Novel Process Analytical Technological Approaches of Dynamic Image Analysis for Pharmaceutical Dry Particulate Systems

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Prof. Dr. Martin Spiess

Dekan

This thesis work is dedicated to my wonderful parents and my lovely wife

Measure what is measurable, and make measurable what is not so.

Galileo Galilei (1564-1642)

Abstract

With the introduction of Process Analytical Technology (PAT) and Quality by Design (QbD) concepts by the Food and Drug Administration (FDA) the pharmaceutical industry is thriving towards improved process understanding. Subsequently, the pharmaceutical industry shifted the focus on the implementation of new technologies for real-time process control of various unit operations. Enhanced process understanding will result in a robust process and eventually enable quality by design into the product.

Inline with this PAT concept of improving process understanding and enhancing manufacturing efficiency, the objectives of this research work were to introduce and implement novel technologies of dynamic image analysis (DIA). The novel DIA approaches would allow for real-time (on-line) particle size and shape monitoring in a pharmaceutical dry milling unit operation and subsequently flowability characterization (at-line) of the milled material for pharmaceutical powders and granules.

For the first objective we employed a pilot-scale conical mill and investigated two DIA sensors, one as on-line mode and the other as in-line mode, for real-time particle size and shape monitoring. We selected different pharmaceutical excipients and placebo granulates, spanning a wide range of particle characteristics, for milling. Various mill parameters such as feeder speed, impeller speed, and screen sizes were considered. The particle size distribution results obtained from both the on-line and in-line modes were compared with a commercially available DIA instrument, which served as an at-line reference. Additionally, the data was also compared with the traditional sieve analysis. The results from the on-line, in-line and at-line DIA measurement modes showed similar particle size distributions for the various

materials studied. However, few differences among the different DIA modes were observed that were mainly attributed to sampling and particle 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}. Finally, the on-line sensor was chosen as it provided robust results. A novel concept of time evolving size and shape analysis (TESSA) was successfully proposed for the first time in dry milling. The TESSA approach 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.

In the second objective we introduced a modern instrument, which combines powder avalanching with DIA to enable a comprehensive understanding of the flow behaviour of pharmaceutical powder formulations. The flow characterization of such formulations is essential as they can pose a challenge for upstream solid dosage manufacturing such as tabletting (die filling) and capsulation (weight variation). A commercial powder avalanching instrument existed earlier, but it lacked dynamic image analysis and further provided very few avalanching parameters such as mean time to avalanche and scatter values. The novel instrument used in this study provides image analysis of the motion of a powder inside a rotating drum and results in several parameters associated with powder avalanching such as avalanche time, avalanche angle, and avalanche power in addition to several other parameters. We initially tested the suitability of this modern instrument for flow characterization of binary blends, comprising of a coarse excipient and fine drug particles, and further introduced the concept of critical flow concentrations (CFCs). At least three drug concentrations were identified for which the flow behaviour, of the binary blends, essentially changed. Accordingly, different flow regions were identified, which were

explained on the basis of changed particle packing configurations. A theoretical model successfully provided a first estimate of the initial two CFCs. The novel avalanche testing instrument used in this work provided complementary information to conventional flowability methodologies such as flow through an orifice. A thorough assessment of pharmaceutical blends is needed to avoid CFCs in view of a robust formulation development and hence with respect to building quality into the design of the solid dosage forms. Later, we used the powder avalanching instrument for characterizing the flow behaviour of the milled materials produced from the conical mill.

In the third objective we implemented the on-line DIA sensor in the conical mill and further tested the feasibility of the avalanching instrument as a potential at-line PAT tool for powder flow characterization. We conducted a response surface design in combination with robustness testing (Taguchi design). Both of these designs employed the conical mill, together with the on-line DIA sensor and the powder avalanching instrument. The mill process parameters, namely impeller speed and screen sizes significantly affected the particle size distribution and flow rate of the milled placebo granules. Feeder speed did not affect the particle size, but displayed a statistically significant influence on the flow responses. Robustness testing was able to capture the effect of assigned noise factors (different placebo lots and temperature conditions) on the responses and showed clear differences between different lots of the placebo granulates in addition to temperature-dependent changes in flow behaviour. Eventually, the powder avalanching instrument was proved to be a successful at-line PAT tool.

The dynamic image analysis PAT tools investigated in this research work provided a novel source of understanding the particle characteristics (size and shape) and flow

behaviour of pharmaceutical powders and dry milled granules. Adequate characterization of particle size as well as shape and flowability is essential for upstream solid dosage form manufacturing. Thus, on-line particle size monitoring and at-line flowability characterization using the presented novel DIA techniques together, as complementary process analytical tools, provides valuable information for industrial characterization of pharmaceutical dry particulate systems, namely powders and granules.

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The timely support of several people at the University of Applied Sciences enabled this research work to be completed in time. I would like to thank Dr. Amina and Mr. Helmut Fally for helping with the SEM analysis and laser diffraction studies. Dr. Michael de Wild for permitting to use the tabletop SEM instrument; Mr. Roger Lievre, Mrs. Edith de Vittori, Mr. Christoph Jeiziner, Mrs. Petra Eckert (librarian) and several others are greatly acknowledged.

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Venkateshwar Rao Nalluri

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List of Peer-reviewed Publications

The following peer-reviewed publications were extracted from this thesis and are referred to in the text by their Roman numerals (I-III).

I. Nalluri VR, Schirg P, Gao X, Virdis A, Imanidis G, Kuentz M. Different modes of dynamic image analysis in monitoring of pharmaceutical dry milling process. **Int. J. Pharm.** 2010; 391:107-114.

II. Nalluri VR, Kuentz M. Flowability characterization of drug-excipient blends using a novel powder avalanching method. **Eur. J. Pharm. Biopharm.** 2010; 74:388-396.

III. Nalluri VR, Kuentz M. Advancing pharmaceutical dry milling by process analytics and robustness testing. **J. Pharm. Innov.** 2010; 5:100-108.

List of Abbreviations

ANOVA	Analysis of Variance
ATEX	Atmosphere Explosibles
CCD	Charge-coupled device
CFC	Critical Flow Concentrations
CQA	Critical Quality Attribute
DIA	Dynamic Image Analysis
DOE	Design Of Experiments
FBRM	Focused Beam Reflectance Measurement
FDA	Food and Drug Administration
LD	Laser Diffraction
MCS	Major Consolidation Stress (σ_1)
NIR	Near-Infrared
QbD	Quality by Design
PAC	Process Analytical Chemistry
PAT	Process Analytical Technology
PSD (s)	Particle Size Distribution (s)
PVM	Particle Vision and Measurement
RH	Relative Humidity
SEM	Scanning Electron Microscope
SFT	Spatial Filtering Technique
SFV	Spatial Filtering Velocimetry
SIA	Static Image Analysis
TESSA	Time Evolving Size and Shape Analysis
UYS	Unconfined Yield Strength (σ_c)
XPT-CV	XenParTec-Cell and Venturi
XPT-P	XenParTec-Probe

List of Symbols

ε	Surface energy of the wall of a crack
ε_f	Void fraction
Φ	Angle of internal friction
c	Critical crack depth
d	Mean particle diameter
ff_c	Flow-index
g	Acceleration due to gravity
ρ_b	Bulk density of the powder
ρ_{RD}	Relative density of the drug particles
ρ_{RE}	Relative density of the excipient particles
ρ_{RDBulk}	Relative bulk density of the drug
ρ_{REBulk}	Relative bulk density of the excipient
ρ_{TD}	True density of the drug
ρ_{TE}	True density of excipient
$\rho_{RDVoids}$	Relative density of the drug particles in the voids
m_c	Mass fraction of coarse particles
m_f	Mass fraction of fine particles
m_D	Mass of drug particles
m_E	Mass of excipient particles
n_D	No. of drug particles
n_E	No. of excipient particles
r_D	Radius of a drug particle
r_E	Radius of an excipient particle
r_{EVoids}	Excipient void volume
r_{Bulk}	Ratio of excipient and drug bulk density
V_{total}	Total void volume
V_o	Untapped (original) apparent volume
V_f	Tapped (final) apparent volume
A	Particle area
C	Dimensionless Constant in Beverloo's equation
C	Cohesion in shear measurements

CI	Carr's Compressibility Index
C_R	Rittinger's Constant
C_K	Kick's Constant
C_B	Bond's Constant
D_o	Hopper orifice diameter
D_1	Diameter of the original material
D_2	Diameter of the milled material
E	Energy consumed in a milling operation
H	Hurst exponent
HCF	Heywood Circularity Factor
HR	Hausner Ratio
K	A constant for particle shape
P_{real}	Perimeter of the original particle
T	Tensile stress
W	Mass flow rate of particles
WDD	Waddel Disk Diameter
X	Mixing fraction of a binary blend
X_{C1}	First critical flow concentration
X_{C2}	Second critical flow concentration
X_{C3}	Third critical flow concentration
Y	Young's Modulus

1 **INTRODUCTION**

1.1 Motivation

The FDA initiated PAT to encourage the voluntary development and implementation of innovative methods of pharmaceutical manufacturing. PAT based innovations promote continuous improvement and enhance manufacturing while maintaining or improving the current level of product quality. Subsequently, process analytics has become an important topic in the pharmaceutical development as well as manufacturing. Process analytics involves real-time monitoring of a process by the use of novel technologies to improve process understanding and enhance manufacturing efficiency while ensuring final product quality. A more distant goal of PAT is to enable real-time product release.

In the last decade several new technologies, in the form of sensor systems, have been introduced into pharmaceutical research for real-time process monitoring of various unit operations, particularly in the areas of high shear granulation (Whitaker *et al*., 2000; Rantanen *et al*., 2005), fluidized bed granulation and drying (Findlay *et al*., 2005; Portoghese *et al*., 2008; Burggraeve *et al*., 2010), coating (Andersson *et al*., 2000), blending (Hausman *et al*., 2005; Sulub *et al*., 2009) and lubrication (Hagrasy *et al*., 2006). A typical pharmaceutical unit operation is dry milling for which no published literature exists for real-time particle size monitoring. Recent advances in particle image analysis technology now allow rapid characterization of size as well as shape of particles that are either stationary or mobile. In pharmaceutical development, dynamic image analysis has been used for acquiring size and shape information of particles in motion, but the mode of analysis was mostly referred to as either at-line or off-line (Yu and Hancock, 2008). Therefore, the need of a suitable instrument for real-time particle size and shape monitoring formed the basis for initiating this work. A main objective of this thesis is, therefore, to introduce a novel PAT sensor in a

pharmaceutical dry milling unit operation, based on the principle of dynamic image analysis. This novel DIA sensor will provide real-time size and shape information of particles during milling. Since, flowability is also an important characteristic of the milled material; a modern instrument is introduced for the first time as an at-line PAT tool for monitoring the flow behaviour. This modern instrument combines powder avalanching and dynamic image analysis for detailed assessment of the powder inside a rotating drum. The complementary use of these novel process analytical sensors enables a thorough characterization of the milled powders and granules.

1.2 Current state of research

Particle size is an important quality marker since it affects vital quality parameters such as powder flow (Liu *et al.*, 2008), which in turn affects weight variation in tablets (Fassihi and Kanfer, 1986) and filling performance of capsules (Tan and Newton, 1990). Particle size is also known to impact the rate of drug release (Jinno *et al*., 2006; Shekunov *et al.*, 2007) and dosage unit content uniformity (Zhang and Johnson, 1997). Therefore, particle size needs to be thoroughly characterized using suitable analytical tools. Recently, quite a few advanced technologies of particle size estimation have become available and are being continuously evaluated for their use in pharmaceutical unit operations. In high shear wet granulation, a focused beam reflectance measurement (FBRM) probe was investigated for in-line particle characterization for enhanced process understanding (Huang *et al*., 2010). State-of-the-art particle size measuring devices based on focused beam reflectance measurement (Lasentec® FBRM®, Mettler-Toledo, Greifensee, Switzerland) and particle vision and measurement (Lasentec® PVM®, Mettler-Toledo, Greifensee, Switzerland) have been deployed in many different processes such as crystallization

(Schirg and Wissler, 2000; Kougoulos *et al*., 2005), fluidized bed granulation (Tok *et al*., 2008), and microparticle characterization (Zidan *et al*., 2010). A laser diffraction system was evaluated both in-line and at-line for the possibility of employing PAT for particle sizing during spray drying (Chan *et al.*, 2008). An ATEX approved laser diffraction instrument (Insitec® D, Malvern instruments, Worcestershire, UK) was developed for on-line particle size measurement of dusts and powders in potential explosive environments (Pugh, 2006). A real-time particle size analyzer (Parsum® IPP70, Malvern instruments, Worcestershire, UK) working on the principle of spatial filter velocimetry (Aizu and Asakura, 1987) has been developed for fluid bed applications (Burggraeve *et al*., 2010; Dietrich *et al*., 2010). Devices, working on the principle of DIA are, however, available as either at-line or off-line tools. Examples of such DIA devices include the CAMSIZER® (Horiba, Kyoto, Japan) and QICPIC™ (Sympatec, Clausthal-Zellerfeld, Germany). There is barely any published scientific literature mentioning the use of DIA as an on-line or in-line process analytical tool.

Flowability characterization of particulate systems (powders and granules) is quite challenging due to the physical properties of the particle bulk. Because of their inherent heterogeneity and segregation tendencies during processing and handling, it is difficult to predict their flow behavior in a given process. In spite of gaining a lot of experience and having traditional methods in place, stoppages and problems with processing of powders are still commonly encountered. Traditionally flowability has been characterized using classical methods like angle of repose, flow rate through an orifice, compressibility index etc. Rheological methods such as shear cell have also been widely used to measure and to predict powder flowability (Guerin *et al*., 1999). Nevertheless, these methods are most suitable for free flowing powders. Cohesive material characterization is still a challenge for the pharmaceutical researcher. In the

last years technological advancements were made in characterizing powder flow. Freeman (2004) described several parameters that could serve as specific indices of powder flowability derived from a series of experiments using a powder rheometer (FT4 Powder Rheometer, Freeman Technology, Worcestershire, UK). The powder rheometer was equipped with a twisted blade rotating and moving in a powder bulk system. Navaneethan *et al* (2005) used a texture analyzer-powder rheometer assembly to understand the behavior of particulate systems under different conditions of shear dynamics. Benedetti *et al* (2007) developed a PAT method based on NIR spectroscopy for in-line powder flow characterization of pharmaceutical formulations to avoid powder segregation or agglomeration. Later, Beach *et al* (2010) used a similar methodology to characterize improved flow behaviour of APIs and their blends. Nevertheless, PAT applications for real-time powder flow monitoring are very limited. Although, Brian H. Kaye (1995) mentioned the potential use of the powder avalanching method for quality control monitoring of powders, there is barely any experimental work with such an instrument reporting it as a viable PAT tool.

1.3 Objectives

There are three main specific objectives for this thesis work, which are described as follows:

Specific aim I

To introduce a novel PAT sensor in pharmaceutical dry milling unit operation for real-time particle size and shape characterization. A sensor system working on the principle of DIA is to be adapted for testing in two modes namely, on-line and in-line. Subsequently, the particle size data is to be compared with a commercially available DIA instrument (QICPIC™), which served as an at-line reference. The data is also to

be compared with the traditional sieve analysis. To evaluate as well as compute correlations between the three modes of DIA analysis, namely on-line, in-line and at-line, to understand various process effects, and eventually choose one of the two modes (on-line or in-line) for routine particle size and shape characterization to enable a quality product. To propose a novel concept of time evolving size and shape analysis and its application.

Specific aim II

In this aim, a novel powder avalanching instrument is to be tested for its suitability as a flow characterization device for pharmaceutical powders. A commercially available device, combining the principles of powder avalanching and DIA is employed to initially evaluate various materials to understand the methodology. Subsequently, the evaluation of binary blends comprising of several mixtures of coarse and fine materials is undertaken to define critical flow concentrations (CFCs). A theoretical model based on the concepts of binary mixtures is proposed. This methodology of powder avalanching characterization and identifying CFCs would enable a robust formulation development and further help in quality by design evaluation.

Specific aim III

In this final aim, we implemented the on-line DIA sensor as a PAT tool for particle size measurements in the conical mill. Additionally, the avalanching instrument is tested for its suitability as an at-line PAT tool for powder flow characterization. A response surface design in combination with robustness testing (Taguchi design) is conducted and several material and process factors and their responses are considered. This would result in a comprehensive understanding of the particle characteristics of the milled material and its corresponding flow behaviour.

2 THEORETICAL SECTION

The theoretical section is divided into four subchapters. The chapters include (1) milling, (2) particle size, shape, and distribution analysis, (3) flowability characterization, and (4) process analytical technological concepts. A special emphasis is placed on conical mill and powder flow characterization using avalanche testing.

2.1 Milling

Size reduction is a process in which the breakage of particles is brought about by the application of mechanical stress (Parrott, 1974). This process is also commonly known as milling, comminution, or grinding. Milling is the principle means of achieving size reduction, which involves shearing, compressing, impacting or attrition. Milling has always been one of the important unit operations in pharmaceutical solid dosage manufacturing because of the need to obtain varying particle size characteristics. Usually raw materials as received or synthesized do not have the required particle size and surface area. To attain a desired particle size (distribution) the raw materials are milled and therefore milling is often the first unit operation that is encountered in pharmaceutical development and production. The significance of milling has been recognized for many years (Parrott, 1974; Bauer-Brandl and Becker, 1996; Vendola and Hancock, 2008). Particle size, obtained through milling, is an important intermediate quality parameter, which 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). Product quality is also influenced by the critical material properties so that interaction of process and material parameters should be thoroughly studied as part of the pharmaceutical

development (Schofield *et al*., 1991; Hlinak *et al*., 2006). Therefore, monitoring the particle size 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).

2.1.1 Physics of Milling

Milling is carried out by a process of crack propagation, whereby localized stresses produce strains in the particles, which are large enough to cause bond rupture and thus propagate the crack (Staniforth 2002). In general, cracks are propagated through regions of a material that possess the most flaws or discontinuities, and are related to the strain energy in specific regions according to Griffith's theory. The Griffith theory (Griffith 1921) of cracks and flaws assumes that all solids have flaws and microscopic cracks, which increase the applied force according to the crack length and focus the stress at the atomic bond of the crack apex. The Griffith theory is commonly accepted and allows the estimation of the theoretical strength of brittle solids. It also gives the correct relationship between fracture strength and flaw size. The Griffith theory may be expressed as (Parrott, 1974):

$$T = \sqrt{\frac{\mathrm{Y}\varepsilon}{c}} \tag{2.1}$$

where T is the tensile stress, Y is Young's modulus, ε is the surface energy of the wall of the crack, and c is the critical crack depth required for fracture.

In general, when a crystalline solid is exposed to stress it will first deform elastically (elastic deformation) according to Hooke's law (Eq. 2.2), where Y is the modulus of elasticity (Young's modulus or Tensile modulus).

$$Strain = Y * Stress \tag{2.2}$$

Beyond a certain point, the yield point, the elastic limit is exceeded, and the solid will deform. This is called the plastic deformation (Fig. 2.1). In this region, the crystal

lattice is strained, and in some cases amorphicity might result. In the region beyond the plastic limit, the particle will not return to its original shape when the applied stress is released. Finally, the crystal breaks at a point called the 'fracture point' (Carstensen, 2001).

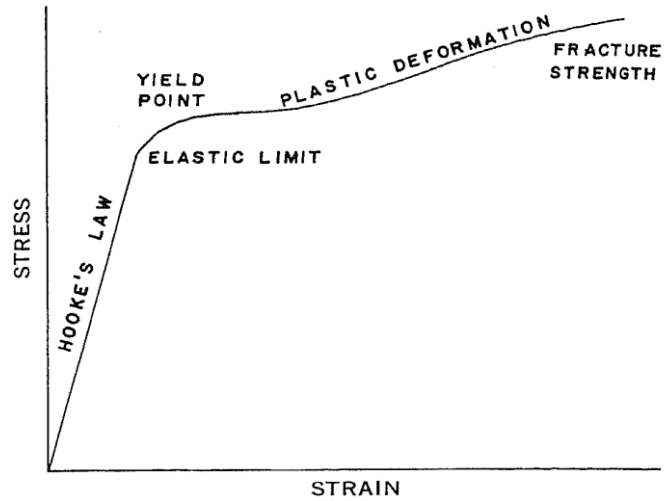


Figure 2.1 Stress-strain diagram for a solid, with the area under the curve representing the energy required to fracture the solid (*Adapted from Parrott, 1974*)

2.1.2 Energy consumption in a milling operation

Three early theories which describe the energy requirement as a function of particle diameter, namely Rittinger's, Kick's, and Bond's theory have received much attention. Rittinger (1867) proposed that the energy required for particle size reduction was directly proportional to the area of new surface created. This relationship can be expressed as:

$$E = C_R\left(\frac{1}{D_2} - \frac{1}{D_1}\right) \tag{2.3}$$

where E is the energy consumed, C_R is a constant; D_1 and D_2 are the diameters of the original material and milled material, respectively. However, Rittinger's relationship is most applicable to fine grinding. Kick (1885) proposed that the energy spent in size reduction is related to the reduction ratio D_1/D_2, where C_K is a constant (Parrott, 1974).

$$E = C_K \ln\left(\frac{D_1}{D_2}\right) \tag{2.4}$$

Bond (1952) suggested a more useful formula in which the total energy that is required for size reduction is inversely proportional to the square root of the particle diameter (C_B is a constant).

$$E = C_B\left(\frac{1}{\sqrt{D_2}} - \frac{1}{\sqrt{D_1}}\right) \tag{2.5}$$

A certain minimal energy is required for size reduction, which begins with crack fracture. However, milling conditions are so random that many particles receive impacts that are insufficient to fracture them and some particles are fractured by excessively forceful impact. Therefore, Tavares (2004) has rightfully mentioned that industrial comminution processes are typically inefficient in their use of energy, since considerably more energy is consumed by the operating equipment than is actually required to break the particles. Nevertheless, in pharmaceutical applications where relatively small quantities of materials are available during development stages and the influence of size and shape are more relevant for the efficacy and physical stability of the drug substance, energy consumption is not a major factor. Vogel and Peukert (2003) developed a model to describe the breakage behaviour of brittle materials. The model successfully correlated energy available for fracture and breakage probability of particles.

2.1.3 Methods of size reduction (dry milling)

Currently, there are several different types of dry milling equipment available in the pharmaceutical industry. Dry milling is typically described as the process of reducing particle size in the absence of any liquids. The various mills can be classified

according to the principal method employed. The selection of milling equipment appropriate for a target particle size distribution varies depending upon the initial particle size distribution, the breadth of the distribution, the friability of the crystal, and other machine operating parameters (Burcham *et al*., 2009). The following sections describe various dry milling equipments based on principle of operation.

2.1.3.1 Cutting methods

A cutter mill consists of a series of knives attached to a horizontal rotor which act against a series of stationary knives attached to the mill casing (Staniforth, 2002). Size reduction, during milling, occurs by fracture of particles between the two sets of knives, which have a clearance of a few millimeters. A screen is fitted in the base of the mill casing and acts to retain material in the mill until a sufficient degree of size reduction is achieved. In the cutter mills, the high shear rates are useful for producing coarse size reduction of dried granulations prior to tabletting.

2.1.3.2 Impact methods

Hammer mills by far are the most commonly used for comminution. Size reduction by impact is carried out by using a hammer mill, which consist of a series of four or more hammers, hinged on a central shaft which is enclosed within a rigid metal case (Fig. 2.2). During milling the hammers swing out radially from the rotating central shaft. The angular velocity of the hammers produces high strain rates so that most particles undergo brittle fracture. Attrition of particles is realized through the impact of the particles with hammers and the mill internals. Particles are retained within the mill by a screen, which allows only adequately comminuted particles to pass through.

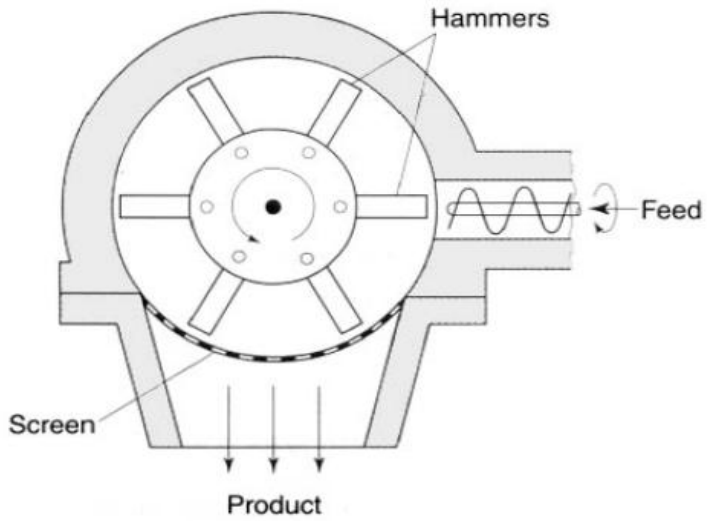


Figure 2.2 Schematic representation of a hammer mill (*Adapted from Staniforth, 2002*)

The energy of the milling can be changed by altering the speed of the hammers and/or the direction of the hammers. In hammer mills there is a relationship between the size of the screen opening and the material feed rate (Carstensen, 2001). The screen size opening is a function of the degree of reduction of the original particles. If the original particles are large relative to the screen size opening, then the residence time in the milling chamber must be longer, which means that the feed rate must be lower. Hammer mills are not typically used for the reduction of particle sizes to below 10 µm (Burcham *et al.*, 2009). An alternative to hammer milling which produces size reduction is vibration milling.

Pin mills work by similar action to hammer mills, but with typically faster tip speeds and lower tolerances between rotating and stationary pins. The milling chamber typically contains a high speed rotor configuration of intermeshing pins which impact the particles as solids are directed through the intermeshing pins (Burcham *et al.*, 2009).

Jet mills are an alternative to hammer or pin milling, where the primary mode of action is the mechanical impact with the particle. Particle size reduction is achieved

through the action of fluid energy (high pressure air), resulting in high energy collisions between particles as well as with the particles and the mill internals, thereby fracturing the particles to micron and submicron size. However, for reduction of particle size to submicron range, dry milling strategies are not adequate and therefore wet milling strategies are typically employed. Since a conical mill is extensively used in this work, a detailed description of the same is given in the following section.

2.1.4 Conical mills

Conical Screen Mills (also referred to as Cone Mills) are gentle size reduction mills which are often used to precondition the material prior to its entry into a process, either by delumping or coarse size reduction. Conical mills belong to the class of compressive force mills in which particles are compressed against a screen wall by means of a rotating impeller or rotor (Fig. 2.3). Other examples include oscillating granulators and rotating sieve mills.

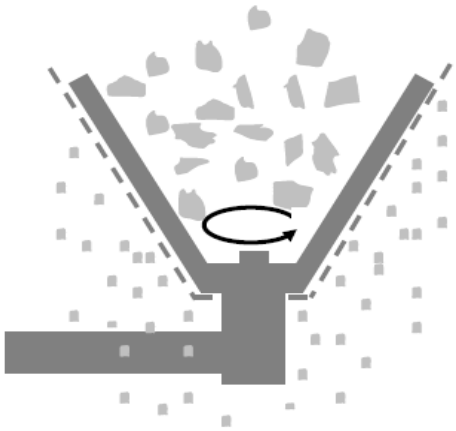


Figure 2.3 Method of operation of a Conical Mill (*redrawn with courtesy of Frewitt)*

The size reduction in a conical mill is caused by forcing the material through a perforated screen and some minor interparticle collisions (Fig. 2.4). This gentle action is ideal for applications which require minimum energy with low heat generation.

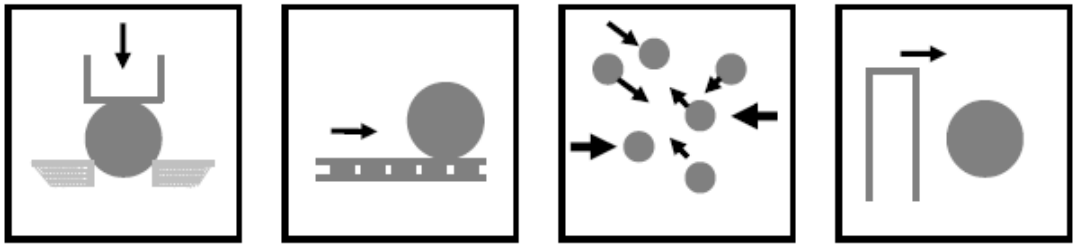


Figure 2.4 Size reduction in a conical mill (*redrawn with courtesy of Frewitt*)

In the conical mill, the material enters the milling chamber via gravity or with the help of a material feeder and exits through the screen holes. Vacuum conveying is often used to move material through the conical mill, which helps in improving overall throughput of the process, contains dust or exposure, and also assists in improvement of end product quality. Two main parameters influence the resulting particle size in a conical mill, namely, screen configuration such as size and shape of the holes and impeller (rotor) speed. The conical mill is also suitable for wet milling prior to fluid bed drying in which case the impeller needs to be changed to a round arm profile. The gentle action of the impeller results in deagglomeration of the product, thereby increasing the surface area and reducing the overall drying times. Most commonly, many mills are equipped with controlled-feeding devices. This is to avoid the filling up of the milling chamber if the material is fed too rapidly. In some cases, the mill cannot handle the load and might break down or stop functioning. Therefore, the optimum feed rate is the maximum rate that will permit milling without blocking the milling chamber. In this work, we wanted to control the rate of material being fed into the milling chamber and for this purpose we used a controlled-feeding device. We studied the affect of feeder speed on particle size responses.

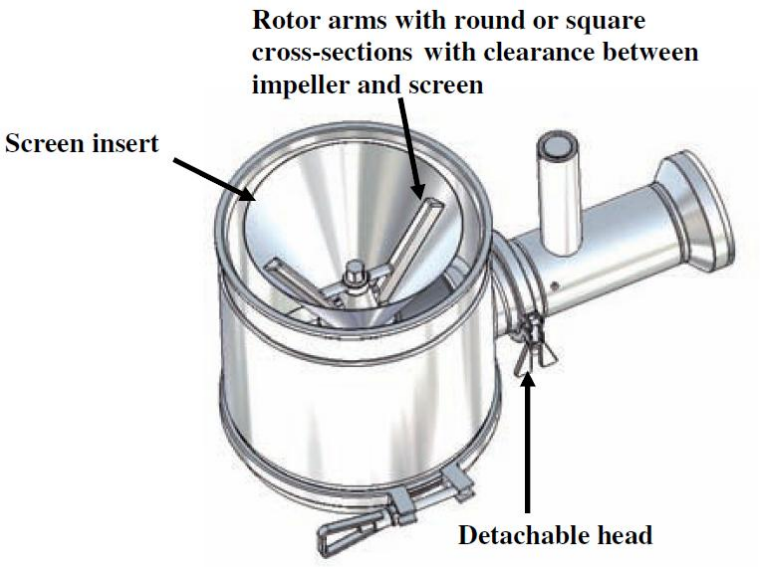


Figure 2.5 Description of the conical mill (*Courtesy of Frewitt*)

One of the main advantages of a conical mill is low heat generation. However, its limitations lie in the inability to mill to a fine particle size, usually less than 150 µm, which will be explained in this thesis in a later chapter. The conical mill employed in this thesis work was a ConiWitt-150^{TM} (Frewitt SA, Fribourg) pilot scale mill. The design of the conical mill *per se* reduces the number of moving parts to a minimum. Because the impeller (rotor) does not touch the screen (Fig. 2.5), one major advantage of the conical mill is that the chances of screen breakage and introduction of unwanted metals are greatly reduced (Poska *et al*., 1993).

Schenck *et al* (2002) investigated size reduction mechanisms in a conical mill for wet granulation before and after drying. While wet milling effectively broke down large agglomerates, dry milling predominantly resulted in fines. Impact attrition was identified as the primary mechanism governing dry granule breakage. Verheezen *et al* (2004) reported that both the size of the particles before granulation and the amount of binder used determined the breakage behaviour in a conical mill. They established a relation between the strength of granules and the degree of size reduction. Reynolds

(2010) developed a mechanistic model to investigate the mode of granule breakage in a conical mill and predict the size distribution of granules.

2.1.5 Milling induced changes in materials

Milling causes many changes in materials such as exposing new surfaces, creating lattice defects and in some cases producing partially or totally amorphous material, thus affecting the physical and chemical properties of the resulting powders (York *et al*., 1998). Impact milling typically imparts mechanical stress and quite often generates heat thereby inducing phase transitions such as polymorphic transitions, dehydration/desolvation, or vitrification via solid-state or melt mechanisms (Zhou *et al.*, 2009). The rate and extent of the phase transitions depends on original material characteristics, the type of mill employed, and on the milling conditions. In a study by Chikhalia *et al* (2006), β-succinic acid crystals with plate like morphology were found to be more prone to crystallinity loss on milling when compared to the needle like morphology. If sufficient energy is provided during milling so that the energy barrier to crystallization is overcome, the resultant crystalline product may impart different functionality and performance, such as altered flow properties and aggregate formation. Pirttimaki *et al* (1993) investigated the polymorphic transformation of anhydrous caffeine as a function of grinding time and compression pressure. The measurements showed that both grinding and compression induce the transformation from the metastable form I into the stable form II and the degree of transformation is greater near the surface than in the middle part of the tablet. The effect of milling and milling intensity also influenced the flow properties and the physico-chemical characteristics of lactose crystals for dry powder inhalation formulations (Steckel *et al.*, 2006). Milling induced polymorphic changes have also been observed for many

small drug molecules, such as ranitidine hydrochloride, famotidine, and indomethacin (Chieng *et al*., 2006; Lin *et al*., 2006; Crowley and Zografi, 2002). Erizal *et al* (2008) concluded that milling process with different milling times, using a ball mill, did not bring about a polymorphic transformation and amorphisation but created crystal lattice defects in sulfamethoxazole form 1.

2.1.6 Influence of milling on particle size distribution

During milling, the particles of the starting material will be broken down and particles in different size ranges undergo different amounts of breakage. With progressive milling, the particle size distribution has a narrower range and a finer mean particle diameter (Staniforth, 2002). If the staring material has a monomodal size distribution, as milling progresses it develops into a bimodal distribution through differences in the fracture behaviour of coarse and fine particles as experimentally observed by Heywood (1950-52) for the case of coal. The primary mode, in the bimodal distribution, gradually decreases in magnitude while the secondary mode increases in magnitude (Fig. 2.6). If milling is further continued the monomodal distribution reappears, since the energy input is not sufficient enough to cause further fracture of the finest particle fraction (Staniforth, 2002). As the particle size distribution (PSD) changes, so does the milling characteristics (Parrott, 1974). However, Rubinstein and Gould (1987), unlike the results of Heywood, did not observe a gradual decrease in magnitude of the primary mode with increased milling time with the pharmaceutical materials investigated. Although the initial stages of milling did eventually produce a bimodal distribution, subsequent milling did not in all cases completely reduce the magnitude of the primary mode (coarse particles) and continually increase that of the secondary mode (fine particles), as found by Heywood (Rubinstein and Gould, 1987).

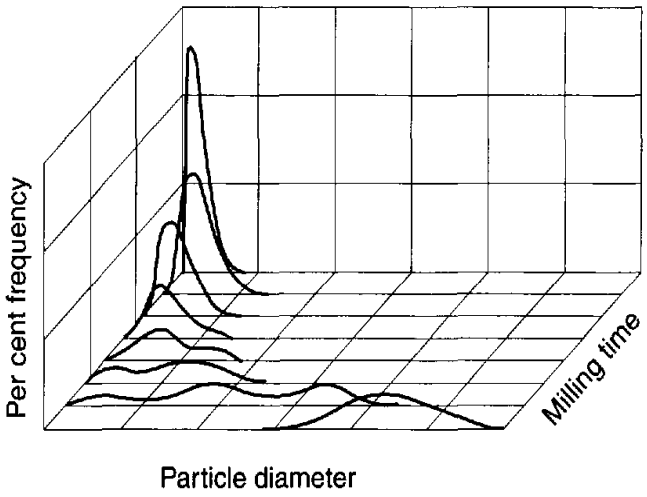


Figure 2.6 Changes in particle size distributions with increased milling time (*Adapted from Staniforth, 2002*)

2.2 Aspects of particle size, shape and distribution analysis

After selecting an appropriate milling equipment to obtain a desired particle size distribution (PSD) it is important to characterize the milled particles to understand if the really desired PSD is being achieved. There are several ways and methods for characterizing the size of a particle. However, particle size analysis is something of a paradoxical subject. Rumpf (1964) was one of the first to realize that the PSD significantly influences nearly every unit operation that involves mechanical processing of particles. Likewise, in many of the unit operations in the pharmaceutical industry particle size monitoring and controlling has received much attention, since it has proven to affect vital quality parameters such as powder flow (Ikekawa and Kaneniwa, 1968; Kaerger *et al*., 2004; Liu *et al.*, 2008), drug release rate (Jinno *et al*., 2006; Shekunov *et al.*, 2007) and dosage unit content uniformity (Zhang and Johnson, 1997; Rohrs *et al*., 2006). Hence, it is important to characterize the particles adequately. Additionally, the collection of a representative sample is of critical importance.

2.2.1 Particle size estimation methods

The growing need for particulate analysis and determination of PSD in the quality control of pharmaceutical products emphasizes the need for efficient and reproducible methods (Beaubien and Vanderwielen, 1980; Allen, 1981). Currently, several methods are available for PSD estimation, which includes both classical and modern instruments. Nevertheless, only objects of simple geometry, namely spheres, can be unambiguously described by a single numerical descriptor (Etzler and Deanne, 1997; Burgess *et al.*, 2004). The sizing of irregularly shaped particles is typically expressed in terms of equivalent spherical diameters (Heywood, 1963) (Fig. 2.7). Some of the particle size (dry) estimation methods will be discussed in the following sections.

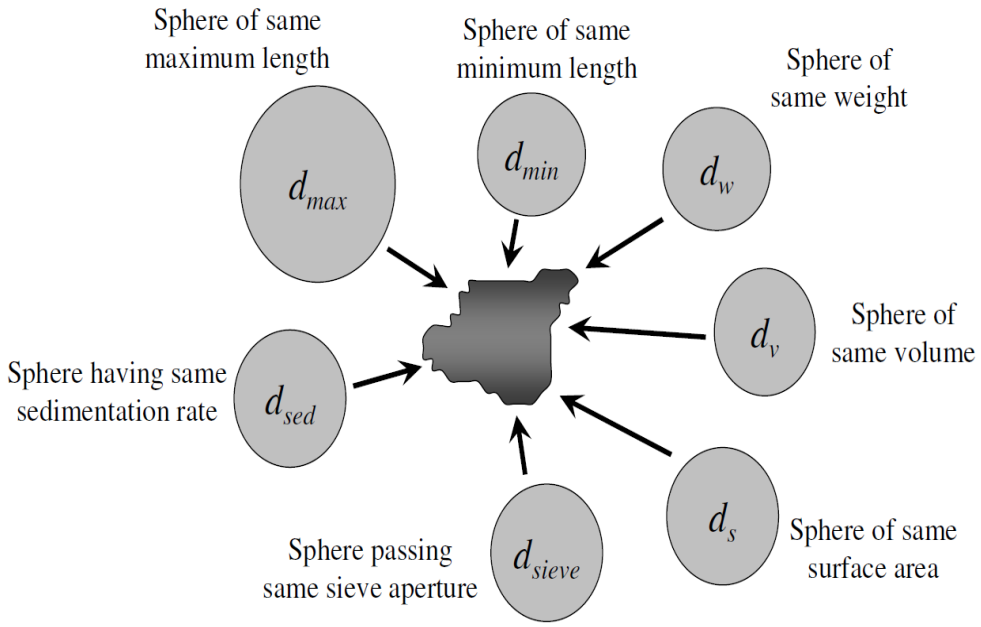


Figure 2.7 Various equivalent sphere interpretations for an irregularly shaped particle (*redrawn and adapted from Kippax, 2005*)

2.2.1.1 Particle size estimation by analytical sieving

Particle size estimation by sieve analysis is the classical and least expensive methods of particle sizing in the pharmaceutical industry. In sieving analysis, a sample is simply passed through wire meshes that have openings of various sizes and then the amount of the sample retained on each sieve is measured. Sieving is one of the

fundamental methods for the classification of powders, and it is the method of choice for determining the size distribution of coarse powders (Brittain, 2002). Conducting analytical sieving for the classification of pharmaceutical materials has been fully described in *USP* General Test <786>. The general method describes the use of both dry sieving method (Method I) and wet sieving method (Method II) procedures. Sieve analysis employs a different method of size analysis, it represents the minimum square aperture through which the particle can pass and hence is influenced by particle shape. Sieve analysis has its own drawbacks; longer measurement times give the particles ample time to orient themselves to fall through the sieve (Rawle, 1993). Particles having the form of thin flakes or long needles are difficult to sieve to finality, because they will only pass the apertures when presented in a favorable position (Heywood, 1963). The general consensus is that sieving is most suitable for granular solids or powders whose average particle size exceeds about 50 µm.

2.2.1.2 Particle size estimation by microscopy

Optical microscopy, also known as static image analysis (SIA), is the only commonly used method in which individual particles are viewed and measured. Examination of a particle under a microscope provides a two-dimensional image. An advantage of this method is that both size and qualitative or quantitative shape information can be obtained simultaneously (Houghton and Amidon, 1992). Particle shape has special importance for pharmaceutical powders, since it affects surface area, bulk density, permeability, flow characteristics and the pharmacological function (Heywood, 1961; Staniforth and Hart, 1987). Various instruments exist for measuring individual particle dimensions of which image analysis is a widely applied technique. Optical microscopy is generally applied to particles of 1 µm and greater while the lower limit

of estimation depends on the resolving power of the microscope. The *USP* General Test <776> describes the particle characterization using optical microscopy. The General Test also states that "For irregularly shaped particles characterization of particle size must include information on particle shape". There are a number of diameters that can be measured in order to characterize particle size (Fig. 2.8). The SIA technique is adequate enough for acquiring a general idea of particle shape, but it is insufficient when using particle shape analysis as a means to control a process.

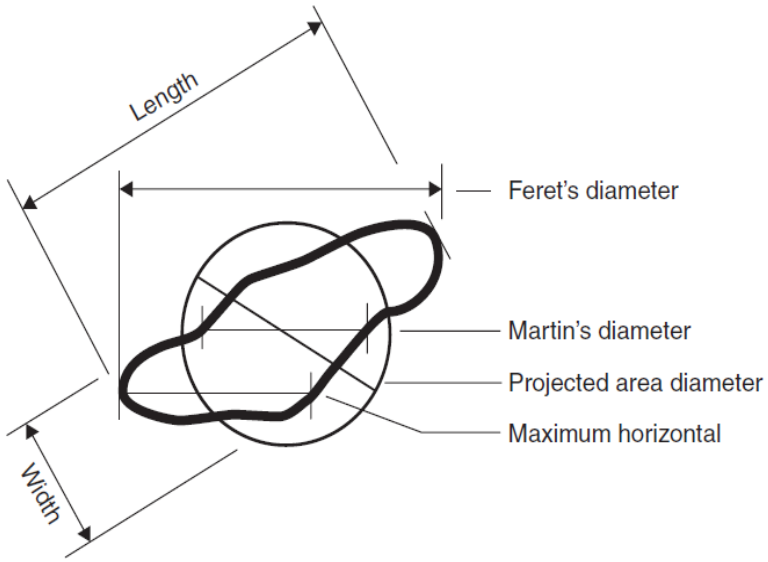


Figure 2.8 Commonly used statistical diameters for particle size (*Adapted from USP General Test <776>*)

Unlike sieve analysis, both size and shape information are made available by the optical microscopy. However, the analysis is slow, tedious and often inaccurate due to operational error or bias if the visual investigation was manually performed (Yamamoto *et al.*, 2004). Also, as relatively few particles are examined, there is a real danger of unrepresentative sampling; therefore limiting its suitability as a quality or production control technique.

Scanning electron microscopy (SEM) is another electron optical imaging technique used quite frequently in the pharmaceutical industry that yields both topographic

images and elemental information of a sample. The SEM instrument produces a large magnified image by using electrons instead of light. A beam of electrons is generated at the top of the microscope by using an electron gun. The electron beam follows a vertical path through the microscope, which is held within a vacuum. The beam travels through electromagnetic fields and lenses, which help in focusing the beam onto the sample. When the beam hits the sample, electrons and X-rays are ejected. Detectors collect these X-rays, backscattered electrons, and secondary electrons and convert them into a signal that is sent to a computer screen to produce the final image. The SEM has many advantages over traditional microscopes. It has a large field depth, which allows more of a specimen to be in focus at one time. The SEM also has a higher resolution, enabling closely spaced specimens to be magnified at much higher levels. Since the SEM uses electromagnets rather than lenses, the operator has a good control over the degree of magnification. All of these advantages, as well as the actual strikingly clear images, make the SEM one of the most useful instruments in current research. Nevertheless, SEM is not a convenient tool for routine particle size estimation but can be very helpful when specific shape information is required.

2.2.1.3 Particle size estimation by laser diffraction

Laser diffraction (LD) particle size analysis is arguably the most popular particle size analysis technique within the pharmaceutical industry, especially in the quality control laboratories (Kelly *et al*., 2006). It offers a wide dynamic range (Fig. 2.9) and is very flexible. Dry powders can be measured directly. Other benefits are rapidity, typical analysis time of less than a minute, small sample requirement, repeatability for reliable results, and high resolution (Tinke *et al*., 2008). Both the Mie and Fraunhofer

optical models are frequently used for the determination of PSDs (Etzler and Deanne, 1997).

The Fraunhofer approximation, used in early diffraction instruments assumes that the particles being measured are opaque and scatter light at narrow angles. It is only true, however, when the particles are large compared to the wavelength of light (de Boer *et al*., 2004). As a result, it is only applicable to large particles and will give an incorrect assessment of the fine particle fraction. The Mie optical model provides a more rigorous solution for the calculation of PSDs from light scattering data. It predicts scattering intensities for all particles, small or large, transparent or opaque. The Mie optical model allows for primary scattering from the surface of the particle, with the intensity predicted by the refractive index difference between the particle and the dispersion medium (Merkus, 2009).

Many international and national standards for using LD to analyze particulate matters in dry and wet forms have been established (Xu and DiGuida, 2003). Nevertheless, as an important argument, LD assumes particles to be spherical, which is in practice never the case. In certain extreme cases, the results of using a spherical model on nonspherical particles will be very different from the truth (Heffels *et al*., 1996; Tinke *et al*., 2005). For smaller sample quantities, laser light scattering has become the method of choice for rapid and reproducible particle sizing (Ma *et al*., 2001). Recent advances in sophisticated data processing and automation have allowed LD to become the dominant method used in industrial PSD determination.

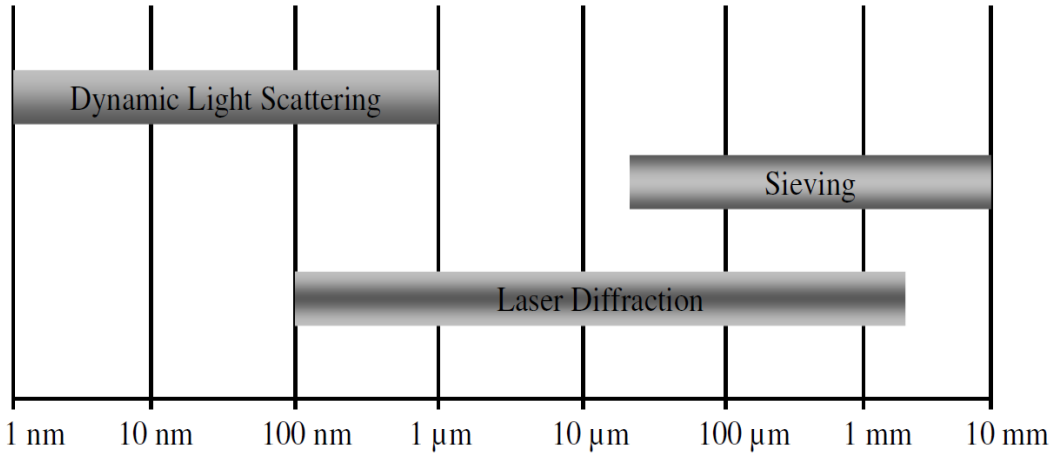


Figure 2.9 Measurement range for different particle size analysis methods (*redrawn and adapted from Malvern Instruments*)

2.2.1.4 Particle size estimation using dynamic image analysis

Dynamic image analysis (DIA) is a recent and rapidly advancing technique and is currently being explored for its use in pharmaceutics (Yu and Hancock, 2008). Compared with other 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 sizing in various processes (Rabinski and Thomas, 2004). The use of DIA was found to be particularly suitable in sizing non-spherical particles (Xu and Santana, 2002; Xu and Di Guida, 2003; Almeida-Prieto *et al*., 2004).

This new DIA technique takes advantage of the progress in microelectronics, such as fast frame grabbers (charge-coupled devices), and combines them with advanced image analysis algorithms to provide users a powerful means of obtaining both size and shape information of particles (Xu and DiGuida, 2003). A DIA instrument (Fig. 2.10) analyses images of the projected area and perimeter of each particle cross-section and based on the choice of size parameter provides a volume or number weighted size distribution of the entire particulate system. Additionally, the risk of

bias caused by subjective sample selection is eliminated, since operator selection of images does not enter the measurement procedure.

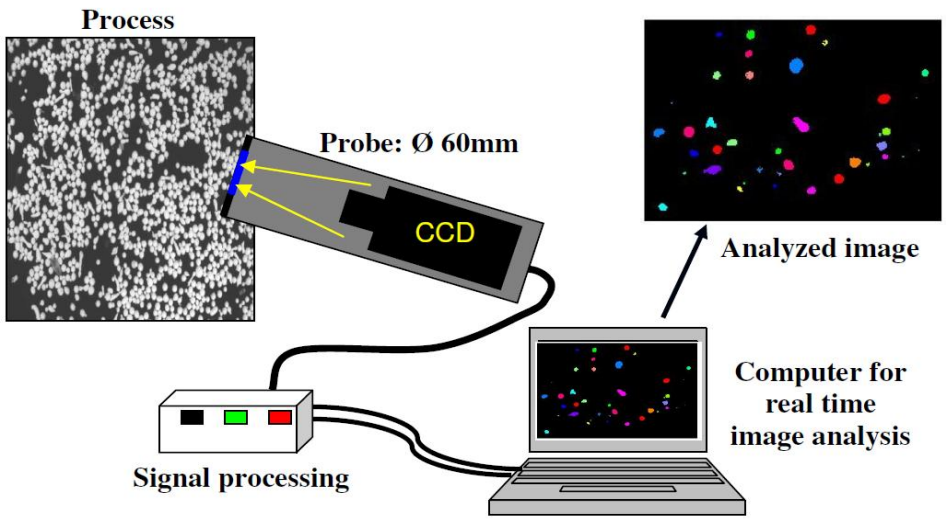


Figure 2.10 Schematic diagram of a DIA sensor

The result's still depend on particle orientation, but the images are analyzed individually without any assumption of particle shape. Xu and DiGuida (2003) mentioned that to reduce the orientation effects the particles in the sample may be circulated during measurement in which case, either each singe particle will be imaged multiple times, or many different particles will be imaged at different orientations. Random orientation provides a better representation of the sample and is the preferred method when true particle shape is critical to the efficacy of the final product. This method of reducing orientation effects has found its way into the designing of on-line and in-line DIA applications for pharmaceutical processes as explained in the case of dry milling in this work.

2.2.1.5 Alternative techniques of particle size estimation

Quite recently alternative techniques based on the principle of focused beam reflectance measurement (FBRM) (Greaves *et al.*, 2008) and spatial filtering

technique (SFT) (Petrak, 2002; Naervaenen *et al*., 2009) have become available and were evaluated for characterizing the particle size distribution.

FBRM, a popular in-line measurement technique, utilizes a focused beam of laser light that scans across a particle passing in front of the probe window (Fig. 2.11) to measure the chord length *s* as the product of the measured crossing time Δt and the beam velocity v_b (Ruf *et al*., 2000; Li *et al*., 2005). The advantages of this technique include ease of use, minimum maintenance requirements and capability of on-line and in-situ measurements. However, the precise interpretation of FBRM data is still debated, because it is difficult to transform the measured chord length into its corresponding PSD accurately (Li *et al*., 2005; Yu *et al*., 2008).

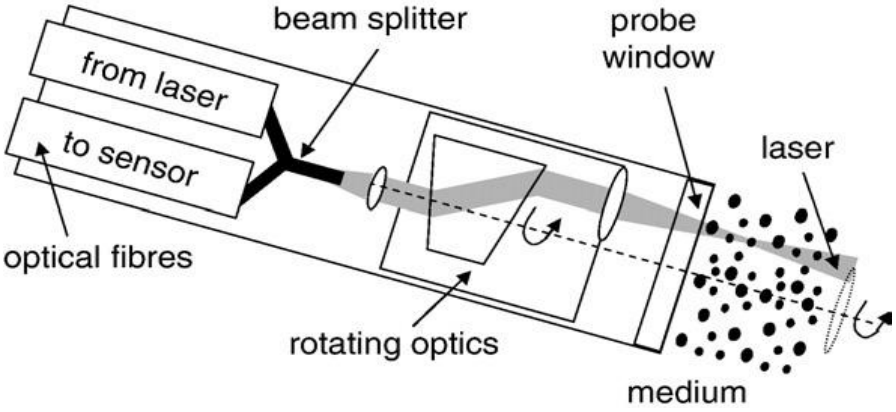


Figure 2.11. Schematic drawing of an FBRM probe (*Adapted from Kail et al., 2008*).

The principles of fibre-optical spot scanning and the fibre-optical spatial filtering velocimetry have been used for determining the size and the velocity of particles simultaneously (Petrak, 2002). Such a technique, employing these principles, called the SFT, measures the chord length distributions of particles (Fig. 2.12). Naervaenen *et al* (2009) applied the SFT method to determine the granule size in a fluid bed granulation process. However, the reported applications of the SFT probe in the pharmaceutical field have been limited.

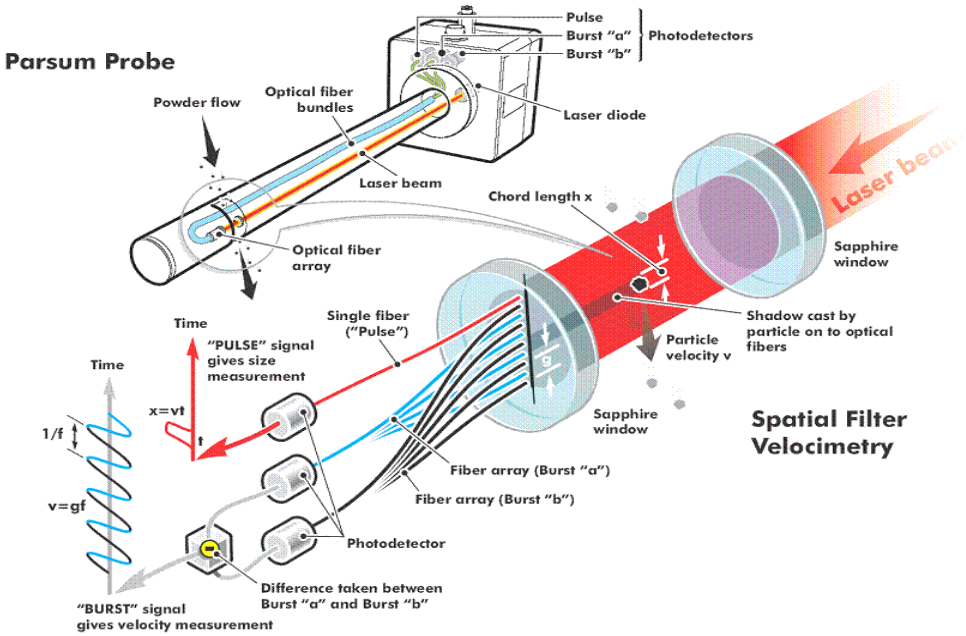


Figure 2.12 Schematic representation of the SFT methodology (*Courtesy of Malvern instruments*)

In past years, several advancements have been made with respect to the instrumentation of such particle sizing methods and there are now a number of possibilities of obtaining reliable estimates of PSDs in real-time. However, it is important to realize that such methods will normally yield different results when applied to a particular system and which does not necessarily mean that one method is more accurate than the rest. Additionally, depending on the operator settings and experimental conditions such as particle optical properties and concentration, particle sampling, particle dispersion markedly different results may be obtained. A thorough knowledge of the possibilities and limitations of every method is necessary in order to obtain reliable results. Therefore it is very obvious, that for meaningful comparison of measurements, analysis by using the same technique is required. Needless to mention, the particle size estimation in different measurement modes, especially using a single technique has not been adequately reported in the scientific literature, which forms the main focus of this work.

2.3 Powder flow characterization

The study of powder flow properties dates back to Coulomb [1773], Mohr [1882], Reynolds [1885], and Prandlt [1921]. In the last decades, powder flowability has become an important topic and has been a subject of extensive research in the pharmaceutical industry, especially with respect to preformulation and development of solid dosage forms. A considerable effort has been spent in understanding and obtaining free flowing powders and granules for tablet and capsule manufacturing (Gold *et al*., 1966). The affects of poor flow, for instance, were observed in the weight variation of tablets (Fassihi and Kanfer, 1986) and in the filling performance of capsules (Tan and Newton, 1990). Hence, poor flow behaviour significantly influences the quality of the final product. Therefore, the pharmaceutical industry realized that an effective powder characterization is the only means of obtaining core knowledge that informs powder understanding and control. In response, many powder measurement methods have been developed. Powder characterization is also growing in importance because innovation in the industry is increasingly reliant on technological advancements, which intensify powder handling challenges. Highly potent actives incorporated in small proportions pose one set of issues; new delivery technologies, such as dry powder inhalers, another (Freeman, 2010). Due to the complexity of powder flow and the various factors influencing flowability, no single measure is currently adequate for defining flow.

2.3.1 Factors influencing powder flow

Several factors are known to influence powder flow behaviour. Primary factors such as particle size and distribution, particle shape, surface energy, cohesion, adhesion, and surface roughness have been shown to influence flowability (Podczeck and Miah,

1996). Secondary or system variables for example, the degree of aeration and the level of moisture, will also have a profound impact (Freeman, 2010). Bulk and tapped densities can serve as indicators of poor flow. Bonding index and internal friction coefficient can also be used as predictors of poor flow (Amidon *et al.*, 2009). External conditions such as relative humidity of the environment, previous storage conditions, degree of consolidation also have a large impact on the flowability. These influencing factors are discussed further in the following section.

When particle size is reduced to such a range that Van der Waals forces increasingly dominate then the powder behaviour will be affected. Particles larger than 250 µm are usually relatively free flowing, but as the size falls below 100 µm powders become cohesive and flow problems are likely to occur. Powders having a particle size of less than 10 µm are usually extremely cohesive and resist flow under gravity. In general, gravitational forces may be dominant for particles having diameters of the magnitude of a millimetre whilst dispersion forces may be dominant for particles of the order of a micrometer. Particulate systems exhibiting narrower particle size distributions flow more easily compared to systems having a broader size distribution (Fan *et al.*, 2005).

Particles having a more irregular shape exhibit much higher porosities in powder beds than spherical particles both before and after tapping (Fukuoka and Kimura, 1992). Particle shape has been shown to affect the flow properties and tabletting performance of ibuprofen, with plate like particles, having better flow properties and tabletting properties compared to needle like particles (Gordon and Amin, 1984).

Solids possess a net imbalance of surface forces and therefore have a surface energy, which is unevenly distributed over the surface (Zeng *et al*., 2001). Some regions may possess a higher surface energy, for example at the edges, than other regions, such as

plane surfaces. The mixing properties of binary and ternary blends can be predicted based on surface energy calculations (Ahfat *et al.,* 1997).

Cohesive forces acting between particles in a powder bed are composed mainly of short-range non-specific van der Waals forces (most important for majority of pharmaceutical powders), which increase as particle size decreases and vary with changes in relative humidity. Cohesion provides a useful method of characterizing the drag or frictional forces acting within a powder bed to prevent powder flow (Staniforth, 2002). Some researchers prefer to use the inverse of cohesion as a measure of a powder's flowability (Geldart *et al.*, 2009).

Adhesion is also commonly encountered in the handling of pharmaceutical solids, leading to the adhesion of powder to the walls of containers, transport tubes, etc. The problems arising from powder adhesion is aggravated by reduction in particle size. The degree of surface roughness of pharmaceutical solids also has importance for several reasons, for example, in dry powder formulation development; the surface roughness of carrier particles has been shown to affect drug product *in vitro* performance (Iida *et al*., 2004). Additionally, surface roughness can influence tablet compression pressure and adhesion of film-coatings (Seitavuopio *et al.*, 2006).

The sensitivity of a particulate system to environmental humidity is, in turn, determined by its hygroscopicity, which is defined as the potential for and the rate of moisture uptake. In general, the higher the relative humidity, the more a solid will sorb water vapour at a higher uptake rate. Absorbed moisture, in turn, can exist either in the unbound state or as part of crystal structure (Howard, 2007). As the moisture content of a powder increases, the adhesion (Craik and Miller, 1958) and also cohesion (Faqih *et al.*, 2007) tend to increase. Even a small change in moisture

content can substantially affect the frictional properties (e.g., wall friction angle, internal angle of friction) of material (Marinelli and Carson, 1992).

As a solid material remains at rest in a bin or hopper, it can become more cohesive and difficult flowing. Hopper and bin load levels, vibratory forces, time in storage, temperature of storage as well as the intrinsic cohesiveness of the material will alter a materials flow characteristics (Howard, 2007).

2.3.2 Flow characterization methods

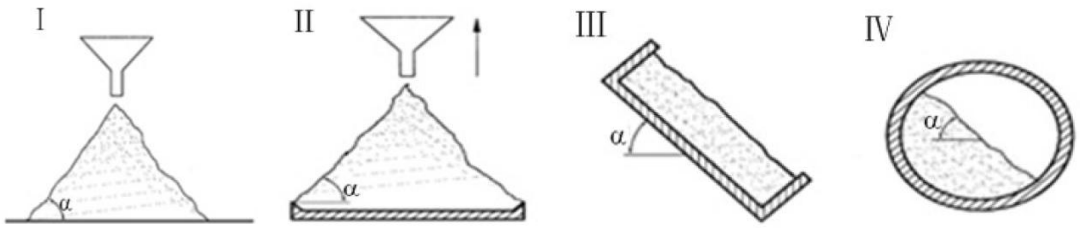
Measuring an array of powder properties is essential because powders have many characteristics. There are a variety of simple techniques that attempt to quantify powder flow. The compendial methods include measurement of angle of repose (USP General Chapter <1174>), bulk and tapped density (USP General Chapter <616>), Hausner ratio (Hausner, 1967) or Carr's compressibility index (Carr, 1965), flow through an orifice (USP General Chapter <1174>) and the shear properties (Jenike, 1964). Innovative flow characterization methods such as cohesivity determination under unconfined conditions (Faqih *et al.*, 2006), dielectric imaging (Dyakowski *et al.*, 1999), atomic force microscopy (Weth *et al.*, 2001) and penetrometry (Zatloukal and Sklubalova, 2007) are a result of technological advances.

Some techniques pursue flow behaviour by measuring forces acting on a blade moving through a powder bed. Cowell *et al* (2005) and Freeman (2007) used a powder rheometer (Manumit powder rheometer and FT4 powder rheometer respectively) to measure axial and rotational forces acting on the rheometer blade while the propeller is penetrating a bed of powder. Some researchers utilize powder avalanching to determine flow characteristics. By measuring chaotic powder avalanches inside a rotating drum Kaye *et al* (1995) and Hancock *et al* (2004) were

able to investigate the rheological behaviour of powders and powder mixtures. This avalanching characterization method appears to be promising for manufacturing related studies.

2.3.2.1 Angle of repose

The angle of repose has long been used to characterize bulk powders. Angle of repose is a characteristic related to inter-particulate friction or resistance to movement between particles. When a powder is allowed to flow through a funnel onto a horizontal plane, it forms a cone. The angle between the side of the cone and the horizontal plane is referred to as the angle of repose. The angle of repose can be reported as the 'drained angle of repose' or the 'dynamic angle of repose'. The four most common methods in use until recently are shown in Fig. 2.13. A free flowing powder will form a cone with shallow sides, and hence a low angle of repose, while a cohesive powder will form a cone with steeper sides. Since the angle of repose measurements are highly dependent on the testing conditions, it is not a very robust means of quantifying powder flow (General chapter <1174>).



fixed height cone fixed base cone tilting table rotating cylinder

Figure 2.13 Measurement of static (I - III) and dynamic (IV) angle of repose (*Modified and adapted from Geldart et al., 2006*)

Jones and Pilpel (1966) tested a number of devices and concluded that the measurements obtained were highly dependent on the device. Table 2.1 describes the different angle of repose values and the corresponding flow characteristics. As a

rough guide, angles less than 30° are usually indicative of good flow, while powders with angles greater than 40° are likely to be problematic. Although the measurement of angle of repose has sometimes met industrial and academic needs for a simple and quick test, Geldart *et al* (1990) pointed out that there was no general agreement as to the best design or size of equipment, for the way that a test should be done, or the optimum amount of powder that should be used.

Table 2.1 Flowability scale (modified and adapted from General chapter <1174> of *USP*)

Flow character	Angle of repose (°)	Compressibility index (%)	Hausner ratio
Excellent	25-30	≤10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very, very poor	>66	>38	>1.60

2.3.2.2 Bulk, tapped and true densities

Bulk density is the mass per unit volume of a loosely packed powder bed. The volume includes the spaces between particles as well as the envelope volume of the particles themselves. The bulk density is an essential parameter for process development and solid dosage manufacturing, since it is used to determine the capacity of mixers and hoppers. Tapped density is the bulk density of a powder that has been compacted by tapping for a definite period of time. The tapped density of a powder represents its random dense packing. Tapped density values are generally higher for more regularly shaped particles (spheres) as compared to irregularly shaped particles such as needles (Amidon *et al.*, 2009). The true density of a substance is the average mass of the particles divided by the solid volume, exclusive of all voids that are not a fundamental part of the molecular packing arrangement. The true density is independent of the method of determination. A powder can only possess a single true density, but it can

have many different bulk density values, depending on the way in which the particles are packed and depending on the bed porosity.

2.3.2.3 Carr's compressibility index and Hausner ratio

Carr's compressibility index (CI) or simply Carr's index is a measure of the capacity of the powder to consolidate. It is a measure of the relative importance of the inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in value and vice versa (Amidon *et al.*, 2009). These differences in particle interactions are reflected in the Carr's index. Compressibility index can be expressed as in Eq. 2.6, where V_o is the untapped apparent volume and V_f is the tapped apparent volume.

$$CI(\%) = 100\left(\frac{V_o - V_f}{V_o}\right) \tag{2.6}$$

It is easy to calculate the CI once bulk and tapped density measurements are performed. Fassihi and Kanfer (1986) found that for directly compressible pharmaceutical powders, when the compressibility index exceeded a value of about 20% a significant increase in tablet weight variation resulted irrespective of the powder flow rate. Podczeck and Newton (1999) demonstrated a correlation between the minimum coefficient of (capsule) fill weight variation and CI. Lee *et al* (2000) demonstrated that the Carr's index is related to the mean time to avalanche. The Hausner ratio is closely related to CI and can be calculated according to Eq. 2.7.

$$HausnerRatio(HR) = \left(\frac{V_o}{V_f}\right) \tag{2.7}$$

The high the Hausner ratio, the poor the flow. The general accepted scale of flowability for Carr's index and Hausner ratio is given in Table 2.1. Carr's index and

Hausner ratio are continued to be used, in combination with other tests, to characterize and predict the flow of pharmaceutical excipients and formulations.

2.3.2.4 Flow through an orifice

Flow through an orifice is an important measure of a powders flow characteristics because of its wide application in several of the pharmaceutical solid dosage manufacturing process. Such processes include granules or powders flow though the opening in a hopper or bin used to feed powder to tabletting and capsule filling machines or sachet filling machines. Because of such importance in producing unit doses, the behaviour of particles being fed through an orifice was extensively studied. Flow rate through an orifice is generally measured as the mass of material per unit time flowing from containers such as cylinders, funnels, and hoppers. However, determination of flow rate through an orifice provides useful information only with free-flowing powders. Dahlinder *et al* (1982) reported that, for cohesive materials the minimum orifice diameter necessary to induce free flow was a better index of flowability.

Beverloo's correlation (Beverloo *et al.*, 1961) is perhaps the most reliable for general calculations of mass flow rate in a silo. The Beverloo's correlation can be expressed as $W = C\rho_b \sqrt{g}\left(D_o - kd\right)^{5/2}$ (2.8)

where W is the mass flow rate of particles, C is an empirical constant, ρ_b is the bulk density of powder, g is the acceleration due to gravity, D_o is the hopper orifice diameter, k is an empirical constant for particle shape, and d is the mean particle diameter. C and k are dimensionless constants and C takes values between 0.55 and 0.65 whereas k takes a value of approximately 1.5 ± 0.1 (Ahn *et al.*, 2008). However, the Beverloo's correlation fails when the particle size is great enough for mechanical

blocking of the orifice to occur and this happens when the particle diameter is about one-sixth of the orifice diameter. Besides, the flow rate is different for small and large orifices. In conclusion, the Beverloo's correlation is reliable in the range $D_o/6 > d >$ 400 µm.

Beverloo's correlation applies well with large powder quantities flowing out of a hopper or silo, but it may not be applicable for small powder quantities. Seppälä *et al* (2010) devised a novel flowability testing method for rapid determination of flow characteristics of powders and granules at a small scale of 1 to 2 g. Flow rate through an orifice is, however, the simplest methods of determining powder flowability and can be used for quantitative comparison of different powders.

2.3.2.5 Shear cell measurements

Jenike pioneered the application of shear cell techniques for measuring powder flow properties. The Jenike's shear cell is widely used in the design of silos for bulk solids. In conjunction with the measured property data, Jenike applied two-dimensional stress analysis in developing a mathematical methodology for determining the minimum hopper angle and hopper opening size for mass flow from conical and wedge shaped hoppers (Jenike, 1964). The measured flow properties used in this methodology are the cohesion, the angle of internal friction, the angle of wall friction, and the flowfunction.

The results of shear cell measurements are classically interpreted as yield loci in the Mohr space. The intercept of the yield loci with the τ-axis (Fig. 2.14) gives the cohesion parameter C, and the slope gives rise to the angle of internal friction Φ (Guerin *et al.*, 1999). Cohesion is a measure of particle to particle bonding strength. Angle of internal friction is a measure of the force required to cause particles to move

or slide on each other. Internal friction is influenced by many parameters including particle surface friction, particle shape, hardness, and particle size distribution. The angle of wall friction represents the adhesive strength between the powder and the wall material; the higher the angle the more difficult it is to move the powder along the wall surface, hence the hopper or chute walls must be made steeper.

Mohr circles tangent to the yield loci give rise to the major consolidation stress (MCS) and to the unconfined yield strength (UYS). The UYS is the shear stress needed to fail or fracture a consolidated powder mass to initialize flow. The force used to consolidate the powder mass is called the MCS. Subsequently, a flowfunction (Fig. 2.15) can be obtained, by plotting the MCS (σ_1) at steady state flow against the UYS (σ_c). A flowfunction lying towards the bottom of the graph represents easy flow, and as the flowfunction moves upward in an anticlockwise direction, more difficult flow is experienced. The flow function can be analyzed to determine the minimum outlet diameters for bins, press hoppers, blender outlets etc to prevent arching and ratholing (Prescott and Barnum, 2000). The flow index (ff_c) is defined as the inverse slope of the flowfunction at the selected range of normal stresses. Jenike classified powders based on their ff_c values and Tomas and Schubert (1979) further extended his classification, which is summarized in Table 2.2.

Table 2.2 Classification of powder flow based on flow index values

Flow index ranges	Flow behaviour
$ff_c < 1$	Non-flowing
$1 < ff_c < 2$	Very cohesive
$2 < ff_c < 4$	Cohesive
$4 < ff_c < 10$	Easy-flowing
$10 < ff_c$	Free-flowing

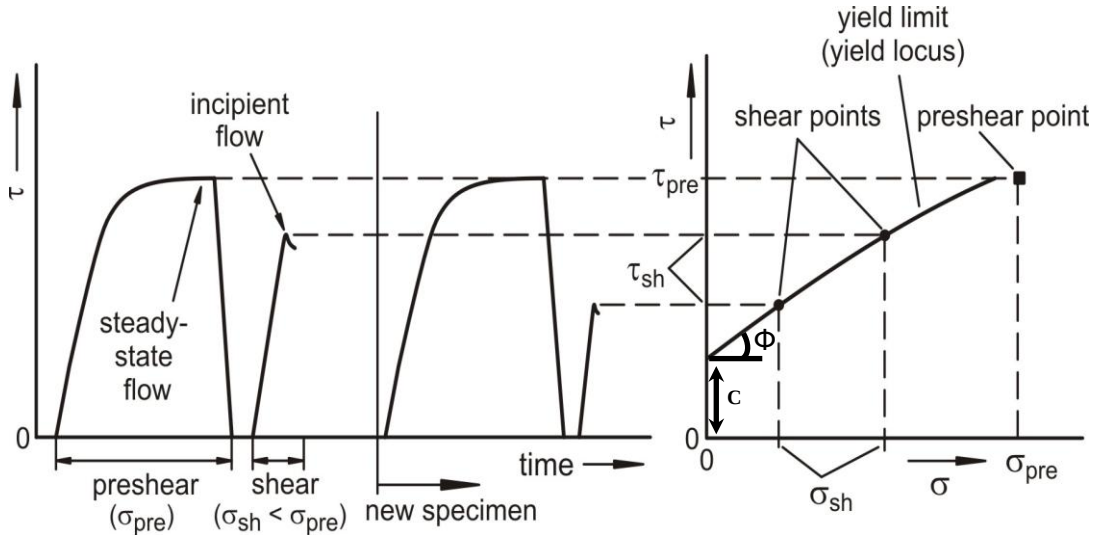


Figure 2.14 Plot of shear stress vs. time; Yield locus. C is cohesion and Φ is angle of internal friction (*Modified and adapted from Schulze, 2007*)

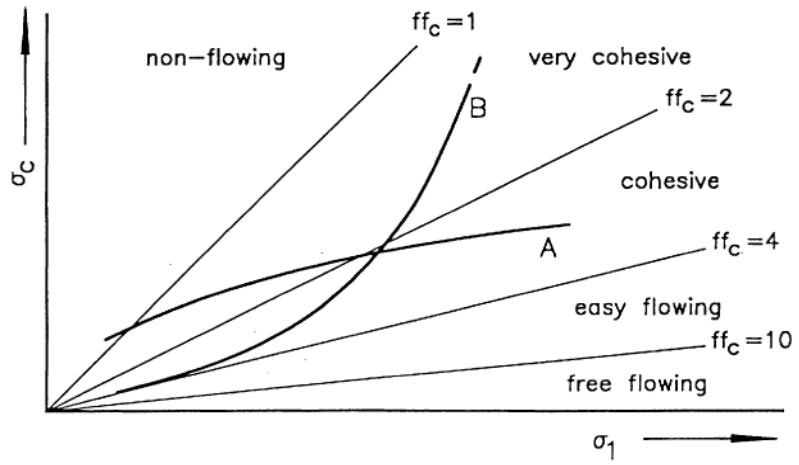


Figure 2.15 Flow function and ranges of different flowability levels (*Adapted from Schwedes 2003*)

Lately, several refined versions of the shear cell instruments, namely, translational, annular, and split rotational cells are commercially available. The shear cell measurements are, however, time and material consuming; correct and reproducible preparation of samples is quite difficult to achieve. Further, the results can be very operator and know-how dependent. Finally, this apparatus should be used if time is not a critical factor and if the flow function of the material is required.

2.3.2.6 Dynamic flow characterization methods (Powder avalanching)

Dynamic flow characterization methods, unlike static methods, have a major advantage in that they closely represent the process under investigation. The rotating drum is one of the most frequently cited dynamic flow characterization systems. Physicists studied the rotating drum for many years long before it was adopted by the pharmaceutical community (Crowder and Hickey, 2000). A pioneering work of Rastogi and Klinzing (1994) used a rotating drum for avalanche characterization of alumina powders. The tests based on avalanches characterize the flowability of a powder by measuring the time interval between avalanches in a rotating drum. It was assumed that the shorter the time between avalanches, the better the flowability of the powder. Later, several authors studied the avalanching behaviour of various powders in a modified version of the rotating drum in an attempt to understand, compare and rank them with respect to their flow characteristics (Kaye *et al.*, 1995; Lee *et al.*, 2000; Lavoie *et al.*, 2002; Hancock *et al.*, 2004; Thalberg *et al.*, 2004). Quintanilla *et al* (2001) looked into the critical behaviour in avalanches of slightly cohesive powders whereas Alexander *et al* (2006) reported the flow dynamics of substantially cohesive powders in rotating cylinders.

The Aeroflow® device (Fig. 2.16) was the first generation, commercially available (Crowder *et al.*, 1999) powder avalanche testing instrument, which consisted of a slowly rotating plexiglass drum and an optical sensor system to detect the powder avalanches as they occur. The optical sensor system consisted of a light and photocell arrangement. The photocell, located behind the drum, collected the light passing through the drum and recorded light variations resulting from cyclic formation of avalanches. The Aeroflow® device analyses data by means of theoretical concepts based on deterministic chaos theory and fractal geometry (Kaye, 1997). Results were

then displayed in terms of "strange attractor plots" and the mean time to avalanche (MTA).

Subsequently, several authors employed the Aeroflow® device for characterizing the avalanching behaviour of their powder systems. Pharmaceutical powder mixtures with poor flow were tested regarding flowability using various methods (Lindberg *et al.*, 2004) and most recently new indices for characterizing the powder flow based on avalanching behaviour were reported (Soh *et al.*, 2006). This information has significantly helped the scientific community to better understand powder avalanching behaviour in a rotating drum. Crowder and Hickey (2000) mentioned that in addition to its use as a platform for studying granular flow, the rotating drum is relevant to dynamic powder characterization and process such as mixing and milling of powders.

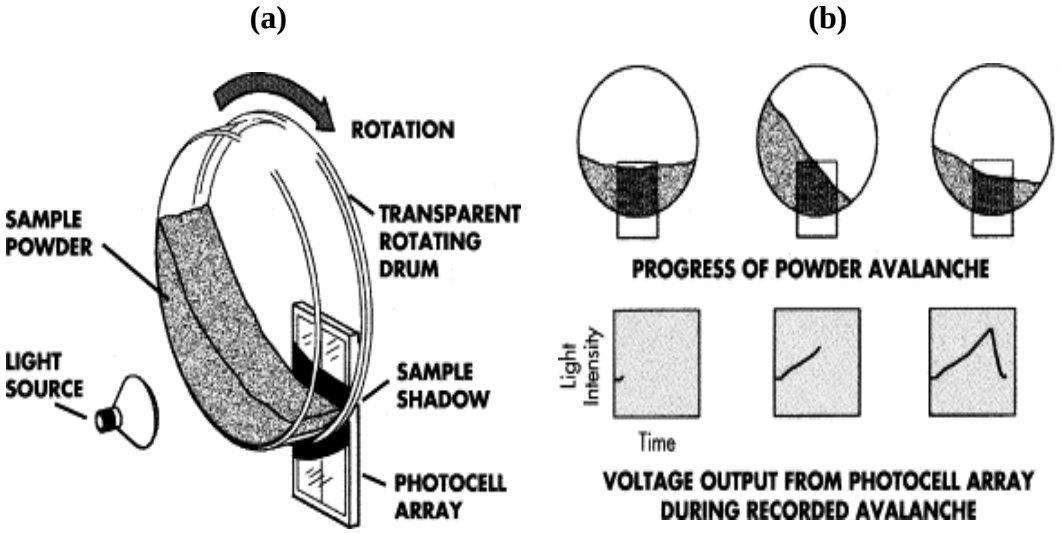


Figure 2.16 Schematic representation of (a) Aeroflow® instrument and (b) the principle of operation (*Adapted from Hancock et al., 2004*)

However, the Aeroflow® device suffers from a few limitations. The most important limitation is that only a small portion of the drum is accessible by a simple optical sensor system. The device can only count avalanches without a proper characterization of the whole avalanching event. Another limitation is the narrowness of the disk which makes significant particle-wall friction and is not a true

representation of pharmaceutical mixing or filling process (Shah *et al.*, 2008). Further drawbacks include the use of a rough boundary surface (*e.g.* sand paper or mesh) to prevent slipping at the drum walls; the need to minimize electrostatic forces at the observation windows to prevent erroneous light obscuration due to sticking particles. Additionally, it is not recommended for testing cohesive powders (Thalberg *et al.*, 2004).

Because of the limitations intrinsic to its own design, the Aeroflow® device is being less frequently studied. On the other hand, a new and technologically advanced powder avalanching instrument (Revolution®, Mercury Scientific Inc., SC, USA), which features a powerful detection system based on dynamic image analysis (Fig. 2.17), is currently being used in many avalanching powder characterization applications (Krantz *et al*., 2009; Huang *et al*., 2009; Hansuld *et al*., 2009; Bonfichi *et al*., 2009). Unlike the Aeroflow®, this advanced instrument is coupled with an image analysis system enabling the determination of diverse parameters characterizing the avalanches. A digital video camera, with the assistance of a cold-cathode back-light illumination, interfaced to a computer and controlled with image processing software captures images (at a predetermined rate) of the whole sample contained in the drum during the rotation process. For every image taken, the software calculates multiple parameters associated with powder avalanching such as mean avalanche time, avalanche power, power average, avalanche angle, avalanche Hurst, and surface fractal among several other parameters (Table 2.3).

Table 2.3 Parameters associated with an avalanche

Avalanche parameter	Definition
Mean avalanche time	The sum of all avalanches divided by the total number of avalanches in the test.
Avalanche angle	The angle of the powder at the maximum power prior to start of the power avalanche occurrence and is displayed as the average value of all the avalanche angles.
Avalanche power	The changes in potential energy of the powder before and after an avalanche.
Power average	The power of the powder calculated by multiplying the height of every pixel by the volume of the powder at that pixel. It is an approximation of the potential energy of the powder in the drum.
Avalanche Hurst	A measure of whether the analysis is purely random or has underlying trends. The Hurst exponent is estimated for an avalanche power set.
Surface fractal	The fractal dimension of the surface of the powder, which provides an indication of roughness of the powder surface.

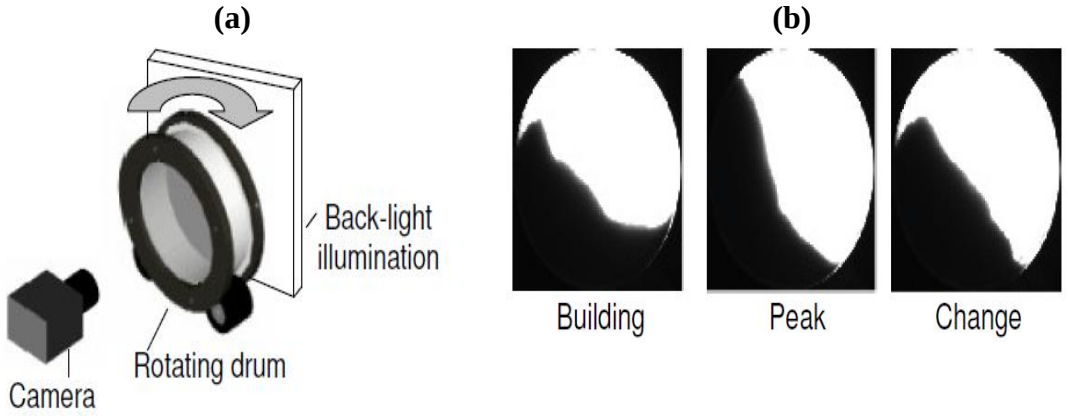


Figure 2.17 Schematic representation of (a) Revolution® instrument and (b) detection of an avalanche using captured images

There are at least six different types of flow regimes (Fig. 2.18) identified for powders whilst inside a rotating drum (Boateng and Barr, 1996; Hancock *et al.*, 2004). The flow of pharmaceutical powders needs to be tested, ideally, under conditions that correspond to the "rolling" or "cascading" flow regimes to obtain meaningful data (Boothroyd *et al.*, 2000; Hancock *et al.*, 2004). Hence, it is important to consider both the visual images and the numerical data to interpret a samples avalanching behaviour

because different samples with similar MTA values may have different flow properties (Boothroyd *et al.*, 2000; Lee *et al.*, 2000). With the Revolution® instrument the operator can, initially, select the desired flow regime by altering the drum rotation speed, which is a major advantage.

Because of its advanced image analysis technique and the potential to calculate diverse avalanching parameters, the Revolution® powder analyzer has drawn the attention of several scientists from various fields. Krantz *et al* (2009), in his study, measured the avalanche angle of fine polymer based powders and Huang *et al* (2009) investigated the fluidization behaviour of fine paint powders. Hansuld *et al* (2009) employed the technique to pharmaceutical granules made form high-shear wet granulation and the authors determined the avalanche power and avalanche time for assessing flowability. However, it was Bonfichi *et al* (2009) who pioneered the work by using the Revolution® instrument for assessing flowability and quality of fine cohesive β-lactam antibiotics.

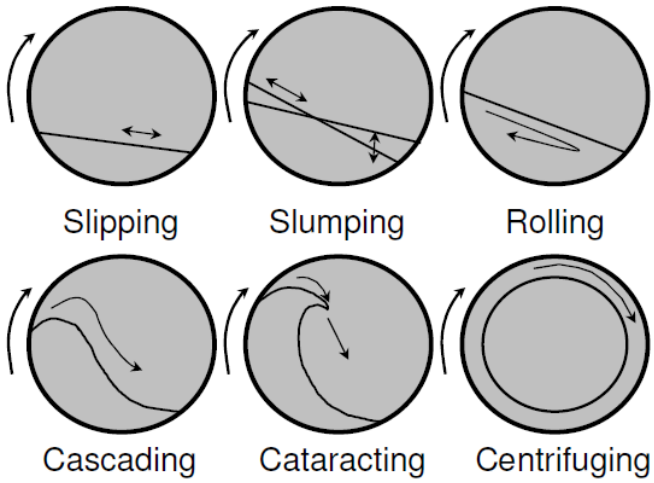


Figure 2.18 Different flow regimes observed inside a rotating drum (*Redrawn and adapted from Hancock et al., 2004*)

2.3.3 Flowability of binary powder mixtures

Flowability of binary powder mixtures consisting of coarse and fine materials is essentially complex, since flow properties are not only influenced by the physico-chemical material factors, but also to a great extent by the particle packing. The particles in multi-component mixtures can assume various packing organizations. The simplest pharmaceutically relevant mixture is binary blends of a drug with an excipient. Such blends provide packing of multisized particles for which empirical equations were derived to calculate the packing density (Carstensen and Puisieux, 1978; Yu and Standish, 1987; Zheng *et al*., 1995). The prediction of the packing properties is even more complex, if interaction between the particles is assumed. Several investigations were made to understand the affects of interparticulate interactions on mixing homogeneity in binary powder blends consisting of fine and coarse particles (Ikekawa and Kaneniwa, 1968; Egermann *et al*., 1985, 1992; Mort and Riman, 1995; Vachon and Chulia, 1998; Sundell-Bredenberg and Nyström, 2001). Barra *et al* (1998) questioned, whether the organization of a binary powder mix can be predicted based on surface energy, cohesion parameter and particle size of its components? The authors were successfully predicting a possible adherence of small particles to a coarse excipient, which is also known from inhalation technology (Clarke *et al*., 2001) but the attempts were not able to reliably predict any packing configuration of binary blends. This was partially due to the effects of particle shape (Wong and Pilpel, 1988; Podczeck and Sharma, 1996), which increased the heterogeneity in powder mixtures. Attempts were made to model these effects of heterogeneity in binary mixtures by means of percolation theory (Consiglio *et al*., 2003), which mainly focused on the geometry of the particle packing. Thus, the physics of binary particle mixtures is still not well understood (Crowder and Hickey,

2000). However, the packing organization defines the material flow properties. These technical blend properties can greatly change, if the packing organization is altered at different mixture ratios. Such changes of flowability with different mixing ratios are important to understand. It is a required knowledge to adequately formulate pharmaceutical powder blends that need designing quality into the product (Wargo and Drennen, 1996; Storme-Paris *et al*., 2009; Sun *et al*., 2009).

2.3.3.1 Ordered mixtures

If a powder consisting of two materials, both having identical physical properties (e.g. size and density), is mixed for a sufficient time, random mixing (Fig. 2.19) will eventually be achieved. However, most pharmaceutical powders consist of mixtures of materials with different properties. This leads to segregation, which means particles of similar properties tend to collect together in part of the mixture. Differences in particle size are the most common cause of segregation in pharmaceutical powders. One exception to this is when one component of the powder mixture has a very small particle size (microfine) and is cohesive and the other component is relatively large (Yeung and Hersey, 1979; study II). In such circumstances, the fine powder may coat the surface of the larger particles (Hersey, 1975), and the adhesive forces will prevent segregation. This is known as ordered mixing, and using this technique it is possible to produce greater homogeneity than by random mixing. The rate of ordered mixing follows first order kinetics, since the rate of mixing will be proportional to the number of fine particles remaining to adhere onto the larger particles. Ordered mixtures, consisting of a microfine drug adsorbed onto coarser excipient particles, offer significant advantages in the manufacture of certain solid dosage forms, especially those containing very small quantities of the drug (Yeung and Hersey, 1979).

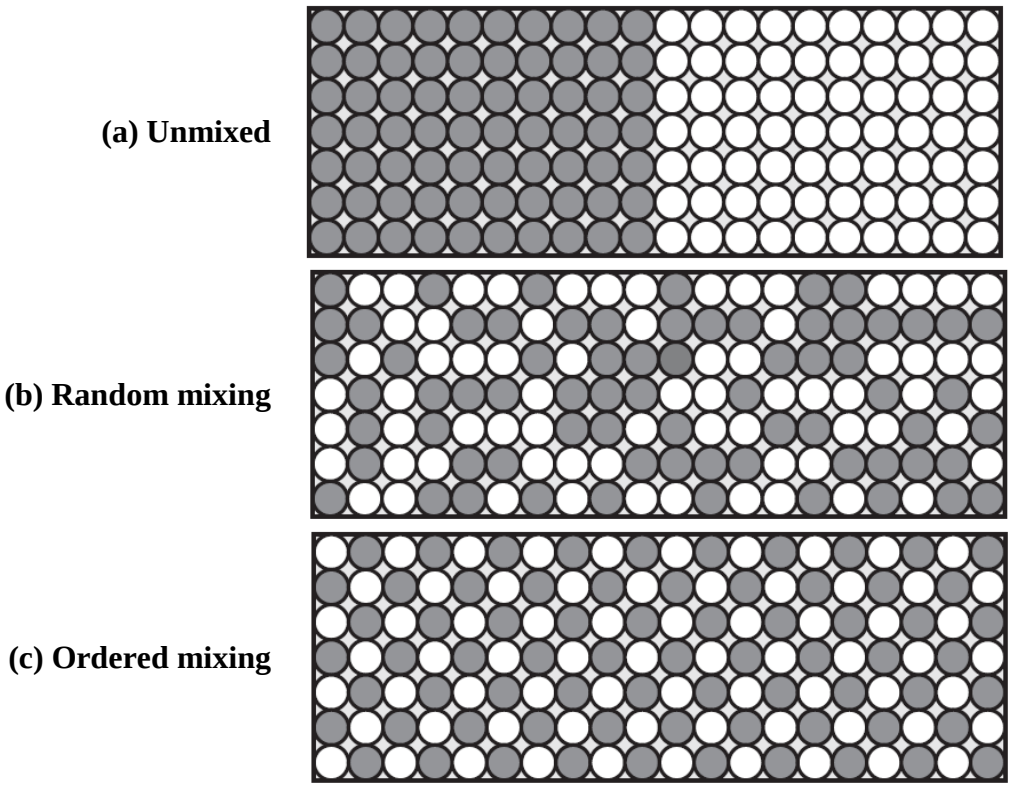


Figure 2.19 Schematic diagram of powder mixing (a) two components before mixing, (b) randomized mixture of equal proportions of black and white particles, and (c) ordered mixture of equal proportions of black and white particles (*Adapted from Zeng et al., 2001*).

2.3.3.2 Effect of fines on flow properties of binary mixtures

In the context of solid dosage forms, addition of fines is usually done to improve flowability of powders. These materials are extremely fine and are added in small quantities of upto 1% w/w (Elbicki and Tardos, 1998). These fine particles generally have poor flowability due to the cohesion force arising mainly from Van der Waals attraction. The addition of a flow agent is an effective way to improve the flowability as discussed in the pioneering work of Molerus (1978) and other researchers (Kaye *et al.*, 1983; Kono *et al.*, 1990; Elbicki and Tardos, 1998; Valverde *et al.*, 2000). Some investigations have been carried out to find the critical concentration at which flowability of materials is predominantly controlled by the fines. Lefebvre *et al* (1988) pointed out that if the amount of smaller (disintegrant) particles in a binary mixture was continuously increased, a more or less critical concentration was observed for

which the mechanical properties such as flowability and compressibility of the mixture and the resulting tablets changed. Tasirin (2000) reported that with the increase of weight percent of fines added to the binary mixture, the flowability properties shifted towards cohesiveness. Kaerger *et al* (2004) investigated the effect of size and shape of paracetamol particles on the flow and compressibility behaviour of binary blends in microcrystalline cellulose. The authors concluded that small, spherical drug particles may result in improvement in the bulk density, densification and compactibility of the binary blends. In a similar study, Soppela *et al* (2010) reported that the flowability of the binary blends was affected both by the amount of paracetamol and the physical properties of microcrystalline cellulose and additional factors such as charging, surface moisture, carrier payload and particle size. Carrier payload originally comes from inhalation products. Carrier payload for a binary mixture can be calculated based on the assumptions of Dickhoff *et al* (2003) and can be defined as the ratio between the total projection surface area of microfine drug particles and the total outer particle surface area of coarse carrier particles (van Veen *et al*., 2005). At low carrier payload, the drug particles find shelter in the carrier surface irregularities and they require time to relocate to other sites on the carrier particle. At higher payload, relocation for the coarse carrier particle is of less interest, because there exists a multilayer of drug particles around the carrier particles (Dickhoff *et al*., 2005). This emphasizes the effect of mixing time on the location of drug particles on the surface of the carrier particles.

A pioneering work of Molerus (1984) involved the study of the effect of fines on the flowability of binary mixtures consisting of spheres. He derived equations to calculate the critical fines content that determine the overall flowability. A fine particle content, which defines the flow properties of the mixture, is reached when the coarse particles

are completely embedded in the fine particles. The appropriate ratio of the mass m_f of the fine particles to the total mass $m_f + m_c$ of the mixture is given by the expression:

$$\frac{m_f}{m_f + m_c} = \frac{1}{1 + \frac{1}{(1-\varepsilon_f)\left(\frac{6}{\pi} - 1\right)}} \tag{2.9}$$

where ε_f is the void fraction of the fine particles surrounding the coarse particles. However, Molerus calculations include simple geometrical considerations and do not take into account the cohesion between the particles. This approximation is less valid for real powder processing operations particularly in DPI formulations, in which micronized drug particles exhibit high cohesion.

In conclusion, powder flowability is *per se* a unique field and requires much attention for better understanding of the flow characteristics. All current techniques for determining powder flow are based on different principles and have advantages and disadvantages. The choice of an appropriate technique to assess powder flow should be made in relation to the technological process to be studied (Prescott and Barnum 2000; Schwedes 2003). Additionally, both static and dynamic characterization techniques must be employed to completely understand the flow properties of a powder to enable predicting its behaviour under different process conditions (Krantz *et al.*, 2009). The results obtained from any individual characterization technique should not be simplified into a universal index or classification. Finally, powder flow properties should be measured and optimized as part of every development program.

2.4 Process analytics and the pharmaceutical industry

The conventional pharmaceutical manufacturing typically employs batch processing, with laboratory analysis of samples collected at predetermined time intervals and processing steps, particularly in-process and end product testing. This conventional approach requires that the quality testing systems are in place to ensure that the final product meets predetermined specifications. These current quality testing systems include process/method/equipment validation, process control using standard operating procedures (SOPs), process instructions/master recipes, and off-line testing of samples at the end of each batch (Scott and Wilcock, 2006). The petrochemical industry has long been using process analytical chemistry (PAC) and most of the process analytical instruments, originally developed by oil and petrochemical industries have been in due course adopted by several other industries. PAC is the technique of gathering analytical information in real-time at the point of manufacture (Hailey *et al*., 1996) and places an emphasis on the process rather than the final product. However, pharmaceutical industry continues to use the traditional quality testing systems to test their finished product quality. This paradigm has changed in the recent years, with the introduction of process analytical technology (PAT) and eventually, process analytics has become a central topic in the pharmaceutical industry. The US Food and Drug Administration (FDA) drafted guidelines for encouraging or requiring the adoption of PAT in the pharmaceutical industries. The following sections will discuss the PAT initiative by the FDA, elements and tools of PAT, and finally the benefits of implementing PAT.

2.4.1 The FDA process analytical technology (PAT) initiative

With the aim of improving pharmaceutical manufacturing, in August 2002 the FDA has announced a new initiative entitled, "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach". This initiative emphasized the early adoption of new technological advances by the pharmaceutical industry. Later, the cGMPs initiative was followed by a more detailed guidance for the industry (Guidance for industry-PAT, 2004). This guidance document was followed by similar elements of continuous product and manufacturing development process, quality risk management, effective quality management, which were subsequently incorporated into ICH guidelines (ICH Q8, 2006; ICH Q9, 2005; ICH Q10, 2008).

The FDA defines PAT to be "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality." PAT is an innovative measure, since it is centered on simultaneous introduction of higher quality into both the product and its manufacturing processes. PAT also represents a framework that helps to harmonize compliance with regulatory requirements. The PAT guidance document provides four types of tools for generation of process data: (1) *Multivariate tools for design, data acquisition and analysis* such as statistical design of experiments, response surface methodologies, principal components analysis, multiple linear regression, partial least squares, neural networks, process simulation, and pattern recognition tools (2) *Process analyzers* which may include in-line (where the sample is not removed from the process stream), on-line (where the sample is diverted, quickly analyzed and returned to the process stream), at-line (where the sample is removed and analyzed close to the process stream) and off-line (where the sample is completely removed

from the process area) (3) *Process control tools* and (4) *Continuous improvement and knowledge management tools*.

PAT enables a better understanding of the process and optimizes the quality of the final product. The concept of process analyzers, within the framework of PAT, has been encouraging pharmaceutical manufacturers to experiment with new approaches and technologies to better comprehend and control their processes (MacGregor and Bruwer, 2008; Yu, 2008). However, to advance PAT it is not only important to introduce new process analyzers, but also study implementation factors of existing technologies. This approach is hoped to bridge the existing gap between initial research applications and current industrial practice. Implementing PAT, however, signifies a thorough scientific understanding of all manufacturing processes, acquired not only by experience but also by extensive data collection and the use of suitable analytical tools. These are among today's most effective solutions for process integration in manufacturing companies and, therefore, have direct relevance to PAT. Fortunately, FDA is lending strong support by encouraging the use of PAT. The FDA supported PAT initiative appears to have gathered significant pace and momentum during the past years and will have a major impact upon the way pharmaceutical manufacturing is conducted in the future.

2.4.2 Benefits of PAT

Implementing PAT is expected to result in three main benefits (a) increase in process as well as product understanding, (b) increase in manufacturing process control and, (c) quality built into the product right from the design stage (Scott and Wilcock, 2006). Additional benefits of PAT are summarized in Table 2.4. The implementation of PAT can lead to quality improvements as a direct result of continuous monitoring

and the use of process tools. Real-time monitoring of batch processing steps decreases product variability, reduces the number of batch failures, and increases batch-to-batch consistency. This will also change the paradigm from blind compliance to science and risk based compliance.

Table 2.4 Benefits of implementing PAT in the pharmaceutical industry (*modified and adapted from Scott and Wilcock, 2006*)

Benefits category	Specific PAT benefits
Reduced operating costs	Increased operating efficiencies
	Improved cycle time (reduced release times, parametric release, reduced sample preparation time, minimized reliance on end product testing, faster analysis times)
	Decreased operating costs
	Possible continuous processing
	Real-time monitoring, feedback controls and results
	Inventory reduction (through parametric release and improved cycle times)
	Increased capacity utilization
	Attain production schedule
	Reduced reprocessing expenses.
Quality improvements	Increased quality (decreased product variability; decreased number of rejections; scrap, batch failure and systems failures; and increased product reliability
	Increased product uniformity (ensure batch to batch consistency, decrease variation)
	Process fingerprinting
	Increased process understanding
	Quality designed into the process
	Use of scientific, risk-based approach in decision making
	Recall prevention/avoidance
	Minimized patient risk including security of supply
	No sampling required or reduced sampling requirements (eliminates sampling error)
	Critical process control provided
	Rapid identification of counterfeit drug substances
Positive regulatory impact	Increased regulatory compliance
	Moderate regulatory burden on FDA
	Improved scientific basis for regulatory functions
Increase occupational safety	Decreased occupation exposure to toxic substances
Positive research and discovery impact	Reduced product development lifecycle/time to market
Minimize environmental impact	Reduced environmental impact (assurance that process and plant environments are maintained within environmental regulations)
	Minimize waste generation during manufacturing

2.4.3 Quality by design and the design space

Quality by design (QbD) is essentially an approach to process development that emphasizes the need for a good understanding of both the process and the product, based on sound science and quality risk management (Garcia *et al.*, 2008). It is important to identify those parameters that have an impact on the process. Further, identification of operating ranges, which are safe and do not result in out-of-specifications (OOS) product is essential. QbD encompasses the application of elements such as: critical quality attributes (CQAs), design of experiments (DOE), risk assessment, and PAT to the development of pharmaceuticals (Verma *et al*., 2009). Accordingly, quality is built into the product and not merely established by testing the finished product. A QbD scientific approach, compared with traditional development, significantly expedites improved process understanding. Additionally, QbD approach facilitates cost reduction and time savings, minimizes impact to the environment and most importantly improves quality, safety and confidence of the process and product.

In recent years diverse process analytical technologies were introduced to pharmaceutical unit operations. The importance of defining CQAs and investigating material properties (Hlinak *et al*., 2006) together with critical process parameters is now widely recognized (Ende *et al*., 2007; Verma *et al*., 2009). 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; Medendorp and Lodder, 2006; Schmidt-Lehr *et al*., 2007; Chan *et al*., 2008; Hui *et al*., 2008; Huang *et al.*, 2010; Tewari *et al.*, 2010), to achieve the quality by design objectives in the pharmaceutical industry.

Design space as defined by ICH Q8 as "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality." A design space (Fig. 2.20) can be created for each unit operation or for a process as a whole. Additionally, design space is produced through a well organized set of design of experiments. The ICH Q8 also states that "working within the design space is not considered as a change; movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process". The control space is suggested as some region, lying within the design space, within which a company will try to operate the process (MacGregor and Brewer, 2008). The concepts of design space and PAT are inherently linked. The knowledge gained from pharmaceutical development studies and manufacturing experiences provide scientific understanding to support the establishment of the design space.

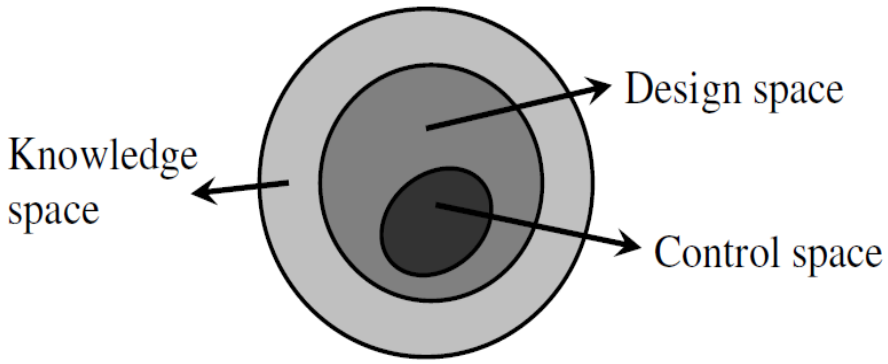


Figure 2.20 Conceptual representation of knowledge, design, and control spaces (*Redrawn and modified from MacGregor and Brewer, 2008*)

2.4.4 Design of experiments

The information gained from properly planned, executed and analyzed experiments can be used to improve functional performance of the products, reduce scrap, lower product development life cycle time, and minimize excess variability in production

process. This can be achieved by using experimental design or design of experiments (DOE), which refers to the process of planning, designing and analyzing experiments for determining the relationships among factors affecting a process and its output (ICH Q8). It is very important to identify factors or parameters, in the initial stage, which can be altered to influence the responses. It is these responses that define the essential properties of a system. The two main applications of DOE are screening and optimization. Screening refers to the identification of factors that influence the experiment and optimization is to find the optimal settings or conditions for an experiment. Commonly used are the fractional factorial (used in initial stage of a project) and full factorial designs. Response surface methodologies (RSM) are multivariate techniques that mathematically fit the experimental domain studied in the theoretical design through a response function (Hanrahan and Lu, 2006). The two most commonly used designs in RSM are the central composite and Box-Behnken designs. The result of an appropriate RSM can be a response contour plot which can be used for the construction of a design space.

The pharmaceutical industry has complex manufacturing processes that would benefit from the multivariate techniques and DOE framework. Indeed, the pharmaceutical sector has long been at the forefront of applying such technology. However, this was mainly at the laboratory and pilot scale, but has been historically much less widespread in manufacturing. The main explanation for this dichotomy is that the pharmaceutical industry has been obliged to operate in a highly regulated environment. This environment has reduced the opportunity for change which in turn has limited the applications of multivariate techniques and DOE in manufacturing. Besides, few experiments can be performed on full scale as opposed to laboratory or pilot scale owing to the large costs involved.

PAT based tools for real-time monitoring of dry milling unit operation (as discussed in this work) or any other pharmaceutical process can decrease process variability, reduce the number of batch failures, and increase batch-to-batch consistency, thus ultimately leading to faster and better manufacturing.

3 **EXPERIMENTAL SECTION**

3.1 Investigation of dynamic image analysis as a suitable process analytical tool for monitoring particle size in a dry milling unit operation (Study-I)

3.1.1 Introduction

This part of the thesis involves study of different measurement modes, employing dynamic image analysis (DIA), for real-time monitoring of particle size distribution in a pharmaceutical comminution process. A further objective is to investigate the concept of time evolving size and shape analysis (TESSA). A conical mill is employed and the real-time particle size is monitored using a DIA sensor system with xenon flash light and CCD camera. The DIA sensor is modified for testing in two modes, on-line and in-line. Results from the different DIA measurement modes namely, on-line, in-line and additionally at-line (reference mode) are compared using pharmaceutical model excipients and granulates. Broad range of material characteristics and process parameters are considered for better understanding of the comminution process. 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. In TESSA experiments, particle size and shape are evaluated in two-dimensional (2D) cluster analysis and the sigma bands are considered. One-sigma intervals provide the sigma bands. 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 in-process analytics. Such early detection of a process deviation is important to avoid impaired product quality and subsequent loss of material.

3.1.2 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 3.1. Placebo II was expected to have the least specific surface area, intuitively, but it was observed that because of higher intragranular porosity it exhibited slightly larger specific surface area value (Table 3.1) which was confirmed from scanning electron micrographs (Fig. 3.1). The rationale in selecting these four materials for this 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.

Table 3.1 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

3.1.3 Methods

3.1.3.1 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 hours at 40°C to condition the surface. All the reported results were measured in triplicate.

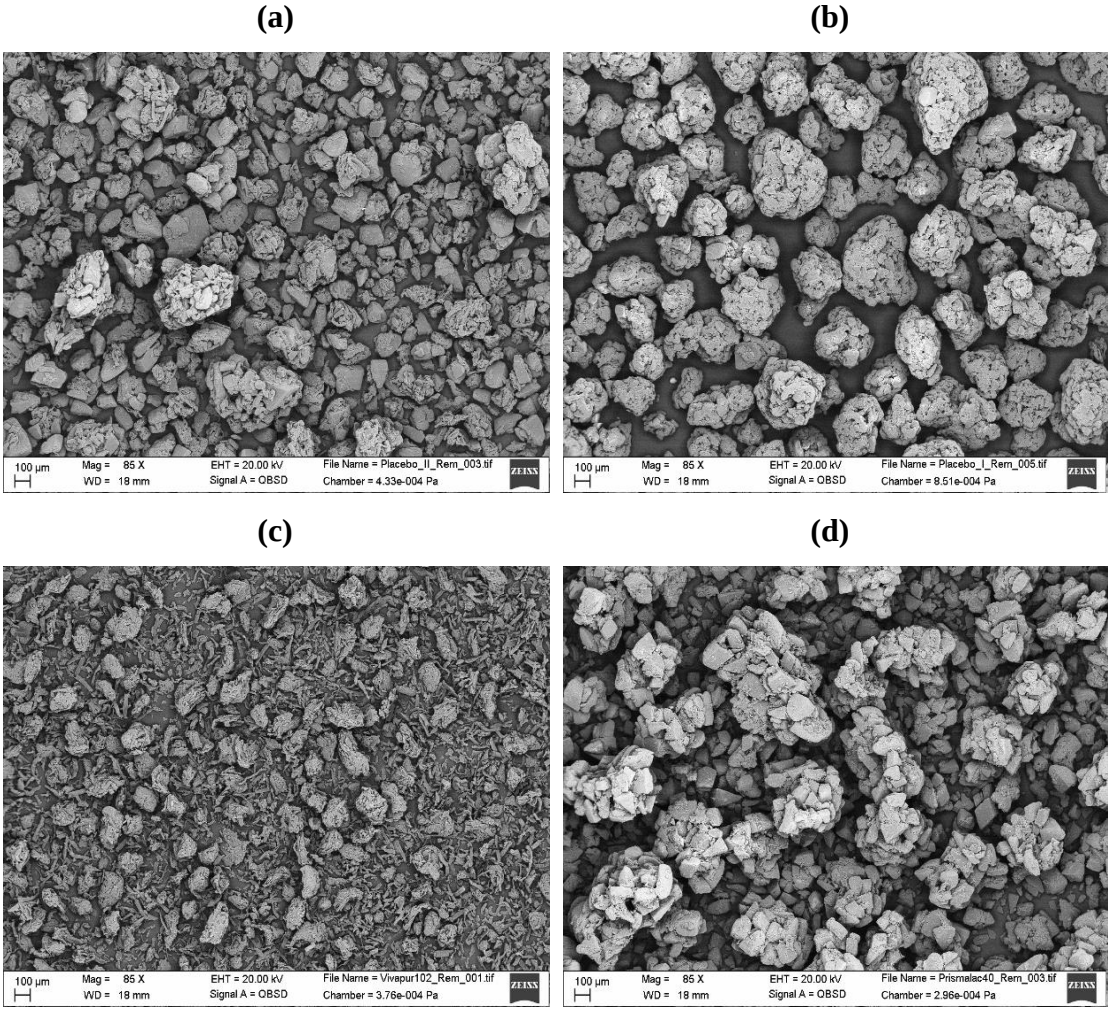


Figure 3.1 Scanning electron micrographs of (a) Placebo I (b) Placebo II (c) Vivapur® 102 (d) PrismaLac® 40 (the unit scale corresponds to 100 µm)

3.1.3.2 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 √2 progression and vibrated at 1.5 amplitude for 10 minutes. 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.

3.1.3.3 Scanning electron microscopy

The morphology of the starting samples was investigated with scanning electron microscopy. The samples were dispersed on a carbon tape and coated with gold/palladium in a sputter coater (Polaron SC7620) prior to imaging. The analysis was performed on a field emission scanning electron microscope (GEMINI® FESEM, Zeiss, SUPRA™ 40VP) at an accelerating voltage of 20 kV in a backscattered detection mode (QBSD).

3.1.3.4 Dynamic image analysis using XPT® sensors

Two dynamic XPT® image analysis sensor systems (PS Prozesstechnik GmbH, Basel, Switzerland) were used to be employed 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-basis for both measurement modes, i.e. on-line and in-line.

3.1.3.5 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 1024x1024 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 to 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.

3.1.3.6 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 kg 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.

3.1.3.7 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 3.2. 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. 3.2a). 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 bars 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 degrees and additional air was blown at a pressure of 0.5 bars on its surface to keep the sensor lens clean during the entire process (see Fig. 3.2b). 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.

Table 3.2 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*	10	1500	2.2	8.5	--	--
In-line	7.5*	10	1500	--	--	25°	0.5

* 7.5 rpm feed speed corresponds to approximately 55 kg/h of material throughput

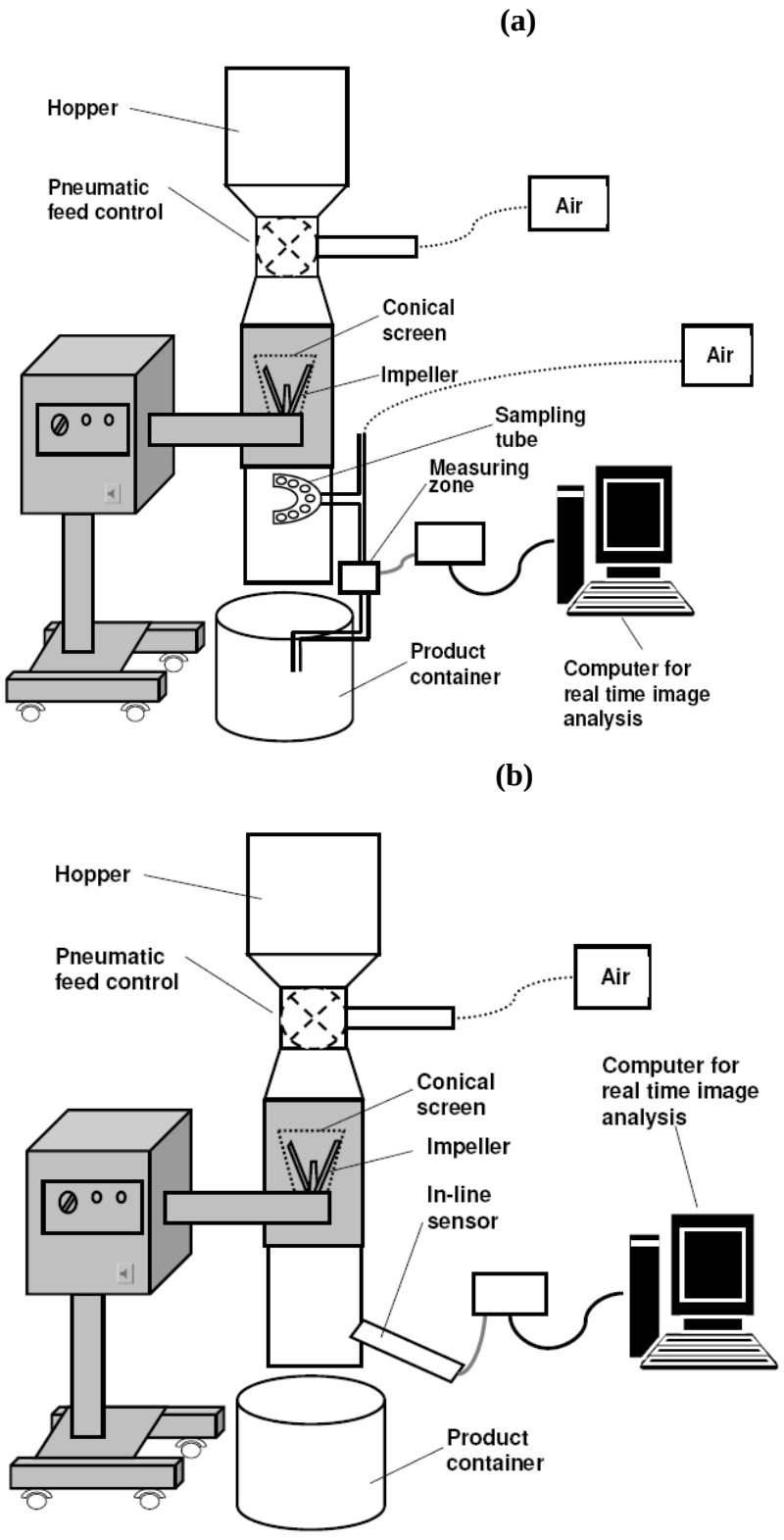


Figure 3.2 Schematic representation of the (a) on-line sensor system (b) in-line sensor system

3.1.3.8 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.

3.1.3.9 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

$$HCF = \frac{P_{real}}{2\sqrt{\pi \cdot A}} \tag{3.1}$$

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 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

$$WDD = 2\sqrt{\frac{A}{\pi}} \tag{3.2}$$

3.1.4 Results and discussion

3.1.4.1 Dynamic image analysis and different measurement modes

3.1.4.1.1 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 3.1. 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. 3.3a through 3.3d. 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. This can be directly visualized by comparing the sieve particle size data of the milled material from Table 3.3 with the sieve particle size data of the unmilled material from Table 3.1. It is important to note that sieve analysis employs a different classification principle than the image analysis. A 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. 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. 3.3a-d). This was particularly observed with Vivapur® 102, which was probably due to 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 were also in fair agreement with the reference values obtained from at-line as well sieve analysis in case of the coarse materials (Fig. 3.3c and 3.3d). 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 3.3. A better understanding of these analytical gaps is of particular interest. Accordingly, there are different potential mechanisms that can theoretically 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 3.3), 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 3.4 and is further discussed in detail on a qualitative basis.

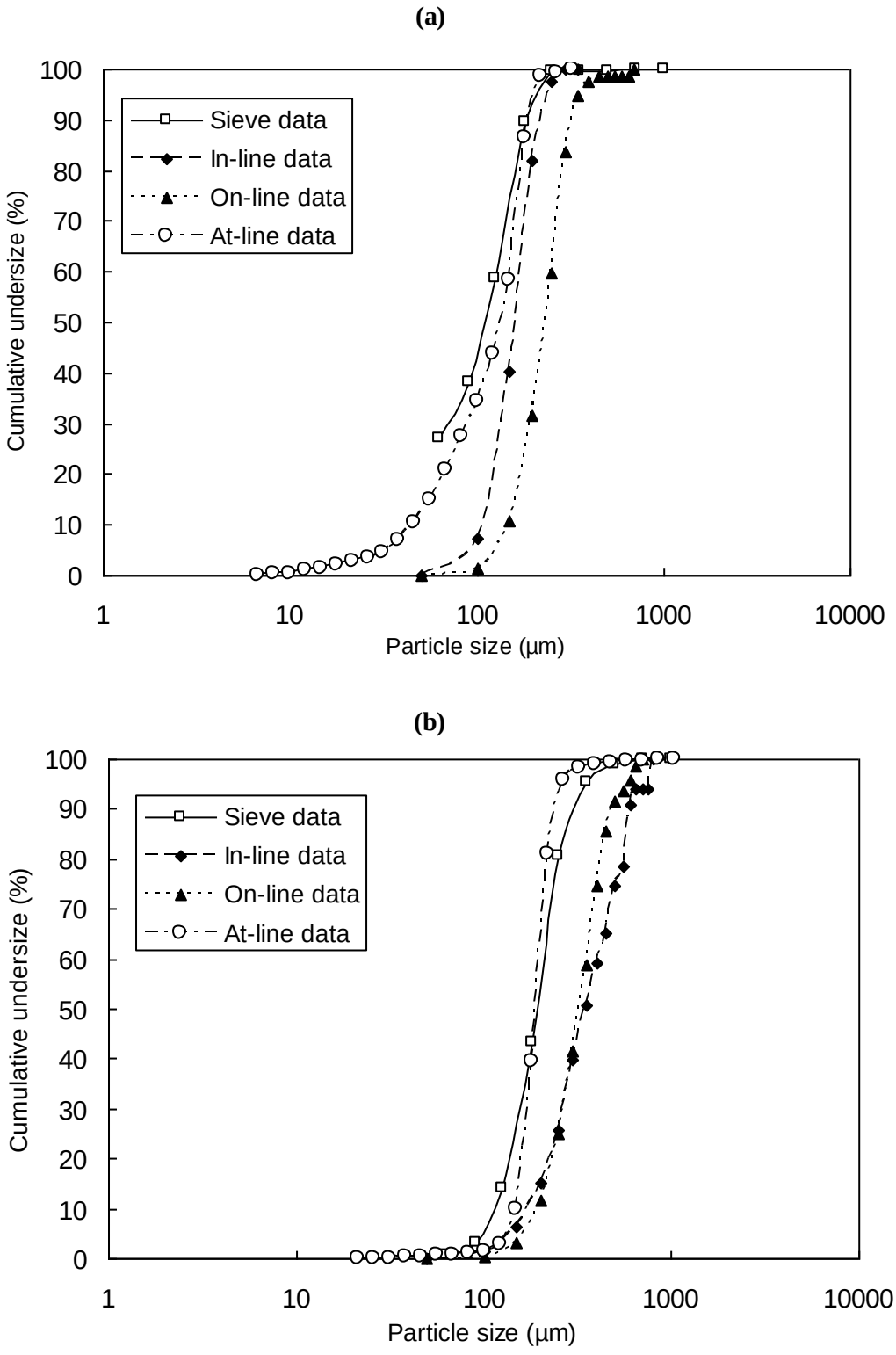


Figure 3.3 Particle size distributions of the milled material measured using the four different modes of analysis for (a) Vivapur® 102 (b) Placebo I

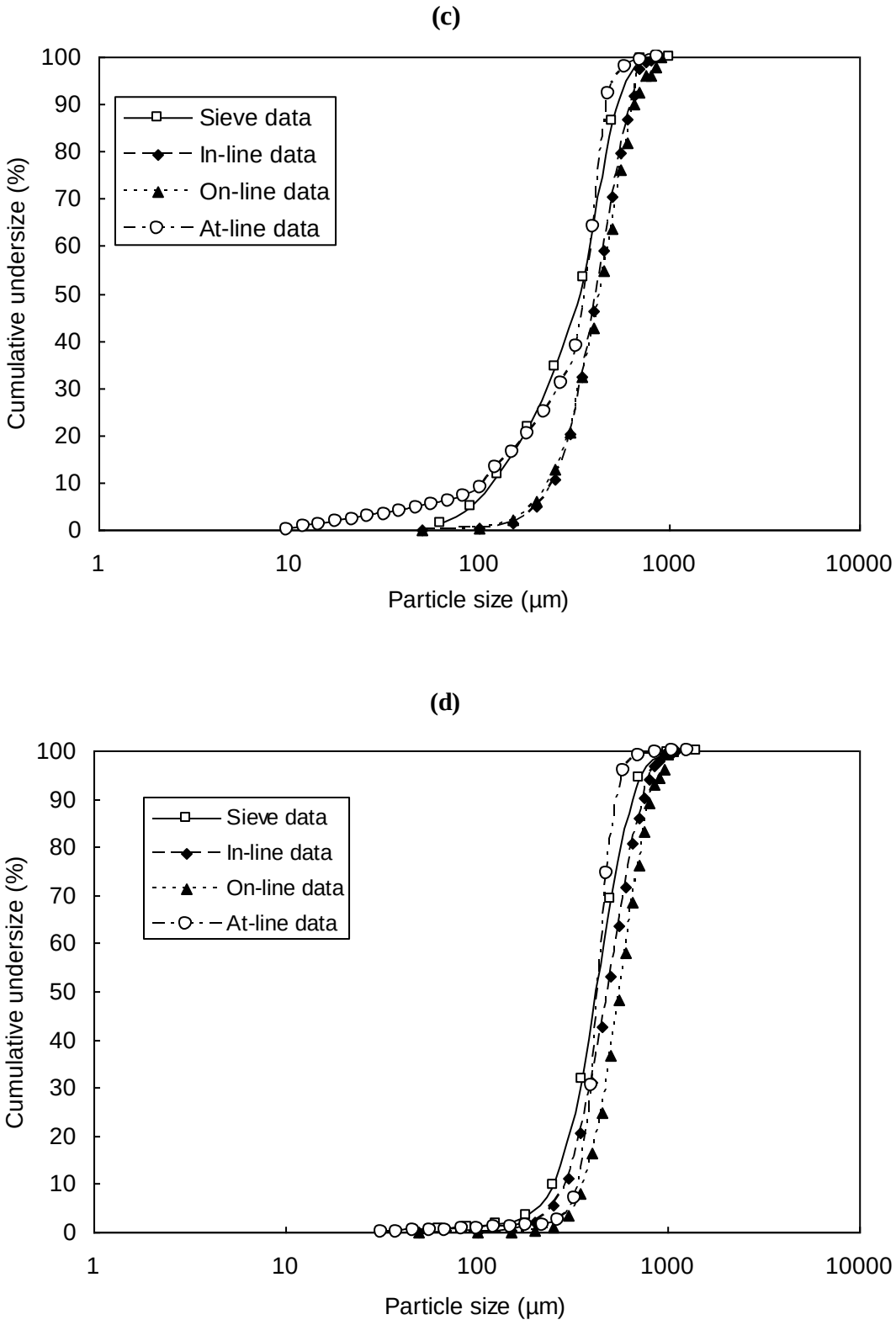


Figure 3.3 Particle size distributions of the milled material measured using the four different modes of analysis for (c) PrismaLac® 40 (d) Placebo II.

Table 3.3 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

The on-line system sucked the material quickly from the process stream following which the particles travelled through a small bent tube. The latter curvature may have caused artefacts 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.

Table 3.4 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*
On-line	Potential effect of sampling device	Potential effects of venturi location and air pressure	Risk of motion blur depending on dispersion	WDD*
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*

* Projected area diameter of disk (circle)

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 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.

3.1.4.1.2 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 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 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 observed 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.

3.1.4.2 Time evolving size and shape analysis (TESSA)

3.1.4.2.1 Monitoring the changes in milling process

Measuring the shape of materials 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 3.2 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 minutes and the data for particle size and shape was collected for a period of 20 seconds 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) would help detecting changes in the milling process like when the milling process reaches equilibrium and when it falls out of the 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 minutes. 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. 3.4 shows that changes in the milling process over time were not very 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 four minutes of milling (Fig. 3.4c) and then changed again towards the end of the process (Fig. 3.4e). This can be observed by inspecting the shape of the 3-sigma box. In Fig. 3.4c the sizes of the 1-sigma and 3-sigma boxes shrank with respect to particle size (x-axis) compared to Fig. 3.4a, when the process reached equilibrium and further expanded as seen in Fig. 3.4e. 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 (values) 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. 3.4a to 3.4e was found to be helpful for monitoring the process changes in the conical mill. At this point it is fair enough to mention that different materials can be conceived 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 where a standardized material feed was present however, further research need to be done in real production shop floor to investigate if the process changes in milling (equilibrium conditions) can be observed also in case of a standardized material feed. This 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.

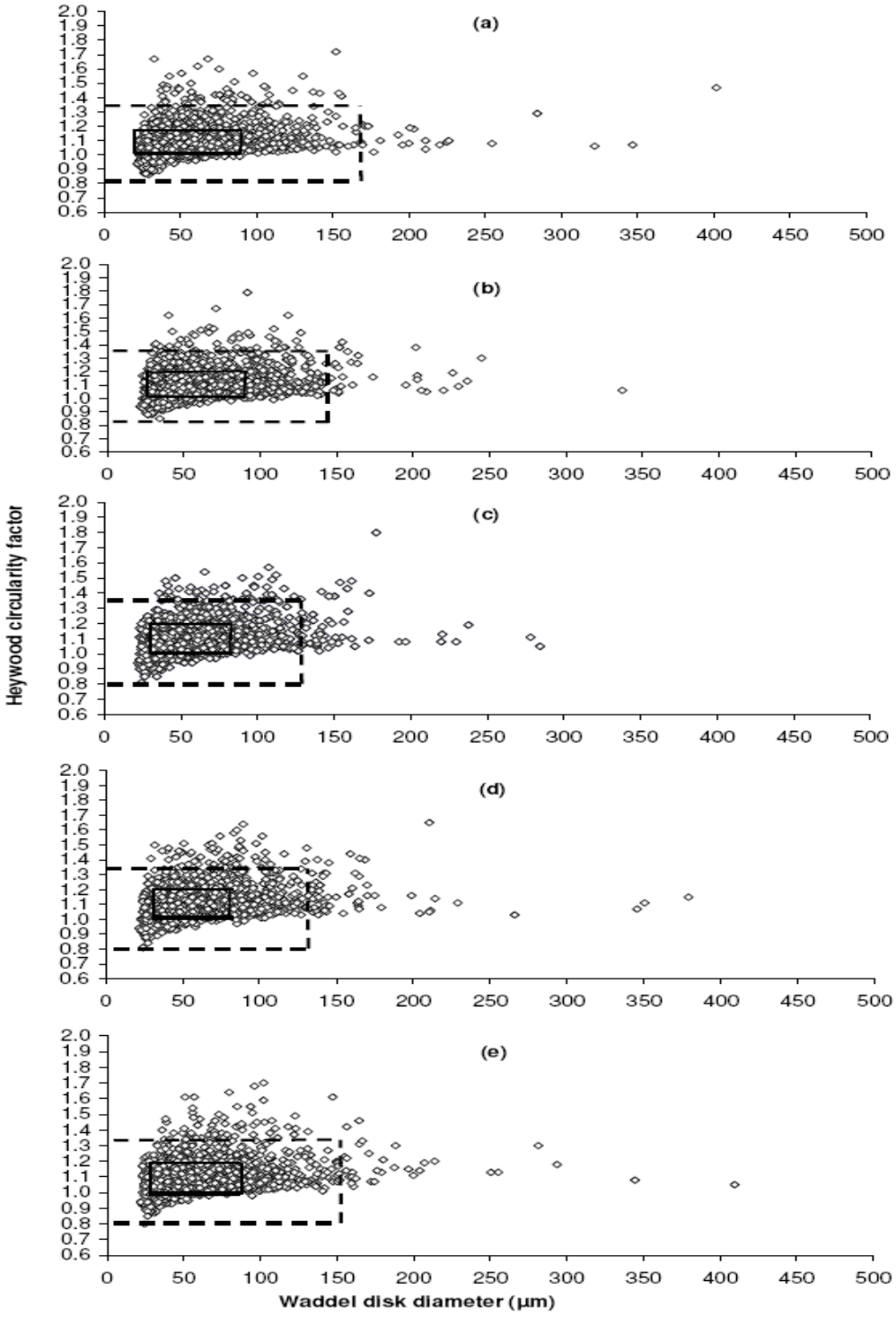


Figure 3.4 Time evolving size and shape analysis of Placebo II (a) 2 minutes after start (b) after 4 minutes (c) after 6 minutes; at equilibrium (d) after 8 minutes; at equilibrium (e) after 10 minutes; end of process [thick lines represent 1-sigma box and dashed lines represent 3-sigma box]

3.1.4.2.2 TESSA applied to a damaged screen

The concept of time evolving size and shape analysis (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 may 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 seconds, every minute over a time period of six minutes. The data, interaction plot, were 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 at all. The sensor was not able to differentiate between intact and broken screens (Fig. 3.5a) at the beginning of the process; this situation is comparable to the observation in Fig. 3.4a 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. 3.5b, after five minutes of milling the on-line sensor system was able to differentiate between broken and intact screens and this is the reason, which was reflected by the almost borderline statistical significance of p=0.056. This situation can also be compared to that of equilibrium process conditions like was seen in Fig. 3.4c. 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. 3.5b. 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 with the given process analytics in the interaction plot 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.

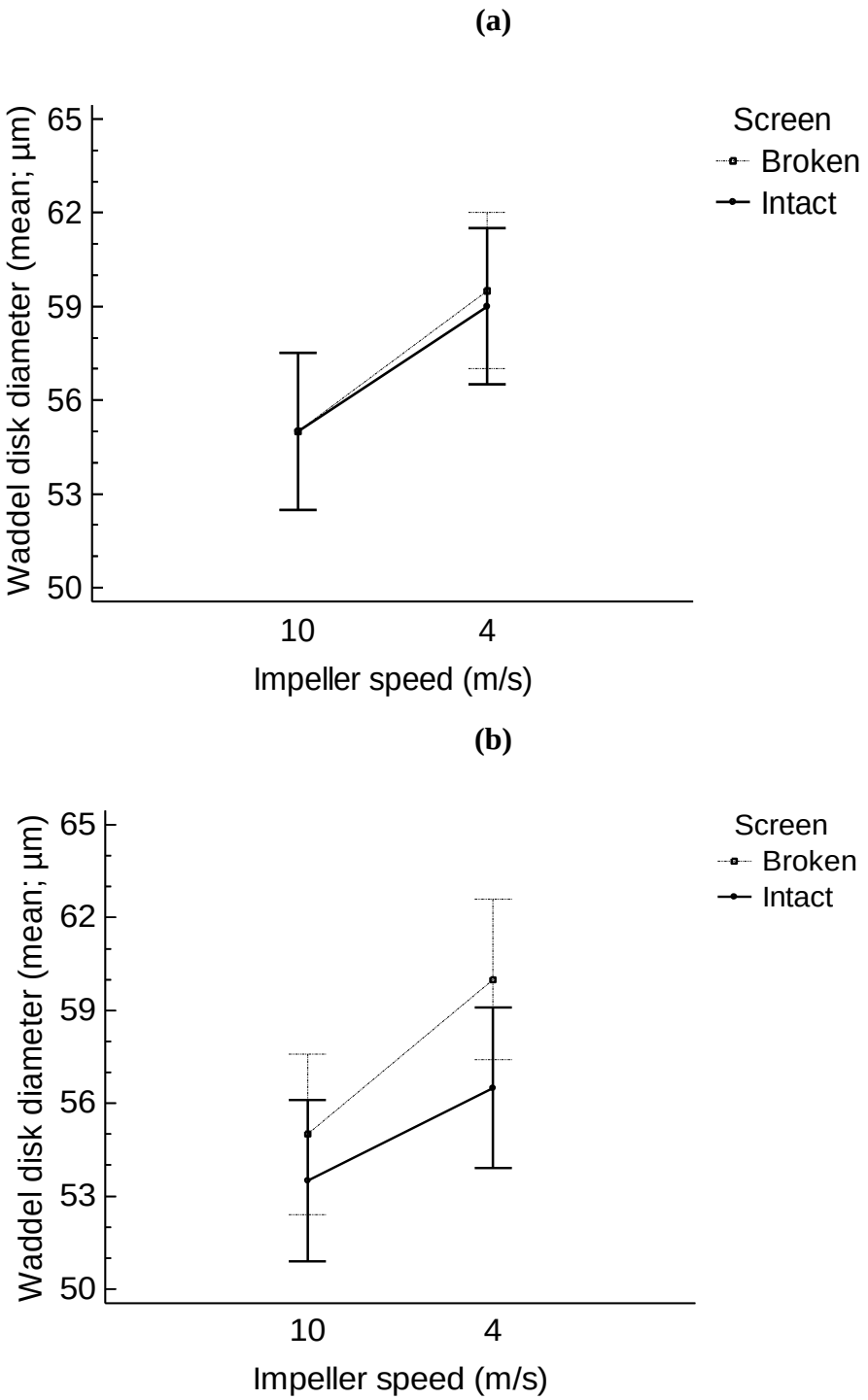


Figure 3.5 Interaction plot of impeller speed and screen (a) at the first minute (T_1) and (b) after five minutes (T_5) of milling.

3.1.5 Conclusions

DIA was successfully tested for its use as a suitable process analytical tool for real time particle size monitoring. The different DIA measurement modes in this study, namely on-line, in-line, and at-line (reference mode) were shown to provide similar

particle size distributions, especially for coarse materials. Eventually, the on-line sensor system was found to be particularly a 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.

3.2 Flowability characterization of drug excipient blends using a novel powder avalanching method

3.2.1 Albendazole-lactose model (Study-II)

3.2.1.1 Introduction

This part of the study has two objectives. The first objective is to introduce a novel powder avalanching instrument, which constitutes a rotating drum and image analysis allowing for a complete powder avalanching characterization. Unlike the powder avalanching devices used in the past, this advanced instrument is coupled with an image analysis system enabling the determination of diverse parameters characterizing the avalanches. This enables a better understanding of the powder avalanching behaviour.

A second and equally important aim of this study is to investigate the flowability of binary powder blends consisting of coarse and fine materials, using the powder avalanching instrument. This is of special interest because flowability of blends is essentially complex. Flow properties are not only influenced by the physico-chemical material factors, but also to a great extent by the particle packing. The particles in multi-component mixtures can assume various packing organizations. The simplest pharmaceutically relevant mixture is binary blends of a drug with an excipient. It is a required knowledge to adequately formulate pharmaceutical powder blends that need designing quality into the product.

The significance of the first objective is to enable a comprehensive understanding of the powder avalanching behaviour with the aid of image analysis. Testing of flowability of pharmaceutical blends and granules is important in view of filling performance of tablets and capsules. Additionally, this new methodology bears the potential of an at-line process analytical technology (PAT) as the measurements can

be performed quite quickly. In line with this consideration, the second aim of the study is directed towards an enhanced understanding of powder blends regarding their flow performance. A rational choice of mixing ratios should be enabled so that both objectives of this study would contribute towards a quality by design (QbD) concept.

3.2.1.2 Materials

A commonly used pharmaceutical excipient, PrismaLac® 40 (MEGGLE, Wasserburg, Germany), which is coarse grade lactose was chosen for the study due to its good flow performance. Albendazole (Satwik Drugs Limited, Hyderabad, India) was chosen as the model drug because of its poor flow and cohesiveness. The materials used were from single lots for all the work reported and were used as received. The physical characteristics of the materials are compiled in Table 3.5.

Table 3.5 Physical characteristics of materials

Material	Description	Particle size distribution (µm)	Bulk Density (g/cc)	Tapped density (g/cc)	True density (g/cc)
Albendazole	USP grade	D_5 : 3.5 D_{50}: 4.5 D_{95}: 5.8	0.238 ± 0.005	0.341 ± 0.004	1.345 ± 0.001
PrismaLac® 40	Coarse sieved crystalline alpha-lactose monohydrate	D_{10}: 260 D_{50}: 478 D_{90}: 705	0.535 ± 0.012	0.596 ± 0.003	1.528 ± 0.001

3.2.1.3 Methods

3.2.1.3.1 Primary characterization of powders

The true densities of the powders were determined with MultiPycnometer® (Quantachrome GmbH, Odelzhausen, Germany) 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 particle size distribution (PSD) of the powders was determined using a Sympatec Helos/Rodos® laser diffraction particle size analyzer (Sympatec GmbH, Clausthal-Zellerfeld, Germany) using a dry powder disperser operated at 3 bar for albendazole. PrismaLac® 40 was dispersed in ethanol and 50 mL cuvette was used for analysis.

3.2.1.3.2 Preparation of binary mixtures

A broad range of concentrations of binary mixtures were prepared for studying the flowability. The concentrations were 0%, 1%, 2.5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80% and 100% w/w of albendazole in the blend. In order to break down agglomerates albendazole was initially sifted through a 250 µm sieve and PrismaLac® 40 through an 850 µm sieve. These materials were then weighted and added into 500 mL amber plastic bottles and mixed for 10 minutes in a TURBULA® T2A shaker-mixer (Willy A. Bachofen AG, Muttenz, Switzerland) at 52 rpm. We selected a common mixing time of 10 minutes and further checked the range of 5 to 15 minutes with respect to altered flow properties using different mixing ratios (Appendix III).

3.2.1.3.3 Avalanche testing of binary mixtures

The flowability of the binary mixtures was tested in a rotating drum using a commercial powder avalanching tester (REVOLUTION®, Mercury Scientific Inc., SC, USA). The instrument was provided with a bigger sample drum assembly, which consisted of an anodized aluminium ring (110 mm diameter, 35 mm wide) and two

borosilicate glass plates on either side. A powder sample measuring device having a volume of 118.3 mL was provided with the instrument and was used to standardize the sample volume of the different measurements. The drum assembly was mounted centrally on two silicone rollers fixed to a horizontal drive shaft, which was run by a motor that rotated the drum. A digital video camera interfaced to a computer and controlled with image processing software captured images of the sample. For every image taken, the software calculated multiple parameters associated with powder avalanching. The images were captured at the rate of 10 frames per second. After loading the powder into the sample drum, a preparation time of 30 seconds was allowed before the analysis was started following which the sample drum was rotated at a speed of one rotation per minute. This rotation speed was chosen after evaluating a broad range of drum speeds (0.5, 0.7, 1.0, 1.5 and 2.0 rpm) and subsequently looking at the corresponding flow regimes exhibited by the mixtures. At higher speeds (> 2 rpm) no pronounced differences were seen between the samples studied. The time for data collection for this instrument can be chosen based on number of avalanches or number of data points. In this study the data collection was limited to 2048 data points (run time: 234 s) and this duration was selected to ensure a sufficient number of data points for analysis. The avalanche was the discharge of the particles inside the rotating drum. Such collective sudden particle movement was identified by the software using the cross-section image and a certain threshold has to be defined. This avalanche threshold was maintained at a minimum in order to collect all of the avalanches. All tests were performed in triplicate and mean and standard deviation are reported. All the experiments were done at ambient conditions with an average relative humidity of roughly 45%. Avalanche time was measured as the time taken for the event. Mean avalanche time was computed by dividing the observation time by

the total number of avalanches in a test. For the avalanche power, the software calculated the changes in the potential energy before and after an avalanche and the dimensions were cm^3.mm (volume of the bulk times the height) as defined by the manufacturer. The avalanche angle (degrees) was computed by collecting the angle of the powder at the maximum position prior to the start of the avalanche occurrence and the result was reported as the average value for all the avalanche angles. The rest angle was the angle at the rest position of the powder at the end of an avalanche occurrence also reported as the average value of all the rest angles.

3.2.1.3.4 Shear cell testing of binary mixtures

The ShearScan TS12® (Sci-Tec Inc, CT, USA), is an automated shear cell and for this entire study a rotational split cell was used for determining the powder flow behaviour of the mixtures. The rotational split cell consisted of a base ring with attached inner and outer sides, upper floating inner and outer rings, and a twisting lid. Samples were compressed between the rings by force on the lid and were sheared by rotational motion between the upper floating rings and lower fixed rings. The shear force was transmitted through the lid and measured as torque in the base. The samples were prepared by carefully pouring the powder mixtures into the gap between the rings followed by scraping the excess powder using the rotating scraper provided with the cell and the sample weight noted. The cell was then placed on the mounting device and the twist-top carefully positioned on the sample surface, taking care not to exert any stress on the sample bed. The failure stress was measured at a normal consolidation stress of 8 kPa. The measurements of a yield locus were repeated in triplicate using fresh samples and the angle of internal friction as well as the cohesion was calculated automatically by the instrument software.

3.2.1.3.5 Powder flow through an orifice

A commercially available powder flow testing instrument (COPLEY Scientific, Nottingham, UK) was used for monitoring the flow rate of material through an orifice. A truncated cone with a circular orifice diameter of 15 mm was used. The flow rate was measured in discrete samples by observing the time it took for a constant volume of the sample to pass through the orifice to the nearest hundredth of a second. Volume flow rate was used in order to avoid the bias of the results in favour of high-density materials. No vibrator was attached to the instrument.

3.2.1.3.6 Scanning electron microscopy of binary mixtures

Scanning electron microscopy (SEM) (TM 1000® Tabletop Microscope, Hitachi, Japan) was used to access the surface morphology and texture of pure materials and binary mixtures. The instrument consisted of a pre-centred cartridge filament for the electron gun and operated at an accelerating voltage of 15 kV. High-sensitive solid-state backscattered electron (BSE) served as the detector. Two vacuum pumps (turbo molecular pump and diaphragm pump) operated to evacuate the chamber prior to sample observation. Samples were sprinkled on a double-sided sticky tape (on metal holders), mounted on the SEM stage and observed under the microscope.

3.2.1.3.7 Statistical Analysis

STATGRAPHICS Centurion XV, version 15.2.06 was used for analysis of the data including the calculation of the Pearson product moment correlations.

3.2.1.4 Results and discussion

3.2.1.4.1 Flow behaviour and trend analysis in the rotating drum

Different flow regimes were differentiated in a rotating drum. Fig. 3.6 depicts the various flow regimes observed during the analysis of the samples. The cascading behaviour was observed for most of the samples, but mixtures containing higher albendazole amounts showed a tendency toward cataracting and this flow behaviour was clearly observed for the pure drug, due to its high cohesiveness. Finally, a slumping behaviour of the samples was also occasionally seen.

Apart from the flow regime it was interesting to analyze trends in a series of avalanches for a given sample. The Hurst exponent (*H*) (Gouyet, 1996), in this study the "avalanche Hurst exponent", was estimated for an avalanche power set by the instrument software and it provided a measure, whether there were memory effects inspecting a series of sequentially following avalanches. All *H* values of the different blends were in a close range of about 0.1 to 0.2 being clearly below 0.5. Such flow behaviour can be called as being "anti-persistent" (Wang *et al*., 2000). Thus, an avalanche with a smaller avalanche power will most likely follow the avalanche with a larger avalanche power.

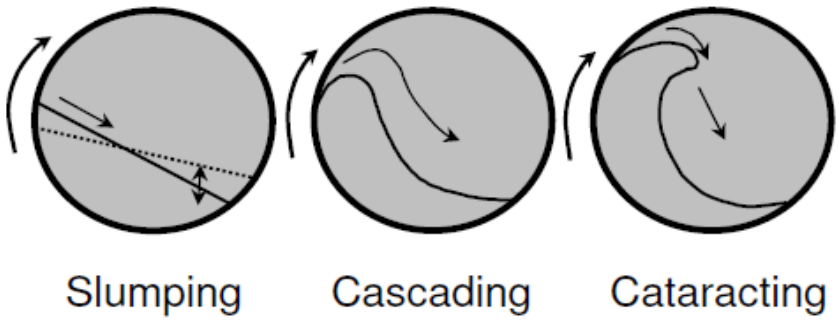


Figure 3.6 Types of powder flow regimes observed in this study (*modified and adapted from Hancock et al., 2004*)

3.2.1.4.2 Interpretation of the avalanche test parameters together with the results of SEM

Lower avalanche times and narrower avalanche time distributions are an indication of easy and consistent flow. Pure PrismaLac® 40 flowed evenly and with a smooth surface, while the cohesive pure albendazole flowed inconsistently with an irregular surface. Powders exhibiting sharp and narrow avalanche time distribution spectrums are more preferable to work with than those displaying a plateau and broader distributions. We observed as the albendazole concentration in the blend increased, the avalanche time spectrum exhibited a flat peak and broader distributions. Fig. 3.7 shows the change in flow behaviour of the blends by means of the mean avalanche time. Different ranges were clearly observed and the transition was not sharp so as to precisely determine the true infliction points. A first critical flow concentration (CFC) was assigned to a very small amount of drug concentration, which for the first time showed altered flow behaviour of the blend as compared with the pure excipient (the theoretical concepts of CFCs are explained in chapter 3.2.1.4.5). This first concentration (X_{C1}) must occur below 1% w/w, since here already an altered flow was observed compared with the pure PrismaLac® 40.

From a technological viewpoint, the second critical concentration (X_{C2}) appears to be of a higher interest and it was revealed close to 15-20% w/w of drug regarding the mean avalanche time (Fig. 3.7). This result was in good agreement with the findings of the avalanche power (Fig. 3.8) as well as with the results of the avalanche angle (Fig. 3.9). Considering the results of the mean avalanche time and avalanche power it was possible to assign a third critical concentration (X_{C3}) between 35% and 45% w/w.

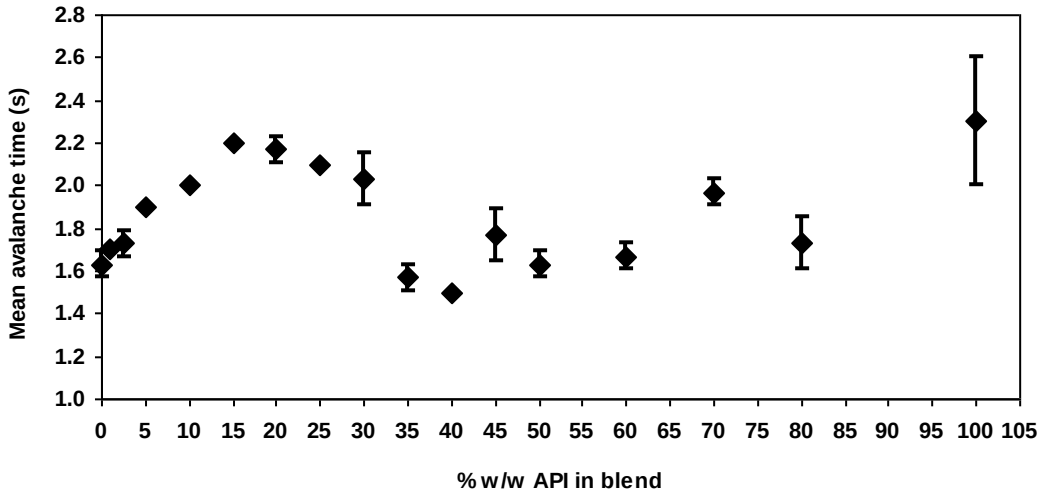


Figure 3.7 Mean avalanche times of various concentrations of albendazole in PrismaLac® 40

However, this transition was rather smooth with respect to avalanche power and when comparing with the results of the avalanche time. Such transition could hardly be observed with the data of avalanche angle and it appears that this parameter could be less discriminating the flow behaviour. Beyond the critical concentration X_{C3}, the different flow parameters all displayed higher variability. In this range the drug increasingly dominated leading to erratic flow performance. Further, abrupt changes of flow behaviour can also exist in this range of drug dominance, but their analysis was problematic due to the high experimental variability and this range appears to be also of a lesser technological importance.

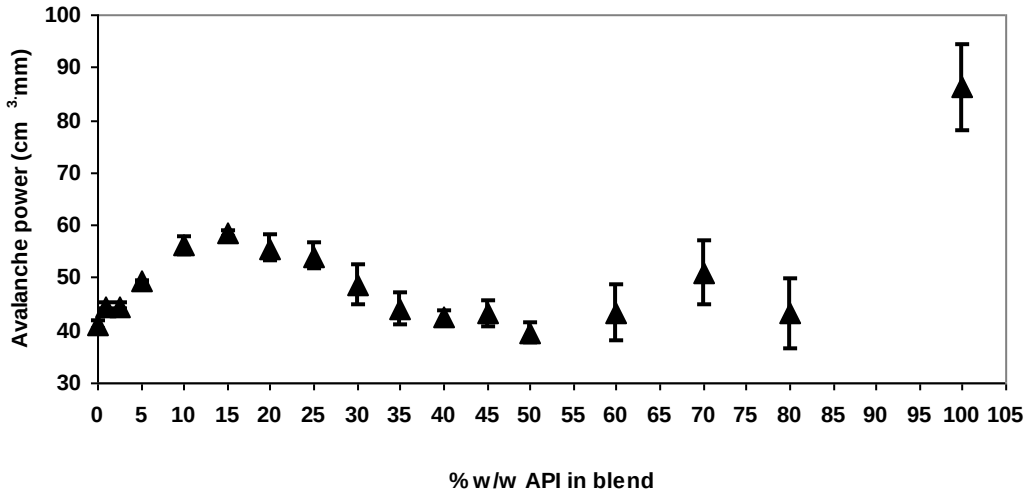


Figure 3.8 Avalanche powers of various concentrations of albendazole in PrismaLac® 40

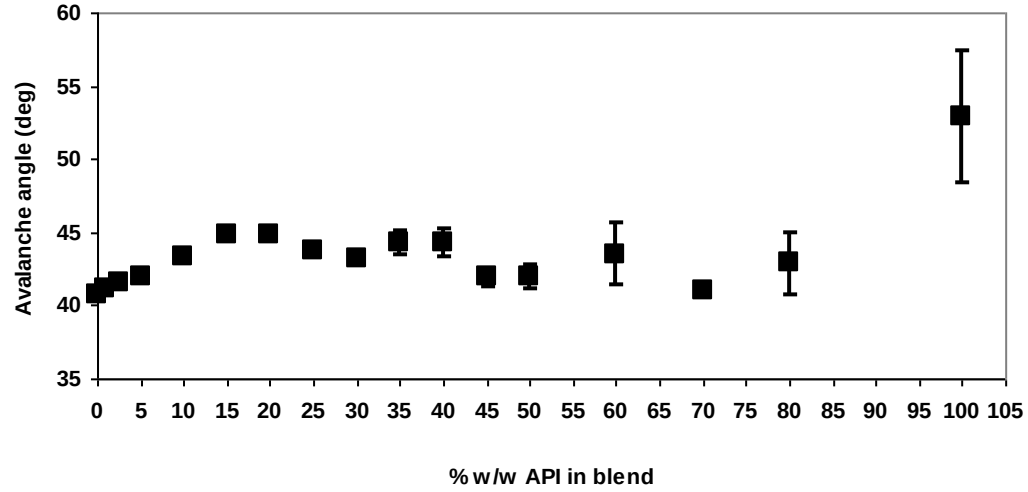


Figure 3.9 Avalanche angles of various concentrations of albendazole in PrismaLac® 40

Different packing configurations were also seen by scanning electron microscopy (Fig. 3.10). Comparing the blend of 20% w/w (Fig. 3.10c) with the pure components (Fig. 3.10a and 3.10b) indicate that smaller drug amounts mainly fill the voids of the excipient particle packing, while some of the albendazole particles were also adhered to excipient surfaces. This initial drug adhesion was not too pronounced so that the excipient particles still displayed their original shape. Certainly, the filling of particle

voids can not be entirely reflected by SEM pictures like Fig. 3.10c, since the sample preparation under vacuum partially removed some of the drug in the voids.

The drug adhesion to the lactose was prevailing in a further range from ~20% to about 40% w/w giving rise to the formation of large and round apparent particles. As an effect of this layering, as seen in the change from Fig. 3.10c to Fig. 3.10d, the observed flow behaviour in the drum was dominated by the coated particles. The size and nearly spherical shape facilitated the overall flowability so that the flow performance in this range was improved to a level that was comparable with the pure excipient. Beyond 40% w/w (Fig. 3.10e and 3.10f) the coating of the lactose particles also continued resulting in the formation of even larger apparent particles. At 80% w/w concentration, a few perfectly round particles were observed some of which had a diameter of as large as ~2000 µm as seen in Fig. 3.10f. A fraction of the drug particles was not part of the excipient coating process and was expected to influence the overall flow behaviour. This dominance of drug particles is the likely reason why beyond 40% w/w, the observed flow in the drum was increasingly impaired.

These results of the avalanching analysis together with images of SEM can be summarized in the following way. A small amount of drug <1% w/w was already sufficient enough to alter the flow performance of the pure excipient. The more drug was added, the poor the flowability became since the small drug particles filled the voids of the excipient particles, while the excipient particles still retained their shape. This could have affected the overall flow performance. However, at a second critical concentration there was a trend towards lower mean avalanche time and avalanche power that was paralleled by an increasing process of drug particles layering the excipient particles. This process led to more ordered structures with round excipient particles of a bigger apparent size. These changes of apparent size and shape were

most likely the cause of the decreasing mean avalanche time and power, which was indicative for improved flowability. This improved flowability ended at a concentration of about 40% w/w albendazole and higher drug amounts gradually worsened the flow. We observed further increase of the avalanching parameters beyond a concentration of about 80% w/w; however, such higher concentration is of lesser technological importance for powder blends. At very high drug amounts a powder blend formulation would be strongly discouraged, as it would be predominantly defined by the drug particle performance and a granulation step would be required.

3.2.1.4.3 Comparison with results from flow through an orifice

The flow of powders through a flow through an orifice instrument is under the influence of gravity and most telling of the flow behaviour. Fig. 3.11 shows the flow behaviour through a 15 mm orifice. On a first glance the flow rate appeared to be corresponding to that observed with the mean avalanche time of the powder avalanching tester. The flow rate was highest at the 1% w/w concentration followed by a continuous and gradual decrease until ~20% w/w. Further the flow rate started to increase up until ~40% w/w but did not increase beyond the pure excipient flow rate. Beyond ~40% w/w the flow rate appeared to become erratic. Pure albendazole did not flow through the orifice as it was very cohesive. This behaviour was in good agreement with the data observed with mean avalanche time (Fig. 3.7).

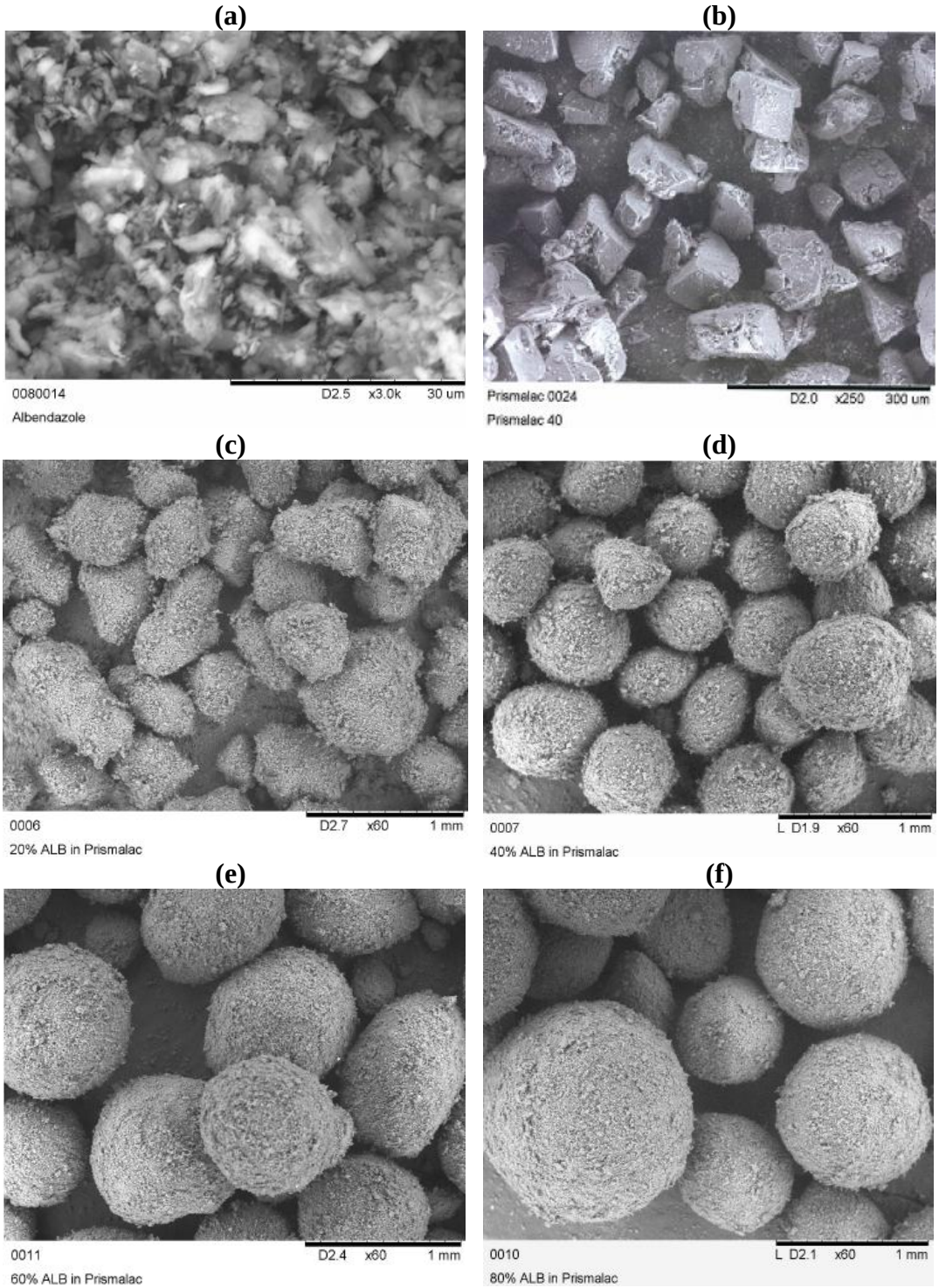


Figure 3.10 Scanning electron micrographs of a) Albendazole b) PrismaLac® 40 c) 20% w/w Albendazole in PrismaLac® 40 blend d) 40% w/w Albendazole in PrismaLac® 40 blend e) 60% w/w Albendazole in PrismaLac® 40 blend and f) 80% w/w Albendazole in PrismaLac® 40 blend.

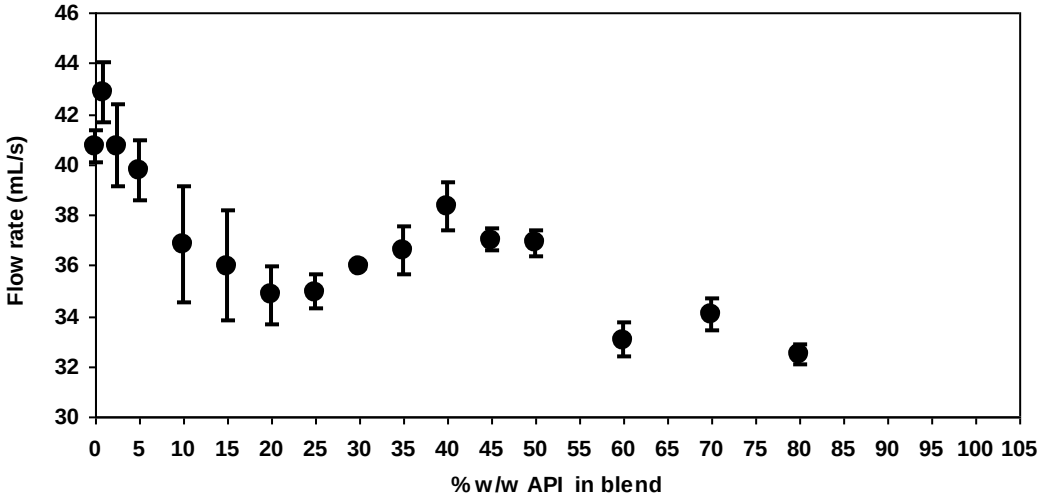


Figure 3.11 Flow rates of the albendazole-lactose binary blends through a 15 mm orifice

3.2.1.4.4 Comparison with shear cell data

It should be recalled that the powder blends inside the rotating drum were under the influence of small shear forces, whereas in a shear cell the same were under the influence of an externally applied large normal stress. The results are discussed in light of cohesion and angle of internal friction. We observed with increasing drug concentration in the blend the cohesivity increased with pure albendazole displaying highest cohesivity of 3 kPa. On the other hand the angle of internal friction exhibited a constant decrease from 25% to 70% w/w implying this mixture region flowed better than the other regions observed. However, a direct comparison between the parameters studied in powder avalanching tester and that of shear cell would be simply misleading the information since these are two extreme cases of consolidation. While, in the powder avalanching tester the blends flow under practically unconsolidated conditions, the shear cell measures at a largely consolidated state. The binary mixtures, after analysis with shear cell, were observed under SEM and we found that the round structure of the particles was destroyed, because of the large normal stress applied during measurements. An example of such a phenomenon is

shown in Fig. 3.12 in which the destruction of the round particles after consolidation is obvious.

The results indicated that an applied normal stress may profoundly alter the structure in a powder system. A comparison of material flow properties under such differing conditions is therefore *a priori* of only limited value. This should be kept in mind, if the flow in a process is considered. A measured flowability parameter can only be expected to be predictive for a process, in which the underlying structure is not substantially changed.

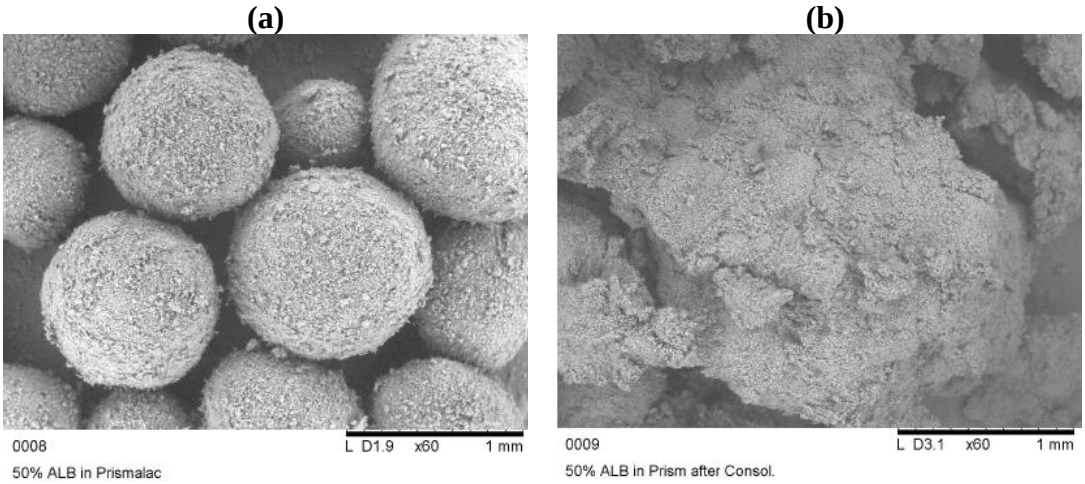


Figure 3.12 Scanning electron micrographs of 50% w/w albendazole in PrismaLac® 40 blend a) before consolidation under shear cell b) after consolidation at 8 kPa.

3.2.1.4.5 Theoretical aspects of critical mixing ratios

Molerus (1984, 1985) described the theoretical aspects of the influence of finer particle content on the flow behaviour of a coarse bulk material. Based on similar theoretical concepts, we have extended his theoretical considerations to powder mixtures. In a binary blend, the mass of the drug, m_D can be expressed by visualizing n_D spherical particles of radius r_D, having a particle density that shall equal to the true density, ρ_{TD}:

$$m_D = \frac{4}{3}\pi \cdot {r_D}^3 \cdot n_D \cdot \rho_{TD} \qquad (3.3)$$

A similar expression can be proposed for n_E excipient particles with a mass m_E and radius r_E having the corresponding true density of ρ_{TE}. Thus, Eq. (3.4) is directly obtained for a mixing fraction X of the blend:

$$X = \frac{m_D}{m_D + m_E} = \frac{1}{1 + \left(\frac{r_E}{r_D}\right)^3 \cdot \frac{n_E}{n_D} \cdot \frac{\rho_{TE}}{\rho_{TD}}} \tag{3.4}$$

For very low values of X, it is expected that the flow behaviour of the excipient is not perturbated by the few drug particles. It is interesting to ask as to how many drug particles can be accommodated by a coarse excipient to show practically unaltered excipient flow performance. Molerus studied a similar problem of particle packings having coarse and fine fractions. It was rationalized that in a cubic packing, a unit cell can be imagined having the dimension of the coarse particles. The fine particles may then theoretically cover three edges of this unit cell without affecting the cubic packing. For a micronized drug and a coarse excipient the Molerus assumption leads to the following ratio of particle numbers:

$$\frac{n_E}{n_D} = \frac{1}{3\left(\frac{r_E}{r_D}\right)} \tag{3.5}$$

Using this Eq. (3.5) in combination with Eq. (3.4) leads to a critical mixing ratio X_{c1}, with an analogous expression as previously found by Molerus for the blends of coarse and fine particle fractions of a single material.

$$X_{C1} = \frac{1}{1 + \frac{1}{3}\left(\frac{r_E}{r_D}\right)^2 \cdot \frac{\rho_{TE}}{\rho_{TD}}} \tag{3.6}$$

For increasing amounts of drug $X > X_{c1}$ it is expected that the packing of the excipient is increasingly perturbated by the amount of drug, but still the excipient dominates overall flow behaviour. A second critical concentration can be defined assuming that

the voids of the excipient packing are entirely filled by the drug particles. Molerus estimated also this critical concentration from packings of coarse and fine particles in a single powder sample however, his estimation was based on a cubic packing of the coarse particles. In the following modified approach, we did not assume any specific packing configuration of the excipient particles and Eq. (3.7) is proposed for the excipient void volume that is entirely filled with the drug:

$$V_{EVoids} = \frac{4}{3}\pi \cdot r_D{}^3 \cdot n_D \cdot \rho_{RDVoids}{}^{-1} = V_{tot} \cdot (1-\rho_{RE}) \tag{3.7}$$

The relative density $\rho_{RDVoids}$ denotes the volume fraction of the drug particles relative to the entire void volume in the excipient packing.

On the other hand the relative density of excipient particles, ρ_{RE} is given by Eq. (3.8)

$$\rho_{RE} = \frac{4/3 \cdot \pi \cdot r_E{}^3 \cdot n_E}{V_{tot}} \tag{3.8}$$

Combination of Eq. (3.4), (3.7) and (3.8) leads to:

$$X_{C2} = \frac{1}{1+\rho_{RDVoids}{}^{-1} \cdot \frac{\rho_{RE}}{1-\rho_{RE}} \cdot \frac{\rho_{TE}}{\rho_{TD}}} \tag{3.9}$$

The relative density of the drug in the voids ($\rho_{RDVoids}$) can be approximated by its relative bulk density, ρ_{RDBulk} and the relative bulk density of the excipient, ρ_{REBulk} may hold for the value of the relative excipient density (ρ_{RE}) at the critical mixing ratio:

$$X_{C2} \cong \frac{1}{1+\rho_{RDBulk}{}^{-1} \cdot \frac{\rho_{REBulk}}{1-\rho_{REBulk}} \cdot \frac{\rho_{TE}}{\rho_{TD}}} \tag{3.10}$$

Eq. (3.10) can alternatively be written by using the ratio of the excipient bulk density to that of the drug, r_{Bulk}:

$$X_{C2} \cong \frac{1}{1+\frac{r_{Bulk}}{1-\rho_{REBulk}}} \tag{3.11}$$

Table 3.5 lists the physical characteristics of the materials and using Eq. (3.6) results in X_{C1} = 0.02%, whereas Eq. (3.11) yields X_{C2} = 22.4%. The first calculated critical concentration was too low to be precisely visualized from Fig. 3.7 through Fig. 3.10. However, it is in agreement with the observation that addition of 1% w/w drug generally displayed a difference in the measured flow parameters of the pure excipient.

The theoretical model is certainly simple in the way that it does only consider the drug filling into the excipient voids, while parallel adhesion of drug particles is ignored. Given the simplicity of the theoretical arguments, the calculated second critical concentration was in close agreement with the findings of the different avalanche flow parameters for which a change at around 15-20% w/w drug was observed. A slightly higher theoretical value of 22.4% was in good agreement with the flow through orifice experiments in which a change at ~20% w/w was observed (Fig. 3.11). There must be further critical concentrations for which the particle packing undergoes fundamental change. However, basic theoretical assumptions were at least shown to roughly predict the initial two critical concentrations of the model blends.

3.2.1.4.6 Correlation of parameters obtained from powder avalanching analyzer and flow through orifice

Pearson product moment correlations were computed to get an insight of the various significant correlating parameters. Focusing on some of the statistically significant parameters, a correlation of 0.87 (p=0.000) was observed between avalanche angle and avalanche power. The avalanche angle and rest angle had a correlation of even 0.94 (p=0.000). This high correlation suggests the use of either of the parameters for interpreting the angle during avalanching. Additionally, a correlation of 0.83

(p=0.000) between avalanche power and avalanche time was also seen. Significant correlations of flow parameters were also found with respect to the variance of some avalanche parameters. Negative correlations were seen between flow rate through the orifice and with both the mean of avalanche power variance [-0.72 (p=0.002)], as well as the mean of avalanche time variance [-0.57 (p=0.021)].

3.2.1.5 Conclusions

A novel instrument for characterizing powder flow was introduced and successfully applied to pharmaceutical binary blends consisting of micronized drug and a coarse excipient. This novel instrument, combining powder avalanching and image analysis, was helpful in characterizing the model blends. The different avalanche parameters were consistent and to some extent also comparable to the results of the flow through an orifice. No meaningful comparison could be made with the shear cell since the applied normal stress significantly altered the structure of the powder system. With respect to the second aim of the study, which is the characterization of the binary blends, we observed critical changes in the flow behaviour. A simple theoretical approach was provided to calculate the two initial critical flow concentrations (CFCs), which successfully provided a good agreement with the experimental findings.

High avalanche values in combination with a drastic change close to a critical flow concentration should be avoided for the design of a robust formulation thus enabling researchers to build quality into the design of the dosage form. Mixing ratios during formulation development could be chosen on a rational basis, also in production avalanche parameters could be monitored making powder avalanching analyzer a viable at-line PAT tool. This new approach could help in avoiding issues of flow performance during upstream manufacturing namely tabletting and capsule filling.

3.2.2 Ketoprofen-lactose model

3.2.2.1 Introduction

Flowability characterization of binary blends consisting of coarse and fine materials was repeated with another model drug. Ketoprofen was studied in binary mixtures of the excipient lactose (PrismaLac® 40).

3.2.2.2 Materials

Ketoprofen (Betapharma, Shanghai, China) was micronized prior to preparing binary blends. Micronization was carried using a jet mill (JMRS 80, ESCO-Labor® AG, Riehen, Switzerland). The physical characteristics of the materials are summarized in Table 3.6. Micronized ketoprofen is very cohesive, unlike the albendazole used in previous study, and is very poor flowing. The materials used were from single lots for all the work reported. All experiments were carried out in triplicate and at ambient conditions (20 to 30°C and 35 to 60% RH).

Table 3.6 Physical characteristics of materials

Material	Description	Particle size distribution (µm)	Bulk density (g/cc)	Tapped density (g/cc)	True density (g/cc)
Ketoprofen	White crystalline powder	D_5 : 0.3 D_{50}: 2.2 D_{95}: 4.8	0.157 ± 0.005	0.200 ± 0.007	1.282 ± 0.005
PrismaLac® 40	Coarse sieved crystalline alpha-lactose monohydrate	D_{10}: 260 D_{50}: 478 D_{90}: 705	0.535 ± 0.012	0.596 ± 0.003	1.528 ± 0.001

3.2.2.3 Methods

3.2.2.3.1 Primary characterization of powders

The true densities of the powders were determined with MultiPycnometer® (Quantachrome GmbH, Odelzhausen, Germany) 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. Particle size distribution (PSD) of ketoprofen was determined using a Sympatec Helos/Rodos® laser diffraction particle size analyzer (Sympatec GmbH, Clausthal-Zellerfeld, Germany) using a dry powder disperser operated at 1 bar. PrismaLac® 40 was dispersed in ethanol and a 50 mL cuvette was used for analysis to estimate the PSD.

3.2.2.3.2 Preparation of ketoprofen-lactose binary mixtures

A broad range of concentrations of binary mixtures were prepared for studying the flowability. The concentrations were 0%, 0.5%, 1%, 2.5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, 90%, and 100% w/w of ketoprofen in the blend. In order to break down agglomerates ketoprofen was initially sifted through 875 µm sieve and PrismaLac® 40 through 1000 µm sieve. These materials were then weighted and added into 500 mL amber plastic bottles and mixed for 10 minutes in a TURBULA® T2A shaker-mixer (Willy A. Bachofen AG, Muttenz, Switzerland) at 52 rpm.

3.2.2.3.3 Avalanche testing of ketoprofen-lactose binary mixtures

The flowability of the ketoprofen-lactose binary mixtures was tested using the powder avalanching tester (REVOLUTION®, Mercury Scientific Inc., SC, USA). The bigger

sample drum assembly and the powder sample measuring device were used. Images were captured at the rate of 10 frames per second. After loading the powder into the sample drum, a preparation time of 30 seconds was allowed before the analysis was started following which the sample drum was rotated at a speed of 0.5 rotations per minute. This rotation speed was chosen after evaluating various drum speeds (0.5, 0.8, 1.0 rpm) and subsequently 0.5 rpm was selected as it was found to be most discriminating the powders. The data collection was limited to 2048 data points. All the experiments were done in triplicate at ambient conditions.

3.2.2.3.4 Powder flow through an orifice of ketoprofen-lactose binary mixtures

The powder flow testing instrument (COPLEY Scientific, Nottingham, UK) was used for monitoring the flow rate of material through a 15 mm orifice. Flow rate was measured in discrete samples by observing the time it took for a constant volume of the sample to pass through the orifice to the nearest hundredth of a second. Volume flow rate was used in order to avoid the bias of the results in favour of high-density materials. No vibrator was attached to the instrument.

3.2.2.3.5 Scanning electron microscopy of ketoprofen-lactose binary mixtures

Scanning electron microscopy (SEM) (TM 1000® Tabletop Microscope, Hitachi, Japan) was used to access the surface morphology and texture of pure materials and binary mixtures. Samples were sprinkled on a double-sided sticky tape (on metal holders), mounted on the SEM stage and observed under the microscope.

3.2.2.4 Results and discussions

Different flow regimes were observed inside the rotating drum. Most of the samples exhibited slumping and cascading behaviour (see Fig. 3.6). Pure ketoprofen could not be measured due to its high cohesiveness and as it was heavily sticking to both the glass plates of the rotating drum. All the Hurst exponent (*H*) values for the different mixtures were below 0.5, which meant anti-persistent behaviour (Wang *et al*., 2000).

The mean avalanche times (Fig. 3.13) decreased initially upto 1% (w/w) concentration and further on increased until 5% w/w. In the range from 5% to 15% (w/w) the mean avalanche times remained more or less constant. A sudden change was observed at 15% w/w following which the mean avalanche time decreased rapidly upto 20% w/w. Beyond 20% w/w, the mean avalanche times gradually and slowly increased upto 35% w/w and further on remained constant until 50% w/w. Beyond 50% w/w concentration the mean avalanche times became erratic with large standard deviations. This trend observed with the mean avalanche times was not clearly seen with other avalanching parameters such as avalanche power and avalanche angle.

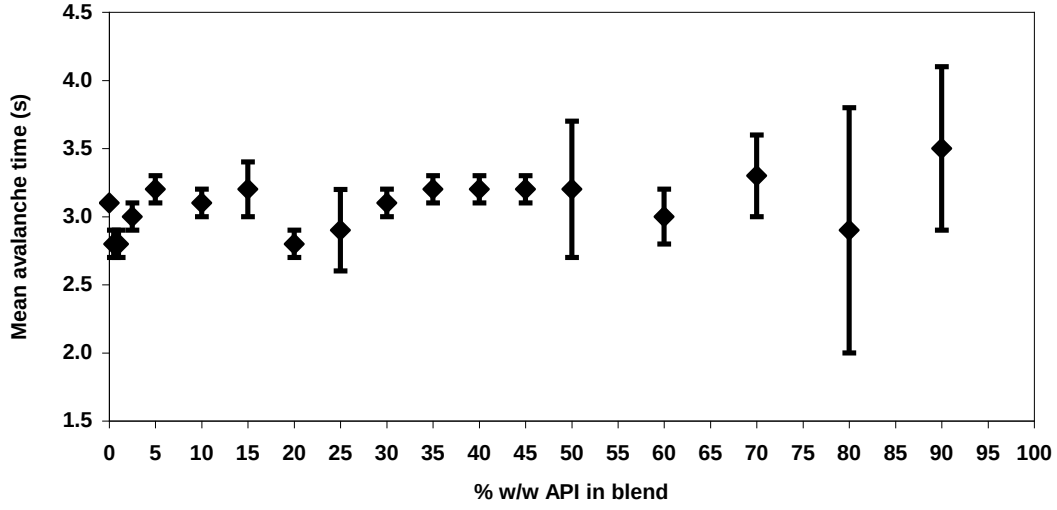


Figure 3.13 Mean avalanche times of various concentrations of ketoprofen in PrismaLac® 40

The flow rate of the various mixtures followed a different trend than observed with mean avalanche times. The flow rate increased until 2.5% w/w after which a gradual decrease was observed upto 30% w/w (Fig 3.14). Beyond 30% w/w, the flow rate started to increase until 50% w/w but did not get any better than the pure PrismaLac. At approximately 50% w/w drug concentration the flow rate almost equals that of the pure excipient and thereafter started to decrease at higher drug concentrations. In general, the flow rate appeared to be higher in the drug concentrations below 15% w/w and was even higher when compared with the pure PrismaLac and all other binary mixtures.

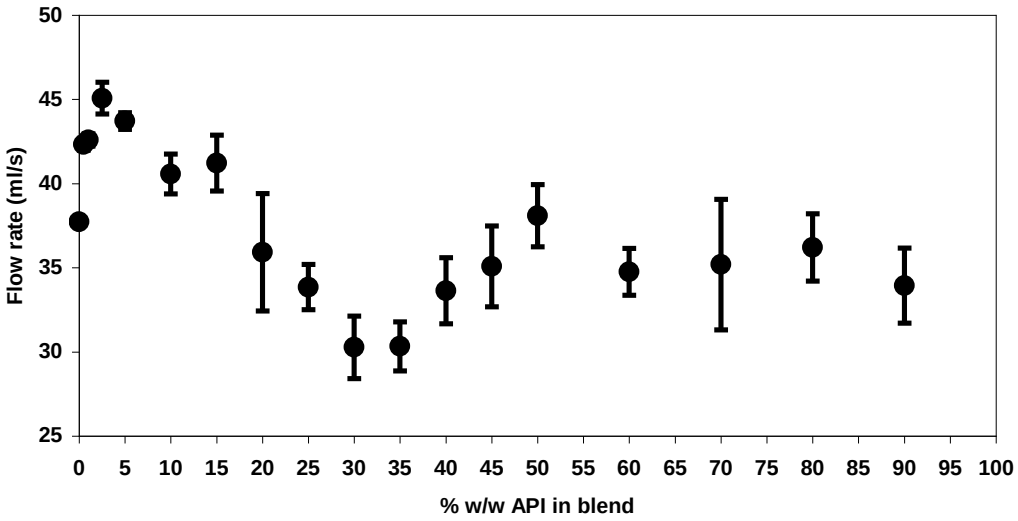


Figure 3.14 Flow rates of the ketoprofen-lactose binary blends through a 15 mm orifice

The ketoprofen drug particles in this study did not strongly adhere to the lactose particles as seen in the case of albendazole-lactose model. The drug particles initially adhere to the coarse lactose particles, as can be seen in the SEM images, causing a slightly lubricative action thereby improving the flow rate (Fig 3.15c-f). When more drug was added the drug particles remain seated in the excipient voids and additionally formed drug-drug particle agglomerates. These drug-drug particle

agglomerates increased in size at higher drug concentrations and subsequently hindered the overall flow of the blend.

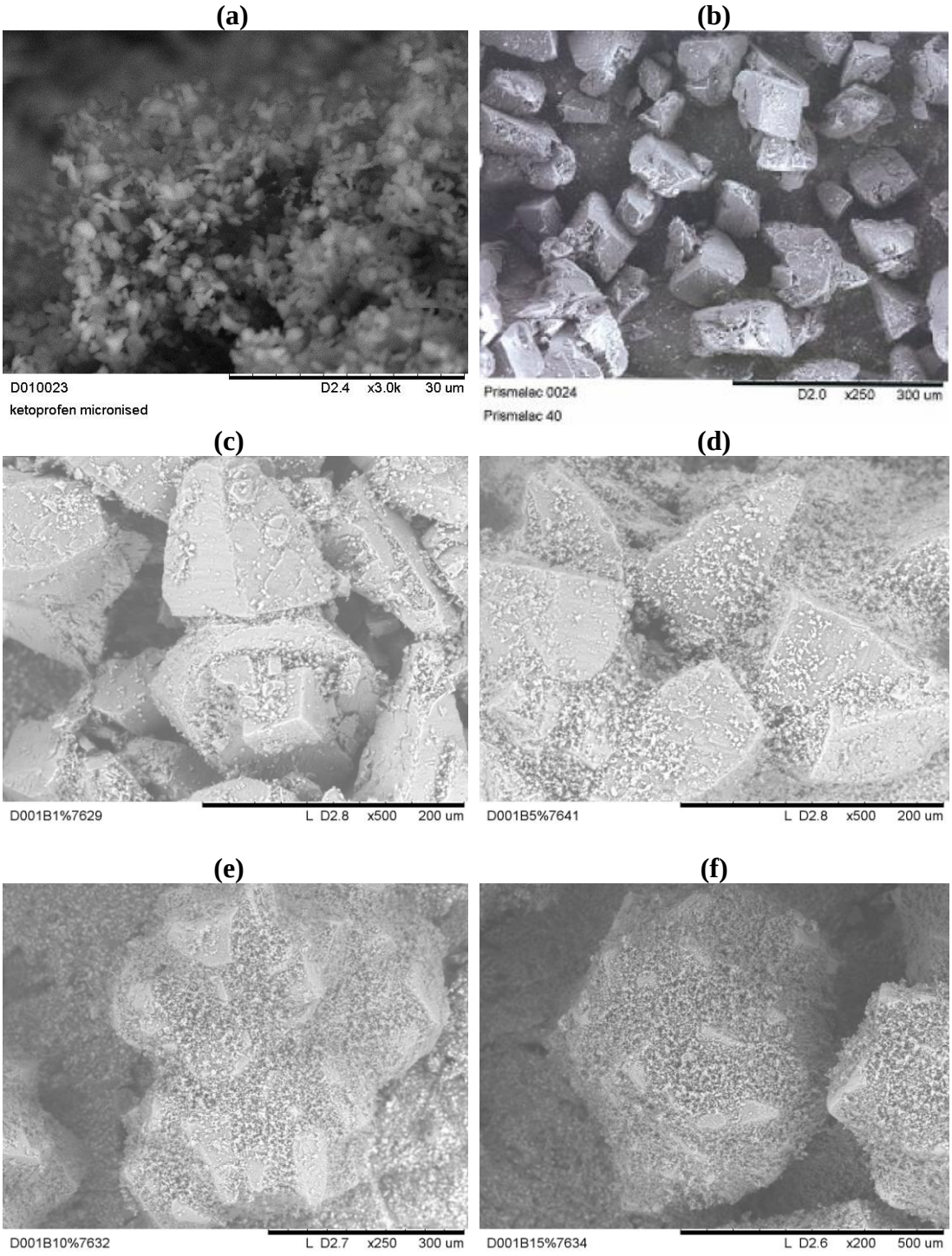


Figure 3.15 Scanning electron micrographs of a) Ketoprofen b) PrismaLac® 40 c) 1% w/w Ketoprofen in PrismaLac® 40 blend d) 5% w/w Ketoprofen in PrismaLac® 40 blend e) 10% w/w Ketoprofen in PrismaLac® 40 blend and f) 15% w/w Ketoprofen in PrismaLac® 40 blend.

The increase in size of the drug-drug particle agglomerates was due to the high cohesive nature of the ketoprofen drug particles, which had a mean particle diameter almost half of that of albendazole. The ketoprofen micronized drug particles coat the coarse lactose particles, but the coating was not as predominant as observed in the albendazole-lactose case. Calculations for the critical flow concentrations using Eq. (3.6) resulted in X_{C1} = 0.005%, and Eq. (3.11) yielded X_{C2} = 15.99%. The first CFC was not clear from Fig. 3.13 and 3.14. However, the second CFC was of higher technical importance. The second CFC was identified from Fig. 3.13 where a decrease in mean avalanche time was seen close to 15% w/w. Such an effect was not so obvious from Fig. 3.14, but a sudden drop in the flow rate was observed at 15% w/w drug concentration. A high negative Pearson product moment correlation was observed between flow rate and mean of avalanche time variance [-0.87, p<0.001].

Some differences were observed in this study when compared to albendazole-lactose model. It is not clear why parameters such as avalanche power and avalanche angle could not show a clear trend in the flow characteristics. The high cohesive nature of ketoprofen and the formation of drug-drug particle agglomerates could be possible reasons. Because of the agglomerate formation there could have been segregation in the mixtures. Further research has to be carried out to understand the segregation effects. However, in both model systems the second CFC i.e. $X_{C2,}$ predicted by the theoretical model agreed well with the experimentally observed changes in flow behaviour.

3.2.2.5 Conclusions

A study was carried out to investigate the flow characteristics of binary blends consisting of a micronized drug ketoprofen and a coarse lactose excipient. The results

obtained were different from those of albendazole-lactose model as seen in the previous chapter. The drug ketoprofen used in this study had a mean particle diameter of 2.2 µm when compared to albendazole, which had a mean particle diameter of 4.5 µm. Besides, ketoprofen was found to be comparatively more cohesive than albendazole because of its fine particle size. Additionally, the micronized drug particles carried large electrostatic charges. Due to the reasons owing to the particular drug particle characteristics and drug-excipient packing organization, some changes in flow behaviour in the binary blends were observed with respect to avalanche time and flow rate. The theoretical CFC calculations successfully predicted the second CFC at which altered flow behaviour in the binary blends was observed. This particular study signifies the importance of drug particle characteristics and particle organizations in binary blends. Further research is needed into the drug-excipient interactions and packing organizations of binary blends.

3.3 Implementation of the on-line dynamic image analysis sensor in dry milling and introduction of the powder avalanching instrument as an at-line PAT tool (Study-III)

3.3.1 Introduction

To advance PAT it is important not only to introduce new process analyzers but also focus on the implementation of existing technologies. This approach was aimed to bridge the existing gap between initial research applications and current industrial practice. Therefore, in this part of the work we implement the on-line dynamic image analysis in pharmaceutical dry milling and introduce the powder avalanching instrument as a novel at-line flowability analyzer. We pioneered testing the feasibility of using the powder avalanching instrument as a PAT tool.

Implementation of the DIA sensor requires a feasibility study of a broad range of process conditions. To achieve this objective, we conducted experiments using a response surface method, which is also widely used in the pharmaceutical industry (Sastry *et al.*, 1997; Rambali *et al.*, 2001). As response variables, different measures of the particle size distribution are selected. However, particle size alone does not fully characterize a particulate system and further aspects such as cohesion, density, and moisture content in the bulk material are of significance for further processing. It is, therefore, also interesting to characterize the flow behaviour of granules after milling to emphasize the influence of particle size on flowability. Hence, we introduced powder avalanching instrument as a novel at-line PAT tool for flowability analysis. In a pioneering work, Kaye *et al* (1995) already mentioned the potential use of this avalanching method for quality control monitoring of a powdered product, but PAT applications for this method were not reported so far. A possible reason is that initial powder avalanching enabled only the counting of avalanches, whereas the

current instrument analyzes the whole avalanching event and yields a series of parameters characterizing the flow. To have a reference for these parameters, conventional flow through an orifice was determined as well.

Process analytics aim to improve process development. Activities at this stage of development also include scale-up as well as investigation of further variables such as environmental factors, supplier changes, or lot-to-lot variability (PAT-Guidance for industry, 2004). Looking at the different variables, there are controllable factors as well as other factors that cannot be controlled. Such uncontrollable factors, otherwise called "noise factors", were earlier differentiated from controllable factors by Genichi Taguchi who proposed statistical designs for robustness testing. The Taguchi method is widely used in engineering (Hou *et al.*, 2007; Gopalsamy *et al.*, 2009; Shahbazian *et al.*, 2009) and has quite recently found its way into biotechnology (Houng *et al.*, 2003; Rao *et al.*, 2008). Nonetheless, its pharmaceutical application can be barely found. In this study, we complemented the response surface design by robustness testing and addressed possible means of advancing unit operation of dry milling by the new process analyzers together with the statistical methods.

3.3.2 Materials

Two lots of a pharmaceutical placebo formulation were manufactured and used as model granulates. The placebo mixture comprised lactose (GranuLac® 200, 62.6% w/w), microcrystalline cellulose (Avicel® PH-101, 31.3% w/w), and polyvinylpyrrolidone (Kollidon® K90, 6.1% w/w). Table 3.7 lists the physical characteristics of the two lots. GranuLac® 200 was obtained from MEGGLE, Wasserburg, Germany. Avicel® PH-101 was purchased from FMC BioPolymers, Brussels, Belgium. Kollidon® K90 was from BASF, Ludwigshafen, Germany. These

placebo granulate lots were manufactured by Glatt GmbH (Binzen, Germany) in a GPCG 60 fluidized bed granulator/dryer.

Table 3.7 Physical characteristics of placebo granulate lots (mean ± standard deviation, n=3)

Material	Particle size distribution by sieve analysis (µm)			Bulk density (g/mL)	Tapped density (g/mL)	True density (g/mL)	Specific surface area (m^2/g)	Loss on drying (% w/w)	
	d_5	d_{50}	d_{95}					Before drying	After drying
Lot I	44 ± 19	810 ± 355	2674 ± 133	0.472 ± 0.005	0.512 ± 0.005	1.671 ± 0.002	0.660 ± 0.01	4.0 ± 0.2	2.5 ± 0.1
Lot II	254 ± 2	528 ± 10	989 ± 9	0.334 ± 0.004	0.395 ± 0.007	1.681 ± 0.012	0.460 ± 0.04	3.7 ± 0.2	2.8 ± 0.1

3.3.3 Methods

3.3.3.1 Characterization of raw materials

Particle size of granulates was analyzed using a Retsch® sieve shaker type AS200 control (Retsch GmbH, Haan, Germany). A 100-g sample was placed on top of a pile of sieves (range 180-2000 µm) arranged according to a √2 progression. The sieves vibrated for 10 min, and data analysis was in line with the dry sieving method (method I of USP). The bulk and tapped densities of the granulates were measured in a graduated cylinder using a type SVM 102 bulk density instrument (Erweka® GmbH, Heusenstamm, Germany) that was operated according to USP method II. A MultiPycnometer® (Quantachrome GmbH, Odelzhausen, Germany) was used to determine the true densities using helium as the displacement gas. Finally, the BET-specific surface area was measured using a Gemini V (Micromeritics Instrument Corporation, Norcross, USA), and 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 nitrogen flow for 16 h at 40°C to condition the surface. Loss on drying of granulates was measured before and after drying. Granules were tray-dried for 1 week at 40°C in a convection oven (Heraeus® model UT12, Thermo Scientific, Germany). A halogen moisture analyzer, type HB43 (Mettler Toledo, Greifensee, Switzerland) was used for measuring the loss of drying. All the reported results were obtained in triplicate.

3.3.3.2 Dry milling equipment

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

3.3.3.3 On-line dynamic image analysis

The on-line dynamic image analysis sensor (XPT® -CV, PS Prozesstechnik GmbH, Basel, Switzerland) was employed for monitoring the milling process. This image analysis system is capable of measuring particle sizes in the range of 1-3000 μm. The image update rate was kept constant at 160 ms (six images per second with 780,000 pixels). As the particles pass through the detecting zone, the xenon flash light illuminates the particles and a charge-coupled device (CCD) camera acquires images of the fast-moving particles. The flashlight and CCD camera were synchronized and the images were transferred to the analyzer computer. The software (version 4.8.19) analyzed the images in real-time to display and store the results. All particle size distributions were calculated on a volume basis. The size parameter "equivalent

rectangle short side" (National Instruments manual, 2005) was chosen for this study. Equivalent rectangle short side is defined as the length of the short side of the rectangle that has the same area and same perimeter as the particle. The perimeter and the area are based on two-dimensional projection of the individual particles onto the plane of the image.

3.3.3.4 At-line flowability testing using powder avalanching analyzer

Flowability of the milled materials was tested in a rotating drum using the powder avalanching analyzer (REVOLUTION®, Mercury Scientific Inc., SC, USA). The bigger sample drum assembly (110 mm in diameter, 35 mm wide) was employed for all the tests. A powder sample measuring device (volume of 118.3 mL) provided with the instrument was used to standardize the sample volume of the different measurements. The images were captured at a rate of ten frames per second. During milling, a sample of standardized volume was quickly transferred to the instrument for analysis which was located in close proximity of the conical mill. After loading the powder into the sample drum, a preparation time of 60 s was allowed. Subsequently, the sample drum was rotated at a speed of 0.6 rotations per minute. This rotation speed was chosen after evaluating a broad range of drum speeds (0.4, 0.6, 0.8, 1.2, and 1.6 rpm) and subsequently looking at the corresponding flow regimes exhibited by the mixtures. The avalanching data collection was limited to 2048 data points. This duration was selected to ensure a sufficient number of data points for analysis. Tests were performed in triplicate, and means and their standard deviations were reported. All experiments were done at ambient conditions with an average relative humidity of 40 ± 5%.

A commercially available powder flow testing instrument (COPLEY Scientific, Nottingham, UK) was used as a reference for monitoring the rate of flow of the samples through an orifice. A truncated cone with a circular orifice diameter of 15 mm was used. Flow rate was measured in discrete samples, and the mass flow rate was reported. No vibrator was attached to the instrument.

3.3.3.5 Design of experiments and statistical analysis

The response surface design was fully randomized and conducted in a single block as 3^3 factorial design which studied the effects of three factors in 30 runs, including three center points per block. The design had 20 degrees of freedom for the error. Table 3.8 summarizes the three process parameters and their corresponding levels. The design of experiments and selected responses are compiled in Table 3.9. The Granulate lot I was used in this factorial design.

Table 3.8 Process parameters and corresponding levels for the response surface method

Process parameters	Levels		
	Low	Medium	High
A: Feeder speed (rpm)[a]	4	7.5	11
B: Impeller speed (m/s)	4	10	16
C: Screen size (mm)	0.5	1.0	1.5

[a] Low, medium, and high feeder speed correspond to approximately 35, 55, and 90 kg/h of material throughput, respectively.

Subsequently, a robustness design was applied. Two control factors and two noise (uncontrollable) factors were considered for the robustness method (Taguchi), as shown in Table 3.10. The design resulted in a total of 16 runs that were randomized to avoid any bias. Noise factors were chosen from a practical view point since lot-to-lot

variations and storage temperature fluctuations are commonly observed in the pharmaceutical industry. Table 3.11 summarizes the results of all measurements.

Table 3.9 Response surface method: design of experiments and measured responses

Process parameters				Responses			
Run no.	Feeder speed (rpm)	Impeller speed (m/s)	Screen size (mm)	d_{50} (µm)	Avalanche angle (deg)	Avalanche power (cm^3.mm)	Flow rate (g/s)
1	7.5	4	1.5	264	44	47.1	15.2[a]
2	11	16	0.5	92	49	57.8	6.6[b]
3	7.5	10	1	235	47	59.7	8.7[a]
4	11	10	0.5	100	49.3	63.7	7.0[b]
5	4	16	0.5	93	48.8	53.8	7.0[b]
6	4	4	0.5	121	47.9	56.2	7.5[b]
7	7.5	4	0.5	130	47.4	56.4	7.6[b]
8	7.5	10	1.5	244	46.2	59.2	10.7[a]
9	4	4	1.5	215	43.7	40.5	15.4
10	7.5	16	1.5	259	46.6	60.6	9.3[a]
11	7.5	10	1	129	46.8	59	9.9[a]
12	7.5	10	1	151	46.9	54.7	9.5[a]
13	4	4	1	254	43.8	44.9	12.5
14	7.5	4	1	293	46.2	55.4	11.9[a]
15	7.5	10	0.5	106	47.9	53.2	6.3[b]
16	4	10	1	268	46.5	55.7	9.3[a]
17	11	16	1.5	144	46.9	55.2	9.9[a]
18	7.5	10	1	138	46.1	55.2	10.8[a]
19	7.5	16	0.5	93	48.8	54.9	5.3[b]
20	11	4	1	190	46.1	60.2	11.7[a]
21	11	10	1	158	47.6	63.6	10.6[a]
22	4	16	1	167	46.7	55.1	8.9[a]
23	4	16	1.5	133	44.2	49	11.1
24	7.5	16	1	199	48.1	63.1	8.4[a]
25	11	4	1.5	410	45.6	56.7	15.4
26	4	10	1.5	182	44.4	49.5	14.1
27	11	16	1	116	48.3	60.2	8.7[a]
28	4	10	0.5	103	48.9	54.9	6.9[b]
29	11	4	0.5	126	46.5	55.1	9.6[b]
30	11	10	1.5	194	45.2	49.9	10.8[a]

[a] One single tap was necessary to initiate powder flow through the orifice.
[b] Continuous tapping was necessary to make the powder flow.

Statistical data analysis was done with STATGRAPHICS® Centurion XV (version 15.2.06, StatPoint, Inc., Virginia, USA) throughout. The fit of the regression models underlying the designs was checked by the coefficient of determination (R^2). Analysis

of variance (ANOVA) was conducted to determine the significant parameters at the 95% confidence level.

Table 3.10 Control and noise factors for the Taguchi method

	Levels	
Inner array (control factors)		
B: Impeller speed (m/s)	4	10
C: Screen size (mm)	1.0	1.5
Outer array (noise factors)		
D: Lots	I	II
E: Temperature conditions	Ambient	40°C

Table 3.11 Taguchi method for robustness testing: design of experiments and measured responses

Process variables					Responses			
Run no.	Impeller speed (m/s)	Screen size (mm)	Lot	Temp. (°C)	d_{50} (µm)	Avalanche angle (deg)	Avalanche power (cm^3.mm)	Flow rate (g/s)
1	10	1.5	I	40	258	56.5	82.0	5.0
2	10	1.5	II	Ambient	267	42.6	57.4	15.7
3	10	1.5	II	40	285	43.3	66.3	13.8
4	10	1.5	I	Ambient	205	45.5	53.6	11.7
5	4	1	I	Ambient	248	45.3	49.7	11.5
6	4	1	I	40	224	56.1	79.7	4.6
7	4	1	II	40	293	43.4	61.9	13.7
8	4	1	II	Ambient	282	42.5	55.2	15.8
9	4	1.5	II	Ambient	328	42.8	65.1	14.6
10	4	1.5	II	40	334	43.5	68.3	12.9
11	4	1.5	I	40	314	54.7	82.1	7.0
12	4	1.5	I	Ambient	288	42.9	42.5	17.4
13	10	1	I	40	159	58.5	91.2	2.9
14	10	1	I	Ambient	207	46.9	49.3	9.8
15	10	1	II	40	260	42.4	45.5	13.4
16	10	1	II	Ambient	257	41.7	46.2	16.1

3.3.4 Results and discussion

3.3.4.1 Response surface design

3.3.4.1.1 Particle size data monitored by on-line dynamic image analysis

We chose the on-line configuration of the sensor for the present work. The size measure was the equivalent rectangle short side which has an advantage with respect to image analysis of moving particles. Equivalent rectangle short side is less affected by motion blur (apparent streaking of rapidly moving particles) than other commonly used size parameters. Motion blur might result in overestimation of the particle size because of particle elongation due to high air pressure employed in the venturi systems.

The data obtained from on-line DIA were analyzed to find statistically significant process parameters that affect particle size distribution. Data were obtained for d_5, d_{50}, and d_{95}. Impeller speed (p=0.0036) and screen size (p<0.0001) were statistically significant at the 95% confidence level even with the fine particle fraction (d_5). On the other hand, feeder speed was not significant for all particle size responses. Changes in the coarser size fractions were mainly of interest in a milling process. Fig. 3.16 shows the mean particle size (d_{50}) as a response plot. The model had an R^2 of 0.69, and only the significant factors are shown. The nonlinear decline of the size as a function of increasing impeller speed (p=0.0034) agreed with the expectation that an increased amount of energy was brought into the milling process. It is known from the literature (Parrott, 1974) that size and energy needed for comminution share a highly nonlinear relationship. Impeller speed not only introduced more local energy but also increased the rate of milling. Moreover, the screen size had a significant effect on the d_{50} values (p=0.0001). Arising from smaller screen sizes, the milled product became coarser

with increasing size and levelled off at 1.5 mm. The results were analogous to the findings of Carstensen (2001) who earlier studied the case of hammer mills.

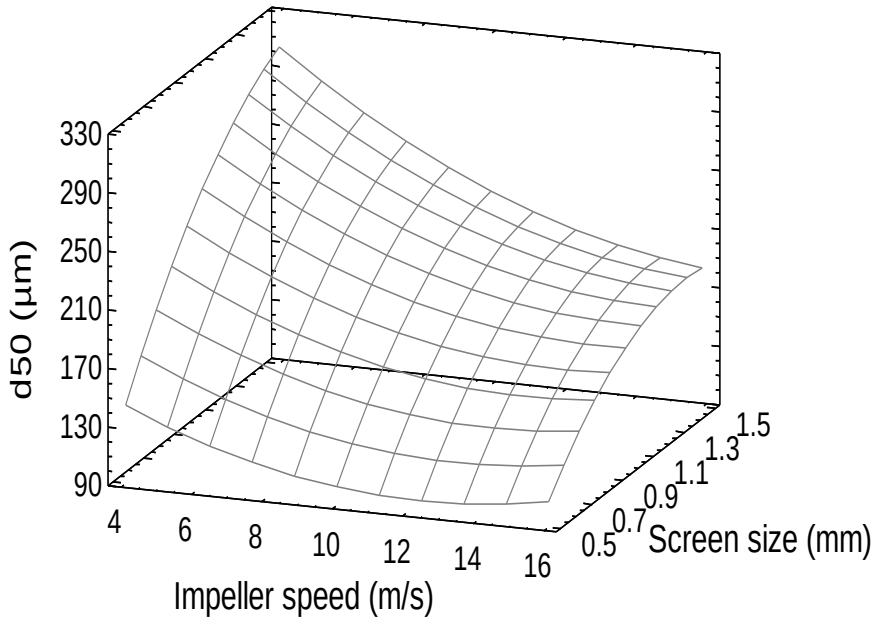


Figure 3.16 Response surface plot for the effect of impeller speed and screen size (at a constant feeder speed of 7.5 rpm) on d_{50}.

It is interesting that the feed rate was not statistically significant even with d_{50} and d_{95}. Theoretically, it would be expected that feed rate influences milling rate. However, milling rate is the outcome of the comminution characteristics of a given material. A material that breaks or deagglomerates easily will, for example, less likely lead to material accumulation in the milling chamber and thus will not display a pronounced feed rate effect on size distribution. The results of our model granulate can be compared with findings from a previous study by Motzi and Anderson (1984) who investigated an aspirin granulate in a Comil®. This study also failed to show the effect of feed rate on particle size. An absent effect of feeder speed was also seen with the d_{95} values, but statistical significance was observed with the impeller speed (p=0.0103) and screen size (p<0.0001). The d_{95} model had an R^2 of 0.79.

The observed particle size distributions obtained from image analysis exhibited a normal distribution, but some samples displayed a tendency toward bimodal distribution. These observations were in agreement with Heywood's (Staniforth 2002) experimental finding of the effect of milling time on particle size distributions. Heywood mentioned that as the milling continued, materials which originally exhibit normal particle size distribution transform to a size-reduced bimodal distribution. The material properties of the granules also play a role in size reduction. Material characteristics such as density, hardness, cohesiveness, and moisture content among others influence mill performance and particle size. Furthermore, the type of mill has a major effect on the size and shape of particles, as stated by Holt (1981).

In the current study, on-line DIA provided reliable size information in a broad range of milling conditions. The use of response surface methodology appears especially useful to develop a process for a given material. Process analytics contribute to monitoring any deviation from a reference state during production. However, measuring size is only one aspect of a particle bulk. To better assess surface properties and cohesion, flowability is an interesting parameter to monitor as it is highly relevant for further processing.

3.3.4.1.2 At-line flowability characterization using powder avalanching analyzer

After milling, the different granules were characterized with the powder avalanching tester to evaluate its usefulness as an at-line monitoring tool. In the present study we focused on the avalanche angle and avalanche power. Both parameters can be advantageous with respect to the interpretation of avalanches. Thus, some particle systems exhibit double or multiple avalanches rather than a clear single discharge.

Since we also observed some double avalanches, it was less adequate to simply count the avalanches for sample comparison. Avalanche angle is measured before the discharge at peak position and is therefore hardly affected by the type of discharge. Avalanche power is a measure for the potential energy of the mean avalanche.

The avalanche angle had a model R^2 of 0.88, with all process parameters namely, feeder speed (p=0.0028), impeller speed (p<0.0001), and screen size (p<0.0001), being statistically significant. The avalanche angle decreased as the screen size increased from 0.5 to 1.5 mm, indicating that coarse particles flow better. High impeller speed produced rather fine particles which have a relatively poor flow, thus exhibiting high avalanche angles. Accordingly, Fig. 3.16 and Fig. 3.17a were in good agreement, but flowability parameters include factors in addition to particle morphology. Aspects of surface roughness and cohesion play a role. Flowability parameters may therefore include a potential surface amorphisation or loss of solvent that could occur during the milling process.

It was remarkable that the avalanching method revealed the significance of feeder speed. Effects of feeder speed can be inferred from Fig. 3.17b as a function of the screen size for which an interaction was revealed (p=0.0139). Accordingly, the effect of feeder speed was different at a smaller screen size when compared to screens having a comparatively large opening of 1.5 mm. It should, however, be noted that these differences were rather subtle. While avalanche angle is a dynamic angle of response, avalanche power is a measure of the potential energy of particles in the avalanche and is measured in cubic centimetres times height (cm^3 x mm). High values of avalanche power indicate the formation of a large avalanche before avalanching. Again, feeder speed (p=0.0010), impeller speed (p=0.0336), and screen size (p=0.0292) were statistically significant for avalanche power. However, the model R^2

was comparatively low for this descriptor at 0.65, which was mainly due to a scattering of values. The avalanche angle and avalanche power were correlated as expected, and the Pearson product moment correlation was 0.7 between the two descriptors. Accordingly, a high potential energy of the avalanche was mainly seen with samples having comparatively high avalanche angles. Such samples were associated with comparatively poor flowability.

In order to compare the powder avalanching data with the most widely used flow characterization technique, the flow rate through an orifice was additionally determined. The samples milled through the fine screen at high impeller speed resulted in very poor flow (Fig. 3.18). Conversely, samples milled through the coarse screen at low impeller speed flowed freely. The flow rate model resulted in a high R^2 of 0.95. Impeller speed and screen size affected flow rate through the orifice and were statistically significant, with both parameters having a p value<0.0001. Moreover, an interaction (p=0.0006) between the two factors was found (p=0.018). Thus, the interaction of feeder speed and screen size observed earlier was confirmed by the flowability parameter (p=0.018). A good Pearson product moment correlation of -0.88 was observed between flow rate and avalanche angle. This implies that the smaller the avalanche angle, the higher the flow rate of the milled granules. Besides, a Pearson correlation of 0.70 between mean particle size and flow rate was also observed.

The avalanching method provided useful information in addition to the monitoring of the particle size alone. Avalanching flowability values were in good agreement with the results of the conventional flow rate that served as a reference rather than as an at-line PAT tool. The avalanching method is more advanced compared to the conventional flow through orifice since it provides dynamic images of the flowing

powder. Hence, the avalanching technique is a potential at-line PAT tool, and future applications could even include automated filling and emptying of the rotating drum. Process analyzers also provided the means to establish a design space for the product in dry milling. Impeller speed and screen size were the two main process parameters found to be significantly influencing particle size as well as flowability. High impeller speed combined with the fine screen resulted in a fine particle size and subsequently in poor flow. Therefore, an impeller speed of 4-10 m/s and a screen size of 1.0-1.5 mm were considered to obtain coarse particles with a good flow. Since the feeder speed only slightly affected the particle size, it was left to operate at average speed of 7.5 rpm in subsequent experiments. These conditions were used for robustness testing which is described in the following chapter.

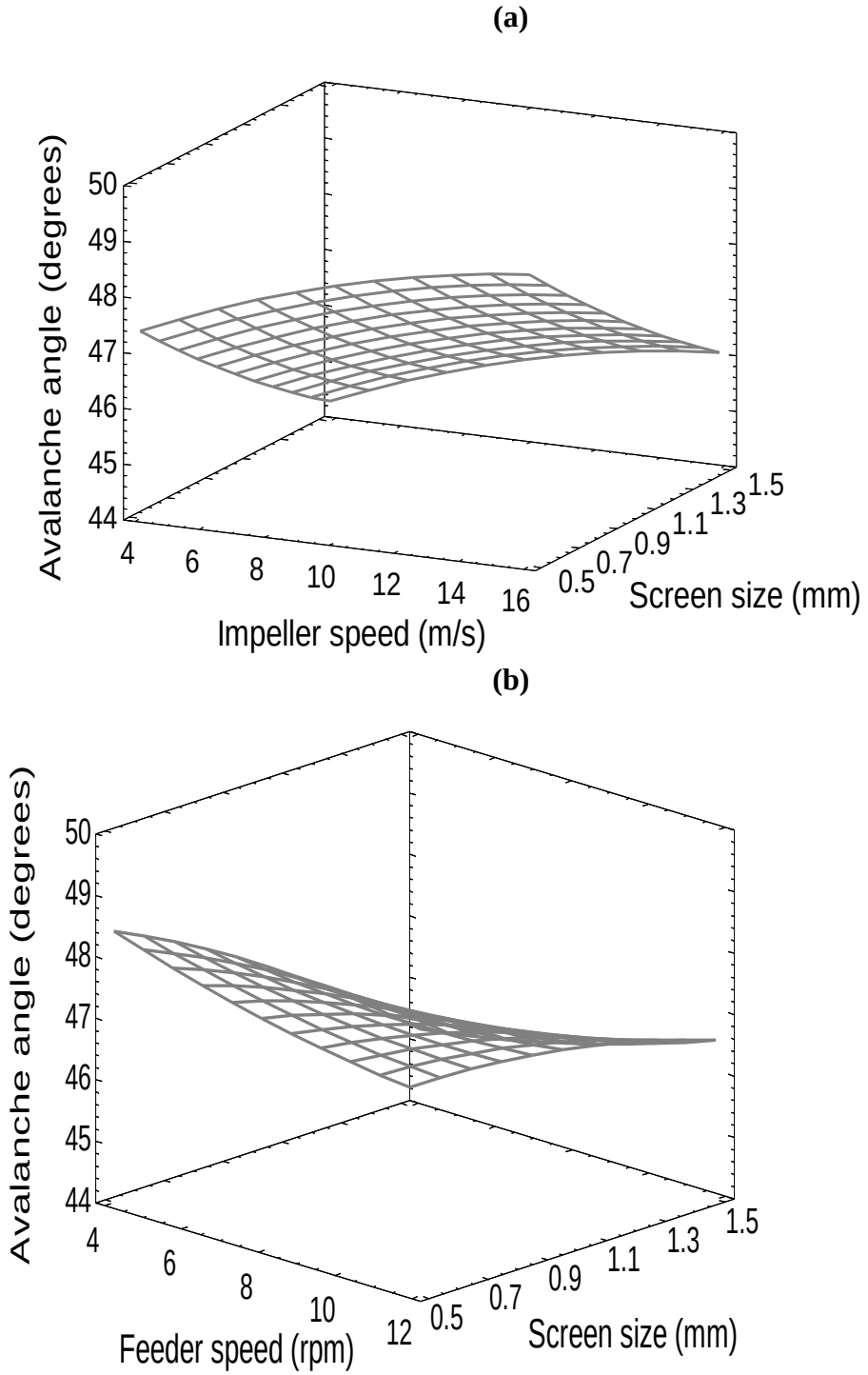


Figure 3.17 Response surface plots for (a) the effect of impeller speed and screen size (at a constant feeder speed of 7.5 rpm) on avalanche angle and (b) the effect of feeder speed and screen size (at a constant impeller speed of 10 m/s) on avalanche angle.

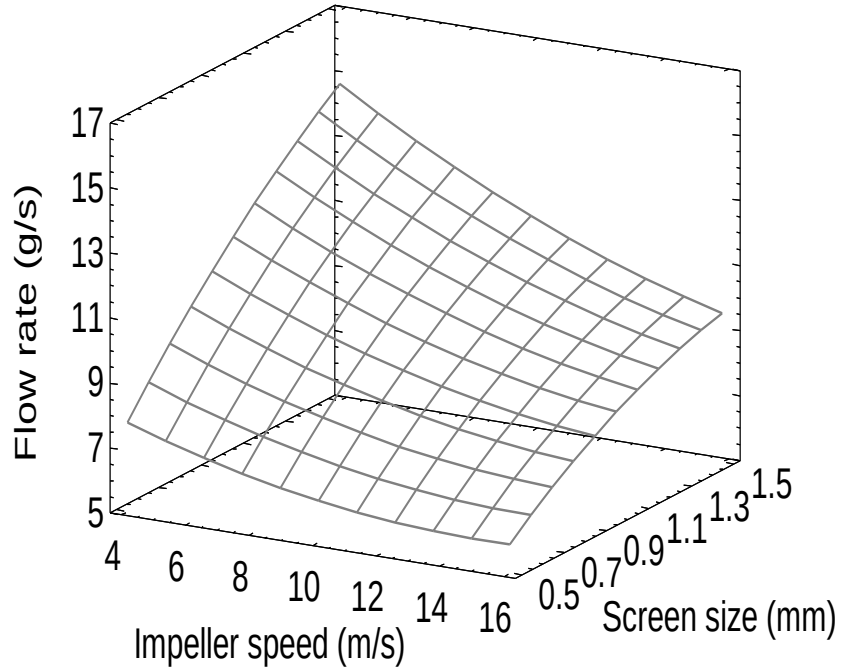


Figure 3.18 Response surface plot for the effect of impeller speed and screen size (at a constant feeder speed of 7.5 rpm) on flow rate through a 15 mm orifice.

3.3.4.2 Robustness testing

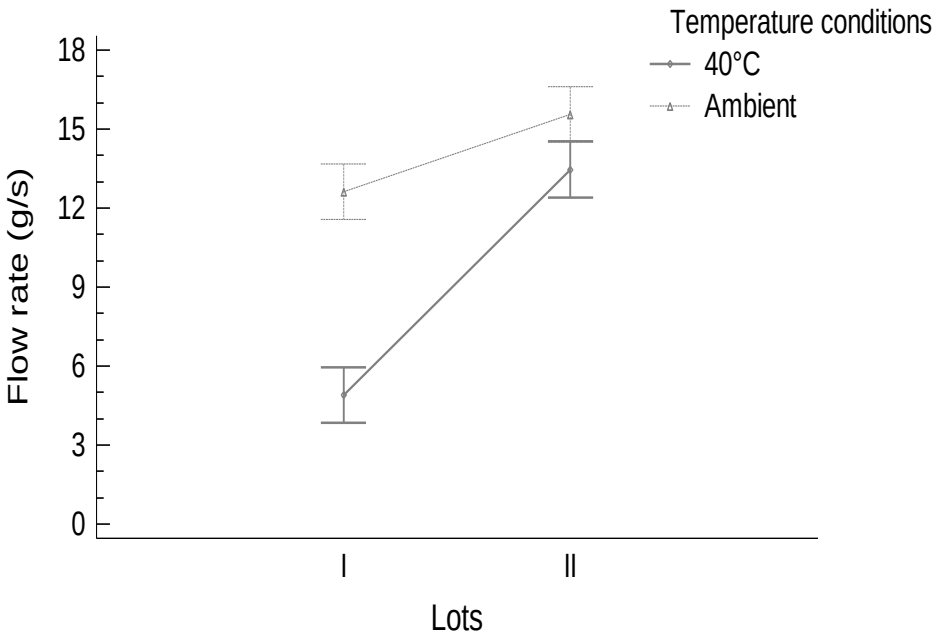
The robustness test (Taguchi design) focused on a part of the response surface that was of interest for processing. A classical ANOVA was used to evaluate the effects instead of considering the signal-to-noise ratio. The latter method reduces the degrees of freedom and should primarily be conducted with Taguchi designs having sufficient experimental runs. However, since material is usually a limiting factor, such larger Taguchi designs have a limited importance for pharmaceutical process development.

The control factors impeller speed and screen size had a statistically significant effect on d_{50} and d_{95}. Impeller speed showed a stronger influence on d_{50} (p=0.0023) than on d_{95} (p=0.0189). In addition, screen size showed a stronger influence on d_{50} (p=0.0048) than on d_{95} (p=0.0104). These data were in good agreement with the observations of the response surface method. Impeller speed (p=0.0030) and screen size (p=0.0073) also showed statistical significance for avalanche angle. Both control factors resulted

in comparatively low *p* values for flow rate, but the effects were not significant at the 95% confidence level. This was indicative of the importance of noise factors.

The two noise factors, namely, different lots and temperature conditions (Table 3.10), strongly affected the avalanching parameters and flow rate. Avalanche angle ($p<0.0001$), avalanche power ($p=0.0189$), and flow rate ($p=0.0002$) were statistically significantly influenced by the factor of granulate batches. The two batches had a different particle size distribution and therefore exhibited variable flow characteristics. Temperature also influenced avalanche angle ($p<0.0001$), avalanche power ($p=0.0004$), and flow rate ($p=0.0004$). Additionally, strong interactions were observed between the two noise factors for all flowability responses. Examples of such an interaction between the two noise factors affecting flow rate (Fig. 3.19a) and avalanche angle (Fig. 3.19b) are presented. Large differences depending on the temperature conditions were seen in lot I when compared to lot II with respect to avalanche angle and flow rate. Flow rate in Fig. 3.19a decreased drastically for lot I when the temperature was increased to 40°C. This can be attributed to the fact that the material that was dried at 40°C for 1 week became fluffy upon milling and flowed inconsistently, thus leading to a lower flow rate. On the other hand, lot II did not show any major change in flow rate or decreased only slightly with increasing temperature and had a better flow rate than lot I. Fig. 3.19b shows a large increase in avalanche angle with increasing temperature in the case of lot I. This is a marker of poor flowability. As for flow rate, avalanche angle did not change much for lot II. A slight difference, both in flow rate and avalanche angle, for the two lots was observed at ambient temperature, which had become more marked at higher temperature. The optimal choice would then be to mill lot II at ambient conditions to maximize the output responses, namely, high flow rate and low avalanche angle.

(a)



(b)

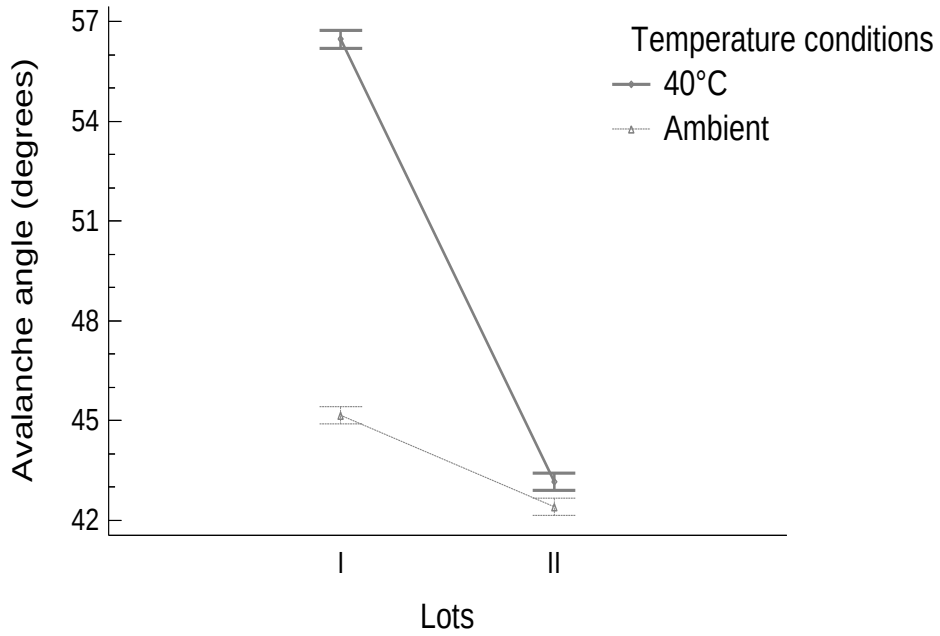


Figure 3.19 Interaction plots showing the effect of noise factors on (a) flow rate and (b) avalanche angle.

Our results emphasize the importance to balance process factors with potential noise factors. A Taguchi design may be performed as part of process development. A knowledge database may be generated for a product, which is important for later manufacturing. Issues of lot-to-lot variability or storage conditions can be avoided. Thus, embedding process analyzers into the design and implementing robustness testing optimize the quality of resulting granulates.

3.3.5 Conclusions

On-line dynamic image analysis was implemented in the dry milling process. By using at-line powder avalanching, a new process analyzer was introduced for the first time. The different methods provided complementary information relevant for further processing. Therefore, both process analyzers were needed for a full characterization of the milled material.

Process analyzers already help during process development, thus providing a sound basis for later manufacturing. Since noise factors were shown to be of relevance, part of this basic knowledge should include robustness testing. Influencing factors, such as lot-to-lot variability for example, are often not sufficiently considered during development. This necessitates the balancing of such noise factors against process factors for clarification. Combined use of process analyzers and statistical methods as reported here for dry milling can be part of a broader concept of solid dosage form manufacture. In conclusion, advancing the individual mechanical unit operations is a prerequisite for optimizing the quality of the final dosage form.

4 GENERAL CONCLUSIONS AND OUTLOOK

A novel on-line dynamic image analysis sensor was introduced and implemented in pharmaceutical conical mill that measured particle size and shape in real-time. Advantages of this DIA sensor include ease of use and minimum maintenance. A main advantage of the sensor system is that it can provide digital images of the particles, which can especially be used for a quick assessment of shape information. By simultaneously monitoring multiple size and shape parameters, enabled by the sensor system, the operator can obtain correlations of size as well as shape. A new concept, TESSA was proposed that enabled to measure changes during milling. The TESSA concept can be used for collecting information regarding equilibrium milling condition for a particular material, which is beneficial for obtaining homogenous particle characteristics. The TESSA concept is particularly beneficial in the early detection of an altered mill performance. A feedback control system for the conical mill can be set-up in the future employing the DIA sensor. This would enable enhanced understanding and control of the pharmaceutical dry milling process. The monitoring of particle size and shape distribution in real-time using the DIA sensor is not only limited to dry milling but can also be extended to other operations involving powder processing. Additionally, the DIA sensor could also be used in ATEX environments after making a few alterations to the sensor system. Thus the safety of the operators will be assured when working in potentially explosive dust atmospheres.

A novel powder avalanching method for characterizing dynamic powder flow based on image analysis was initially applied to pharmaceutical powder blends and later the device was introduced as an at-line PAT tool. The novel powder avalanching method was helpful in characterizing the different drug-excipient model blends consisting of micronized drug and a coarse excipient. Critical changes in the flow behaviour of the

model binary blends were observed and a new concept of critical flow concentrations (CFCs) was developed. A simple theoretical approach was provided to calculate critical flow concentrations (CFCs), which successfully provided a good agreement with the experimental findings. The introduced flowability characterization concepts are useful in the design of a robust and quality formulation. Moreover, the powder avalanching device can be used on a regular basis for charactering powder flow and eventually help in avoiding issues of flow performance during upstream solid dosage manufacturing namely tabletting and capsule filling.

The two DIA process tools, presented in this thesis, provided complementary information relevant for particulate systems processing. Hence, both the process analyzers are needed for a thorough characterization of a milled material. The introduced process analytical concepts provided an improved understanding of material characteristics and process factors. Combination of complementary DIA process analyzers and statistical methods as reported in this work for a dry milling unit operation can be extended to other unit operations employed in solid dosage form manufacturing. Thus, a reliable and practical approach for characterizing particulate systems and their flow properties would be beneficial in assessing and predicting their performance during handling and scale-up operations.

Appendix

I. Study of discontinuous material flow using the conical mill

Several pretesting studies were carried out in the initial screening experiments in order to identify critical to process parameters for the conical mill. In one of the pretesting studies, material dumping experiments were carried out by removing the pneumatic controlled-feeding device. This is rather a realistic approach, since a controlled-feeding device is usually not available in pharmaceutical production. The experiments were conducted to check if the sensor system is able to realize sudden changes in PSD due to agglomeration of particles on the sensor glass incase of in-line sensor and accumulation of particles inside the venturi measuring zone incase of on-line sensor. In each case approximately 20 kg material was used.

The experiments were performed by manually dumping the material, Prismalac® 40, into the hopper of the conical mill. The impeller speed was set to 4 m/s and a screen size of 500 µm was used. The in-line sensor was positioned at 25° and pressurized air of 0.5 bars was applied to blow away the particles sticking to the sensor glass. The drastic changes in the PSD, due to some particles sticking to the sensor glass, were identified by the in-line sensor system rather quickly, after about 400 s of milling. This is because the pressurised air was not sufficient enough to completely blow away the particles sticking to the sensor glass. This kind of situation was most clearly observed with the fine particle sized material, Vivapur 102. Increasing the air pressure was not feasible because it blew away most of the particles out of the focal depth of the camera lens. When the impeller speed was increased to 10 m/s and the experiment restarted with fresh material, the in-line sensor system was again able to capture the drastic changes in the particle size distribution in this case even quicker (at about 100 s time point) than at an impeller speed of 4 m/s.

Similar experiments were repeated with on-line sensor system. The impeller speed was set to 4 m/s and a screen size of 500 µm was used. The large sampling orifice (Ø 8.5 mm) was employed and the venturi air pressure was set to 3 bars. No major deviations in the PSD were observed in this case, which is probably due to the good dispersion achieved inside the venturi measuring zone. The observed higher-end particle sizes (d_{95}) were below 500 µm except at 39 s and 60 s time points where the d_{95} was close to 600 µm. The observed particle sizes were also below 500 µm when the impeller speed was increased to 10 m/s. These studies speak in favour of the on-line sensor system because even in the absence of a controlled-feeding device the observed PSDs were within the expected limits. There was no accumulation of particles observed inside the measuring zone.

II. Powder avalanching- pretesting studies with several excipients

To enable a better understanding of the powder avalanching instrument a broad range of commercially available excipient grades were initially studied, in their original available form, to understand the flow behaviour. The drum was rotated at 0.5 rpm. Mean avalanche time was interpreted to understand the differences among the flow characteristics of the measured excipients. Measurements were performed in triplicate and the mean and 95% LSD intervals were reported. LSD forms a confidence interval for each pair of means at the selected confidence level using Student's t-distribution. This procedure is due to Fisher and is called the Least Significant Difference procedure, since the magnitude of the limits indicates the smallest difference between any two means that can be declared to represent a statistically significant difference.

The mean avalanche time varied for different excipients (Fig. I). A one-way ANOVA was calculated. The *p* value of the F-test was <0.0001 indicating a statistically significant difference between the mean avalanche times from one level of excipient to another at the 95.0% confidence level.

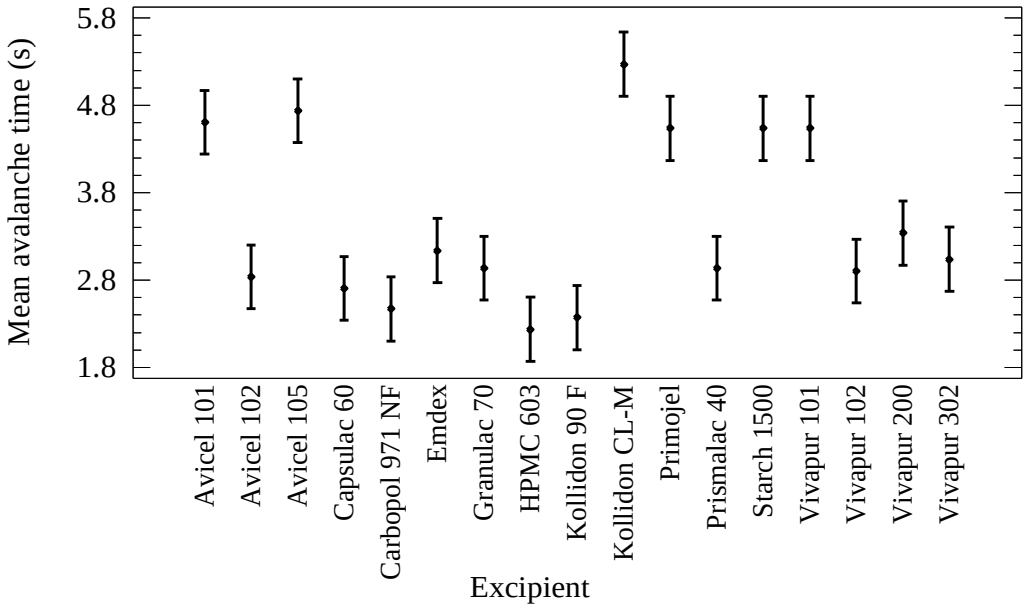


Figure I Mean avalanche times of different excipients (means and 95% LSD intervals)

Thus, the analysis of the variance enabled a good differentiation between several excipients with respect to the avalanche parameter.

III. Investigation of the effect of mixing ratio and mixing time for albendazole-lactose binary powder blends

To evaluate the effect of mixing ratio and mixing time on the flow responses, a randomized 2^2 factorial design was conducted. The design resulted in six runs including two centerpoints and two error degrees of freedom. Binary blends were prepared by the addition of 10%, 30% and 50% w/w albendazole to lactose (PrismaLac® 40) and mixed at 52 rpm in a Turbula for 5, 10, 15 minutes according to the sequence provided by the design of experiments. Response parameters such as

mean avalanche time, avalanche power, avalanche angle were evaluated and additionally the flowrate through a 15 mm orifice was also studied. Analysis of variance was conducted and as a result, mixing ratio was found to be significant, at 95% confidence level, for avalanche power (p=0.0205). Mean avalanche time and avalanche angle did not show a statistical significant affect. Mixing time did not affect any of the response parameters studied. Besides, no significant interaction was observed between the two mixing factors.

Bibliography

Ahfat N.M., Buckton G., Burrows R., Ticehurst M.D., 1997. Predicting mixing performance using surface energy measurements. Int. J. Pharm. 156, 89-95.

Ahn H., Basaranoglu Z., Yilmaz M., Bugutekin A., Gül M.Z., 2008. Experimental investigation of granular flow through an orifice. Powder Technol. 186, 65-71.

Aizu Y., Asakura T., 1987. Principles and development of spatial filtering velocimetry. Appl. Phys. B 43, 209-224.

Alexander A.W., Chaudhuri B., Faqih A.M., Muzzio F.J., Davies C., Tomassone M.S., 2006. Avalanching flow of cohesive powders, Powder Technol. 164, 13-21.

Allen T., 1981. Particle size measurement, 3rd ed., London: Chapman and Hall. pp. 107-120.

Almeida-Prieto S., Blanco-Mendez J., Otero-Espinar F.J., 2004. Image analysis of the shape of granulated powder grains. J. Pharm. Sci. 93, 621-634.

Amidon G.E., Secreast P.J., Mudie D., 2009. Particle, powder, and compact characterization. In: Developing solid oral dosage forms: pharmaceutical theory and practice. Academic press, Burlington, USA, pp 169.

Andersson M., Folestad S., Gottfries J., Johansson M.O., Josefson M., Wahlund K.G., 2000. Quantitative analysis of film coating in a fluidized bed process by in-line NIR spectrometry and multivariate batch calibration. Anal. Chem. 72 (9), 2099-2108.

Barra J., Lescure F., Falson-Rieg F., Doelker E., 1998. Can the organisation of a binary mix be predicted from the surface energy, cohesion parameter and particle size of its components? Pharm. Res. 15, 1727-1736.

Bauer-Brandl A., Becker D., 1996. Evaluation of a conical mill for screening of direct compression formulations. Drug Dev. Ind. Pharm. 22, 417-430.

Beach L., Ropero J., Mujumdar A., Alcalà M., Romañach R.J., Davé R.N., 2010. Near-infrared spectroscopy for the in-line characterization of powder voiding part II: Quantification of enhanced flow properties of surface modified active pharmaceutical ingredients. J. Pharm. Innov. 5, 1-13.

Beaubien L.J., Vanderwielen A.J., 1980. Particle size analysis of pharmaceutical powders. J. Pharm. Sci., 69, 651-655.

Benedetti C., Abatzoglou N., Simard J.-S., McDermott L., Leonard G., Cartilier L., 2007. Cohesive, multicomponent, dense powder flow characterization by NIR. Int. J. Pharm. 336, 292-301.

Beverloo W.A., Leniger H.A., van de Velde J., 1961. The flow of granular solids through orifices. Chem. Eng. Sci. 15, 260-269.

Boateng A.A., Barr P.V., 1996. Modelling of particle mixing and segregation in the transverse plane of a rotary kiln. Chem. Eng. Sci. 51, 4167-4181.

Bond F.C., 1952. The third theory of comminution. Transactions of AIME, Miner. Eng. 193, 484-494.

Bonfichi R., Cloralio G., Rainoldi A., 2009. Dynamic avalanching accurately assesses flowability and quality. Pharm. Technol. (Europe). http://pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?id=607093&pageID=1&sk=&date. Accessed 31 May 2010.

Boothroyd E.M., Doherty R.A., Poynter R., Ticehurst M., 2000. Comparison of blend flow measured on the Aeroflow with tablet weight uniformity. J. Pharm. Pharmacol. 52, 174S.

Brittain H.G., 2002 December. Particle-size distribution, Part III. Determination by analytical sieving. Pharm. Technol. 56-64.

Burcham C.L., Collins P.C., Jarmer D.J., Seibert K.D., 2009. In: Zheng J. Formulation and analytical development for low-dose oral drug products. New Jersey: John Wiley & Sons, Inc., pp. 205-219.

Burgess D.J., Duffy E., Etzler F., Hickey A.J., 2004. Particle size analysis: AAPS workshop report, cosponsored by the Food and Drug Administration and the United States Pharmacopeia. AAPS J., 6, Article 20.

Burggraeve A., Van Den Kerhof T., Hellings M., Remon J.P., Vervaet C., De Beer T. 2010. Evaluation of in-line spatial filter velocimetry as PAT monitoring tool for particle growth during fluid bed granulation. Eur. J. Pharm. Biopharm. 76(1), 138-146.

Carr R.L., 1965. Evaluating flow properties of solids. Chem. Eng. 72, 69-72.

Carstensen J.T., Puisieux F., 1978. Apparent density versus composition relations in cascaded binary powder beds, Powder Technol. 20, 249-255.

Carstensen J.T., 2001. Comminution. In: Carstensen J.T. Advanced pharmaceutical solids: drugs and the pharmaceutical sciences, vol.110. New York: Marcel Dekker; pp.323-333.

Chan L.W., Tan L.H., Heng P.W.S., 2008. Process analytical technology: Application to particle sizing in spray drying. AAPS PharmSciTech 9, 259-266.

Chieng N., Zujovic Z., Bowmaker G., Rades T., Saville D., 2006. Effect of milling conditions on solid-state conversion of ranitidine hydrochloride form 1. Int. J. Pharm., 327, 36-44.

Chikhalia V., Forbes R.T., Storey R.A., Ticehurst M., 2006. The effect of crystal morphology and mill type on milling induced crystal disorder. Eur. J. Pharm. Sci. 27, 19-26.

Clarke M.J., Tobyn M.J., Staniforth J.N., 2001. The formulation of powder inhalation systems containing a high mass of nedocromil sodium trihydrate, J. Pharm. Sci. 90, 213-223.

Consiglio R., Baker D.R., Paul G., Stanley H.E., 2003. Continuum percolation thresholds for mixtures of spheres of different sizes, Physica A, 319, 49-55.

Cowell A., McGlinchey D., Ansell R., 2005. A CFD analysis of the Stable Microsystems Powder Flow Analyser with an experimental comparison. Abstract, Particulate Systems Analysis, Stratford upon Avon.

Craik D.J., Miller B.F., 1958. The flow properties of powders under humid conditions. J. Pharm. Pharmacol. 10, 136-144.

Crowder T.M., Sethuraman V., Fields T.B., Hickey A.J., 1999. Signal processing and analysis applied to powder behaviour in a rotating drum. Part. Part. Syst. Charact. 16, 191-196.

Crowder T.M., Hickey A.J., 2000 February. The physics of powder flow: Applied to pharmaceutical solids, Pharm. Technol., 50-58.

Crowley K.J., Zografi G., 2002. Cryogenic grinding of indomethacin polymorphs and solvates: assessment of amorphous phase formation and amorphous phase physical stability. J. Pharm. Sci. 91, 492-507.

Dahlinder L.E., Johansson M., Sjogren J., 1982. Comparison of methods for evaluation of flow properties of powders and granulates. Drug Dev. Ind. Pharm. 8, 455-461.

de Boer G.B.J., de Weerd C., Thoenes D., Goossens H.W.J., 1987. Laser diffraction spectrometry: Fraunhofer diffraction versus Mie scattering. Part. Part. Syst. Charact. 4, 14-19.

Dickhoff B.H.J., de Boer A.H., Lambregts D., Frijlink H.W., 2003. The effect of carrier surface and bulk properties on drug particle detachment from crystalline lactose carrier particles during inhalation, as function of carrier payload and mixing time. Eur. J. Pharm. Biopharm. 56, 291-302.

Dickhoff B.H.J., de Boer A.H., Lambregts D., Frijlink H.W., 2005. The interaction between carrier rugosity and carrier payload, and its effect on drug particle redispersion from adhesive mixtures during inhalation. Eur. J. Pharm. Biopharm. 59, 197-205.

Dietrich S., Petrak D., Köhler M., Eckardt G., 2010. Spatial filtering technique as powerful tool for real-time particle size measurement for fluid bed applications in

pharmaceutical industry. Sci. Pharm. 78, 586. Conference abstract LPPT06 (doi:10.3797/scipharm.cespt.8.LPPT06).

Dyakowski T., Luke S.P., Ostrowski K.L., Williams R.A., 1999. On-line monitoring of dense phase flow using real-time dielectric imaging. Powder Technol. 104, 287-295.

Egermann H., Kemptner I., Pichler E., 1985. Effects of interparticulate interactions on mixing homogeneity, Drug Dev. Ind. Pharm. 11, 663-676.

Egermann H., Krumphuber A., Frank P., 1992. Novel approach to estimate quality of binary random powder mixtures: samples of constant volume. III: Range of validity of equation, J. Pharm. Sci. 81, 773-776.

Elbicki J.M., Tardos G.I., 1998. The influence of fines on the flowability of alumina powders in test hoppers. Powder Handling and Processing 10, 147-149.

Ende D., Bronk K.S., Mustakis J., O'Connor G., Santa Maria C.L., Nosal R., *et al*., 2007. API Quality by Design example from the Torcetrapib manufacturing process. J. Pharm. Innov. 2, 71-86.

Erizal, Cahyati S.Y., Nurono S.S., Halim A., 2008. Effect of milling on solid state transformation of sulfamethoxazole. Int. J. Pharmcol. 4, 140-144.

Etzler F.M., Deanne R., 1997. Particle size analysis: a comparison of various methods II. Part. Part. Syst. Charact. 14, 278-282.

Fan A., Parlerla S., Carlson G., Ladipo D., Dukich J., Capella R., *et al*., 2005. Effect of particle size distribution and flow property of powder blend on tablet weight variation. Am. Pharm. Rev. 8, 73-78.

Faqih A.M., Chaudhuri B., Alexander A.W., Davies C., Muzzio F.J., Tomassone M.S., 2006. An experimental/computational approach for examining unconfined cohesive powder flow. Int. J. Pharm. 324, 116-127.

Faqih A.M., Mehrotra A., Hammond S.V., Muzzio F.J., 2007. Effect of moisture and magnesium stearate concentration on flow properties of cohesive granular materials. Int. J. Pharm. 336,338-345.

Fariss G., Keintz R., Okoye P., 2006. Thermal effusivity and power consumption as PAT tools for monitoring granulation end point. Pharm. Technol. 30, 60-72.

Fassihi A.R., Kanfer I., 1986. Effect of compressibility and powder flow properties on tablet weight variation, Drug Dev. Ind. Pharm. 12, 1947-1966.

Findlay W.P., Peck G.R., Morris K.R., 2005. Determination of fluidized bed granulation end point using near-infrared spectroscopy and phenomenological analysis. J. Pharm. Sci. 94 (3), 604-612.

Freeman R.E., 2004. Predicting flowability and characterizing powders. Pharma. Technol. Eur. 16 (1), 41-43.

Freeman R.F., 2007. Measuring the flow properties of consolidated, conditioned and aerated powders: a comparative study using a powder rheometer. Powder Technol. 174, 25-33.

Freeman T., 2010. The importance of powder characterization. Pharma. Technol. Eur. 22 (6), 21-26.

Fukuoka E., Kimura S., 1992. Cohesion of particulate solids, VIII. Influence of particle shape on compression by tapping. Chem. Pharm. Bull. 40, 2805-2809.

Garcia T., Cook G., Nosal R., 2008. PQLI key topics- Criticality, design space and control strategy. J. Pharm. Innov. 3, 60-68.

Geldart D., Mallet M.F., Rolfe N., 1990. Assessing the flowability of powders using angle of repose. Powder Handling & Proc., 2, 341-346.

Geldart D., Abdullah E.C., Hassanpour A., Nwoke L.C., Wouters I., 2006. Characterization of powder flowability using measurement of angle of repose. China Particuology, 4, 104-107.

Geldart D., Abdullah E.C., Verlinden A., 2009. Characterization of dry powders. Powder Technol. 190, 70-74.

General Test <616>, "Bulk density and tapped density," *USP 32–NF 27*, (U.S. Pharmacopeial Convention, Rockville, MD, 2009), pp. 226-227.

General Test <776>, "Optical Microscopy," *USP 32–NF 27*, (U.S. Pharmacopeial Convention, Rockville, MD, 2009), pp. 302-304.

General Test <786>, "Particle-Size Distribution Estimation by Analytical Sieving," *USP 32–NF 27*, (U.S. Pharmacopeial Convention, Rockville, MD, 2009), pp. 307-310.

General Test <1174>, "Powder flow," *USP 32–NF 27*, (U.S. Pharmacopeial Convention, Rockville, MD, 2009), pp. 688-691.

Gold G., Duvall R.N., Palermo B.T., 1996. Powder flow studies I: Instrumentation and applications, J. Pharm. Sci. 55:1133-1136.

Gordon R.E., Amin, S.I., 1984. European Patent, no. 0120587.

Gopalsamy B.M., Mondal B., Ghosh S., 2009. Taguchi method and ANOVA: An approach for process parameters optimization of hard machining while machining hardened steel. J. Sci. Ind. Res. (India) 68, 686-695.

Gouyet J.F., 1996. Physics and fractal structures, Springer-Verlag Berlin, Heidelberg, New York, pp. 46.

Greaves D., Boxall J., Mulligan J., Montesi A., Creek J., Sloan E.D., Koh C.A., 2008. Measuring the particle size of a known distribution using the focused beam reflectance measurement technique. Chem. Eng. Sci. 63, 5410-5419.

Griffith A.A., 1921. The phenomena of rupture and flow in solids. Phil. Trans. R. Soc. Lond. A January 1, 221, 163-198.

Guerin E., Tchoreloff P., Leclerc B., Tanguy D., Deleuil M., Couarraze G., 1999. Rheological characterization of pharmaceutical powders using tap testing, shear cell and mercury porosimeter. Int. J. Pharm 189, 91-103.

Guidance for industry PAT - A framework for innovative pharmaceutical development, manufacturing, and quality assurance. U.S. Department of Health and Human Services Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), Office of Regulatory Affairs (ORA), Pharmaceutical cGMPs. http://www.avarent.com/docs/pat.pdf, September 2004.

Hagrasy A.S. El, Chang S.Y., Kiang S., 2006. Evaluation of risk and benefit in the implementation of near-infrared spectroscopy for monitoring of lubricant mixing. Pharm. Dev. Technol. 11, 303-312.

Hailey P.A., Doherty P., Tapsell P., Oliver T., Aldridge P.K., 1996. Automated system for the on-line monitoring of powder blending processes using near-infrared spectroscopy. Part I. System development and control. J. Pharm. Biomed. Anal. 14, 551-559.

Hancock B.C., Vukovinsky K.E., Brolley B., Grimsey I., Hedden D., Olsofsky A., Doherty R.A., 2004. Development of a robust procedure for assessing powder flow using a commercial avalanche testing instrument, J. Pharm. Biomed. Anal. 35, 979-990.

Hanrahan G., Lu K., 2006. Application of factorial and response surface methodology in modern experimental design and optimization. Critical Reviews in Analytical Chemistry 36, 141-151.

Hansuld E.M., Briens L., McCann J.A.B., Sayani A., 2009. Audible acoustics in high-shear wet granulation: Application of frequency filtering. Int. J. Pharm. 378, 37-44.

Hausman D.S., Cambron R.T., Sakr A., 2005. Application of Raman spectroscopy for on-line monitoring of low dose blend uniformity. Int. J. Pharm. 298, 80-90.
Hausner H.H., 1967. Friction conditions in a mass of metal powder. Int. J. Powder. Metall. 3, 7-13.

Heffels C.M.G., Verheijen P.J.T., Heitzmann D., Scarlett B., 1996. Correction of the effect of particle shape on the size distribution measured with a laser diffraction instrument. Pat. Part. Syst. Charact. 13, 271-279.

Hersey J.A., 1975. Ordered mixing: A new concept in powder mixing practice. Powder Technol. 11, 41-44.

Heywood H., 1950-52. Some notes on grinding research. J. Imp. Coll. Eng. Soc. 6, 26.

Heywood H., 1961. Techniques for the evaluation of powders- I. Fundamental properties of particles and methods of sizing analysis. Powder Metallurgy 7, 1-28.

Heywood H., 1963. The evaluation of powders. J. Pharm. Pharmacol. 15, 56T-74T.

Hlinak A.J., Kuriyan K., Morris K.R., Reklaitis G.V., Basu P.K., 2006. Understanding critical material properties for solid dosage form design. J. Pharm. Innov. 1, 12-17.

Holt C.B., 1981. The shape of particles produced by comminution: A review. Powder. Technol. 28, 59-63.

Hou T.H., Su C.H., Liu W.L., 2007. Parameters optimization of a nano-particle wet milling process using the Taguchi method, response surface method and genetic algorithm. Powder. Technol. 173, 153-162.

Houghton M.E., Amidon G.E., 1992. Microscopic characterization of particle size and shape: An inexpensive and versatile method. Pharm. Res., 9, 856-859.

Houng J.Y., Hsu H.F., Liu Y.H., Wu J.Y., 2003. Applying the Taguchi robust design to the optimization of the asymmetric reduction of ethyl 4-chloro acetoacetate by bakers' yeast. J. Biotechnol. 100, 239-250.

Howard S.A., 2007. Solids: Flow properties, In: Encyclopedia of pharmaceutical technology. Informa Healthcare, USA. pp 3275-3296.

Huang J., Kaul G., Utz J., Hernandez P., Wong V., Bradley D., *et al.*, 2010. A PAT approach to improve process understanding of high shear wet granulation through in-line particle measurement using FBRM C35. J. Pharm. Sci. 99, 3205-3212.

Huang Q., Zhang H., Zhu J., 2009. Experimental study on fluidization of fine powders in rotating drums with various wall friction and baffled rotating drums. Chem. Eng. Sci. 64, 2234-2244.

Hui T.L., Wah C.L., Heng P.W.S., 2008. Rapid and convenient microsphere sizing: using a PAT instrument and pilot-scale spray dryer can provide real-time information regarding process and product size. Pharm. Technol. Asia Pacific 2.

Iida K., Inagaki Y., Todo H., Okamoto H., Danjo K., Leuenberger H., 2004. Effects of surface processing of lactose carrier particles on dry powder inhalation properties of Salbutamol Sulfate. Chem. Pharm. Bull. 52, 938-942.

International Conference on Harmonisation, 2006. ICH harmonised tripartite guideline; Pharmaceutical Development Q8

International Conference on Harmonisation, 2005. ICH harmonised tripartite guideline; Quality Risk Management Q9

International Conference on Harmonisation, 2008. ICH harmonised tripartite guideline; Pharmaceutical Quality System Q10

Ikekawa A., Kaneniwa N., 1968. Influence of particle size on physicochemical properties of pharmaceutical powders. VII Fluidity and packing property of binary mixtures, Chem. Pharm. Bull. 16, 1543-1549.

Jenike A.W., 1964. Storage and flow of solids. Utah. Eng. Exp. Stn. Bull. 123, 1-194.

Jinno J., Kamada N., Miyake M., Yamada K., Mukai T., Odomi M., *et al*., 2006. Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs. J. Control Release 111, 56-64.

Jones T.M., Pilpel N., 1966. Some angular properties of magnesia and their relevance to material handling. J. Pharm. Pharmacol., 18 (Suppl.), 182-189.

Kaerger J.S., Edge S., Price R., 2004. Influence of particle size and shape on flowability and compactibility of binary mixtures of paracetamol and microcrystalline cellulose. Eur. J. Pharm. Sci. 22, 173-179.

Kail N., Briesen H., Marquardt W., 2008. Analysis of FBRM measurements by means of a 3D optical model. Powder. Technol. 185, 211-222.

Kaye B.H., Leblanc J.E., Moxam D., Zubac D., 1983. The effect of vibration on the rheology of powders. International Powder and Bulk Solids Handling and Processing, 324-337.

Kaye B.H., Gratton-Liimatainen J., Faddis N., 1995. Studying the avalanching behaviour of a powder in a rotating disc, Part. Part. Syst. Charact. 12, 232-236.

Kaye B.H., 1997. Characterizing the flowability of a powder using the concepts of fractal geometry and chaos theory. Part. Part. Syst. Charact. 14, 53-66.

Kelly R.N., DiSante K.J., Stranzl E., Kazanjian J.A., Bowen P., Matsuyama T., Gabas N., 2006. Graphical comparison of image analysis and laser diffraction particle size analysis data obtained from the measurements of nonspherical particle systems. AAPS PharmSciTech 7, Article 69.

Kick F., 1885. “Das Gesetz der proportionalen Widerstande und seine Anwendung,” Arthur Felix, Leipzig, Germany.

Kippax P., 2005 March. Appraisal of the laser diffraction particle-sizing technique. Pharm. Technol. 88-96.

Kono H.O., Huang C.C., Xi M., 1990. Function and mechanism of flow conditioners under various loading pressure conditions in bulk powders. Powder Technol. 63, 81-86.

Kougoulos E., Jones A.G., Jennings K.H., Wood-Kaczmar M.W., 2005. Use of focused beam reflectance measurement (FBRM) and process video imaging (PVI) in a modified mixed suspension mixed product removal (MSMPR) cooling crystallizer. J. Cryst. Growth. 273, 529-534.

Krantz M, Zhang H., Zhu J., 2009. Characterization of powder flow: Static and dynamic testing. Powder Technol. 194, 239-245.

Lavoie F., Cartilier L., Thibert R., 2002. New methods characterizing avalanche behaviour to determine powder flow, Pharm. Res. 19 (6), 887-893.

Lee Y.S.L., Poynter R., Podczeck F., Newton J.M., 2000. Development of a dual approach to assess powder flow from avalanching behaviour, AAPS PharmSciTech. 1 (3), Article 21.

Lefebvre C., Barthelemy C., Guyot-Hermann A.M., Guyot J.C., 1988. An attempt at bringing to light a "phase inversion" in a binary mixture of two dimensional rounded particles. Drug. Dev. Ind. Pharm 14, 2443-2465.

Li M., Wilkinson D., Patchigolla K., 2005. Comparison of particle size distributions measured using different techniques. Part. Sci. Technol. 23, 265-284.

Lindberg N., Palsson M., Pihl A.C., Freeman R., Freeman T., Zetzener H., Enstad G., 2004. Flowability measurements of pharmaceutical powders with poor flow using five different techniques, Drug Dev. Ind. Pharm. 30, 785-791.

Lin S.Y., Cheng W.T., Wang S.L., 2006. Thermodynamics and kinetics characterization of polymorphic transformation of famotidine during grinding. Int. J. Pharm., 318, 86-91.

Liu L.X., Marziano I., Bentham A.C., Litster J.D., White E.T., Howes T., 2008. Effect of particle properties on the flowability of ibuprofen powders. Int. J. Pharm., 362, 109-117.

Ma Z., Merkus H.G., van der Veen H.G., Wong M., Scarlett B., 2001. On-line measurement of particle size and shape using laser diffraction. Part. Part. Syst. Charact. 18, 243-247.

MacGregor J.F., Bruwer M.J., 2008. A framework for the development of design and control spaces. J. Pharm. Innov. 3, 15-22.

Marinelli J., Carson J.W., 1992. Solve solids flow problems in bins, hoppers and feeders. Chemical Engineering Progress, 88, 22-28.

Medendorp J., Lodder R.A., 2006. Acoustic-resonance spectroscopy as a process analytical technology for rapid and accurate tablet identification. AAPS PharmSciTech 7, Article 25, E1-E9.

Merkus H.G. 2009. "Laser Diffraction" in Particle Size Measurements: Fundamentals, Practice, Quality. Springer: Netherlands. pp 259-285.

Molerus O., 1978. Effect of interparticle cohesive forces on the flow behaviour of powders. Powder Technol. 20, 161-175.

Molerus O., Nywlt M., 1984. The influence of the fine particle content on the flow behaviour of bulk materials, Powder Technol. 37, 145-154.

Molerus O., 1985. Schuettgutmechanik: Grundlagen und Anwendungen in der Verfahrenstechnik, Springer-Verlag, Berlin, Heidelberg, New York, Tokyo, pp. 82-187.

Mort P.R., Riman R.E., 1995. Determination of homogeneity scale in ordered and partially ordered mixtures, Powder Technol. 82, 93-104.

Motzi J.J., Anderson N.R., 1984. The quantitative evaluation of a granulation milling process. II. Effect of output screen size, mill speed and impeller shape. Drug. Dev. Ind. Pharm. 10, 713-728.

Naervaenen T., Lipsanen T., Antikainen O., Raeikkoenen H., Heinaemaeki J., Yliruusi J., 2009. Gaining fluid bed process understanding by in-line particle size analysis. J. Pharm. Sci. 98, 1110-1117.

National Instruments, 2005. User's manual for LabVision. Austin, Texas, USA.

Navaneethan C.V., Missaghi S., Fassihi R., 2005. Application of powder rheometer to determine powder flow properties and lubrication efficiency of pharmaceutical particulate systems. AAPS PharmSciTech. 6 (3), E398-E404.

Parrott E.L., 1974. Milling of pharmaceutical solids. J. Pharm. Sci. 63, 813-829.

Petrak D., 2002. Simultaneous measurement of particle size and particle velocity by the spatial filtering technique. Part. Syst. Charact. 19, 391-400.

Pirttimaki J., Laine E., Ketolainen J., Paronen P., 1993. Effects of grinding and compression on crystal-structure of anhydrous caffeine. Int. J. Pharm. 95, 93– 99.

Podczeck F., Sharma M., 1996. The influence of particle size and shape of components of binary powder mixtures on the maximum volume reduction due to packing, Int. J. Pharm. 137, 41-47.

Podczeck F., Miah Y., 1996. The influence of particle size and shape on the angle of internal friction and the flow factor of unlubricated and lubricated powders. Int. J. Pharm. 144, 187-194.

Podczeck F., Newton J.M., 1999. Powder filling into hard gelatin capsules on a tamp filling machine. Int. J. Pharm. 185, 237-254.

Portoghese F., Berruti F., Briens C., 2005. Continuous on-line measurement of solid moisture content during fluidized bed drying using triboelectric probes. Powder Technol. 181, 169-177.

Poska R.P., Hill T.R., Schaik J.W.van, 1993. The use of statistical indices to gauge the mixing efficiency of a conical screening mill. Pharm. Res. 10, 1248-1251.

Prescott J.K., Barnum R.A., 2000. On powder flowability. Pharma. Technol. 24, 60-84.

Pugh D., 2006. On-line particle size measurement in ATEX dust environments. Powder Handling and Processing. 18 (2), March/April, 97-99.

Quintanilla M.A.S., Valverde J.M., Castellanos A., Viturro R.R., 2001. Looking for self-organized critical behaviour in avalanches of slightly cohesive powders, Phys. Rev. Lett. 87 (19), 194301(4).

Rabinski G., Thomas D., 2004. Dynamic digital image analysis: emerging technology for particle characterization. Water Sci. Technol. 50, 19-26.

Rambali B., Baert L., Thone D., Massart D.L., 2001. Using experimental design to optimize the process parameters in fluidized bed granulation. Drug. Dev. Ind. Pharm. 27, 47-55.

Rantanen J., Wikström H., Turner R., Taylor L.S., 2005. Use of in-line near-infrared spectroscopy in combination with chemometrics for improved understanding of pharmaceutical processes. Anal. Chem. 77 (2), 556-563.

Rao R.S., Kumar C.G., Prakasham R.S., Hobbs P.J., 2008. The Taguchi methodology as a statistical tool for biotechnological applications: A critical appraisal. Biotechnol. J. 3, 510-523.

Rastogi S., Klinzing G.E., 1994. Characterizing the rheology of powders by studying dynamic avalanching of the powder, Part. Part. Syst. Charact. 11, 453-456.

Rawle A.F., 1993. 'Basic principles of particle size analysis' application note MRK038, Malvern instruments, Malvern, UK. www.malvern.co.uk.

Reynolds G.K., 2010. Modeling of pharmaceutical granule size reduction in a conical screen mill. Chem. Eng. J. 164, 383-392.

Rittinger R.P. von, 1867. "Lehrbuch der Aufbereitungskunde", Ernst and Korn, Berlin, Germany, 19.

Rohrs B.R., Amidon G.E., Meury R.H., Secreast P.J., King H.M., Skoug C.J., 2006. Particle size limits to meet USP content uniformity criteria for tablets and capsules. J. Pharm. Sci. 95, 1049-1059.

Rubinstein M.H., Gould P., 1987. Particle size reduction in the ball mill. Drug Dev. Ind. Pharm. 13 (1), 81-92.

Ruf A., Worlitschek J., Mazzotti M., 2000. Modeling and experimental analysis of PSD measurements through FBRM. Part. Part. Syst. Charact. 17, 167-179.

Rumpf H., Ebert F., 1964. Darstellung von Kornverteilungen zur Ausdeutung der Gesetzmässigkeit der Zerkleinerungswirkung von Zerkleinerungsmaschinen. Chem.-Ing. Techn. 36, 523-557.

Sastry S.V., Reddy I.K., Khan M.A., 1997. Atenolol gastrointestinal therapeutic system: optimization of formulation variables using response surface methodology. J. Control. Release 45, 121-130.

Schenck L.R., Plank R., Zega J., 2002. Investigation of size reduction mechanisms in a conical screen mill for wet granulation before and after drying. In: Proceedings of the AAPS Annual Conference Poster, Toronto.

Schirg P., Wissler P., 2000. Membrane processes for the chemical and pharmaceutical industry and optimization of particulate processes by Lasentec FBRM. Chimia 54, 207-210.

Schmidt-Lehr S., Moritz H., Juergens K.C., 2007. On-line control of particle size during fluidized bed granulation. Pharm. Ind. 69, 478-484.

Schofield T., Bavitz J.F., Lei C.M., Oppenheimer L., Shiromani P.K., 1991. Key variables in dosage form design. Drug. Dev. Ind. Pharm. 17, 959-974.

Schulze D., 2007. Powders and bulk solids: Behaviour, characterization, storage and flow. Springer-Verlag: Berlin, Heidelberg. pp 87.

Schwedes J., 2003. Review on testers for measuring flow properties of bulk solids. Granul. Matter. 5, 1-43.

Scott B., Wilcock A., 2006. Process analytical technology in the pharmaceutical industry: a tool kit for continuous improvement. PDA J. Pharm. Sci. Technol. 60, 17-53.

Seitavuopio P., Heinämäki J., Rantanen J., Yliruusi1 J., 2006. Monitoring tablet surface roughness during the film coating process. AAPS PharmSciTech. 7, Article 31, E1-E6.

Seppälä K., Heinämäki J., Hatara J., Seppälä L., Yliruusi J., 2010. Development of a new method to get a reliable powder flow characteristics using only 1 to 2 g of powder. AAPS PharmSciTech. 11 (1), 402-408.

Shah R.B., Tawakkul M.A., Khan M.A., 2008. Comparative evaluation of flow for pharmaceutical powders and granules. AAPS PharmSciTech. 9, 250-258.

Shahbazian A., Navarchian A.H., Pourmehr M., 2009. Application of Taguchi method to investigate the effects of process factors on the performance of batch emulsion polymerization of vinyl chloride. J. Appl. Polym. Sci. 113, 2739-2746.

Shekunov B.Y., Chattopadhyay P., Tong H.H.Y., Chow A.H.L., 2007. Particle size analysis in pharmaceutics: principles, methods and applications. Pharm. Res. 24, 203-227.

Soh J.L.P., Liew C.V., Heng P.W.S., 2006. New indices to characterize powder flow based on their avalanching behaviour, Pharm. Dev. and Tech. 11, 93-102.

Soppela I., Airaksinen S., Murtomaa M., Tenho M., Hatara J., Raikkonen H., *et al.*, 2010. Investigation of the powder flow behaviour of binary mixtures of microcrystalline celluloses and paracetamol. J. Excipients and Food Chem. 1, 55-67.

Staniforth J.N., Hart J.P., 1987. Particle size characterization for pharmaceuticals. Anal. Proc. 24, 78-80.

Staniforth J.N., 2002. Particle size reduction. In: Aulton M.E., editor. Pharmaceutics: the science of dosage form design. 2nd ed., Churchill Livingstone, New York, pp.166-173.

Steckel H., Markefka P., teWierik H., Kammelar R., 2006. Effect of milling and sieving on functionality of dry powder inhalation products. Int. J. Pharm. 309, 51-59.

Storme-Paris I., Clarot I., Esposito S., Chaumeil J.C., Nicolas A., Brion F., Rieutord A., Chaminade P., 2009. Near infrared spectroscopy homogeneity evaluation of complex powder blends in a small-scale pharmaceutical preformulation process, a real-life application, Eur. J. Pharm. Biopharm. 72, 189-198.

Sulub Y., Wabuyele B., Gargiulo P., Pazdan J., Cheney J., Berry J., *et al.*, 2009. Real-time on-line blend uniformity monitoring using near-infrared reflectance spectrometry: A noninvasive off-line calibration approach. J. Pharm. Biomed. Anal. 49, 48-54.

Sundell-Bredenberg S., Nyström C., 2001. The possibility of achieving an interactive mix with high dose homogeneity containing an extremely low proportion of a micronized drug, Eur. J. Pharm. Sci. 12, 285-295.

Sun C.C., Hou H., Gao P., Ma C., Medina C., Alvarez F.J., 2009. Development of a high drug load tablet formulation based on assessment of powder manufacturability: moving towards quality by design, J. Pharm. Sci. 98, 239-247.

Tan S.B., Newton J.M., 1990. Powder flowability as an indication of capsule filling performance, Int. J. Pharm. 61, 145-155.

Tasirin S.M., 2000. The effect of fines on flow properties of binary mixtures. Chem. Eng. Comm. 179, 101-115.

Tavares L.M., 2004. Optimum routes for particle breakage by impact. Powder Technol. 142, 81-91.

Tewari J., Dixit V., Malik K., 2010. On-line monitoring of residual solvent during the pharmaceutical drying process using non-contact infrared sensor: A process analytical technology (PAT) approach. Sens. Actuators B Chem 144, 104-111.

Thalberg K., Lindholm1 D., Axelsson A., 2004. Comparison of different flowability tests for powders for inhalation. Powder Technol. 146, 206-213.

Tinke A.P., Vanhoutte K., Vanhoutte F., DeSmet M., DeWinter H., 2005. Laser diffraction and image analysis as a supportive analytical tool in the pharmaceutical development of immediate release direct compression formulations. Int. J. Pharm. 297, 80-88.

Tinke A.P., Carnicer A., Govoreanu R., Scheltjens G., Lauwerysen L., Mertens N., *et al*., 2008. Particle shape and orientation in laser diffraction and static image analysis: size distribution analysis of micrometer sized rectangular particles. Powder Technol. 186, 154-167.

Tok A.T., Goh X., Kiong Ng W., Tan R.B.H., 2008. Monitoring granulation rate processes using three PAT tools in a pilot-scale fluidized bed. AAPS PharmSciTech. 9 (4), 1083-1091.

Tomas J., Schubert H., 1979. Particle characterization. Partec 79, Nurnberg, Germany, 301-319.

Vachon M.G., Chulia D., 1998. The use of particle characteristics to elucidate mix homogeneity in binary powder blends, Drug Dev. Ind. Pharm. 24, 961-971.

Valverde J.M., Castellanos A., Ramos A., Watson P.K., 2000. Avalanches in fine, cohesive powders. Physical Review E 62, 6851-6860.

van Veen B., Pajander J., Zuurman K., Lappalainen R., Poso A., Frijlink H.W., Ketolainen J., 2005. The effect of powder blend and tablet structure on drug release mechanisms of hydrophobic starch acetate matrix tablets. Eur. J. Pharm. Biopharm. 61, 149-157.

Vendola T.A., Hancock B.C., 2008. The effect of mill type on two dry-granulated placebo formulations. Pharm. Technol. 32, 72-86.

Verheezen J.J.A.M., Voort Maarschalk K. van der., Faassen F., Vromans H. 2004. Milling of agglomerates in an impact mill. Int. J. Pharm., 278, 165-172.

Verma S., Lan Y., Gokhale R., Burgess D.J., 2009. Quality by design approach to understand the process of nanosuspension preparation. Int. J. Pharm. 377, 185-198.

Vogel L., Peukert W., 2003. Breakage behaviour of different materials - construction of a master curve for the breakage probability, Powder Technol. 129, 101-110.

Wang G., Antar G., Devynck P., 2000. The Hurst exponent and long-time correlation, Phys. Plasmas, 7, 1181-1183.

Wargo D.J., Drennen J.K., 1996. Near-infrared spectroscopic characterization of pharmaceutical powder blends, J. Pharm. Biomed. Anal. 14, 1415-1423.

Weth M., Hoffman M., Kuhn J., Frick J., 2001. Measurement of attractive forces between single aerogel powder particles and the correlation with powder flow. J. Non-Cryst. Solids 285, 236-243.

Whitaker M., Baker G.R., Westrup J., Goulding P.A., Rudd D.R., Belchamber R.M., *et al*., 2000. Application of acoustic emission to the monitoring and end point determination of a high shear granulation process. Int. J. Pharm. 205, 79-91.

Wong L.W., Pilpel N., 1988. The effect of the shape of fine particles on the formation of ordered mixtures. J. Pharm. Pharmacol. 40, 567-568.

Xu R., Andreina Di Guida O., 2003. Comparison of sizing small particles using different technologies. Powder Technol. 132,145-153.

Xu R., Santana J., 2002. Dynamic image analysis: Improving size measurement of non-spherical particles. Powder & Bulk Eng. 16, 24-27.

Yamamoto N., Shinozuka Y., Kumagai K., Fujii M., Yanagisawa Y., 2004. Particle size distribution quantification by microscopic observation. J. Aerosol. Sci., 35, 1225-1234.

Yeung C.C., Hersey J.A., 1979. Ordered powder mixing of coarse and fine particulate systems. Powder Technol. 22, 127-131.

York P., Ticehurst M.D., Osborn J.C., Roberts R.J., Rowe R.C., 1998. Characterization of the surface energetics of milled dl-propranolol hydrochloride using inverse gas chromatography and molecular modeling. Int. J. Pharm. 174, 179-186.

Yu L.X., 2008. Pharmaceutical quality by design: product and process development, understanding, and control. Pharm. Res. 25, 781-791.

Yu A.W., Standish N., 1987. Porosity calculation of multi-component mixtures of spherical particles, Powder Technol. 52, 233-241.

Yu W., Hancock B.C., 2008. Evaluation of dynamic image analysis for characterizing pharmaceutical excipient particles. Int. J. Pharm. 361, 150-157.

Yu Z.Q., Chow P.S., Tan R.B.H., 2008. Interpretation of focused beam reflectance measurement (FBRM) data via simulated crystallization. Org. Process Res. Dev. 12 (4), 646-654.

Zatloukal Z., Sklubalova Z., 2007. Penetrometry and estimation of the flow rate of powder excipients. Pharmazie. 62, 185-189.

Zeng X.M., Martin G.P., Marriott C., 2001. Particulate interactions in dry powder formulations for inhalation. Taylor and Francis: London & NewYork. pp 20, 52-54.

Zhang Y., Johnson K.C., 1997. Effect of drug particle size on content uniformity of low-dose solid dosage forms. Int. J. Pharm. 154, 179-183.

Zheng J., Carlson W.B., Reed J.S., 1995. The packing density of binary powder mixtures, J. Europ. Ceram. Soc. 15, 479-483.

Zhou D., Porter W.R., Zhang G.G.Z., 2009. Drug stability and degradation studies. In: Developing solid oral dosage forms: pharmaceutical theory and practice. Academic press, Burlington, USA, pp 117.

Zidan A.S., Rahman Z., Khan M.A., 2010. Online monitoring of PLGA microparticles formation using Lasentec focused beam reflectance (FBRM) and particle video microscope (PVM). AAPS J. 12 (3), 254-262.

Curriculum Vitae

Personal Details

First name	**Venkateshwar Rao**
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Nationality	Indian
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	CH-4057, Basel, Switzerland
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Ph.D study

December 2007 to actual date	Ph.D studies at Institute of Pharmaceutical Technology (University of Basel) and Institute of Pharma Technology (University of Applied Sciences, Muttenz) under the supervision of Prof. Dr. Georgios Imanidis and Prof. Dr. Martin Kuentz. Ph.D Title: Novel process analytical technology approaches of dynamic image analysis for pharmaceutical dry particulate systems.

Supervision of the following projects:

January to June 2009	Master Thesis: Flowability characterization of binary powder blends using a novel powder avalanching device (Mrs. Doris Hümbelin, University of Basel).
November 2009 to January 2010	Semester project: Process monitoring of pharmaceutical dry milling and characterizing flowability (Mr. Philippe Chavanne and Mr. Michael Müller, University of Applied Sciences).
March 2009 and 2010	Hard gelatin capsules practical's for final year bachelor students of University of Applied Sciences.

Podium presentations

May 2010	PAT concepts in pharmaceutical dry milling: on-line particle size measurements with dynamic image analysis and at-line flowability testing using powder avalanching. EuPAT4, Kuopio, Finland (presented by Prof. Martin Kuentz).
January 2010	A novel powder avalanching method for the flowability characterization of drug-excipient blends. Annual Research Meeting, University of Basel, Switzerland.
June 2009	A novel method for flowability characterization of pharmaceutical blends. PharmSciFair, Nice, France.

Poster presentations

September 2010	Novel process analytical concepts in pharmaceutical dry milling. Swiss Pharma Science Day, Bern, Switzerland.
March 2010	Dynamic image analysis in pharmaceutical dry milling: from different measurement modes to time evolving size and shape analysis (TESSA). 7th PBP World Meeting, Malta.
February 2009	A novel method for flowability characterization of pharmaceutical blends. Annual Research Meeting, University of Basel, Switzerland.

Trainings & Workshops

March 2009	"Fluid bed drying, granulating and coating", a 3-day workshop held by Technology Training Center in Binzen, Germany.
February 2009	"Multivariate Data Analysis-Basic Course" a 3-day course held by Umetrics in Basel.
August 2008	"Meeting the challenges of pharmaceutical innovation and quality by design in the 21st Century: Implementation of PAT", a 2-day IPS Workshop held in Basel.
May 2008	"Erfolgreich formulieren mit modernen Tablettierhilfsstoffen", JRS Pharma Kundenseminar, Basel.
April 2008	"How can we reduce time to market and enhance product quality", held by Ifiip GmbH and Pharmatrans Sanaq AG, Basel.

Educational Background

October 2004 to August 2007	Master of Science in Applied Polymer Science at Martin-Luther-University, Halle-Wittenberg, Germany. Master thesis title: Evaluation of TG-FTIR and TG-MS coupling techniques for characterization of pseudo-polymorphs (thesis performed at Merck KGaA, Darmstadt, Germany from January to June 2007).
July 1996 to June 2000	Bachelor of Pharmacy (Honors) at Birla Institute of Technology and Science, Pilani, India. Bachelor thesis title: In-vitro metabolism studies of Centchroman (thesis performed at Central Drug Research Institute, Lucknow, India).
August 2000	"Registered pharmacist" in the state of Andhra Pradesh, India.

Work Experience

July to August 2007	Internship at Zentrale Forschung Analytik (ZFA-4), Merck KGaA, Darmstadt, Germany.
April to October 2006	Internship at Zentrale Forschung Analytik (ZFA-5), Merck KGaA, Darmstadt, Germany.
September 2000 to October 2004	Research Associate in Formulations Development at Cadila Pharmaceuticals Limited, Ahmedabad, India.

Personal Skills

Language skills	English (fluent); German (fluent); French (basic); Hindi (fluent); Telugu (Mother tongue).
Computer skills	• Design of Experiments (DoE) and statistical evaluation; multivariate data analysis (MVDA). • Competent with Windows environments, Microsoft Office (Word, Excel, PowerPoint, Outlook), Lotus Notes, MassFrontier, Internet and Scientific literature databases.

Achievements

- Second prize "Publications Award, 2011" awarded during PhD by the School of Life Sciences at the University of Applied Sciences, Muttenz, Switzerland
- Passed in distinction (92.7%) in 12^{th} standard in the academic year 1995-1996
- "Best outgoing student" awarded during High School for the academic year 1993-1994

As a PhD student I have attended lectures and courses given by

Prof. Georgios Imanidis, Dr. Silvia Rogers, Dr. Penelope Vounatsu, Dr. Brian Cutting, Dr. Michael Ulmschneider, Dr. Marek Tulej, Dr. Michael Kessler.