIA (PICTIS) have been developed for very fragile particles. The DIA on-line instrument takes benefit from

the experiences of the LD apparatus. That means a start from an advanced point of development.

4.2.2 Matrix of instruments

The new extension of the instruments family encloses the well proven dry disperser as well as the gravity disperser for sensitive materials. Along with the LD and the DIA technique this spans a matrix of on-line particle sizing instruments as shown in Figure 3.

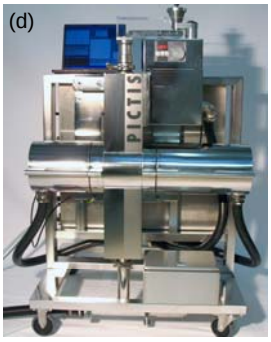
	laser diffraction	image analysis
high dispersion force	integrated samplers e.g. TWISTER or probe	
	(a)  MYTOS	(b)  PICTOS
low dispersion force	Separated samplers and transport necessary	
	(c)  MYTIS	(d)  PICTIS

Figure 3: The matrix of particle size analyzers for GMP applications and the allocation of the suitable sampling methods:

(a) on-/at-line LD sensor MYTOS;
(b) DIA sensor PICTOS, (a)+ (b) with dry disperser.
(c) on-/at-line LD sensor MYTIS and
(d) on-/at-line DIA PICTIS
(c + d) with gravity disperser, mounted on a trolley.
(a,b,c) sensors are shown with a vibratory feeder.

The integration of IA is useful only if the measurement is fast enough to get statistically reliable results and, of course, if the sample is taken representatively. Both premises are valid for the systems PICTOS and PICTIS. Samples of 50000 particles can be taken and calculated every 2 minutes. This means DIA can now provide a measuring frequency which is near to that of LD instruments. This variety of in- and on-line PSA offers the matrix of instruments shown in Figure 3. Samplers suitable for these instruments with low dispersing forces are simple cups which gather the amount of particles for one or the part of one measurement. This works e.g. by holding the cup beneath the output of a mill or a compactor. Transport systems to move the sample to the instrument are in preparation. This can be done manually or by a robot.

4.2.3 Results overview

Due to the strict confidentiality of most of the applications only very few results can be published.

As a result of the newness of the instruments, in field data are not yet available for all types of instruments. So only some impressive results are shown: Figure 4 demonstrates that even very small changes of the mill settings can be detected.

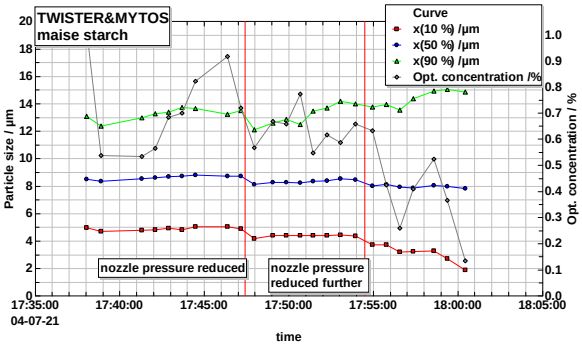


Figure 4: Sampling of maize starch with TWISTER 50 behind a jet mill measured with LD instrument.

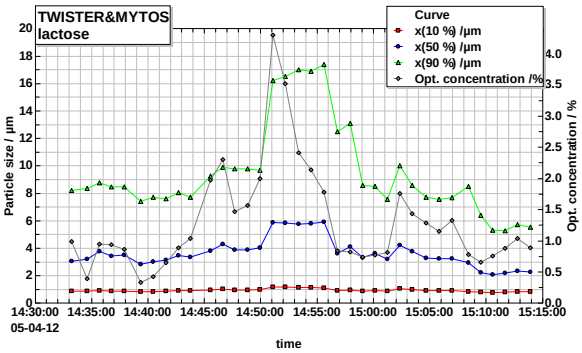


Figure 5: Sampling of lactose with TWISTER 50 behind a jet mill with variations of milling conditions measured with LD instrument.

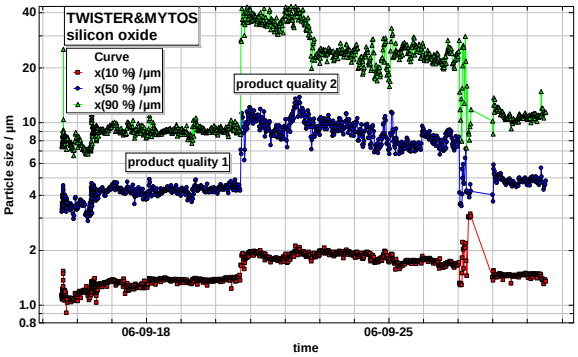


Figure 6: Living data over 2 weeks including quality changes of silicon oxide.

In Figure 5 the immediate reaction of the mill/classifier system on changes is shown. The instant reaction of

the measuring system allows to test different settings to reach the desired PSD. This is valid for even very sticky products, as maize starch is. In the following Figure 6 the process data of the production of silicon oxide is monitored over different product qualities. The immediate response of the measuring system allows for a very short time to reach the new quality specifications.

4.3 Examples for on-line Systems

There are numerous examples of GMP-systems which cannot all be shown. For example the TWISTER mounted behind a spray dryer. The sampler and the PSA were mounted on an elevating rack which allows the mounting of the sampler at different heights in a 250mm product line. Additionally TWISTER and out coupling stage had to be insulated against heat loss. The transport tube between sampler and PSA is heated to provide against condensation in the tube. The rack additionally carries an embedded PC, so that the communication to the process electronics can be provided via LAN.

4.3.2 Behind a small mill, throughput 5 kg/h

The GMP-Module with ATEX compliance (compact designed PSA) together with a ∅50 sampler found its place within an extremely small safety cabinet, see Figure 7.

Figure 7: Very narrow conditions for a ∅50mm sampler TWISTER and GMP-Module; analyser within a mobile rack

4.3.3 Behind a big mill with 1.2 t/h

The sampler behind the big jet mill shown in Figure 8 has enough room to be fixed optimally after 5 times the diameter behind the classifier. The measuring LD on-line system is situated below. Here was made a virtue of necessity and an inserted cyclone into the waste line of the LD analyser delivers the analysed sample out of the line to allow for chemical analysis.

Figure 8: Sampler in 150mm horizontal product line.

5 CONCLUSION

The presented systems and results prove the on-line capability of their combination with a gravity disperser. The calculated particle size distributions of DIA measurements meet all expectations regarding the comparability with laser diffraction results. The identical design of DIA and LD instruments implies the unique possibility to benefit from former experiences with the dry disperser technique. A various number of installations in GMP and ATEX areas have shown that these conditions are no disqualification criteria for a successful implementation of PSA. First industrial applications of the new Sympatec MYTIS and PICTIS systems are now going on.

REFERENCES

[1] Witt, W., Röthele, S.: In-line Laser Diffraction with Innovative Sampling, PARTEC 1998, Nuremberg, Germany

[2] Witt, W., Heuer, M., Schaller, M.: In-line Particles Sizing for Process Control, Particulate Systems Analysis 2003, Harrogate, UK

[3] gempex Co., Ltd. www.gempex.de/e/

[4] Heuer, M., Schaller, Witt, W., In-line Partikel-größenanalyse in neuen Dimensionen GVC-Fachausschuss Bamberg 2002

[5] Witt, W., Köhler, U., List, J.: Direct Imaging of very fast Particles Opens the Application of Powerful (Dry) Dispersion for Size and Shape Characterisation, PARTEC 2004, Nuremberg, Germany

[6] Witt, W., Köhler, U., List, J.: Experiences with Dry Dispersion and High-Speed Image Analysis for Size and Shape Characterisation, Particulate Systems Analysis 2005, Stratford-upon-Avon, England

[7] Witt, W., Köhler, U., List, J.: Current Limits of Particle Size and Shape Analysis with High Speed Image Analysis, PARTEC 2006, Nuremberg, Germany

[8] Köhler, U., List, J., Witt, W.: Comparison of Laser Diffraction and Image Analysis under Identical Dispersing Conditions PARTEC 2006, Nuremberg, Germany