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Particle Size Determination during Fluid Bed Granulation

Tools for Enhanced Process Understanding

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ACADEMIC DISSERTATION

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Abstract

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Fluid bed granulation (FBG) is a widely used process in pharmaceutical industry to improve the powder properties for tableting. During the granulation, primary particles are attached to each other and granules are formed. Since the physical characteristics (e.g. size) of the granules have a significant influence on the tableting process and hence on the end product quality, process understanding and control of the FBG process are of great importance. Process understanding can be created by exploiting the design of experiment studies in well instrumented FBG environment. In addition to the traditional process measurements and off-line analytics, modern process analytical technology (PAT) tools enable more relevant real-time process data acquisition during the FBG.

The aim of this thesis was to study different particle size measurement techniques and PAT tools during the FBG in order to get a better insight into the granulation process and to evaluate possibilities for real-time particle size monitoring and control. Laser diffraction, spatial filtering technique (SFT), sieve analysis and new image analysis method (SAY-3D) were used as particle size determination techniques. In addition to the off-line measurement, SFT was also applied in-line and at-line, whereas SAY-3D was applied on-line. Modelling of the final particle size and the prediction of the particle size growth during the FBG was also tested using partial least squares (PLS).

SFT studies revealed different process phenomena that could also be explained by the process measurement data. E.g., fine particles entrapment into the filter bags, blocking of the distributor plate and segregation in FBG were observed. The developed on-line cuvette enabled SAY-3D image acquisition and visual monitoring throughout the granulations and it performed well even in very wet conditions. Predictive PLS models for the final particle size could be constructed. Based on this information, pulsing of the granulation liquid feed was presented as a controlling tool to compensate for the excessive moisture content during the FBG. A new concept of utilising the process measurement data to predict particle size during FBG was also successfully developed. It was concluded that the new methods and PAT tools introduced and studied will enable enhanced process understanding and control of FBG process.

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Espoo, May 2009

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Contents

List of original publications

This thesis is based on the following publications:

I Närvänen, T., Lipsanen, T., Antikainen, O., Räikkönen, H., Yliruusi, J., 2008. Controlling granule size by granulation liquid feed pulsing. Int. J. Pharm. 357, 132-138.

II Närvänen, T., Seppälä, K., Antikainen, O., Yliruusi, J., 2008. A new rapid on-line imaging method to determine particle size distribution of granules. AAPS PharmSciTech 9 (1), 282-287.

III Närvänen, T., Lipsanen, T., Antikainen, O., Räikkönen, H., Heinämäki, J., Yliruusi, J., 2009. Gaining fluid bed process understanding by in-line particle size analysis. J. Pharm. Sci. 98 (3), 1110-1117.

IV Lipsanen, T., Närvänen, T., Räikkönen, H., Antikainen, O., Yliruusi, J., 2008. Particle size, moisture, and fluidization variations described by indirect in-line physical measurements of fluid bed granulation. AAPS PharmSciTech. 9 (4), 1070-1077.

V Närvänen, T., Antikainen, O., Yliruusi, J., 2009. Predicting particle size during fluid bed granulation using process measurement data. AAPS PharmSciTech., submitted

The publications are referred to in the text by their Roman numerals. Reprinted with permission from the publishers.

Abbreviations

AE	acoustic emission
CCD	charge-coupled device
CCF	central composite face-centred design
EP	European pharmacopoeia
FBG	fluid bed granulation
FBRM	focused beam reflectance method
FDA	Food and Drug Administration
FL	fuzzy logic
GMP	good manufacturing practises
GSDM	grey scale difference matrix
ICH	international conference on harmonisation
NIRS	near infrared spectroscopy
NME	new medical entity
PAT	process analytical technology
PID	proportional, integral, derivative
PCA	principle component analysis
PLS	partial least squares
RGB	red, green, blue
RH	relative humidity
SAY-3D	name of the tested image analysis system
SFT	spatial filtering technique
SOM	self organising map
USP	United States Pharmacopoeia
VIP	variable influence on projection

1 Introduction

The pharmaceutical industry has a growing interest in achieving more robust, efficient and controlled processes in production. One driving force for this is a decreased efficacy of pharmaceutical industry to develop and launch new molecular entities while the development costs have been rapidly increased. For example, the number of the new molecular entities (NME) and biotechnology products first launched worldwide has decreased from an average level of 43 in 1991-1995 to 27 in 2001-2005 (CMR international, 2008). At the same time the estimated full cost of bringing a NME to market has raised to 2-3 folds (DiMasi and Grabowski, 2007). Due to this, much effort has been put to improve the cost-efficacy of the manufacturing processes during the last few years. Methods like Lean manufacturing, Six sigma and Operational excellence programs that have been utilised successfully in other process industries, have also spread to pharmaceutical industry (Shanley, 2006).

The use of more efficient and modern process analytical technologies (PAT) is also encouraged by the regulatory authority (Food and Drug Administration (FDA), 2004). PAT research and development has recently greatly increased, and there are also commercial PAT tools available for different pharmaceutical processes. The shift from traditional off-line quality determination towards real-time quality assurance has, however, not been very rapid. In order to get rid of the quality control analyses after the manufacturing, pharmaceutical industry has a challenge in demonstrating that the analytical methods used during the manufacturing ensure the same product quality as the traditionally used methods. However, when more data from the process is obtained and analysed, it also enables possibilities for quality improvement. PAT tools encouraged to be used include 1) multivariate tools for design, data acquisition and analysis, 2) process analysers, 3) process control tools and 4) continuous improvement and knowledge management tools. The role of product and process understanding, quality risk management and scientific justification of process controls are also emphasized in this new concept (ICH Q8, 2008; ICH Q8 Annex, 2008; ICH Q9, 2005; ICH Q10, 2008). As described in the ICH Q8 guideline, the general target for pharmaceutical development is that the quality should be built-in or should be by design.

Granulation is one of the key processes in pharmaceutical solid dosage form production. Among the various granulation techniques, fluid bed granulation (FBG) is one of the most widely used. One benefit of FBG is that mixing, granulation and drying all occur in the same equipment. The main quality targets for the final granules in pharmaceutical process are usually 1) uniform drug substance content, 2) good processability, and 3) desired drug release profile. Particle size distribution has a major impact on these properties and therefore its reliable determination is of great importance.

To achieve process understanding of a multivariate process like FBG, effective and reliable process-control tools are needed. Air flow rates, air humidity, pressure differences, temperature values and granulation liquid feed rate values are typical process parameters that are determined during the FBG. However, all influencing variables are not necessarily optimally in control. For instance, inlet air humidity can vary significantly during the year and hence influence the particle size growth in FBG if no efficient dehumidifying and moistening systems are in place. By utilizing design of experimental studies, the effects of material and process parameters on critical quality attributes can be understood and the basis for the scientific understanding and justification for relevant real-time process control tools can be created. The selection of appropriate PAT tools for process control and product quality measurements is an important phase and requires deep expertise both in analytical and process perspectives. In addition, good manufacturing practice (GMP) principles applied in pharmaceutical industry necessitate high standards and documentation requirements for any analytical tools to be applied in production environment. Consequently, validation of any PAT tool is also an essential step before implementation.

In this thesis, the approach has been to study the particle size determination techniques in FBG to get better insight into the process and to evaluate potential real-time PAT tools in particle size monitoring and control.

2 Literature review

2.1 Overview of the fluid bed granulation (FBG)

Fluid bed granulation (incl. mixing, wetting and drying) and wet massing in a high shear mixer with subsequent fluid bed drying are the two most important methods to produce granules for pharmaceutical manufacturing (Schæfer, 1988; Wørts, 1998). Fluid bed granulation (FBG) involves three simultaneous rate processes: (1) wetting and nucleation, (2) consolidation and growth, and (3) breakage and attrition (Iveson et al., 2001; Bouffard et al, 2005). Since it is difficult to distinguish these rate processes from each other, some more practical partitioning of the process is required. Thermodynamically, it is reasonable to split the fluid bed granulation process and the modelling in two main stages: 1) binder addition phase and 2) drying phase, since the state of matter in the processing chamber is fundamentally different in these two stages. To get the starting materials mixed, usually a short fluidisation period before the binder addition phase is also performed.

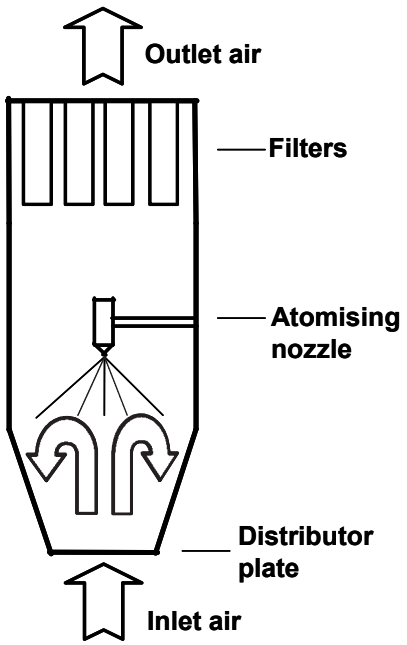


Fig. 1 *Top-spray fluid bed granulator*

A simplified picture of a top-spray fluid bed granulator is shown in Fig. 1. Fluidising air is led through the distributor plate and is consequently removed through the filters. The amount of airflow is controlled by a fan or a lid that is located above the upper filters. The binder solution is sprayed using an atomising nozzle. The powder is fluidised by the air and the forming granules are in continuous movement inside the granulation chamber.

2.2 Granule formation

In order to get granules, bonds must be formed between powder particles. Five primary bonding mechanisms have been suggested (Aulton, 1981):

1. Adhesion and cohesion forces in the immobile liquid films between individual primary powder particles
2. Interfacial forces in mobile liquid films within the granules
3. The formation of solid bridges after solvent evaporation
4. Attractive forces between solid particles
5. Mechanical interlocking

During the granule formation and drying, three states of water distribution can also be separated based on the increasing water amount: pendular state, funicular state and capillary state. According to Flemmer (1991), the moisture content (volume-%) of these stages are 0-13.6%, 13.6-100% and 100%, respectively. During the fluid bed granulation process, granule growth rate and size are influenced by the establishment of a critical dynamic equilibrium between granule wetting and evaporation from the granule surface (Frake et al., 1997). The control of water amount in granulation is important because the water amount greatly affects the granules properties. Kapur and Fuerstenau (1964) divided the granule formation into three stages: 1) Nucleation, 2) Transition and 3) Ball growth. If the water content during the granulation is too high, over wetting of the mass leads to ball growth, which leads to granules with high median particle size and undesired pharmaceutical processing properties. Overview of the granulation mechanism in FBG is given in Fig. 2.

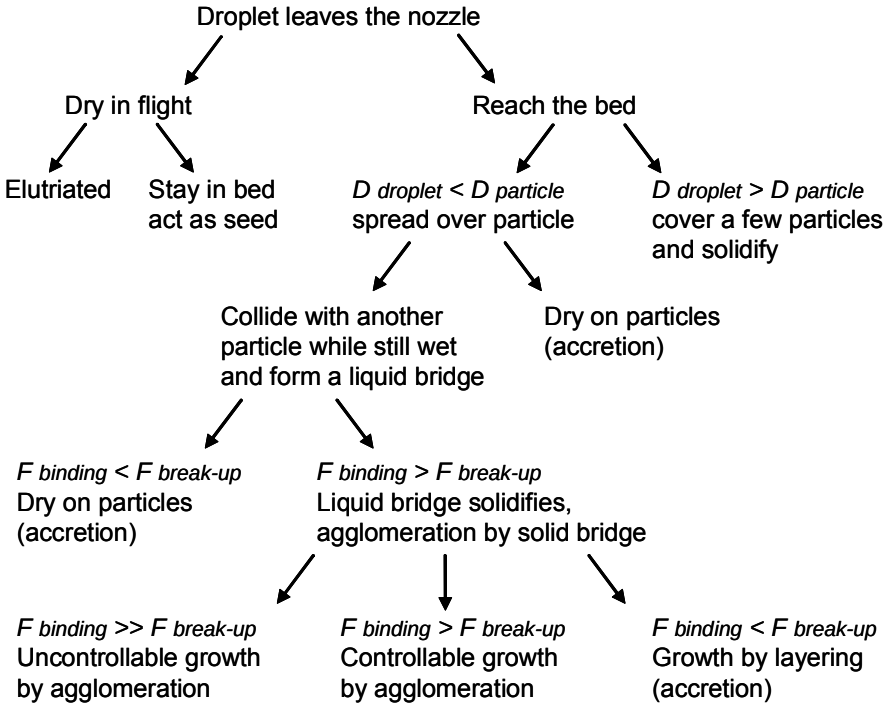


Fig. 2 *Mechanism of granulation in FBG. Modified from Parikh et al (1997) and Maraglou and Nienow (1986).*

2.3 Variables influencing particle size growth in FBG

Strict control of the FBG process is essential in order to get successful operation and desired end product quality in a reproducible way. Because many parameters have significant influence on the process, they are either controlled or monitored in modern FBG equipment. The main material and process variables affecting the quality of final product in FBG are listed in Table 1. It is commonly understood that careful and accurate control and monitoring of this complex set of inter-related parameters in FBG is important, and hence many studies have been carried out to understand these parameters and their effect on the process better. There are several physical and functional testing methods available for granules (Sucker, 1982). Although the variables in FBG have an influence on many granule characteristics, e.g. porosity, bulk and tapped density, surface morphology and flowability, the following overview mainly concentrates on those of the granule size effects.

Table 1. *Main material and process variables affecting product quality in FBG (Modified from Faure et al., 2001).*

Material variables	Spraying phase variables	Drying phase variables
Solid solubility and degree of swelling in binder liquid	Inlet air temperature and relative humidity	Inlet air temperature and relative humidity
Powder particle size distribution	Spray droplet size	Air flow rate
Binder concentration and viscosity	Quantity of solvent	Process time
Wettability of the solid by the liquid	Bed fluidity/air flow rate	
	Equilibrium temperature and relative humidity in bed	
	Spraying surface and rate	
	Process time	

2.3.1 Process

There are several process parameters that can be adjusted in FBG. Although many studies have been carried out for single parameters in FBG it is important to recognise that the parameters do have interrelationships and they may influence each other. The bed moisture content and the droplet size are two important elements in FBG. To prevent the overwetting of the powder mass, there should be an equilibrium between the moisture intake and evaporation during the FBG (Kristensen and Schæfer, 1987). Increase in liquid flow rate and inlet air humidity result to larger droplet size and higher bed moisture and hence larger granules are usually obtained (Davies and Gloor, 1971; Schæfer and Wørts, 1978a; Schaafsma et al., 2000). However, if the air-to-liquid mass ratio is kept at a constant level, the increased liquid flow rate decreases the droplet size (Schæfer and Wørts, 1977b).

Increase in atomising air decreases the droplet size and therefore smaller granules are obtained (Merkku et al., 1993; Juslin et al., 1995a-b; Yu et al., 1999; Hemati et al., 2003; Bouffard et al., 2005). Increased inlet air temperature and excess gas velocity enhance evaporation and hence decrease the granule size (Lipps and Sakr, 1994, Wan et al., 1999). According to pilot scale studies by Cryer and Scherer (2003), binder spray rate and binder droplet size explained 65% and 10% of the granule size variance, respectively. Rambali et al. (2001b) found that granule size can be optimised by using 3 fundamental variables: the powder moisture content, the droplet size and the airflow rate. Too high airflow rate can, however, result to attrition of the granules (Parikh, 1991). The granule breakage during the drying process is also dependent on the moisture content of the granules; dry granules are

more prone for attrition and the fines fraction increases under stress (Nieuwmeyer et al., 2007a). Different testing methods have also been developed to study the attrition and breakage of the granules (Tardos et al., 1997; Airaksinen et al., 2000; Reynolds et al., 2005).

2.3.2 Materials

The properties of the starting material have an important role in FBG process. Since the wetting and the free water present on the surface of the particles are essential in the formation of granules, the particle size of the starting materials affects the granulation. As the decrease in particle size increases the total surface area of the mass, it also results in a smaller granule size (Schæfer and Wørts, 1977a; Ormós and Pataki, 1979b; Abberger et al., 2002). Small particle size and needle-like shape of the particles can also lead to problems in fluidisation (Kristensen and Schæfer, 1987; Juslin and Yliruusi, 1996b). Kristensen and Hansen (2006) used a rotary processor in FBG to compensate the impaired fluidisation activity due to the increased cohesivity of the starting material. Absorbing materials, e.g. starch, result in incomplete wetting of the surface and thus the amount of liquid should be higher (Schæfer and Wørts, 1977a; Schinzinger and Schmidt, 2005). The solubility of the starting material into the binding solution also influences the granule growth. Ormós and Pataki (1979a) compared 5 different materials that had different solubilities and found that the highest growth rate was obtained with the materials having the highest solubility.

Drying is simultaneously occurring during the spraying phase in FBG. When higher binder concentrations are used, the evaporation of the solvent results in more viscous liquid bondings and more stabilised agglomerates. Consequently also the granule size is increased (Kristensen and Schæfer, 1987). Relationship between final granule size and binder concentration has been well established (Davies and Gloor, 1972, 1973; Schæfer and Wørts, 1978b; Alkan and Yuksel, 1986; Wan and Lim, 1991; Wan et al., 1992; Rohera and Zahir, 1993; Liu et al., 1994; Abberger, 2001b; Bouffard et al., 2005; Rajniak et al., 2007). Also, the type of binder has a role in the agglomeration phenomenon. In general, an increase in viscosity also results in increased agglomerates. Gelatin, however, has been found to form a portion of big granules even at low binder concentrations (Schæfer and Wørts, 1978b; Ormós et al, 1979c; Georgakopoulos et al., 1983; Rohera and Zahir, 1993).

High particle-binder-particle bond strength and gelation of gelatine solutions have been suggested to be reason for this.

2.3.3 Equipment

Equipment variables in FBG have not been found to be as relevant as in high shear mixing (Kristensen and Schæfer, 1987). Proper fluidisation can be obtained by different distributor plates as well as by varying FBG container shapes. Davis and Gloor (1971) found that the decrease in the nozzle height increased the average granule size slightly and decreased the friability of the granules. This was explained by the binder's increased ability to wet and penetrate the fluidised solids due to the shorter distance. If the nozzle is located at a too high position, the risk of spray drying and walls wetting also increases (Hemati et al., 2003). In other studies, the height of the atomising nozzle or the nozzle diameter has had only little or no effect at all on the FBG process (Rambali et al., 2001a; Cryer and Scherer, 2003). On the other hand, too low position of the nozzle may result to clogging of the nozzle. The size of the granulator, however, can have a significant impact on the particle size and therefore the moisture content in the bed is the key parameter to be controlled in scale-up studies (Faure et al., 2001).

2.4 Sampling and process measurements

The primary goal of sampling is to withdraw the smallest quantity of the material that can provide a representative particle size distribution (Shekunov et al., 2007). The probability of obtaining a sample which perfectly represents the actual particle size distribution is, however, remote. When several samples are taken their characteristics will deviate and if these samples are representative, the expected variation may be assessed from statistical analysis (Allen, 1990). The sampling technique itself will add further variation to the results, which has to be taken into a consideration. The total sampling error is by far the dominating factor in all analytical activities and therefore practical sampling principles have been suggested (Petersen et al., 2005). However, as it is not always possible to obtain the optimum samples from the process, the two golden rules of sampling should still be adhered to whenever possible (Allen, 1990):

1. A powder should be sampled when in motion.
2. The whole of the stream of powder should be taken for many short increments of time in preference to part of the stream being taken for the whole of the time.

The scoop sampling is widely used in FBG processes due its simplicity and because it can be taken during the fluidisation. The assumption then is that the sample taken from the process is representative of the whole bulk. However, it is well known that scoop sampling is subject to large errors and it tends to be very operator sensitive (ISO 14488, 2007). The axial size segregation phenomenon in fluid bed granulation can be significant and dependent on the fluidisation velocity (Hoffmann and Romp, 1991). Therefore, the influence of the sampling height should be studied for the FBG process. If very large granules (>800 μm) are present in FBG, the radial segregation can also occur (Wormsbecker et al, 2005) and representative sampling is even more complicated. When the optimal sampling location is established the accuracy can be increased by gathering more samples, and then also the variance between the samples can be determined.

Some traditional off-line techniques can, in principle, be utilised as at-line applications too. Then, however, the sample treatment should be quite straightforward and the analysing time rapid enough. The sample used for analysis can be quite small, and therefore the sample obtained from the process should be divided before the analysis in a controlled way. The two golden rules previously stated for sampling are valid also for dividing of samples. In the comparison studies performed for different sample dividing techniques, the spinning riffler has proved to be the best method (Allen and Khan, 1970). According to the experimental results, the estimated maximum sample error for the scoop sampling and the spinning riffling techniques were 17.1% and 0.42%, respectively.

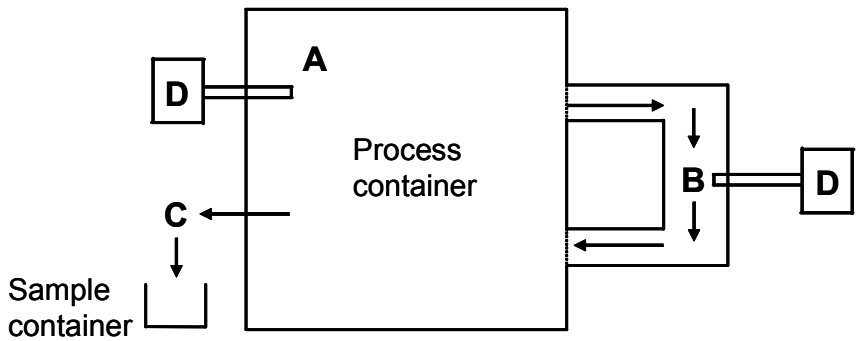


Fig. 3 *Illustration of in-line (A),on-line (B) and at-line (C) sampling applications from a processs (D=measurement equipment).*

Basic principles of the at-line, on-line and in-line sampling techniques are illustrated in Fig. 3 and more detailed descriptions are found in literature (Callis et al., 1987). In an at-line application, the sample is withdrawn from the process, e.g. by scooping. On-line application includes an automatic sampling device that collects the sample and directs it to measurement equipment. Depending on the analysing technique, the sample can be either destroyed or returned to the process. In in-line application, analysis is carried out during the process without any special sampling procedure. These techniques can further be divided into two classes whether they disturb the process or not. In-line analyses are often performed optically through a window or using a probe installed inside the process chamber. The challenge in these applications is to maintain the cleanliness of the optical window throughout the process. The potential sources of errors related to the manual sampling, e.g. poor repeatability, small amount of samples obtained and time-consuming sample treatment, are clear disadvantages of the at-line application compared to the on-line and in-line applications.

2.5 Definition of particle size

When the particles have a regular shape, e.g. ball (Fig 4a), the meaning of particle size is easy to understand. However, even for spherical particles the median volume particle size results can differ 10% between the the measurements techniques (Shekunov et al., 2007). The more irregular the particle shape is, the more the particle size result is related to and dependent on the particular measurement technique used. Although any single linear measurement for an irregular particle (Fig 4c) can be quite irrelevant, the determination of large number of randomly orientated particles can give statistically meaningful size distribution data.

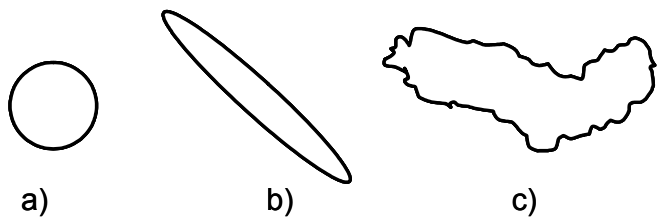


Fig. 4 *Ball (a), acicular (b) and irregular (c) shaped particles*

Different measurement techniques define different particle size diameters. Some typical particle size definitions are shown in Table 2. Depending on the measurement technique, the size distribution is usually represented as number-, volume- or mass-weighted size distribution. The particle size results are usually presented using average diameters, such as median (50%) size and the whole distribution can be visually illustrated as frequency or cumulative size distributions.

Table 2. *Typical definitions of particle size, modified from Allen (1990)*

Symbol	Name	Formula and/or definition
d_v	Volume diameter	$V = \pi/6 \bullet d_v^3$ Diameter of a sphere having the same volume as the particle
d_s	Surface diameter	$S = \pi d_s^2$ Diameter of a sphere having the same surface as the particle
d_A	Sieve diameter	The width of the minimum square aperture through which the particle will pass
d_P	Projected area diameter	Diameter of a circle having area equivalent to that of the particle

2.6 Particle size determination techniques in FBG

2.6.1 Sieving

Different particle size measuring techniques and sampling applications have been utilised in the granule growth and attrition studies. The most commonly used technique is probably analytical sieving. During the FBG samples have been taken and they have been dried before the analysis (Juslin and Yliruusi, 1996a; Watano et al., 1996b; Hemati et al., 2003). This technique is laborious and time consuming, and therefore, not very popular in industrial or academic studies, anymore. There are also potential sources of error for the analysis, e.g. sample treatment before the sieving. Wet granule mass cannot be directly sieved, and during the drying of sample the particle size distribution of the granules may be altered. Sieve analysis is, however, still widely used to determine the particle size distribution of the final dried granules and it is also described in the pharmacopoeia (Ph. Eur. 6, 2.9.38., 2008; USP 32, <786>, 2009).

2.6.2 Image analysis

Optical microscopy for particle characterisation can generally be applied to particles of 1 μm and greater (Ph. Eur. 6, 2.9.37., 2008; USP 32, <776>, 2009). The characterisation using image processing and analysing techniques includes 5 steps: image acquisition, preprocessing, segmentation, extraction, and representation of the characteristic parameters (Nazar et al., 1996). One commercially available image analysis technique is QICPIC™ by Sympatec that uses similar dispersion systems as laser diffraction (Köhler et al., 2007). Many challenges, however, are related to the dispersion of the wet and sticky particles and granules. On the other hand, if very powerful dispersion forces are used to detach the particles from each to other, there is also a risk of breaking the granules. This risk and consequent inaccurate particle size results is highest in the early granulation phase, where no solid bonds yet exist. Therefore, the methods that require little or no sample treatment are suitable for granule growth and attrition studies. Laitinen et al (2002, 2003, 2004) presented an at-line image analysis technique that used grey scale difference matrix (GSDM). Using a partial least squares modelling they developed a model between the GSDM and the particle size distribution measured by sieving. The technique needed no sample treatment or particles dispersing and was therefore suitable during the whole granulation process. Since the method had to take two separate images from different angles and time points it could not, however, be applied as on-line or in-line.

An in-line image processing system has been studied in wet granulation processes (Watano and Miyanami, 1995a; Watano et al., 1997). The body of the system consisted of CCD camera, optical fibres, a telephoto lens and an air purge unit. A stroboscope with a xenon lamp gave light flashes at 1 μs intervals. As it is usual in image processing techniques, pre-processing procedure was needed, such as filtering, binarisation, reduction of noise and segmentation of overlapped particles, before the particle size identification and counting was performed. Using the image processing technique the mass median particle size and the shape factor of the particle could be determined. The particle size results determined by the image processing system corresponded well with the sieve analysis results. Study results also revealed that the position of the image analysis probe influences on the results due to the particles segregation in fluid bed granulator.

2.6.3 Laser diffraction

There are only a few particle size determination techniques that are available for either in-line or on-line application for fluid bed granulation. Laser diffraction technique can be attached into the process by using a specialised sampling device. In the laser diffraction, a dispersed sample at an adequate concentration is passed through a beam of a monochromatic light (Ph. Eur. 6, 2.9.31., 2008). The light scattered by the particles at various angles is measured by a multi-element detector. The scattering pattern values are transformed, using an optical model and mathematical calculation, to yield a volumetric particle size distribution. The commercial laser diffraction equipment suppliers have they own solutions for the optical modelling, and dissimilar particle size results have been reported between different laser diffraction equipment (Etzler and Deanne, 1997). Laser diffraction equipment suppliers have in-line/on-line systems equipped with appropriate samplers (Insitec™ by Malvern, UK; Mytos™ by Sympatec, Germany). Although these techniques have been utilised in milling and different wet processes (Crawley, 2001; Ma et al, 2001; Crawley, 2003; Witt et al, 2003; Crawley and Malcolmson, 2003, 2004), no reports of FBG applications is found in the literature.

2.6.4 Chord length determination

In a focused beam reflectance method (FBRM) a tightly-focused laser beam is projected from a probe into the measurement location through a window (Heath et al., 2002; Gregory, 2008). The laser beam is rotated at high speed (2-8 m/s). Particles passing near the probe window reflect the laser light and the reflected light is detected. Overview of the measurement technique is shown in Fig. 5. The system determines chord length distribution and it has been successfully utilised in suspensions and in crystallisation process (Braatz, 2002; Barrett et al., 2005; Kougoulos et al., 2005; Sistare et al., 2005). Recently, FBRM has also been studied in FBG in comparison with two other PAT tools (Tok et al., 2008). FBRM could detect the three main rate processes (wetting and nucleation, consolidation and growth and breakage), although the sensitivity of the optical signal was susceptible to fouling of the probe window. Due to this well known disadvantage of optical in-line probes, an at-line FBRM application has been developed to enable granule growth studies (Hu et al., 2008). In this application, granules were suspended in the silicon oil. They found that the FBRM and sieve analysis results of the

dried granules were close to each other. Furthermore, the process samples analysed by FBRM and laser diffraction had a similar trend, although the laser diffraction results were clearly bigger.

Spatial filtering technique (SFT) is another method to determine the chord length distribution (Petrak, 2001, 2002; Petrak and Rauh, 2006; Schmidt-Lehr et al., 2007). In SFT the measured particles are dispersed using pressurised air through the measurement zone inside the probe (Fig. 5). The velocity and the chord length size of the particles are measured as they move through the laser beam and hence prohibit light entrance to the detectors. Where FBRM is most suitable in suspensions, SFT cannot be immersed into liquids. The advantage of the SFT over FBRM is, however, that it can also easily be used as an at-line application without any method development, and consequently be utilised in granule growth studies in FBG. Both chord length size techniques are also commercially available (Lasentec™ by Mettler-Toledo and Parsum™ by Malvern). As the chord length distribution is influenced by many variables, e.g. particle orientation and shape, there are study reports that focus on the calculation and transformation of chord length distributions into true particle size distribution. Both empirical (Heath et al., 2002; Giulietti et al., 2003) and theoretical (Simmons et al., 1999; Ruf et al., 2000; Bloemen and De Kroon, 2005) approaches to this are available.

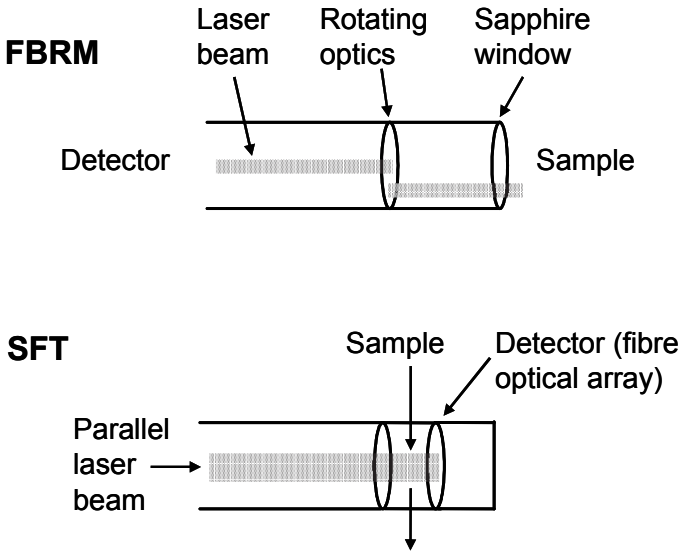


Fig. 5 *Illustration of FBRM and SFT measurement techniques*

2.6.5 Near infrared spectroscopy

Near infrared spectrophotometry (NIRS) is a technique with wide and varied applications in pharmaceutical analysis (Ph. Eur. 6, 2.2.40., 2008; USP 32, <1119>, 2009) and an increasing effort has been put on NIRS applications in pharmaceutical technologies in recent years (Reich, 2005; Roggo et al., 2007). It has been long recognised that NIRS reflectance is influenced also by physical characteristics of the sample (Ciurczak et al., 1986) and therefore particle size of pharmaceutical powders and final granules has been studied by NIRS technique (Frake et al., 1998; Pasikatan et al., 2001; Otsuka et al., 2003, Otsuka, 2006; Niewmeyer et al., 2007b). In FBG studies, where NIRS has been applied real-time, Frake et al. (1997) utilised the change in zero order absorbance of the spectra and were able to have a qualitative comparison with the sieve analysis results. Similarly, Rantanen and co-workers (1998, 2000a) reported that the baseline of apparent absorbance increased when reflectance decreased due to the larger particle size. They studied the particle size in FBG using a four-wavelength near infrared sensor. Goebel and Steffens (1998) obtained a good correlation between the NIRS and particle size data in FBG, however, the range of the particle size was quite limited (20-110 μm). Findlay et al. (2005) developed a NIRS model for FBG that gave comparable results with the off-line image analysis method. As the water also influenced the model, the particle size model had to be corrected when the moisture content was greater than 3% w/w. They also reported that the real-time particle size measurements are less accurate during the first 20 min due to the fouling of the NIRS probe window and to the self-association/agglomeration of the starting material. Nieuwmeyer et al. (2007) developed a partial least squares regression (PLS) model between the NIRS signal and particle size results measured by laser diffraction. Granule samples between the 300 μm and 800 μm were most accurately predicted.

2.6.6 Acoustic emission

Acoustic emission (AE) is a technique that has been studied also in pharmaceutical applications and it can be found also in the pharmacopoeia (USP 32, <1005>, 2009). Manufacturing processes cause vibrations that carry embedded information concerning both physical and chemical parameters (e.g. composition, mixing progress, flow density, particle size). These vibrations can be measured by AE sensors. AE can be applied as non-invasive in-line technique and therefore it is also appropriate for FBG environment.

Belchamber et al. (1986) studied hydration of silica gel granules and found relationship between the AE signal and granules that exceeded 0.5 mm in size. Halstensen and Esbensen (2000) studied AE in the flow segregation studies, where a funnel flow phenomenon was gained using different particle size fractions. Later it was applied in FBG (Halstensen et al., 2005, 2006). In those studies the process trajectories could be obtained and the various particle size distributions could be differentiated. Recently, Matero et al. (2008) studied AE to determine granule size and water content in FBG. Although the AE gives no direct particle size data, the correlations can be developed using chemometric tools and thereby in-line particle size monitoring may be possible. AE studies in high-shear granulation applications have also been carried out (Whitaker et al., 2000; Papp et al, 2008).

2.7 Control and modelling of particle size in fluid bed granulation

PID (proportional, integral, derivative) controller is a commonly used feedback mechanism in industrial control systems. A PID controller attempts to correct the error between a measured and a desired value for a process variable by calculating and then utilizing a corrective adjustment action. In FBG, air flow rate and temperature are typical process variables that can be adjusted by PID controller. The general equation (1) for PID is given below. Term u is the controller output and the 3 terms stand for proportional ($K_p e$), integral ($K_i \int e dt$) and derivative ($K_d\ de/dt$) parts. K in each term represents the gain (tuning parameter) and e is the difference between the targeted and measured process value.

$$u = K_p e + K_i \int e dt + K_d\ de/dt \qquad (1)$$

If the PID controller parameters are selected improperly, the controlled process input can be unstable. Therefore, PID loop should be tuned to each application and there are both manual and commonly used mathematical methods available for that. The control system performance and stability can be further improved by including a feed-forward control system into the PID feed-back control. In a feed-forward system, the knowledge about the system (e.g. the desired acceleration) can be fed forward and combined with the PID output.

According to the PAT guidance (FDA, 2004) the design and optimisation of drug formulations and manufacturing processes can include 4 steps:

1. Identify and measure critical material and process attributes relating to product quality
2. Design a process measurement system to allow real time or near real time (e.g., on-, in-, or at-line) monitoring of all critical attributes
3. Design process controls that provide adjustments to ensure control of all critical attributes
4. Develop mathematical relationships between product quality attributes and measurements of critical material and process attributes

The FBG process and hence the granule properties are influenced by a complex interaction of materials, process and equipment parameters. Data analyses and modelling are usually needed when identifying the critical material and process attributes as well as when the process control systems are established. Given such multivariate relationships, conventional data-processing methods are not best suited for investigation of the process of size enlargement. Therefore, multidimensional modelling methods, such as principle component analysis (PCA), self-organising map (SOM), partial least squares regression (PLS), fuzzy logic (FL) and neural networks have been utilised in FBG studies.

According to Dasykowski et al. (2003) PCA is the most popular linear projection method and it is used to examine structures, observations, similarities and trends of large data tables. The visualisation of the process by PCA or by SOM is a practical and illustrative way to monitor FBG process qualitatively. SOM is an unsupervised artificial neural networks method for observing and visualizing high-dimensional data (Kohonen, 1997). Using process measurements and in-line NIR data Rantanen et al (2001) demonstrated that the path (process trajectory) of a successful granulation batch can be visualised by SOM method. PCA has also been utilised in acoustics applications. Matero et al. (2008) could cluster the different granule size fractions in FBG using PCA. In addition to the granule size clustering, Halstensen et al. (2005, 2006) were able to monitor process trajectory and different process phenomena, such as nozzle clogging by PCA. A generalized regression neural network has also been successfully utilised to predict the granule properties (Behzadi et al., 2005). A series of granulation processes were performed where product and process parameters were investigated. For the five test batches, the predicted results for mean granule size were in good correspondence with the sieve analysis.

PLS is a projection method relating two data matrices to each other by a multivariate model (Haaland and Thomas, 1988; Wold et al., 2001). It can be used e.g. for multivariate calibration and for process modelling and optimisation. PLS has been widely used in NIRS applications for chemical analyses, and recently also in particle size prediction (Nieuwmeyer et al., 2007). FL and fuzzy set theory are mathematical ways to handle uncertainty (Zimmermann, 1991). In order to get rid of the overwetting problems of the mass and consequent too large granule formation in FBG, an automatic process control system utilising FL was developed (Watano et al 1995b, 1996c). The FL system employed the linguistic algorithm of if-then rules that considered the lag and delay elements that were difficult to predict manually. Neurofuzzy logic has also been used for data mining of fractured experimental data in FBG (Shao et al., 2008). Rambali et al. (2003) utilised the deepest regression method for optimisation of FBG when only incomplete process data was available. Model utilising heat transfer and moisture balance measurements have also been used for granule size prediction in FBG (Watano et al., 1996b).

Other theoretical models, such as discrete particle modelling and population balance modelling have been utilised in order to better understand the granule growth and segregation phenomena in FBG (Watano et al., 1995c, 1996a; Abberger, 2001a; Cameron et al., 2005; Dahl and Hrenya, 2005; Deen et al., 2007). The ultimate goal for the modelling should be the establishement of physical models i.e. achieving mechanistic understanding of the FBG. These kind of models may include information e.g. of the elastic/plastic properties of the granules, and the probability of the collisions, coalescences and breakage during the FBG (Iveson et al., 2001).

3 Aims of the study

To aim of this thesis was to study different particle size measurement techniques during the fluid bed granulation in order to get better insight of the granulation process and to evaluate the possibilities of real-time particle size monitoring and control. Specific goals of this study were:

1. to evaluate different particle size determination techniques for granules
2. to study the effect of granulation liquid feed pulsing on the particle size
3. to investigate the feasibility of a novel image analysis method for particle size monitoring during the fluid bed granulation
4. to study the influence of implementing different particle size measurement techniques (off-line, at-line, in-line) on the particle size results of FBG process
5. to test modelling approaches for particle size control and prediction in fluid bed granulation process

4 Experimental

4.1 Materials

Each batch consisting of 2.0 kg theophylline anhydrate (200 M, BASF Aktiengesellschaft, Ludwigshafen, Germany) and 2.0 kg α-lactose monohydrate (200 M, DMV International GmbH, Veghel, The Netherlands) was granulated, using 2 kg of 7.5% aqueous binder solution of polyvinylpyrrolidone (Kollidon K-30; BASF).

4.2 Manufacturing of granules

The granulations were performed in an automated bench scale fluid-bed granulator (Glatt WSG 5; Glatt GmbH, Binzen, Germany). The instrumentation is described in detail by Rantanen et al.. (2000b). The inlet air humidity of the process air was modified using a humidifying system (Defensor Mk4; Brautek Oy, Espoo, Finland). The relative humidity (RH) of the inlet air was measured from the inlet air duct before the heating element. The atomisation pressure was 0.1MPa and the nozzle height set to 45 cm from the distributor plate. The inlet air temperature was 40°C during the mixing and spraying phases and was raised to 60°C during the drying phase. The inlet airflow rates were adjusted to 0.04m^3/s and 0.08m^3/s for the mixing and granulation/drying phases, respectively. A mixing time of 2 min was used in all batches. The final moisture content of the granules, measured by loss-on-drying (Sartorius Thermocontrol MA 100; Sartorius, Göttingen, Germany), was not more than 1.1% in all batches.

A central composite face-centred design (CCF) with three mid-point repetitions was used in this study. Inlet RH, granulation liquid feed rate and granulation liquid feed pulsing were studied at three levels (Table 3). The inlet air humidity levels were >13 g/m^3 (high), 7–12 g/m^3 (medium) and <6 g/m^3 (low). The granulation liquid feed rate values were 90 g/min, 70 g/min and 50 g/min. Granulation liquid feed pulsing was initiated after half of the total liquid amount (2000 g) was sprayed. The granulation liquid feed was interrupted for 1 min every 2nd minute (50% pause time), every 3rd minute (33% pause time) or not at all (0% pause time). The granulations were performed in randomised order. In addition to

the design of experiment studies, additionally batches were manufactured using the same materials, process parameters and factors as in CCF study.

Table 3. *Design of experiments*

Batch	Average water content of inlet air	Granulation liquid feed rate	Pause time in liquid feeding
1	-1	-1	-1
2	1	-1	-1
3	-1	1	-1
4	1	1	-1
5	-1	-1	1
6	1	-1	1
7	-1	1	1
8	1	1	1
9	-1	0	0
10	1	0	0
11	0	-1	0
12	0	1	0
13	0	0	-1
14	0	0	1
15	0	0	0
16	0	0	0
17	0	0	0

4.3 Particle size determination methods

4.3.1 Image analysis method (SAY-3D)

In the image analysis method (SAY-3D) a granule bed surface was illuminated through the window from three sides, using the ultra bright RGB (red, green, blue) leds. Illumination angle to the bed surface was 27°. The maximum luminous intensities of the red, green and blue led were 7,400, 9,500 and 3,500 mcd, respectively. Illumination intensities were adjusted so that each colour contributed to the illumination equally. One colour picture was taken by a 6-megapixel CCD camera (Canon PowerShot S3 IS, Canon Inc.) with 4× close-up lens using 1-ms illumination. The measuring arrangement is schematically described in Fig. 6a. Camera was controlled to take images and send them to a computer (IBM Think Pad, levono T60) by Canon's own software (Remote shooting, Camera Window, Canon Inc.). A topographic picture of the object was constructed based on the colour intensities using Visual Basic 6 (Visual Studio, Microsoft corp.) programming language. Resolution of 14×14 μm was used.

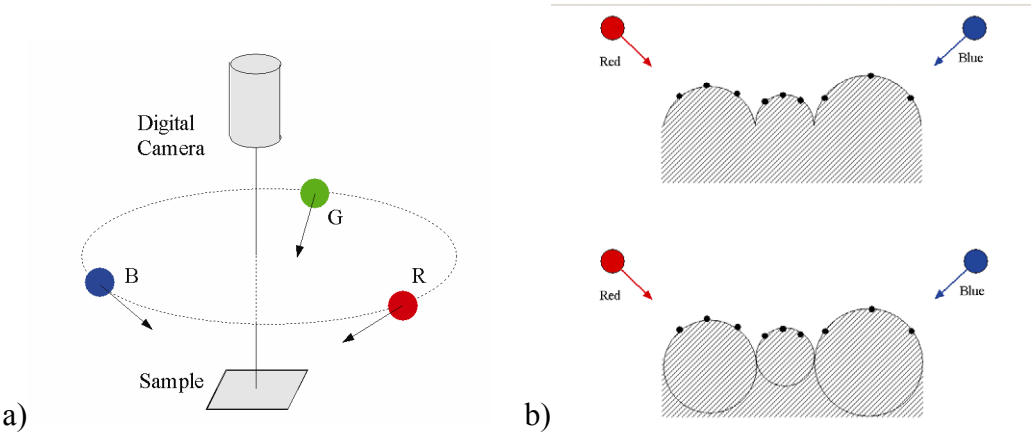


Fig. 6 *The measuring principle of SAY-3D (a) and the particle size determination from topographic data (b).*

After the topography was calculated, the sizes of the individual granules were determined from the topographic data. The granules were approximated to ideal spheres. Using the topographic data, three points were selected to represent each granule (Fig. 6b). Since the height data of the surface were known, the granule size of each particle was obtained. With a computer used here the software was able to determine the sizes of 2,000 particles from one image in a few seconds. Consequently, the number particle size distribution from each image was gathered which was transferred to volume size distribution.

For preliminary accuracy and precision evaluation, 4 sieve fractions (250–355 µm, 355–500 µm, 500–710 µm, and 710–1,000 µm) were used. A standard glass cuvette (40×28×15 mm) was filled with the sample and pictures were taken. 40 images were taken from each fraction for analyses and the sample was mixed before each measurement.

4.3.2 Laser light diffraction

The volume particle-size distribution was determined with laser light diffractometry (Laser Diffraction Particle-size Analyzer LS13 320; Beckman Coulter Inc., Miami, FL, USA), using Fraunhofer theory. A 20-ml sample was dispersed, using air as the medium in the Tornado Dry Powder System; the dispersion pressure was 4.7 kPa. A mean of three measurements was used for data analyses.

4.3.3 Sieve Analysis

A 50-g sample was vibrated with an automatic sieve shaker (Fritsch analysette, Idar-Oberstein, Germany) for 5 min. The sieve analyses (range 71–2,000 μm with √2 increment) were performed in triplicate for each batch and the mean values for mass median particle size were determined.

4.3.4 Spatial filtering technique (SFT)

In the SFT (Parsum® IPP 70; Gesellschaft für Partikel-, Strömungs- und Umweltmesstechnik GmbH, Chemnitz, Germany) the particles passed through an aperture (diameter 4 mm). Pressurized air was used to disperse the particles. Measured raw data was collected via A/D converter to a PC (Pentium II, 2 GHz, 40 GB HDD, 512 MB RAM). The SFT software operated in the Windows® XP environment. The volume particle size distribution calculated by the software was used.

4.4 Other physical characterisation methods

The flowability and the apparent volume values were determined according to the European Pharmacopoeia 5th edition. The Carr's Index was calculated from the bulk and tapped density values. Images of the final granules were recorded with a scanning electron microscopy (Zeiss DSM 962, Oberkochen, Germany).

4.5 Sampling and measurement arrangements

4.5.1 Off-line measurements

After the drying process was finalized, all granules were poured through a 3.15 mm sieve to remove any clumps. The mass was divided using the spinning riffler (Fritsch Sample Divider Laborette 27, Idar-Oberstein, Germany) to the desired sample amount in order to get representative samples for each measurement technique.

4.5.2 At-line measurements

During the fluid bed process, manual sampling was carried out at a height of 13 cm from the distributor plate (Fig. 7). The samples (3–5 g) were analysed by SFT as an at-line application. The measurement arrangement is illustrated in Fig. 8. Each sample was poured manually through the aperture of the SFT probe, using a funnel.

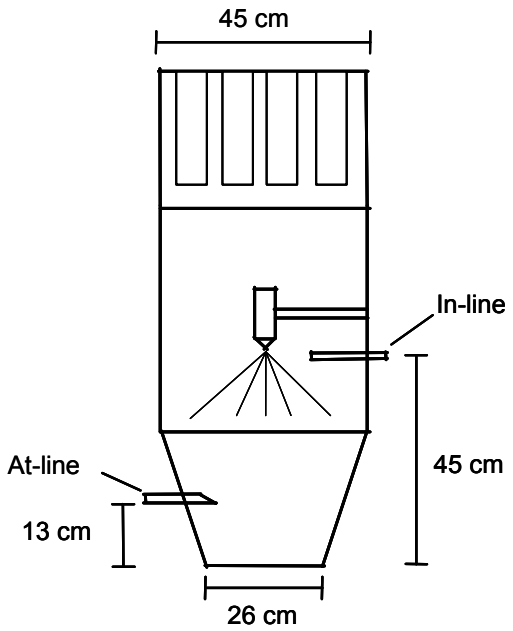


Fig. 7 *In-line and at-line sampling locations in Glatt WSG5 fluid bed granulator*

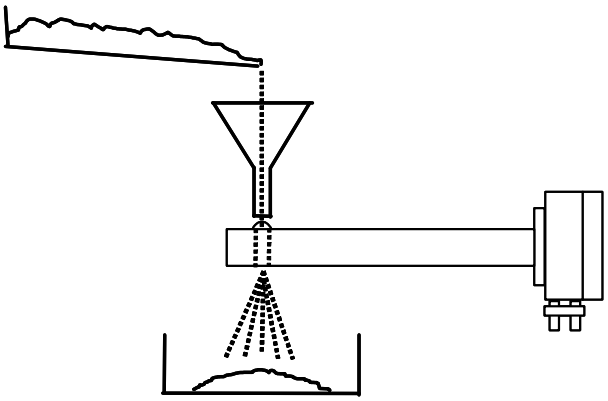


Fig. 8 *At-line measurement arrangement*

4.5.3 On-line measurements

At first, the sampling cuvette was located inside the granulator. However, it was soon found that fouling of the window prevented reliable image acquisition. The final installation system is illustrated in Fig. 4 (in paper II), in which the sampling cuvette is located outside the granulator. System consisted of a digital camera with close-up lens (11×8×13 cm) and the body (6×6×21 cm) where the cuvette and leds were located. The sampler orifice (20×35 mm) was installed at a height of approximately 13 cm from the distributor plate. Cuvette was quickly filled by the granules during the fluidisation and pulsed air pressure was used to return the sample to the process between the measurements. Five images per minute were taken during the process and the pictures were sent to a computer for near real-time image analyses. The image size was 15×20 mm; about 350 pictures were taken during each granulation process.

4.5.4 In-line measurements

An in-line SFT probe was installed in the granulator at a height of 45 cm (Fig. 7). In preliminary studies, lower probe locations were also tested; however, sticking of the particles into the probe influenced the results. During the fluid bed process, an average number and volume particle size distribution data at 10 s intervals was saved. Additionally, a moving average of 6 last median volume particle size values was monitored during the process.

4.6 Data analysis and modelling

The number particle size data determined with SAY-3D were transformed to volume particle size distribution. The median size from the volume particle size distribution was used to compare SAY-3D results with sieve fraction measurement results. Additionally, the moving average median size of ten consecutive images was monitored during the process. Volume particle size distribution results obtained by the SFT software were used.

4.6.1 Off-line model

The 10% (d_{10}), 50% (d_{50}) and 90% (d_{90}) fractiles from the cumulative volume particle-size distribution were used for modelling. In addition, sieve fraction calculation was performed for the SFT and laser diffraction results. The independent variables (factors) in the model were: (1) humidity of the inlet air (Air), (2) granulation liquid feed rate (Liq) and (3) relative time of pauses in the granulation liquid feed (Pau). The average inlet air RH values measured during the process were used for the modelling. The responses included the median volume particle size (GS) of the final product and the relative width (RW) of the size distribution (Equation 2).

$$RW = (d_{90} - d_{10})/d_{50} \quad (2)$$

Both responses were measured using three techniques. Modelling was performed by Modde for Windows (Version 7.0, Umetrics, Umeå, Sweden), using a stepwise regression technique. The effects of the process variables were then modelled, using a second-order polynomial fitting (Eqs. 3-4). The models were simplified with a multilinear backwards, stepwise regression technique. The least significant terms were excluded from the model as long as the predictive power (Q^2) of the model increased.

$$\log [GS(Air, Liq, Pau)] = a_1 \times Air + a_2 \times Liq + a_3 \times Pau + a_4 \times Air \times Liq + a_5 \times Air \times Pau + a_6 \times Liq \times Pau + a_7 \times Air^2 + a_8 \times Liq^2 + a_9 \times Pau^2 + a0 \quad (3)$$

$$RW(Air, Liq, Pau) = a_1 \times Air + a_2 \times Liq + a_3 \times Pau + a_4 \times Air \times Liq + a_5 \times Air \times Pau + a_6 \times Liq \times Pau + a_7 \times Air^2 + a_8 \times Liq^2 + a_9 \times Pau^2 + a_0 \quad (4)$$

4.6.2 Real-time model

Twenty two measured and 19 derived process parameters were used as factors and the in-line d_{50} values were used as a response in PLS modelling. For spraying phase model, the actual d_{50} values were used. The change in d_{50} values from the start of drying phase was used for drying phase model. The complete list of all 41 process parameters is presented in Table 4. At first the process data was synchronized and integrated with the d_{50} data. The process measurement data was saved at every 1 s whereas the d_{50} data was received only at every 10 s, and therefore the process measurement data was filtered to have the same amount of time points. Because one measurement represents quite a small sample from the

total mass, a moving average of 6 consecutive measurements was used. It was found in previous studies that the in-line application systematically underestimates the particle size (Närvänen et al, 2008c). Due to this the d_{50} data was corrected using the equation 5, where X represents the original d_{50} values (μm) and Y the corrected values (μm).

$$Y = (X-14.5)/0.687 \quad (5)$$

Eleven batches from the experimental study set were selected for PLS model development and 4 batches for model testing (Table 1, in paper V). Matlab software (version 7.0 in Windows XP) was programmed to model all possible permutations for any combination of the process parameters using 2-6 parameters. Root mean square error of prediction (RMSEP) and statistical significance evaluation of the PLS coefficient values were used to compare and rank the models. Different models were developed for spraying phase and drying phase.

Table 4. *Measured and derived parameters in Glatt WSG 5 fluid bed granulator.*

Parameter	Abbreviation	Unit
Measured:		
Temperature of process room	T1	ºC
Temperature after heater	T2	ºC
Temperature of air before granulator	T3	ºC
Temperature of air before granulator	T4	ºC
Temperature of mass	T5	ºC
Temperature of granulation chamber	T6	ºC
Temperature of granulation liquid	T7	ºC
Temperature after filters	T8	ºC
Temperature after filters	T9	ºC
Temperature on the chamber wall	T10	ºC
Temperature in the outlet air duct	T11	ºC
Pressure difference over filters	dP1	kPa
Pressure difference over granules	dP2	kPa
Relative humidity of inlet air	U1	RH%
Relative humidity of outlet air	U2	RH%
Flow rate of inlet air	F in	g/s
Flow rate of outlet air	F out	g/s
Fan speed, value of frequency converter	Fan speed	1/s
Control current of heating element	Current	mA
Pump rotation speed of granulating liquid	N1	rpm
Amount of granulation liquid sprayed (scale)	M1	g
Granulation time	Time	s
Derived:		
Absolute humidity of inlet air	AH1	g/m^3
Absolute humidity of outlet air	AH2	g/m^3
Flow rate of inlet air	F1	l/s
Flow rate of outlet air	F2	l/s
Fluidisation parameter, F in/Fan speed	Flow ind	g/rev
Specific enthalpy of water vapour in inlet air	Lat heat	kJ/kg
Cumulative enthalpy of water vapour in inlet air	Lat heat cum	kJ/kg
Average flow of granulating liquid from start	AveM	g
Flow rate of granulation liquid in a second	dM	g/s
Cumulative water amount of inlet air	Water in cum	g
Cumulative water amount of outlet air	Water out cum	g
Water in cum + M1 - Water out cum	Water balance	g
Pressure difference over filters – Pressure difference over filters with empty granulator with equal flow rate	dP1eff	kPa
Pressure difference over granules – Pressure difference over granules with empty granulator with equal flow rate	dP2eff	kPa
U1 – U2	dU	RH%
AH1-AH2	dAH	g/m^3
Specific enthalpy of water vapour in outlet air	Lat heat out	kJ/kg
Cumulative enthalpy of water vapour in outlet air	Lat heat out cum	kJ/kg
Cumulative enthalpy of water vapour in inlet air - Cumulative enthalpy of water vapour in outlet air	Energy balance	kJ/kg

5 Results and discussion

5.1 Evaluation of off-line particle size determination techniques (I)

Granule characteristics of the various batches were very different from each other. The morphology and the median particle size between the batches had noticeable variation (Fig. 3, in paper I). Furthermore, the strength of the granules was not uniform throughout the batches. Therefore, it was not possible to validate a single method, e.g. sieve analysis as a reference method for the two other techniques. Especially in the early screening studies of the formulation and process development phases this kind of large variety of the granule characteristics is usual.

The comparison of the particle size results between the three techniques revealed major differences (Figs 1-2, in paper I). Although the order correlation of the batches remained similar with all techniques, the median values between the techniques were remarkably different. The trend in the results was clear; sieve analysis gave the biggest and laser diffraction the smallest particle size values. When the sieve analysis and laser diffraction results were compared with the SFT results, statistically significant differences were obtained in the fraction of <180 μm and 250-1000 μm. Although the sieve analysis is a widely used and established method, there are also sources of errors for that technique. In sieving the blockage of the sieves is often encountered (Iacocca and German, 1997). Cohesion and adhesion can occur during the sieve shaking and hence the particles do not pass through the sieves as expected. Low moisture content and small particle size facilitate these interaction forces. The original presentation of the particle size distribution is already different between the three methods. Sieve analysis, SFT and laser diffraction results are presented as mass distribution, chord length distribution and volume size distribution, respectively. Chord length distribution data was transferred to volume size distribution by the SFT software, but the transformations do not take into account the morphology differences of the granules. Due to the chord length measurement principle, the size distribution is usually wider compared to the real distribution (Petrak, 2002). Additionally, if there were differences in the porosity and the density of the granules, the mass distribution results would not be fully comparable with the volume size distribution. Due to the large differences obtained in the particle size results between the techniques, modelling was also utilised for further evaluation (section 5.5.2).

5.2 SAY-3D in real-time granule size monitoring (II)

The off-line particle size measurement results determined by the SAY-3D corresponded quite well to those of sieve analysis in the size fraction range 250–1000 μm (Fig. 6, in paper II) and the standard deviations of these determinations were less than 5%. Consequently, the preliminary accuracy of the SAY-3D was regarded to be sufficient for on-line feasibility testing in FBG.

5.2.1 On-line results

Three different batches were manufactured for SAY-3D feasibility testing; slow, fast and modified granule growth processes (Table I, in paper II). It was found that there was plenty of variation between the individual particle size values during the process (Fig. 9). However, when the saved images were examined after the process, it was found that the particle size results obtained represented the actual images quite well. The explanation for the large variation was due to the systematic stopping of the fluidisation that occurs at every minute. During the break the filter bags are shaken to remove the fines stuck into the filters. Consequently, when the SAY-3D on-line cuvette is filled during the filter-shaking period, the fine particles released from the filter significantly influence the size results. In spite of this variation, the moving average data was quite consistent and the particle size trend could be followed during the process.

With a rapid granule growth process the variability between the individual particle size results decreased (Fig. 9, in paper II). This was due to the fact that using the high granulation feed rate the fines attached quickly to the granules and there were little fines left in the granule mass. During the 30-min spraying time, the median particle size measured by the SAY-3D increased to approximately 900 μm. It could also be seen that in the drying phase the median particle size decreased and the variability between individual measurements widened. This phenomenon was probably due to breakage of the weakest granules and the appearance of fines by surface attrition during the drying phase.

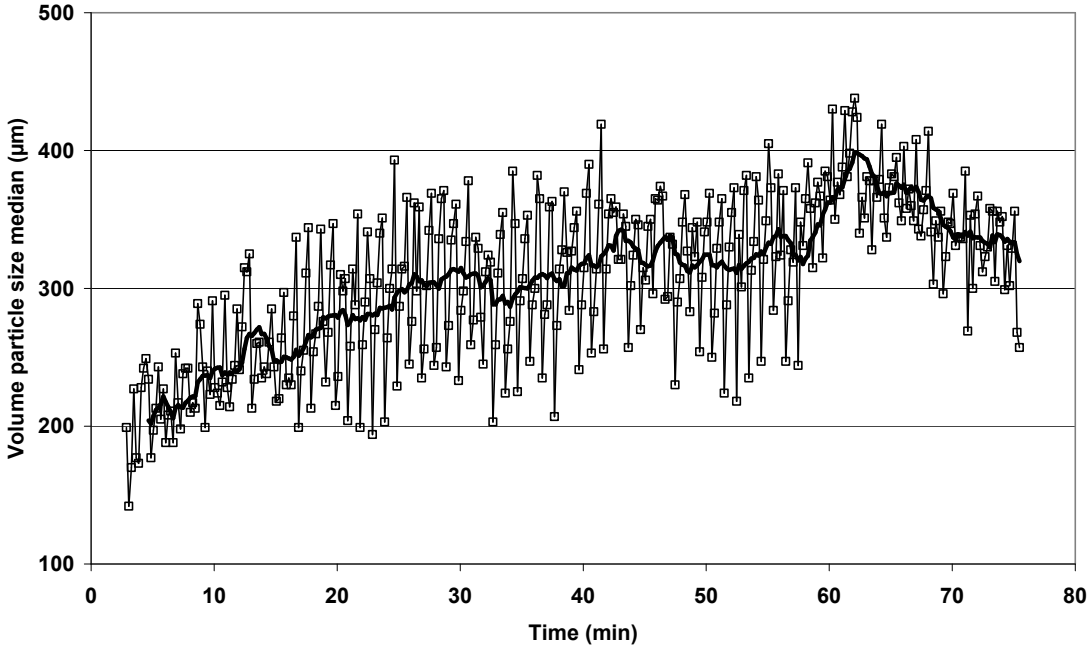


Fig. 9 *SAY-3D particle size results of a slow granule growth batch. Squares illustrate the individual measurements and thick line is a moving average of 10 consecutive measurements. Modified from paper II.*

The average median particle size of the last 10 images from the process was compared with the sieve analysis results determined for the final granules (Table 2, in paper II). Both techniques gave similar results for batches II and IV, whereas significant differences were observed in the median size values for batch III. Further visual examination of the images revealed that the SAY-3D determined the particle size correctly from the pictures, suggesting that the largest granules were not presented representatively in the cuvette. However, this batch was manufactured in extreme conditions in order to generate very big granules and the final particle size was far from the optimum, e.g. for tableting. Nonetheless, the risk of unrepresentative sampling has to be taken into consideration whenever sampling from fluid bed granulation.

5.2.2 Feasibility of the method

Particle morphology and high surface roughness very likely influence the particle size determination by the SAY-3D, since the method assumes particles to be spherical. However, the same assumption is made in many other currently used methods.

Furthermore, because surface topography is constructed by colour intensity data, particles with very high reflective properties, e.g. glass spheres, cannot be determined with SAY-3D. Although high moisture content can affect the reflective properties of the particles, no difficulties were observed in this study with moist granules. The advantage of the image analysis system compared to other particle size techniques is that the images are saved and it is straightforward to verify the results with the original raw data, if needed. It is also important to understand that particle size is not an unambiguous measure in such a dynamic process like fluid bed granulation, where granule growth, breakage and attrition take place simultaneously. Therefore, instead of putting major effort on the absolute accuracy of the particle size method, it is most often adequate to have a possibility to monitor visually the process and to get comparable particle size data from batch to batch. One big advantage of the SAY-3D cuvette system was that no significant fouling occurred even with the water content in the mass was very high. Following such an extreme process and retrieving on-line images during the process has not been previously possible. This approach allows for process monitoring and visual evaluation of the forming granules in FBG in a broad range of experimental design studies. Hence, SAY-3D attached to the on-line cuvette can be regarded as a feasible and promising monitoring method for FBG.

5.3 Improved version of the SAY-3D apparatus (unpublished data)

Based on the promising experiences from the feasibility study, the SAY-3D was further developed. The optics of the SAY-3D was improved and a compact camera (mvBlueFOX-124, Matrix Vision, GmbH, Oppenweiler, Germany) was integrated into the system. Illumination was performed by ultrabright leds. Using this system the resolution was 4.4 µm x 4.4 µm. The SAY-3D was installed into a tandem on-line cuvette that collected granule samples at every 4 s. The cuvette and the orifice diameters were the same as in the feasibility study. One cuvette was used for SAY-3D and the other cuvette for on-line Near Infrared Spectrometer (NIRS). In addition to the increased SAY-3D image quality and acquisition speed, the on-line cuvette also enabled significantly more consistent NIRS signal and decreased noise level compared to the in-line application tested with the same NIRS probe. Due to this much less spectral treatment was needed and the water amount could be followed qualitatively using the raw NIRS specta during the FBG process. Picture of the SAY-3D and NIRS probe attached to the tandem cuvette is shown in Fig. 10.

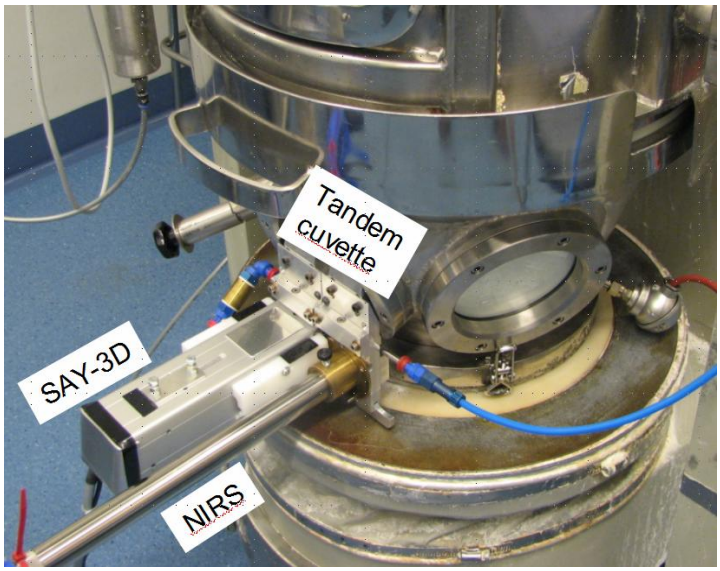


Fig. 10 *Tandem cuvette attached with SAY-3D and NIRS probe in Glatt WSG5 fluid bed granulator*

5.4. Evaluation of SFT measurements (III)

5.4.1 Monitoring of process phenomena

Different phenomena and process failure modes were observed from the in-line SFT data. For example, the influence of the entrapment of the fine particles into the filter bags and the blocking of the distributor plate (Figs. 4-5, in paper III) could be rapidly seen as abnormal particle size trends. Based on the gathered process measurement data, reliable explanations for these process failures could also be established. It was not previously recognized that the fluctuation in particle size values due to the filter shaking period can be notable. Usually high amount of fines in the final granules leads to undesired processability of the granules. Therefore, in-line SFT application could be utilized in process development phase to monitor the amount of the fines during the spraying phase.

5.4.2 Comparison of in-line, at-line and off-line results

The particle size results between the different SFT applications (in-line, at-line and off-line) differed significantly. Only with a batch of relatively small granules (< 200 µm), all the results were close to each other (Fig. 7, in paper III). When bigger granules were

present in the process, the in-line results underestimated and the at-line results overestimated the actual particle size. Another important finding was that variation between the at-line samples was remarkable (Fig. 9, in paper III). This was very likely due to the fact that the samples were taken based on the predetermined amount of granulation liquid sprayed. Hence the actual sampling points did not always occur at the same time point with respect of the filter shaking period. This should be taken into a consideration in future studies; to standardise the sampling times based on the shaking periods and to gather more samples during the FBG process.

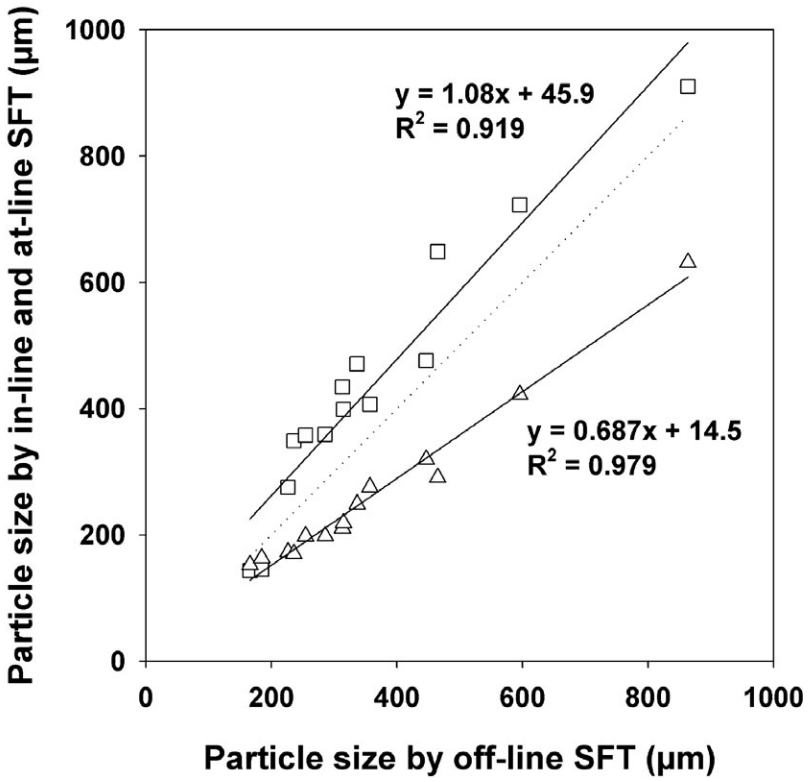


Fig. 11 *Comparison of in-line (triangles) and at-line (squares) median particle size results to off-line (dotted line) results of the manufactured batches. Modified from paper III.*

Fig. 11 compiles the particle size results of all the batches manufactured. All results were determined by SFT, and consequently, the results can be compared with each other. In principle, if the granule mass were homogenously distributed and if no sampling errors occurred, all SFT measurement applications (in-line, at-line and off-line) should have somewhat similar values within a single batch. The dotted line represents the off-line

results of the final granules that can be regarded as the reference values for each batch. The in-line results had a good correlation with the off-line results (R^2=0.98), however, the relatively low slope value illustrates that the in-line results gave systematically smaller particle size results. This is due to the segregation phenomenon; the bigger the granule, the less likely it is to fluidise to the height of the in-line probe location.

5.4.3 Applicability of SFT in fluid bed granulation

In addition to the fast in-line particle size monitoring, different phenomena and process failure modes that relate to particle size can be observed using in-line SFT. The implementation of an in-line probe is not, however, a straightforward operation. Since the location of the probe in the granulator and the process operation, i.e. filter bags shaking, influence the measurement, optimisation studies should be carried out before implementation. If possible, the probe should be installed at the lowest part of the granulator to ensure representative results. The higher the probe is installed, the more the fluidisation activity and the segregation affect the particle size results. On the contrary, the risk of fouling and sticking of the probe increases below the granulation spraying zone area. Using the experimental study set reported here, the probe could not be applied in the lower part of the fluid bed container due to the particles sticking into the probe. However, with dryer FBG processes it may also be possible to install the SFT probe at a lower position.

If reliable in-line data cannot be obtained from the process, SFT can be utilized as an at-line application. One advantage of this is that no new attachements through the FBG container wall are needed. Collected samples can be quickly analysed, and the particle size trend followed. Representative sampling should be carefully considered with this application and the number of the samples should be as high as possible during the process. Because the particle size results obtained by different particle size techniques differ, the versatile (in-line, at-line and off-line) applicability of SFT offers great potential for fluid bed process development and understanding.

5.5 Modelling

5.5.1 Relationships between process measurement data and particle size (IV)

Correlations between single process measurement and particle size were obtained. When an approximate steady state particle growth was achieved, (i.e. 500-2000 g granulation liquid was sprayed) there was a clear relationship (R^2=0.77) between the fluidisation parameter and the median particle size. The description of the fluidisation parameter is found in Lipsanen et al. (2008). More detailed analysis of each manufactured batch revealed that a mathematical model could be constructed. Using this equation, fluidisation parameter served as a somewhat good estimate of the median particle size for the batches manufactured (Fig. 5, in paper IV). However, it should be noted that this equation is dependent on the formulation and the equipment used, and therefore cannot be universily applied. Another finding was that the pressure difference over filters correlated (R^2=0.75) inversely with the particle size; increasing particle size decreases the pressure difference, in general. This is logical since the smallest particles are prone to drift along the fluidisation air to the filters, block the air flow, and thereby elevate the pressure difference. Consequently, both process measurements, i.e. fluidisation parameter and pressure difference over filters, could be used as indicative in-line estimates of particle size during granulation.

5.5.2 Controlling final particle size using predictive models (I)

The influence of granulation liquid feed rate, inlet air humidity and pulsing of granulation liquid feed on the final particle size results were modelled. It was found that using SFT or laser diffraction results, pulsing had a statistically significant impact on the particle size. On the contrary, with sieve analysis results pulsing had no impact on the model (Table 5). This highlights the fact that although there was a linear correlation (R^2=0.97) between the SFT and sieve analysis results, the sieve analysis did not have the same accuracy compared to the other two methods used in this study. Based on these findings predictive particle size model using the SFT results were used for further evaluation.

Table 5. *Coefficients a1..a10, statistical significance (p), goodness of fit (R^2) and goodness of prediction (Q^2) values of modelling the median particle size (Air = humidity of the inlet air, Liq = granulation liquid feed rate and Pau = relative time of pauses in the granulation liquid feed). Statistical significances are marked as asterisks (p<0.05*, p<0.01**, p<0.001***). Modified from paper I.*

	SFT		Sieve analysis		Laser diffraction	
	Coef.	p	Coef.	p	Coef.	p
Air	0.112	***	0.102	***	0.106	**
Liq	0.101	***	0.138	***	0.187	***
Pul	-0.0480	*	-0.0248	NS	-0.0633	*
*Air*Liq*	0.0450	NS	0.0423	NS	0.110	*
*Air*Pul*	-	-	-	-	-	-
*Liq*Pul*	-0.0378	NS	-0.0439	NS	-0.0866	*
*Air*Air*	-	-	-	-	-	-
*Liq*Liq*	-	-	-	-	0.0848	NS
*Pul*Pul*	-	-	-	-	-	-
a_0	2.49		2.63		2.20	
	$R^2 = 0.94$ $Q^2 = 0.90$		$R^2 = 0.89$ $Q^2 = 0.68$		$R^2 = 0.90$ $Q^2 = 0.76$	

Granulation liquid feed pulsing had clear influence on the median particle size (Figs. 5 and 6, in paper I). Pulsing did not influence the bulk and tapped density, Carr's Index, and flowability values of the final granules; however, the size distribution of the granules was broadened. Pulsing extends the spraying phase time, which can generate more fines due to attrition of granule surfaces. Although the spraying phase time was increased, pulsing clearly decreased the drying process times when the inlet air RH was high (>60% at 25°C), and hence no major changes were seen in the total process times (Table 3, in paper I).

The developed model offers large potential for particle size prediction and adjustment. When the influence of all chosen factors is evaluated together, it is clearly seen that granulation liquid feed pulsing is an efficient and straightforward way to control particle-size (Fig. 12). The results of this study suggest that granulation liquid feed pulsing can be used to compensate for the disadvantageous influence of too high a level of moisture in the fluid bed granulation, and hence to be used against seasonal air RH variations.

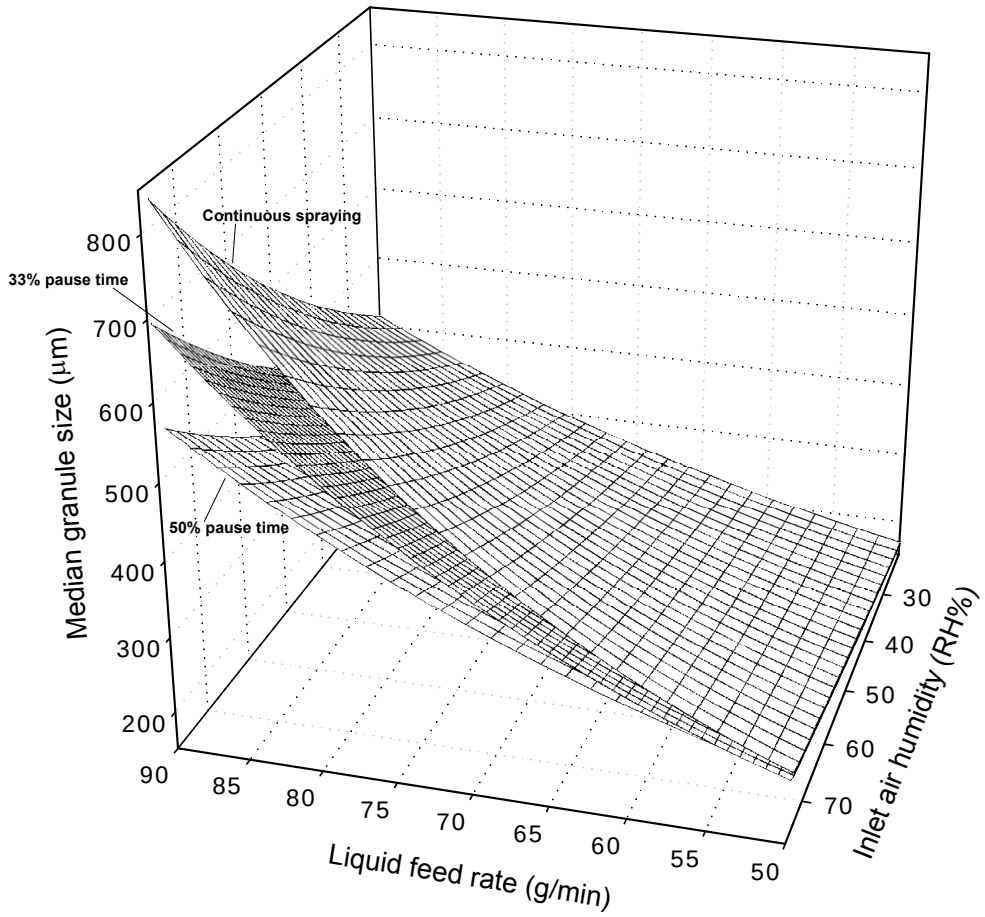


Fig. 12 *Effect of inlet air humidity, granulation liquid feed rate and liquid feed rate pulsing on median particle size. Modified from paper I.*

5.5.3 Real-time particle size prediction (V)

The aim of this study was to evaluate if the particle size could be quantitatively predicted based on the process measurement data during the process. Direct and calculated process measurements were used as factors and in-line SFT particle size results as response. The selected models and the parameters for spraying and drying phases are shown in Table 6. For spraying phase, the number of statistically significant model coefficients was four. Using this model the root mean square error of prediction value was 30.0 µm. The selected spraying phase model included Water balance, Water out cum, F1 and dP2. The goodness of prediction (Q^2) value for the model was 0.86. Water balance and Water out cum had the biggest impact on the model which can be seen as high VIP (variable influence on projection) and coefficient values.

Table 6. *VIP and coefficient values of the selected models*

Spraying phase model	VIP	Coefficient
Water balance	1.40	1.24
Water out cum	1.00	-0.546
F1	0.730	0.178
dP2	0.698	-0.117
Drying phase model	**VIP**	**Coefficient**
dU	1.24	1.66
Water balance	1.14	0.585
AH1	1.05	-1.03
T6	1.01	-1.10
AH2	0.805	0.564
T4	0.636	0.499

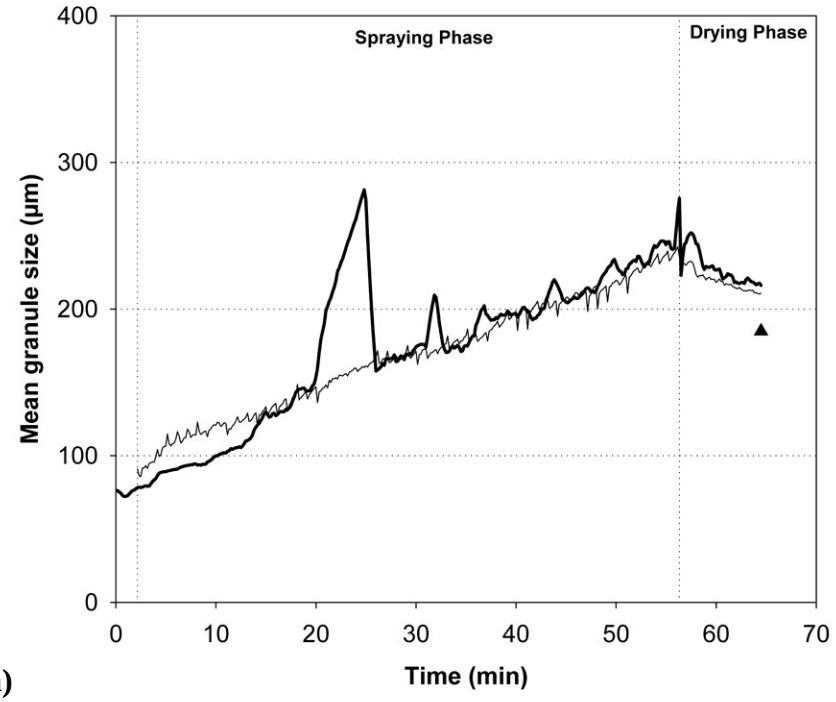
Water balance was actually present in all of the models regardless of the amount of the parameters used and can therefore be regarded as the most significant single parameter for the d_{50}. When the coefficient values of the model are evaluated, it is seen that the increase in *Water balance* increases the d_{50} value and the increase in *Water out cum* decreases it. This is logical since the first parameter describes the amount of the water accumulating in the granulator whereas the second parameter reflects the cumulative water amount released from the process. The influence of the other two parameters, *F1* and *dP2*, on the model was very likely related to the decreased air flow through the smallest particles.

For drying phase, with the model of six parameters, all parameter coefficients had statistical significance on the model. This is probably due to the fact that the amount of data and the particle size changes were clearly smaller in drying phase compared to the spraying phase. Hence, more parameters were needed for particle size prediction. The drying phase model included following parameters: *dU*, *Water balance*, *AH1*, *T6*, *AH2* and *T4*.

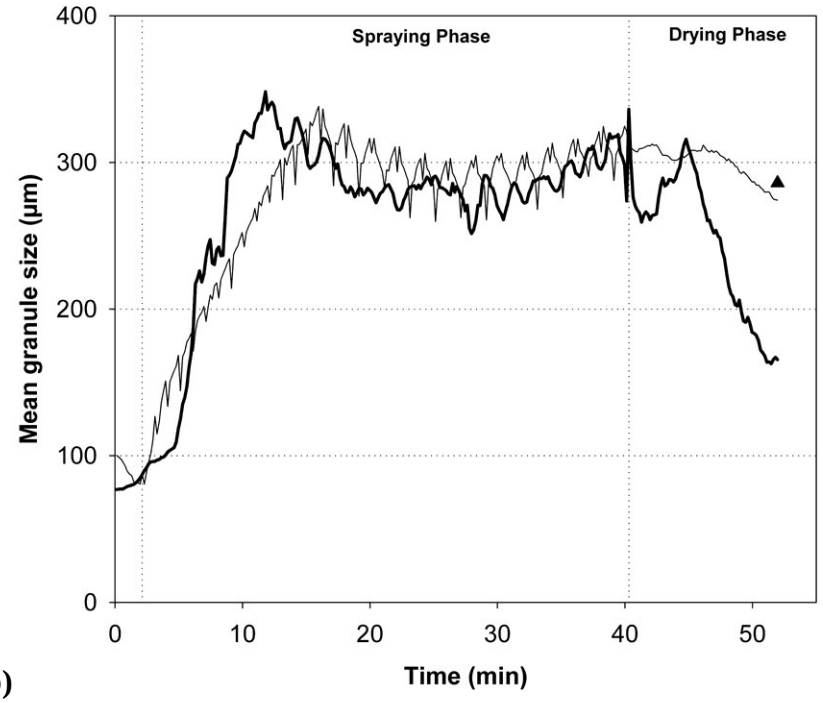
The predicted d_{50} values were in good correspondence with the observed values. For a mid point batch of the experimental design, the predicted values followed particularly well the measured data (Fig. 4, in paper V). One target for the modelling was to evaluate how the particle size prediction results will perform during the process failures. It was found that the model prediction was quite robust against the observed process problems, such as entrapment of fines into the filter bags and diminished fluidisation due to the blocking of

distribution plate (Fig. 13a-b). So, the biased in-line SFT results were not reflected in the particle size values predicted by the model. Furthermore, the model predicted well the turning point in the original d_{50} trend at the time when the drying phase started (Fig 13a). When the final d_{50} values measured off-line by SFT were compared to the predicted level, it was found that the selected model predicted reasonably well the final particle size.

The results of this modelling concept were promising. Although the design of experiment was not optimal for the modelling, the d_{50} predictability was still good. This suggests that the model parameters well covered the most relevant phenomena relating to granule growth and attrition. The possibilities of the modelling concept described here are wide; however, some restrictions exist as well. Design of experimental studies can be utilised to cover the desired variable ranges for the model. Predictive model for particle size growth can be developed in small scale and the design space limits for the growth can be specified. In larger scale the model can be verified and updated. Eventually, the particle size trend could be predicted in real-time without an in-line particle size technique or sampling procedures as long as the process variation obtained is included in the established model (i.e. design space). It must be remembered, however, that the developed model is valid only inside the studied variable ranges. In order to develop this kind of predictive particle size models the FBG environment should be appropriately instrumented and reliable real-time particle size results acquired. If an in-line or on-line particle size technique cannot be applied, SFT is one good choice to be used at-line. In all techniques, however, representative sampling is of uppermost importance when applying any particle size determination method during the process.



a)



b)

Fig. 13 *Observed (thick line) and predicted (thin line) d_{50} values for two batches. Triangle represents the d_{50} value of the final granules measured off-line. Modified from paper V.*

6 Summary and conclusions

Particle size of the final granules was determined using sieve analysis, laser diffractometry and SFT. Most of the differences observed in the results between the techniques were explained based on process understanding, granules characteristics and the principles of the methods. The effects of the studied process variables were modelled best using the SFT data, and therefore that data was utilised for particle size prediction.

An on-line cuvette was developed that enabled reliable image acquisition and particle size determination during the FBG even with the highest moisture processes. Following and retrieving on-line images from such an extreme process has not been previously possible by any other application and hence this is a significant improvement. The granule size determination accuracy of the SAY-3D was verified to be comparable with the sieve analysis using the selected sieve fractions. When used as on-line application, the granule growth trend could be monitored by the SAY-3D in real-time.

The impact of sampling location and the effect of different process phenomena on the particle size results could be studied by SFT. The in-line application of SFT was sensible for detecting fast particle size changes and trends during the process. The comparison of off-line, at-line and in-line results revealed significant differences. The bigger the granules were, the more the results also differed. Process understanding could be increased based on the SFT studies and the method proved to be useful for process development purposes.

Relationships between the process measurements and in-line particle size data were obtained, and hence the measurements could be used as indicative estimates of the particle size. Using the design of experiment studies, predictive models for the final particle size could be constructed. Pulsing of the granulation liquid feed was presented as a controlling tool to compensate for the excessive moisture content during the fluid bed granulation. A new modelling concept for real-time particle size prediction using the process measurement data was also introduced.

Most of the methods studied in this thesis can be applied in FBG process development and they can bring valuable information for the developer. Although there were some challenges in in-line application of SFT, the method itself was proved to be fast and it gave reproducible results. Therefore, SFT could be useful in process development as an at-line technique. In future, the feasibility of the on-line cuvette should be studied in a larger fluid bed granulator. The SAY-3D can already be used successfully in qualitative granule growth monitoring and it has a lot of potential in process development, scale-up and in trouble shooting studies. Optimisation of the quantitative particle size determination of the SAY-3D and demonstrating the particle size prediction concept using the process measurement data by another data set would be appropriate focus areas for future studies. As a conclusion, the new methods and PAT tools introduced and studied in this thesis will enable enhanced process understanding and control of FBG process.

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