International Journal of Pharmaceutics 391 (2010) 107–114

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Different modes of dynamic image analysis in monitoring of pharmaceutical dry milling process

Venkateshwar Rao Nalluri[a,b], Peter Schirg[c], Xin Gao[d], Antoine Virdis[d], Georgios Imanidis[a,b], Martin Kuentz[a,*]

[a] University of Applied Sciences Northwestern Switzerland, Institute of Pharmaceutical Technology, Gründenstr. 40, CH-4132 Muttenz, Switzerland
[b] University of Basel, Institute of Pharmaceutical Technology, Klingelbergstr. 50, CH-4056 Basel, Switzerland
[c] PS Prozesstechnik GmbH, Novartis Areal, K-970.1, CH-4002 Basel, Switzerland
[d] Frewitt SA, Route du Coteau 7, CH-1763 Granges-Paccot, Switzerland

ARTICLE INFO

Article history:
Received 8 December 2009
Received in revised form 16 February 2010
Accepted 19 February 2010
Available online 25 February 2010

Keywords:
Process analytical technology (PAT)
Conical mill
Process analyzers
Dynamic image analysis
Shape factor
Quality by design

ABSTRACT

This article focuses on the process analytical technology (PAT) of pharmaceutical dry milling. The first objective is to compare different modes of dynamic image analysis namely, on-line, in-line and at-line for monitoring powder milling. The second objective is to introduce time evolving size and shape analysis (TESSA). Thus, a conical mill was equipped with a dynamic image analysis system which consisted of a xenon flash light and charge-coupled device (CCD) camera. Different pharmaceutical excipients and granulates were chosen as models. The results from the on-line, in-line and the at-line measurement modes showed similar size distributions for the various materials studied, however differences were observed that were mainly attributed to sampling and dispersion. A high correlation of 0.975 ($p < 0.001$) was observed between on-line d_{50} and at-line d_{50} when compared to 0.917 ($p < 0.001$) between in-line d_{50} and at-line d_{50}. The concept of TESSA was found to be useful in detecting changes in milling conditions including the successful detection of a damaged screen when intentionally introduced in the milling process. This monitoring approach of particle size and shape has potential to reduce product variability, facilitates process development, and ultimately helps in establishing quality by design concept for the manufacture of solid dosage forms.

1. Introduction

Pharmaceutical dry milling is an important unit operation employed in the solid dosage form manufacturing. The process variables in dry milling have to be closely monitored in order to achieve a quality product. Particle size plays a critical role throughout product processing because it influences several product attributes such as powder flow, compressibility, tablet hardness, and uniformity of content, as well as the drug release rate (Shekunov et al., 2007). Hence, monitoring of particle characteristics and a control of the milling process are vital tasks and can avoid issues like over-processing of the product (Scott and Wilcock, 2006).

In recent years diverse process analytical technologies were introduced to pharmaceutical unit operations. Subsequently the Food and Drug Administration initiated the quality by design (QbD) concept, in which process analytics was embedded (Guidance for industry-PAT, September 2004). The importance of defining critical product attributes and investigating material properties (Hlinak et al., 2006) together with critical process parameters is now widely recognized. Study of these factors as well as their interactions will considerably increase the knowledge of the process and so assure quality of the final product. This involves appropriate monitoring of critical process parameters, preferably using in-line or on-line instruments with various PAT tools (Fariss et al., 2006; Schmidt-Lehr et al., 2007; Hui et al., 2008), to achieve the quality by design objectives in the pharmaceutical industry.

Particle size measurement by sieve analysis is the classical and least expensive methods of particle sizing in the pharmaceutical industry. However, for smaller sample quantities, laser light scattering has become the method of choice for rapid and reproducible particle sizing (Ma et al., 2001). Quite recently alternative techniques based on focused beam reflectance measurement (Greaves et al., 2008), spatial filtering technique (Petrak, 2002; Naervaenen et al., 2009), and dynamic image analysis (DIA) (Xu and Santana, 2002; Yu and Hancock, 2008) have become available and were evaluated for characterizing the particle size distribution. Compared with other traditional particle sizing techniques, DIA has the major advantage that the instrument provides images of fast moving particles and is sensitive to differences in size and shape characteristics; therefore, it is being increasingly applied to particle

* Corresponding author. Tel.: +41 61 467 46 88; fax: +41 61 467 47 01.
E-mail address: martin.kuentz@fhnw.ch (M. Kuentz).

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doi:10.1016/j.ijpharm.2010.02.027

sizing in various processes (Rabinski and Thomas, 2004). This use of DIA was found to be particularly suitable in sizing non-spherical particles (Xu and Santana, 2002; Xu and Andreina Di Guida, 2003; Almeida-Prieto et al., 2004).

The importance of milling and its control has been recognized for many years (Parrott, 1974; Bauer-Brandl and Becker, 1996; Vendola and Hancock, 2008), but the particle size estimation in different measurement modes, especially using DIA, has not been adequately reported in the scientific literature. DIA *per se* is a developing field and is currently being explored for its use in pharmaceutics (Yu and Hancock, 2008). The purpose of this article is to study the use of DIA for monitoring pharmaceutical comminution using a conical mill. The first objective is to study and compare the different measurement modes. Results from on-line, in-line and at-line image analysis are compared using pharmaceutical model excipients and granulates. This part of the study addresses, in particular, the ongoing PAT implementation in the pharmaceutical industry, in which effects of the measurement modes are important for technological deployment. A second and equally important objective of this work is to study the concept of time evolving size and shape analysis (TESSA) of the milled material. Particle size and shape are evaluated in two-dimensional (2D) cluster analysis and the sigma bands are considered. These sigma bands provide in the 2D visualization a 'sigma box' and its evolution over process is assessed. Additionally TESSA is also evaluated with respect to detecting a broken screen in the process. This addresses the question, can a process failure, i.e. a hole in the screen, be detected by the use of process analytics. Such early detection of a process deviation is important to avoid impaired product quality and subsequent loss of material. Both objectives would contribute towards building quality by design into the operation of a conical mill.

2. Materials and methods

2.1. Materials

Two widely used pharmaceutical excipients were incorporated in the study namely, PrismaLac® 40 (MEGGLE, Wasserburg, Germany), which is coarse grade, crystalline α-lactose monohydrate and Vivapur® 102 (JRS Pharma, Rosenberg, Germany) a fine grade microcrystalline cellulose. In addition, two pharmaceutical placebo granulates were manufactured and used as models. The Placebo I formulation consisted of lactose (GranuLac® 70, 75% w/w), microcrystalline cellulose (Vivapur® 101, 15% w/w), croscarmellose sodium (Ac-Di-Sol®, 5% w/w) and polyvinylpyrrolidone (Kollidon® 30, 5% w/w). Placebo II formulation was composed of lactose (GranuLac® 200, 62.6% w/w), microcrystalline cellulose (Avicel® PH-101, 31.3% w/w) and polyvinylpyrrolidone (Kollidon® K90, 6.1% w/w). GranuLac® 70 and GranuLac® 200 were obtained from MEGGLE, Wasserburg, Germany. Vivapur® 101 was purchased from JRS Pharma, Rosenberg, Germany. Ac-Di-Sol® and Avicel® PH-101 were from FMC BioPolymers, Brussels, Belgium. Kollidon® 30 and Kollidon® K90 were obtained from BASF, Ludwigshafen, Germany.

The material characteristics are compiled in Table 1. Placebo II was expected to have the least specific surface area, intuitively, but it was observed that because of higher intragranular porosity it exhibited comparatively larger specific surface area value (Table 1) which was confirmed from scanning electron micrographs (data not shown).

The rationale in selecting these four materials for the study was to have two placebos to serve as pharmaceutical model granulates; additionally we chose two commonly used pharmaceutical excipients, one fine and the other coarse, which are typically used in the pharmaceutical industry. The finer excipient (Vivapur® 102) was especially chosen to challenge the performance of the sensors.

2.2. Methods

2.2.1. Characterization of raw materials

A MultiPycnometer® (Quantachrome GmbH, Odelzhausen, Germany) was used to determine the true densities of the powders using helium as the displacement gas. The bulk and tapped densities were measured in a graduated cylinder using a type SVM 102 bulk density instrument (Erweka® GmbH, Heusenstamm, Germany) and was operated according to USP Method II. The BET specific surface area of the samples was measured using a Gemini V (Micromeritics Instrument Corporation, Norcross, USA) and the sample preparation was done on a FlowPrep 060 (Micromeritics Instrument Corporation, Norcross, USA). Prior to measurement, samples were accurately weighed into sample tubes and degassed under the flow of nitrogen for 16 h at 40 °C to condition the surface. All the reported results were measured in triplicate.

2.2.2. Particle size determination by analytical sieving

Sieve analysis of unmilled and milled materials was performed using a Retsch® Sieve shaker type AS200 control (Retsch GmbH, Haan, Germany). A 100 g sample was placed on a broad nest of sieves (range 63–1000 μm), arranged according to $\sqrt{2}$ progression and vibrated at 1.5 amplitude for 10 min. A dry sieving method (Method I of USP) was followed for the analysis and the interpretation of the results. The measurements were performed in triplicate and the mean and standard deviation were reported.

2.2.3. Dynamic image analysis using XPT® sensors

Two dynamic XPT® image analysis sensor systems (PS Prozesstechnik GmbH, Basel, Switzerland) were used as in-line XPT-P and on-line XPT-CV separately (where -P stands for Probe and -CV for flow through Cell and Venturi). This image analysis system is capable of measuring particle sizes in the range from 1 to 3000 μm. The image update rate can be adjusted from a minimum of 50 ms (20 images per second with 780,000 or 1,400,000 pixels) to 5 s. As the particles pass through the detecting zone, the xenon flash light illuminates the particles and a charged-coupled device (CCD) camera acquires images of the fast moving particles. The flash light and CCD camera are synchronized and the images are transferred to the analyzers computer. The software, XenParTec version 4.6.5, analyzed the images in real-time to display and store the results. All particle size distributions were calculated on a volume-base for both measurement modes, i.e. on-line and in-line.

Table 1
Physical characteristics of raw materials, mean ± standard deviation ($n = 3$).

Material	Particle size data by sieve analysis (μm)			Bulk density (g/mL)	Tapped density (g/mL)	True density (g/mL)	Specific surface area (m^2/g)
	d_5	d_{50}	d_{95}				
Vivapur® 102	11 ± 0	107 ± 2	218 ± 1	0.326 ± 0.001	0.468 ± 0.007	1.527 ± 0.003	1.270 ± 0.038
Placebo I	98 ± 2	203 ± 5	460 ± 9	0.544 ± 0.005	0.640 ± 0.002	1.500 ± 0.000	0.276 ± 0.088
PrismaLac® 40	228 ± 5	480 ± 2	773 ± 10	0.535 ± 0.012	0.596 ± 0.003	1.528 ± 0.001	0.185 ± 0.054
Placebo II	252 ± 7	484 ± 23	947 ± 26	0.487 ± 0.003	0.553 ± 0.004	1.471 ± 0.001	0.916 ± 0.051

Table 2
Process variables for on-line and in-line sensor systems.

Type	Feed speed (rpm)	Impeller speed (m/s)	Screen size (μm)	Venturi air pressure (bars)	Sampling orifice (Ø, mm)	Sensor position	Cleaning air pressure (bars)
On-line	7.5[a]	10	1500	2.2	8.5	–	–
In-line	7.5[a]	10	1500	–	–	25°	0.5

[a] 7.5 rpm feed speed corresponds to approximately 55 kg/h of material throughput.

2.2.4. Dynamic image analysis with QICPIC™

A QICPIC™ (Sympatec GmbH, Clausthal-Zellerfeld, Germany) dynamic image analysis instrument equipped with a dry sample disperser RODOS™ and vibratory feeder VIBRI™ (Sympatec GmbH, Clausthal-Zellerfeld, Germany), and Windox 5.4.1.0 software was used in the present study to determine the particle size distribution. In this entire study, QICPIC™ is referred to as an at-line system. The device works in transmission with a parallel light beam. A pulsed light source generates stable visible light pulses with a duration of 1 ns and reduces any motion blur at particle speeds of 100 m/s. The instrument has an adjustable flash rate from 1 to 500 Hz, and is synchronized with the high-speed complementary metal-oxide-semiconductor (CMOS) camera that captures images up to 500 frames per second (fps) with 1024×1024 square pixels. The samples were fed using a high-speed dry sample disperser RODOS™ (pressure 1.0 bar and vacuum 50 mbar) and a dry-feeder VIBRI™ with a 20–30% feed rate. The image analysis evaluation was based on the equivalent projection area of a circle and the volume based particle size distribution was determined.

2.2.5. Dry milling equipment

A conical screen mill, ConiWitt-150™ (Frewitt SA, Fribourg, Switzerland) was used with different screens. The impeller was operated at variable speeds from 4 to 18 m/s and a square shaped two armed rotor blade profile was used. Samples of 1 and 5 kg were filled into the hopper attached to a feeder and the rate was controlled by a pneumatic system, which was operated from 4 to 11 rpm.

2.2.6. Development and setup of the on-line and in-line systems

Preliminary tests were conducted to establish optimal measurement conditions for in-line and on-line process analysis. This was important in order to have a reasonable comparison of the different measurement modes. The resulting parameters are summarized in Table 2. A constant material feed and impeller speed was maintained for both sensor systems. In the case of on-line sensor system, a semi-circular sampling tube was developed. It contained seven equidistant orifices each having a diameter of 8.5 mm (see Fig. 1a). Such a sampling tube facilitated the uniform collection of processed material from the periphery of the milling chamber. An optimized air pressure of 2.2 bar was maintained at the inlet of the venturi system for sucking in the material from the process stream for analysis. In the case of in-line sensor system, the sensor was positioned at 25° and additional air was blown at a pressure of 0.5 bar on its surface to keep the sensor lens clean during the entire process (see Fig. 1b). Prior to the start of the experiments one kg of the material was placed inside the hopper and pneumatically fed into the milling chamber in a controlled manner.

2.2.7. Statistical analysis

The analysis of the data was conducted using STATGRAPHICS® Centurion XV, version 15.2.06 including the calculation of the Pearson product–moment correlations. Pearson product–moment correlation coefficient is a measure of the strength of linear dependence between two random variables. It is defined as the sum of the products of the deviations of the two variable scores from their respective means divided by the square root of the product of their standard deviations.

2.2.8. Image analysis

The shape factor, Heywood Circularity Factor (HCF) (National Instruments, 2005) is the ratio of a particle perimeter to the perimeter of the circle having the same area and is given by

$$\mathrm{HCF} = \frac{P_{\mathrm{real}}}{2\sqrt{\pi \cdot A}} \quad (1)$$

where P_{real} is the perimeter of the particle and A is the particle area. Particles exhibiting shape close to a disk have HCF values close

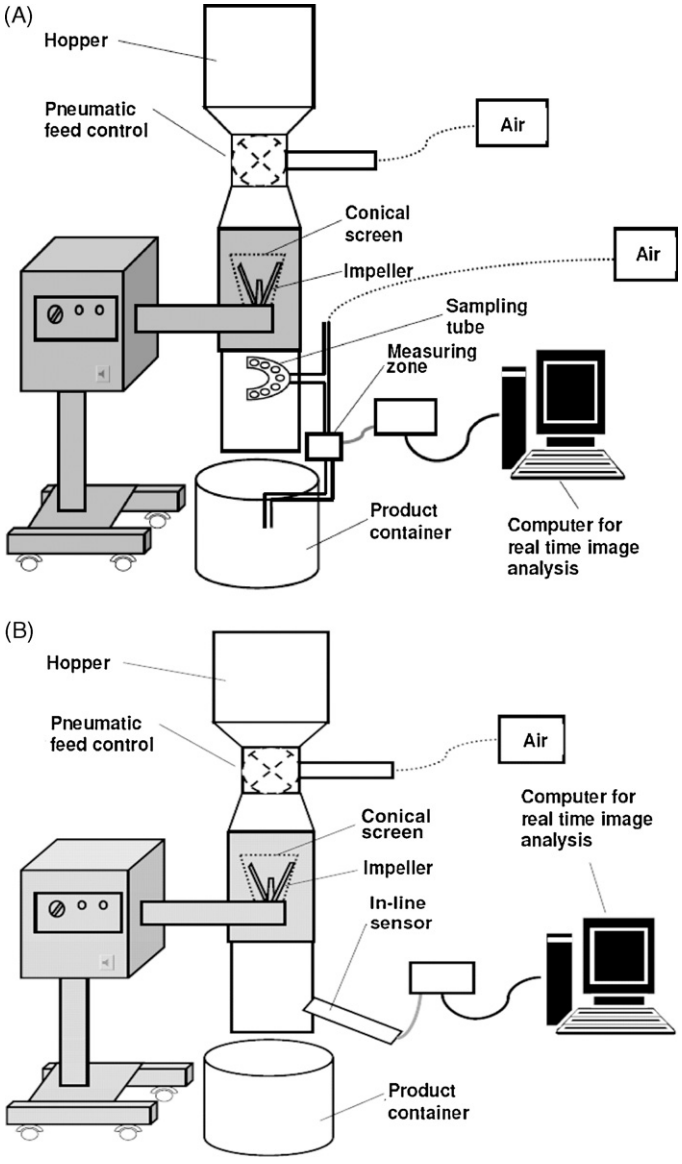

Fig. 1. Schematic representation of the (a) on-line sensor system and (b) in-line sensor system.

to 1 and the HCF value increases as angularity increases. The HCF is independent of particle size. The perimeter and the area of the particle are based on two-dimensional projection of the individual particles onto the plane of the image.

The size parameter, Waddel disk diameter (WDD) (National Instruments, 2005) is the diameter of a disk having the same area as the particle and is given by

$$\mathrm{WDD} = 2\sqrt{\frac{A}{\pi}} \quad (2)$$

3. Results and discussion

3.1. Dynamic image analysis and different measurement modes

3.1.1. Comparison of different measurement modes

Since sieve analysis is a reference method in particle sizing, it was used to characterize all materials before and after milling. The sieve particle size data of the unmilled materials is shown in Table 1. Particle size data of the unmilled materials with on-line and in-line systems was not obtained because the conical mill was designed to work with the screen in place. The cumulative particle size distributions of the four milled materials are shown in Fig. 2a through 2d. The on-line and in-line analysis in the conical mill provided consistent measurements. A strong milling effect was not observed but rather the size changes were due to a comminution process. A reduced size was to some extent seen with the coarse PrismaLac®40 and the Placebo formulations. However, Vivapur® 102, being a fine material, did not undergo any milling effects under the present set-up. This can be directly visualized by comparing the sieve particle size data of the milled material from Table 3 with the sieve particle size data of the unmilled material from Table 1. It is important to note that sieve analysis employs a different classification principle than the image analysis. The main interest was therefore in comparing the results of the different measurement modes having the same classification method namely on-line, in-line and at-line.

Table 3
Particle size data of the milled materials obtained from the four different modes of analysis, mean ± standard deviation ($n = 3$).

Material	Particle size (μm)	On-line analysis	In-line analysis	At-line analysis	Sieve analysis
Vivapur® 102	d_5	119 ± 1	84 ± 1	35 ± 5	12 ± 3
	d_{50}	233 ± 2	162 ± 1	114 ± 24	110 ± 14
	d_{95}	359 ± 10	242 ± 5	228 ± 12	215 ± 12
Placebo I	d_5	162 ± 1	138 ± 9	112 ± 7	96 ± 3
	d_{50}	324 ± 12	347 ± 15	213 ± 4	192 ± 3
	d_{95}	555 ± 81	660 ± 112	436 ± 3	353 ± 3
PrismaLac® 40	d_5	186 ± 8	201 ± 1	74 ± 4	90 ± 10
	d_{50}	432 ± 13	416 ± 19	310 ± 52	337 ± 5
	d_{95}	793 ± 71	669 ± 27	643 ± 35	636 ± 8
Placebo II	d_5	317 ± 5	242 ± 5	230 ± 17	196 ± 22
	d_{50}	558 ± 10	485 ± 16	467 ± 25	426 ± 13
	d_{95}	913 ± 80	818 ± 29	826 ± 64	751 ± 44

Interestingly, it was observed that the on-line and in-line modes resulted in higher particle size than obtained from the at-line reference (Fig. 2a–d). This was particularly observed with Vivapur® 102, which was probably due to the formation of aggregates inside the particle measuring zone.

The on-line and in-line particle size data curves were overlapping to some extent for the different materials, which indicates the possibility of deploying either of the sensors for process monitoring. These real-time process data was also in fair agreement with the reference values obtained from at-line as well sieve analysis in case of the coarse materials (Fig. 2c and 2d). This consistency is notable and it appears that the mode of dynamic image analysis might not be a dominant factor in measuring the particle size of coarse materials.

There were also differences observed among the investigated measurement modes as can be inferred from Table 3. A better understanding of these analytical gaps is of particular interest. Accordingly, there are different potential mechanisms that can the-

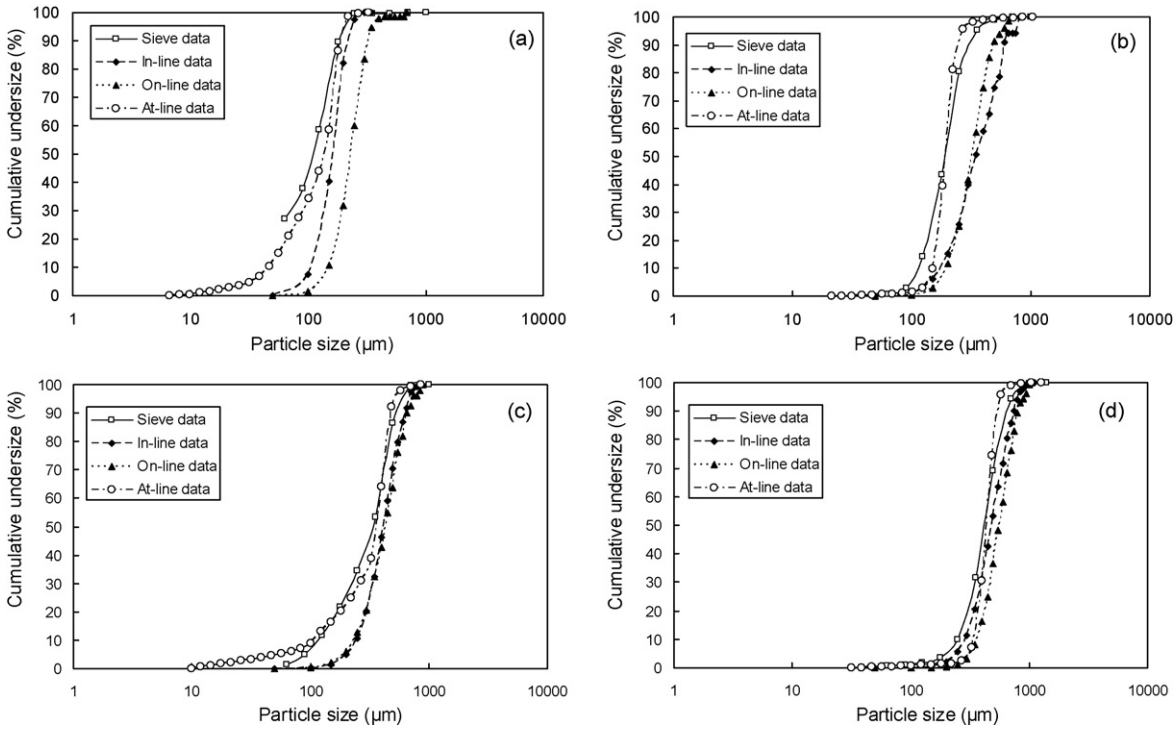

Fig. 2. Particle size distributions of the milled material measured using the four different modes of analysis for (a) Vivapur® 102, (b) Placebo I, (c) PrismaLac® 40, and (d) Placebo II.

Table 4
Aspects of the three types of measurement modes.

Type	Sampling	Dispersion	Image analysis	Selected size parameter
At-line	Optimal in at-line mode	Very good dispersion achieved	Minimized particle overlapping	WDD[a]
On-line	Potential effect of sampling device	Potential effects of venturi location and air pressure	Risk of motion blur depending on dispersion	WDD[a]
In-line	Sensor cleaning, its position and angle can be relevant	Sensor overloading can occur during high product flow (dumping)	Overlapping particles limit individual particle recognition	WDD[a]

[a] Projected area diameter of disk (circle).

oretically affect the measured particle size using DIA. An average difference of about 110 μm was seen between the on-line d_{50} and at-line d_{50} (about 120 μm for d_{95}) for all the materials considered together (see Table 3), whereas an average difference of about 80 μm was observed between in-line d_{50} and at-line d_{50} (about 70 μm for d_{95}). These differences must be attributed to factors of sampling, dispersion (inside the measurement zone), and image analysis, whereas the statistical data treatment was essentially the same. An overview of these potential effects is given in Table 4 and is further discussed in detail on a qualitative basis.

The on-line system sucked the material quickly in from the process stream following which the particles traveled through a small bent tube. The latter curvature may have caused artifacts of particle dispersion. A retrospective analysis of the obtained images indicated that on-line measurements showed motion blur (motion blur is the apparent streaking of rapidly moving particles relative to flash duration in a still image) with respect to Vivapur® 102 resulting in higher particle size values. This effect was later minimized in a modified design of the venturi system, in which the bent of the sampling tube was removed.

The setup of the in-line sensor system was different from that of the on-line configuration. Even though a small thin tube was blowing air on the sensor glass, some particle adhesion was still observed in the in-line system. This effect was especially pronounced with cohesive and fine particles as in the case of Vivapur® 102. An increase of the cleaning air pressure to 1.0 bar was critical because adhering particles were blown away, and much of the milled material was removed from the focal depth of the lens. The risk of too high particle concentrations on the sensor glass, in the present study, was reduced by using a controlled material feed. This enabled a comparison of the different measurement modes, however such a controlled feeding is usually not found in a production environment. The likelihood of particle overloading is, therefore, increased, which limits the robustness of the in-line sensor system.

The choice of a statistical size parameter for evaluation itself can further add to the differences in analytical size measurements. However, this was not the case in the present study as both the QICPIC™ and the XPT® were set to measure the diameter of a circle (or disk) having the same projection area of the particle (Waddel disk diameter).

These outlined effects of the different measurement modes are interesting from an academic viewpoint, but practical PAT is mainly focused on measuring differences in production process conditions. Accordingly, an analytical bias seems to be of lesser importance than the robustness of the measuring system. A PAT tool should be discriminating and must work under the various production conditions. The latter aspect was a particular advantage for the on-line system, because the images never showed an excessive particle concentration and no particles adhered to the sensor glass. For these reasons, we chose the on-line sensor system for further studies described in this article.

3.1.2. Correlations among the different measurement modes

Pearson product moment correlations were computed for the d_5, d_{50} and d_{95} values ($n = 12$) obtained for the various milled materials from on-line, in-line, at-line and sieve analysis. Some of the highly significant correlations are discussed mainly with respect to d_{50}. A correlation of 0.931 ($p < 0.001$) was seen between on-line d_{50} and in-line d_{50}. An even stronger correlation of 0.975 ($p < 0.001$) was obtained between on-line d_{50} and at-line d_{50}, when compared to 0.917 ($p < 0.001$) between in-line d_{50} and at-line d_{50}. The correlation observed between on-line d_{50} and sieve d_{50} was 0.987 ($p < 0.001$), whereas the correlation between in-line d_{50} and sieve d_{50} was 0.938 ($p < 0.001$). Good correlations were also revealed among the d_{95} values. The high correlations indicate the possibility of calculating the size distribution of a measurement mode based on the given data from another. However, these regressions are of lesser practical importance, since the main purpose of the process analytical tool is to measure subtle differences of particle size or shape as it was emphasized in the following section.

3.2. Time evolving size and shape analysis (TESSA)

3.2.1. Monitoring changes in the milling process

Measuring the shape of particles is equally important as measuring particle size. For the shape analysis in this study a modified on-line sensor system was used. This modification was achieved by positioning the inlet of the air supply of the Venturi system directly below the measuring zone, thereby significantly minimizing the effects of motion blur. This motion blur was mostly seen in the past with Vivapur® 102 and we reduced this effect experimentally in the new design by comparing the obtained images (data not shown). The mill was operated as per the conditions for on-line setup mentioned in Table 2 with a few changes made to the sampling tube (single orifice having a diameter of 5 mm and the tube bent was removed). Placebo II was selected to provide model granules. The mill was run continuously for 10 min and the data for particle size and shape was collected for a period of 20 s in every minute. For particle size Waddel disk diameter (WDD) was chosen, and for shape the Heywood circularity factor (HCF) was opted. The time evolving size and shape analysis (TESSA) was applied in view of detecting changes in the milling process like when the milling process reaches equilibrium and when it falls out of equilibrium due to a stopped material feed. Equilibrium for a given material is arbitrarily defined by the process time interval in which no relevant change is observed with respect to particle size and shape. We chose five regular time points to represent the data, namely 2, 4, 6, 8 and 10 min. The changes in standard deviations over time in terms of size and shape provided a “sigma box” in the two-dimensional graph. Similar boxes can also be constructed according to, for instance, 2-sigma or 3-sigma. Fig. 3 shows that changes in the milling process over time were not pronounced. The identification of equilibrium was complicated by the rather short process time, which had to be selected due to the availability of the placebo material. However, the results still showed a trend towards an established equilibrium. The process arrived at the equilibrium condition after about 4 min of milling (Fig. 3c) and then changed again towards the end of the process (Fig. 3e). This can be observed by inspecting the shape of the 3-sigma box. In Fig. 3c the sizes of the 1-sigma and 3-sigma boxes shrank with respect to particle size

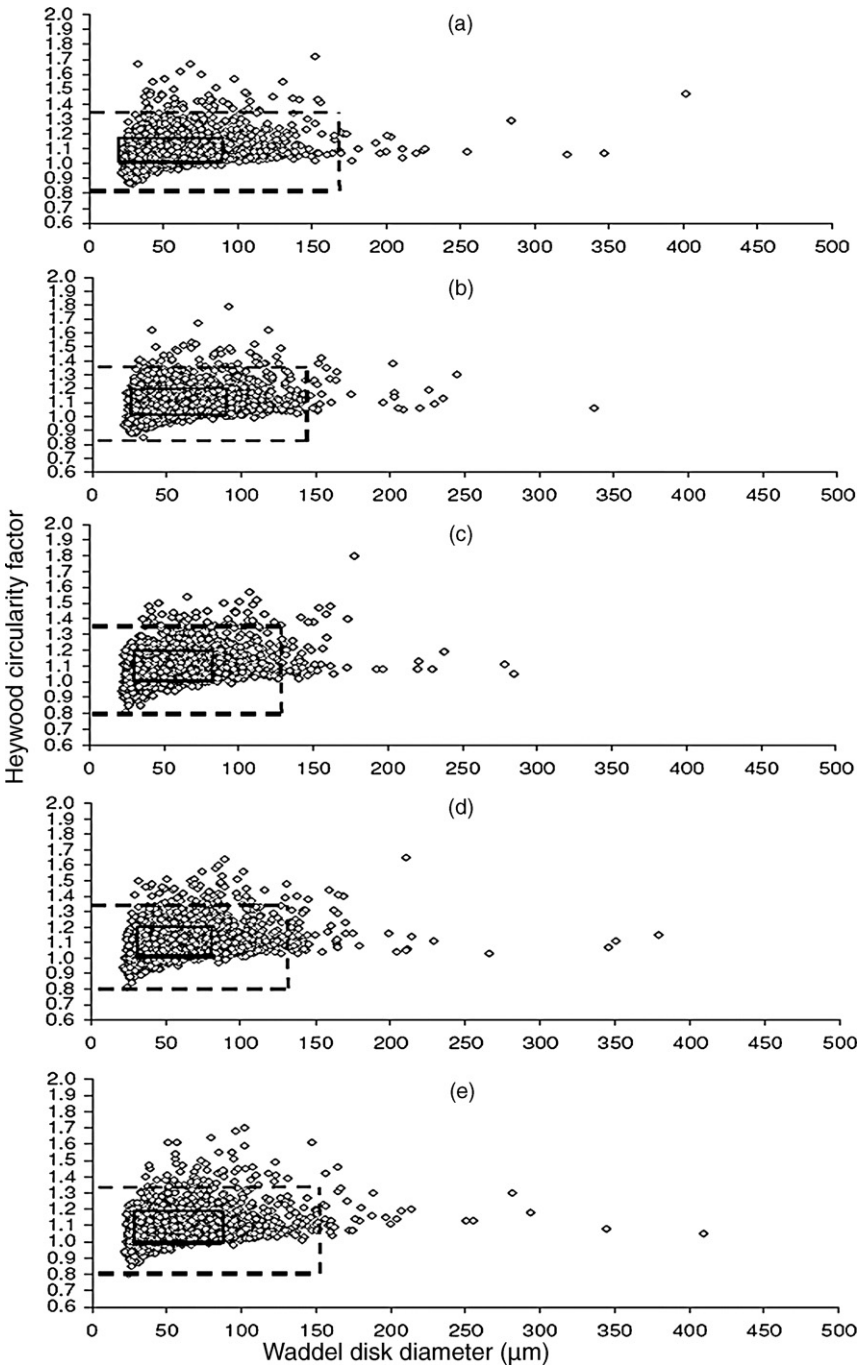

Fig. 3. Time evolving size and shape analysis of Placebo II (a) 2 min after start, (b) after 4 min, (c) after 6 min; at equilibrium (d) after 8 min; at equilibrium (e) after 10 min; end of process [thick lines represent 1-sigma box and dashed lines represent 3-sigma box].

(*x*-axis) compared to Fig. 3a, when the process reached equilibrium and further expanded as seen in Fig. 3e. However, there were quite a few particles lying far outside the 3-sigma box. The coarse particles above the size sigma limits were possibly aggregates. On the other hand, the particles above the limits with respect to the *y*-axis were clearly irregular particles or particles exhibiting larger HCF values. The shape factor did not show a significant change and most of the time remained constant.

The initial cluster distribution in the size and shape plot provided a material characterization. On the other hand the evolution over time as seen from Fig. 3a–e was found to be helpful for monitoring the process changes in the conical mill. At this point it is a short step to assume that different materials are likely to reach equilibrium at different time points. Such knowledge about the equilibrium milling conditions is useful for obtaining homogenous particle characteristics. Traditionally, the shape factor is not adequately defined in product specifications. TESSA could help in setting shape specifications for the milling process by defining the boundary limits for the chosen shape factor. Additionally, TESSA could also help to cope with variability in the starting material. This means that depending on natural starting material variability, the equilibrium process conditions would be adapted to obtain only the material lying within the desired specifications. This also means that the milling product of the first and of the last few minutes could be diverted to a bin. Later on, such a bin could then be excluded from the regular in-process containers ensuring that for

further processing, i.e. lubrication or tabletting, only optimized and uniform granules are present.

The process changes, in this study, were observed using a standardized material feed. However, further research needs to be done in a real production shop floor to investigate how the material scale or discontinous material feed can impact the results. The material and time course analysis is one way of profiting from on-line size and shape analysis, but it is also of interest to evaluate TESSA with respect to detecting a malfunction of the milling process.

3.2.2. Time evolving size and shape analysis (TESSA) applied to a damaged screen

The concept of TESSA was also applied to detect changes in the milling conditions with respect to a reference state. We tested, whether a broken screen could be detected using the on-line data of particle size and shape. Such early detection of critical milling conditions is important from a practical viewpoint and could help to reduce batch failures in manufacturing. The usefulness of TESSA was tested by investigating two potential effects, namely impeller speed (4 and 10 m/s; both speeds were run at a constant material feed speed of 7.5 rpm) and two 500 μm screens, one intact and the other with a hole of 4 cm diameter cut into the screen. The coarse material, Placebo II, was chosen again as model granules and the measurements were performed using the on-line sensor. A 2^2 factorial design in duplicate with three degrees of freedom, resulting in eight runs was selected. All the experiments were performed using 5 kg of the starting material and the data for size and shape was collected for a period of 20 s, every minute over a time period of 6 min. The data, interaction plot, was obtained after the first minute (T_1) and after five minutes (T_5) of the milling process. The interaction plot indicates the effect of one factor (impeller speed) depending upon the levels of the other factor (screen).

As a result, the impeller speed was found to be statistically significant at 95% confidence level ($p < 0.05$) for both time points, T_1 ($p = 0.009$) and T_5 ($p = 0.013$). The screen factor, however was observed to be only very close to that of significance ($p = 0.056$) for T_5 and for the first time point T_1, the screen factor was not found to be significant. The sensor was not able to differentiate between intact and broken screens (Fig. 4a) at the beginning of the process; this situation is comparable to what has been observed in Fig. 3a, when the process did not reach equilibrium. This explains why the screen factor was not found to be statistically significant at the beginning of the process. In Fig. 4b, after 5 min of milling the on-line sensor system was able to differentiate between broken and intact screens leading to a borderline *p*-value of 0.056. This situation can also be compared to that of equilibrium process conditions like was seen in Fig. 3c. The presence of a hole in the screen resulted in an increase in the mean particle size, which was obvious because the on-line sensor system was able to capture images of a few unmilled particles escaping through the hole in the screen. This effect can be more clearly seen at low impeller speed (4 m/s) from the interaction plot in Fig. 4b. However, the mean particle size increased by only a few μm. This inference leads to the conclusion that detection of a broken screen depends on additional factors. Certainly it depends on the size and location of the hole in the screen; additionally the impeller speed was shown to be of relevance. At low speed (4 m/s) the mean particle size difference measured between the intact and broken screen was larger than at higher speed (10 m/s). This small difference in mean particle size observed at higher speed was likely due to the material distribution in the mill. At an increased impeller speed (from 4 to 10 m/s), the material is expected to follow a kind of vortex in the mill so that not all particles fall directly into the sample tube orifice. On the other hand, the number of particles detected naturally depends on the size and location of the hole. The detection of a damaged screen can, therefore, be viewed as a very subtle difference in the reference state and it was remarkable that this could be shown at all with the given process analytics with respect to size. The shape factor (HCF), on the other hand, did not show significant changes in the particles measured, which could be a specific finding for the material studied.

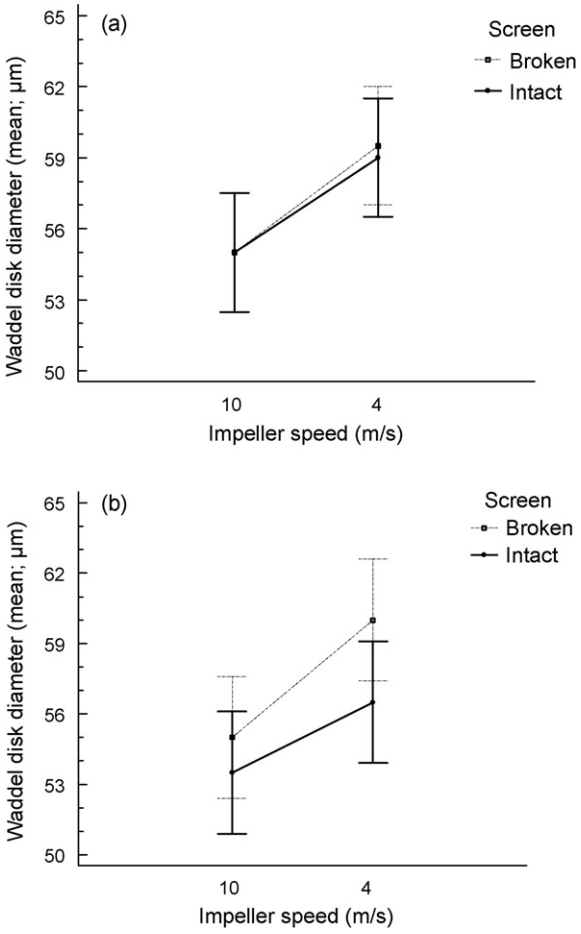

Fig. 4. Interaction plot of impeller speed and screen (a) at the first minute (T_1) and (b) after five minutes (T_5) of milling.

4. Conclusions

Dynamic image analysis was used as process analytical tool in pharmaceutical conical milling. The measurement modes on-line, in-line and at-line were shown to provide similar particle size distributions especially for coarse materials. However, the on-line sensor system was found to be a particularly robust PAT tool in dry milling. The concept of TESSA was introduced and enabled to measure changes during milling. Further research is to be carried out in real production conditions to investigate the potential of TESSA. Thus, early detection of an altered mill performance and potential quality defects could be achieved and appropriate measures could be taken. The introduced process analytical concepts also provide an improved understanding of material and process factors, which is needed to implement the quality by design approach.

Acknowledgements

The authors would like to thank the Commission for Technology and Innovation (CTI), Switzerland for funding this research work under the project no.9025.1 PFIW-IW. The fruitful discussions of Mr. Charles Phillot of Frewitt SA during the course of this work

are gratefully acknowledged. The authors would also like to thank Sympatec GmbH, Basel for their technical support during the measurements with Qicpic. Glatt GmbH (Binzen, Germany) and GEA (Bubendorf, Switzerland) are greatly acknowledged for donating and helping with the manufacture of the pharmaceutical placebo granulates respectively.

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