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**Towards real-time understanding of processes in  
pharmaceutical powder technology**

by

Satu Lakio

ACADEMIC DISSERTATION

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## Abstract

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There is a need for better understanding of the processes and new ideas to develop traditional pharmaceutical powder manufacturing procedures. Process analytical technology (PAT) has been developed to improve understanding of the processes and establish methods to monitor and control processes. The interest is in maintaining and even improving the whole manufacturing process and the final products at real-time. Process understanding can be a foundation for innovation and continuous improvement in pharmaceutical development and manufacturing. New methods are craved for to increase the quality and safety of the final products faster and more efficiently than ever before. The real-time process monitoring demands tools, which enable fast and noninvasive measurements with sufficient accuracy. Traditional quality control methods have been laborious and time consuming and they are performed *off line* i.e. the analysis has been removed from process area. Vibrational spectroscopic methods are responding this challenge and their utilisation have increased a lot during the past few years. In addition, other methods such as colour analysis can be utilised in noninvasive real-time process monitoring.

In this study three pharmaceutical processes were investigated: drying, mixing and tableting. In addition tablet properties were evaluated. Real-time monitoring was performed with NIR and Raman spectroscopies, colour analysis, particle size analysis and compression data during tableting was evaluated using mathematical modelling. These methods were suitable for real-time monitoring of pharmaceutical unit operations and increase the knowledge of the critical parameters in the processes and the phenomena occurring during operations. They can improve our process understanding and therefore, finally, enhance the quality of final products.

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## List of original publications

This thesis is based on the following publications, which are referred to in the text by their respective roman numerals (I-V).

- I**     **Virtanen S**, Antikainen O, Yliruusi J, 2007. Uniformity of poorly miscible powders determined by near infrared spectroscopy. *International Journal of Pharmaceutics*, 345 (1):108-115. doi: 10.1016/j.ijpharm.2007.05.044
  
- II**    **Virtanen S**, Antikainen O, Yliruusi J, 2008. Determination of the crushing strength of intact tablets using Raman spectroscopy. *International Journal of Pharmaceutics*, 360 (1):40-46. doi: 10.1016/j.ijpharm.2008.04.022
  
- III**   **Virtanen S**, Antikainen O, Räikkönen H, Yliruusi J, 2009. Granule size distribution of tablets. *Journal of Pharmaceutical Sciences*, 99(4):2061-2069. doi:10.1002/jps.21945
  
- IV**    **Lakio S**, Heinämäki J, Yliruusi J, 2009. Colorful Drying. *AAPS PharmSciTech*. doi:10.1208/s12249-009-9351-x
  
- V**     **Lakio S**, Siiriä S, Räikkönen H, Airaksinen S, Närvänen T, Antikainen O, Yliruusi J. New insights into segregation during tableting. (Submitted to *International Journal of Pharmaceutics*)

## Abbreviations

API	Active pharmaceutical ingredient
$a_w$	Water activity
CBZ	Carbamazepine
CCD	Charge-coupled device (detector)
cel200	Cellet with particle size 200 $\mu\text{m}$
cel700	Cellet with particle size 700 $\mu\text{m}$
cel1000	Cellet with particle size 1000 $\mu\text{m}$
CIE	Commission Internationale de l'Eclairage, International Commission on Illumination
CZ	ChromaZone
CZ31	ChromaZone granules with activation temperature of 31°C
CZ35	ChromaZone granules with activation temperature of 35°C
CZ40	ChromaZone granules with activation temperature of 40°C
$d_{50}$	The particle diameter at which 50% of the particles have diameters that are greater or smaller than the $d_{50}$ value
FDA	United States Food and Drug Administration
$F_e$	Ejection force
$F_{eff}$	The effective force
$F_{lp}$	Lower punch force
$F_{up}$	Upper punch force
HPMC	Hydroxypropyl methylcellulose
InGaAs	Indium gallium arsenide (detector)
$L^*a^*b^*$	$L^*a^*b^*$ colour space
LMH	$\alpha$ -lactose monohydrate
LP	Non-contact laser profilometry
M	Mesh
MMFD	Multichamber microscale fluid bed device
MS	Magnesium stearate
MSC	Multiplicative scatter correction
NIR	Near infrared
NIRS	Near infrared spectroscopy
PAT	Process analytical technology
PbS	Lead(II) sulfide (detector)
PCA	Principal component analysis
Ph. Eur.	European Pharmacopoeia
PIT	Process induced transformation
PLS	Partial least squares regression
PVP	Polyvinyl pyrrolidone
$Q^2$	Test set validation coefficient (estimate of the predictive ability of the model)
$R^2$	Correlation coefficient (quantitative measure of the goodness of fit)
Ra	Average roughness
RH	Relative humidity
Rq	Root-mean-square roughness
SD	Standard deviation
SEM	Scanning electron microscopy
SFT	The spatial filtering technique
SNV	Standard normal variate transform
$s_{rel}$	The standard deviation of the relative error
TP	Theophylline anhydrate
USP	United States Pharmacopoeia
UV	Unit variance
UV-Vis	Ultraviolet-Visible
v/v	volume / volume
w/w	weight / weight
XRPD	X-ray powder diffraction



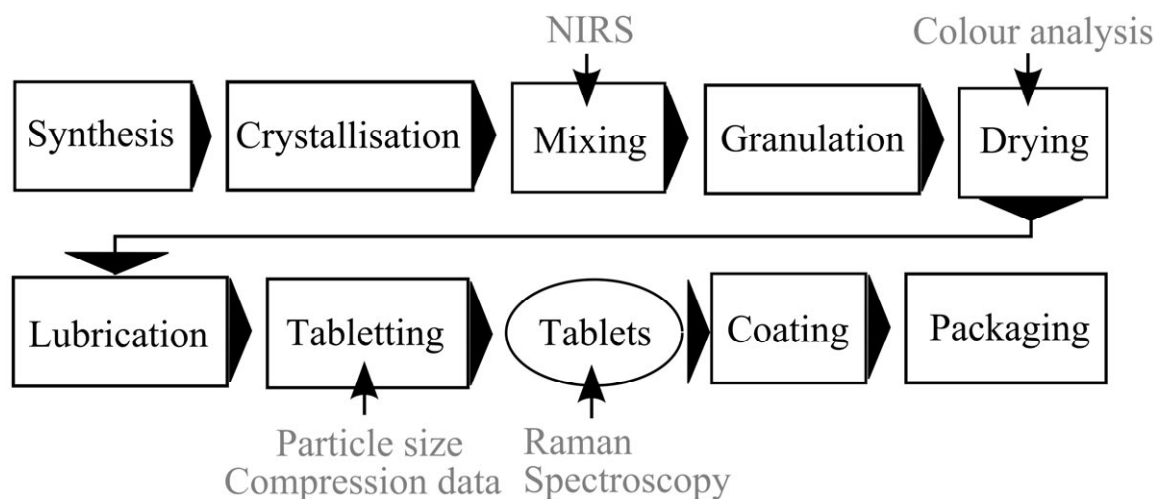
## 1. Introduction

The field of pharmaceutical powder technology is under continuous changes and researchers have to be able to respond this challenge. The goal for pharmaceutical industry is to increase the quality of products, decrease the production costs and reduce the time of new products to come on market.

Formulations that are manufactured from powders and granules, such as tablets and capsules, are the most used dosage forms (Lieberman et al., 1993; Muzzio et al., 2002; Wells and Aulton, 2007). Therefore the knowledge of the physical properties of solid materials is crucial. However, pharmaceutical powder technology is still mainly considered more as an art than a science (Lanz, 2006). Thus behaviour of powders and granules during pharmaceutical processing is only partly known and profound understanding is needed from behaviour of powders and granules (Muzzio et al., 2002). For instance the tableting process is invented already over 150 years ago, and tablets are the most used dosage form in the world (Alderborn, 2007). Nevertheless, it is still a challenging task to assure the reproducible quality of tablets from batch to batch.

As pharmaceutical products become more complex, regulatory requirements for product will also become demanding, requiring much better understanding and control of product properties and process attributes. There is a need for better understanding of the processes and new ideas to develop traditional manufacturing procedures. Recent developments in the pharmaceutical technology are related to process analytical technology (PAT). PAT has been developed to improve our understanding of the pharmaceutical process and to monitor and to control critical process parameters (US Food and Drug Administration, 2004). The interest is in maintaining and even improving the whole manufacturing process and the final products at real-time. The real-time process monitoring demands tools, which enable fast and noninvasive measurements with sufficient accuracy. Traditional quality control methods have been laborious and time-consuming and they are performed *off line* i.e. the analysis has been removed from process area. Vibrational spectroscopic methods, such as near infrared and Raman spectroscopies, are responding this challenge and their utilisation has increased a lot during the past few years. The methods are fast, they do not demand sample preparation, both qualitative and quantitative information from chemical and physical properties of the sample can be

retrieved at real-time. All this can be gained with only one measurement! However, spectroscopic methods demand multivariate data analysing methods, in order to systematically differentiate the useful information. Multivariate methods can reveal information about interactions and correlations between variables and between variables and observations (Eriksson et al., 2001). Spectroscopic and other real-time monitoring methods can be attached to all of the unit processes in pharmaceutical powder technologies described in Figure 1.



**Figure 1.** The unit processes of manufacturing of tablets. The arrows represent the unit processes which were studied in this thesis. Analysing methods are marked with grey.

The whole processing cycle demands attention to enhance the quality of final products. In this thesis means for real-time monitoring were developed for three different unit processes: mixing, drying and tabletting. Real-time monitoring methods can be implemented also to other unit processes. The methods increase the knowledge of the critical parameters in the processes and the phenomena occurring during operations. In addition, amount of waste would decrease substantially if powder behaviour would be known better and the changing circumstances could be responded at real-time. In the best case they can even increase process understanding. Process understanding can be a foundation for innovation and continuous improvement in pharmaceutical development and manufacturing. New, fast and accurate methods are craved for to increase the quality and safety of the final products faster and more efficiently than ever before. However, one cannot forget the importance of traditional parameters such as temperature, pressure and moisture even if new methods are established for real-time monitoring.

## **2. Literature review**

### **2.1 Pharmaceutical powders**

A large proportion of pharmaceutical products consist of powdered material. Therefore there is a great deal of interest to study the behaviour of solids and acknowledge the importance of these properties.

A powder is a heterogeneous system of dry solid particles and air. The maximum particle size in a material classified as a powder is less than 1000  $\mu\text{m}$  (Staniforth and Aulton, 2007). Powders behave partly as liquids and partly as solids; they can flow like liquid and fragment as a solid. Powders can be electrostatic especially in dry conditions. This can induce challenges for powder processing in pharmaceutical industry because particles are sticking to each other and walls of the handling chambers. Pharmaceutical powders are usually organic materials and they are used as mixtures. Most commonly powders are compressed to tablets or capsulated.

Powders can be granulated to increase the particle size before other processing. Granulation increases flowability, makes particle size uniform, reduces dust and can even control the rate of drug release and improve compression characteristics. By definition a granule has a specified particle size of 2–4 mm (Summers, 2007). In practise, even smaller particles than 2 mm can be said granules too. Granules are not as electrostatic as powders and they are much easier to handle.

### **2.2 Mixing of powders**

Mixing is defined as a process that tends to result in a randomisation of dissimilar particles within a system (Rippie, 1970). Mixing is a crucial but complex process for manufacturing of solid dosage forms. Many variables, such as the characteristics of the solid or of the mixer type, and the operation conditions, can influence the degree of mixing (Fan et al., 1970). This explains why optimum operation conditions are unique to every product (Sindel et al., 1998).

Mixing has been the target of research for decades. Poux et al. (1991) studied various kinds of mixers. Johnson (1975) investigated the influence of powder characteristics such

as particle size and size distribution on the segregation of mixtures. Speiser and Tawashi (1962) attempted to determine how various type of mixers influence the mixing time and the homogeneity of a mixture.

The uniformity of mixture has been controlled by assembling samples from the processing mass at different stages. Sampling has been a major problem in the mixing studies. It has been challenging to obtain representative sample from the container. When any kind of probe or thief sampler is pushed in the mass it will affect the mass. The API content of these samples has been determined with chromatographic or ultraviolet-Visible (UV-Vis) spectroscopic methods (Wargo and Drennen, 1996). Conventional operations are time consuming and laborious. Recently, spectroscopic methods have been coupled with mixing. Especially near infrared spectroscopy (NIRS) is overtaking previous methods because of its advantages.

### **2.3 Fluid bed drying**

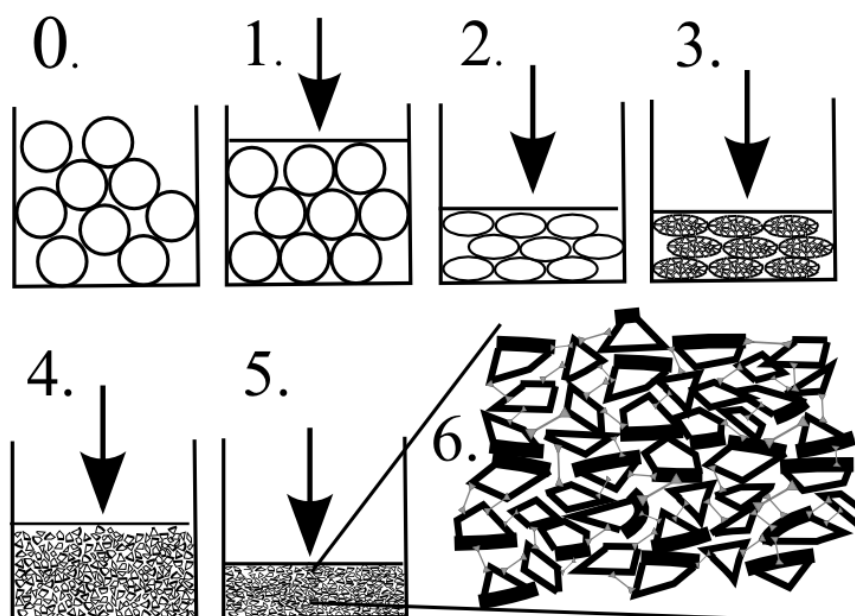
The temperature is raised in many pharmaceutical processes such as wet granulation, drying and tableting processes. Increase of the temperature can accelerate hydrolysis and oxidation reactions dramatically (Florence and Attwood, 2006). In addition, thermal stress that pharmaceutical solids are exposed to during manufacturing can induce various processing-induced phase transitions in bulk drug APIs and/or excipients (Miroshnyk et al., 2006). Because drying is one of the standard unit operations in the pharmaceutical industry, that typically involve raised temperature, it is important to understand the transitions that may take place upon exposure of pharmaceutical solids to thermal stress. For these reasons the formulation of heat sensitive APIs is a challenge for the pharmaceutical industry.

Fluid bed drying is a common method to dry pharmaceutical materials. The contact between the drying gas (usually air) and the particles is good which leads to fast heat transform and drying (Rankell et al., 1986). The parameters such as moisture or the speed of the inlet air can be optimised during the process. The material can flow in many different ways during the fluid bed drying. The fluidisation type is dependent on the material properties for example its density, triboelectricity and particle size. There are also challenges in fluid bed drying. The movement of the air and therefore the heat transfer is yet unsolved.

## 2.4 Tableting

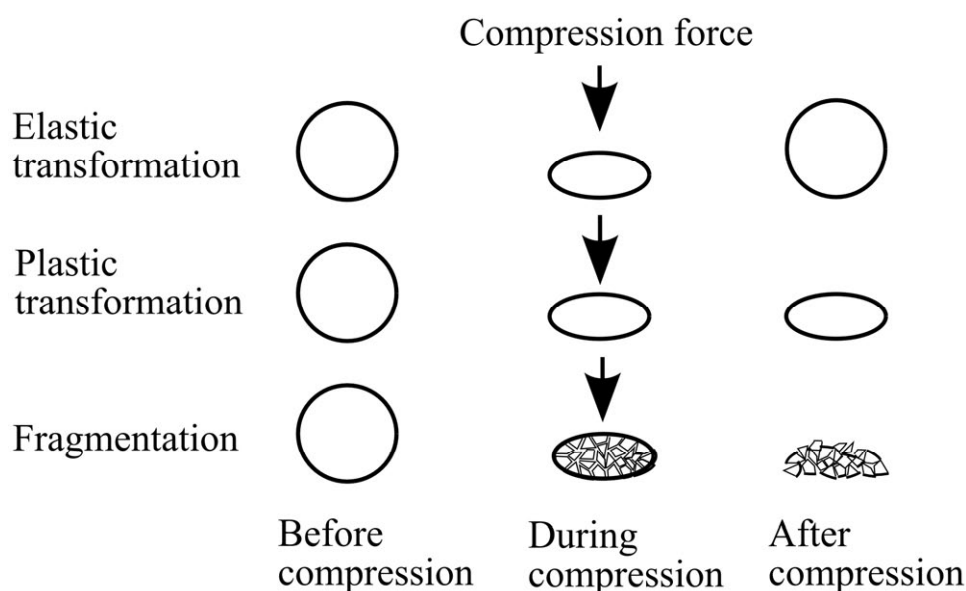
European Pharmacopoeia (2005) defines tablets as: "solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration." A tablet should possess following attributes: 1) ability to stand mechanical treatment such as production and packaging, 2) it should not have faults such as cracks and discoloration, 3) it should have desired chemical, physical and microbiological stability, and 4) it should release the drug in a reproducible and predicted manner (Gunsel et al., 1970).

Tablets are the most common pharmaceutical dosage form (Alderborn, 2007). They have many advantages such as ease of handling, good patient compliance, they are relatively easy and inexpensive to manufacture, safe to administer and they are really versatile. Compression process includes several phases (Train, 1957; Duberg and Nyström, 1986) (Fig. 2): A) filling of the die, B) rearrangement of particles, C) elastic or plastic transformation of particles (Krycer and Pope, 1982), D) fragmentation, E) rearrangement of fragments, F) elastic or plastic transformation of fragments (Duberg and Nyström, 1986) and G) formation of bonds. Phases from D to F can occur several times during compression. The elastic and plastic transformation and fragmentation of particle is presented in Figure 3.



**Figure 2.** Compression of particles. A. The die has been filled, B. Rearrangement of particles, C. Elastic or plastic transformation of particles, D. Fragmentation, E. Rearrangement of fragments, F. Elastic or plastic transformation of fragments, G. Formation of bonds (magnification from the figure F.). The arrow represents compression force.

Tablet machines can be equipped to measure punch forces and displacements. This enables real-time monitoring of the compression process. However, the compression data has usually been evaluated by studying compression force profile for single tablet (Marshall, 1989; Hoblitzell and Rhodes, 1990; Schmidt and Vogel, 1994; Yliruusi et al., 1997; Nicklasson and Alderborn 2000; Palmieri et al., 2005; Patel et al., 2007). Force, time, and displacement curves have broadly been studied to get information of compaction properties of pharmaceutical materials. Equations, such as Heckel, Kawakita and Cooper-Eaton, have been generated to describe force profiles (Heckel, 1961; Cooper and Eaton, 1962; Kawakita and Lüdde, 1970/1971).



**Figure 3.** Transformation of particles during compression.

#### 2.4.1 Effect of particle size on tableting

The role of initial particle size in the compression process was already recognised in the 1950s (Hersey et al., 1967). Control of particle size and size distribution is important because they influence the flowability (Fan et al., 2005; Li, 2008; Deanne and Etzler, 2009), tablettability (Sun and Himmelsbach, 2006), content uniformity (Yalkowsky and Bolton, 1990; Rohrs et al., 2006), tablet weight variation (Laitinen et al., 2004; Fan et al., 2005), tensile strength of tablet (Olsson and Nyström., 2001), drug release (Heng et al., 2001) and dissolution properties of tablets (Carless and Sheak, 1975; Jilavenkatesa et al., 2002; Yu, 2008; Deanne and Etzler, 2009).

The effect of particle size on flowability has been widely studied, but the results are often contradictory depending on the original particle size and size distribution. Fan and coworkers (2005) noted that flowability was improved with larger particles and narrower particle size distribution. However, there is an increase in flowability as the size of granules decreases in some cases (Jillavenkatesa et al., 2002). Nevertheless, when the particle size was reduced even more the flowability decreased. This can be explained with changes in forces which influence the flow. As particle size decreases, several interparticulate forces such as mechanical interlocking, hydrogen bonding, electrostatic, and van der Waals forces can predominate over gravity (Marks and Sciarra, 1968). These forces act on the surface of the particles and smaller particles have larger surface area in relation to their mass than larger ones. In addition, these varying results may be due to differences in the flowability measurement set-ups, humidity of the air, and/or particle properties such as original particle size.

The particle rearrangement during compaction is affected by the particle size and size distribution (Patel et al., 2006). The smaller particles can enter into the voids between the larger particles therefore a closer packing arrangement is obtained during the tableting process. The particle surface area capable of forming interparticulate bonding is increased when particle size is decreased (Nyström et al., 1993; Fichtner et al., 2008). For most pharmaceutical powders, compaction of smaller particles results in stronger tablets because they have larger surface area for bond formation (Hersey et al., 1967; Yajima et al., 1996; Sun and Grant, 2001ab; Fichtner et al., 2005; Patel et al., 2006; Lee and Kuo, 2006). The initial particle size can affect both the number and the bonding force of the interparticulate bonds (Eriksson and Alderborn, 1995). However, fragmentation of larger particles can equalise the particle size and reduce the influence of size difference (Sun and Grant, 2001a). Particle size plays a crucial role in the tensile strength of tablets especially when compressing materials that form solid bridges (such as sodium chloride) during compaction (Adolfsson et al., 1999). In addition, particle size enlargement causes reduction in tablettability of microcrystalline cellulose (MCC) powders, according to Sun and Himmelspach (2006).

The particle size distribution of granules during tableting has not previously been studied using intact granules or tablets. For example Carless and Sheak (1975) and Khan and Rhodes (1975) have used broken tablets after tableting process.

## **2.4.2 Segregation during tableting**

Reliable and uninterrupted flow of uniformly mixed material is crucial for manufacturing high quality tablets. Segregation can cause weight variation in tablets and therefore quality problems for the final dosage form. Segregation of powders can occur as a result of differences in the physical and mechanical properties of the particles. If the segregation phenomenon occurs due to the sifting mechanism, in which smaller particles move through a matrix of larger particles, changing the particle size ratios of the components to within 1.3:1 or decreasing the mean particle size below 100  $\mu\text{m}$  will reduce sifting segregation (Carson, 1988; Prescott and Hossfeld, 1994). Granule segregation can eventually cause weight variation in tablets and therefore quality challenges for the final dosage form. Antikainen and others (2006) found a distinct trend between segregation tendency and weight variation in tablets when they used a single punch tableting machine. In general, segregation tendency increases with the particle size (Xie et al., 2008). Segregation is more likely to occur in wide size distributions than in narrow size distributions. When the size of the granules is similar, segregation does not occur and there is no significant change in the drug content of tablets.

## **2.5 Tablet properties**

### **2.5.1 Mechanical strength of tablets**

The mechanical strength of a tablet provides a measure of the bonding potential of the material. It means the ability of tablet to resist breakdown or the force which is needed to break the tablet (European Pharmacopoeia, 2005). Tablets must remain intact until administration. However, they must be soft enough so that the active pharmaceutical ingredient can be released in the alimentary tract.

The factors that influence the mechanical strength of tablets can be divided into three groups: 1) material and formulation factors, 2) process factors, and 3) environmental factors. Formulation factors are due to the physical and chemical properties of particles. A process factor may include the equipment used and environmental factors the relative humidity (RH) and temperature of the air. In pharmaceutical systems interparticular interactions, triboelectricity, liquid and solid bridges, porosity, particle size and shape, and wetting may also be essential with regard to the mechanical strength of granular



systems (Alderborn and Nyström, 1996). In addition, the size and shape of the tablet influence the mechanical strength.

The mechanical properties of pharmaceutical tablets can be divided to friability and hardness or crushing strength of tablets. Friability testing is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. The weight loss due to abrasion is a measure of the tablet friability. The term crushing strength and hardness of the tablet are used in a disorganised manner in the literature. Usually crushing strength means the force that is needed to break the tablet by diametral compression (Fig. 4). Tensile strength is an extension for crushing strength. It takes the dimension of the tablet into account on the contrary to crushing strength. However, if one wants to reliably compare the strength of the tablets, only tablets with the same dimensions and other attributes, such as material and density, can be compared to each other. The measuring method, friability or strength, must be chosen depending on subject of interest.



**Figure 4.** Diametral compression of a tablet.

The mechanical strength of tablets can be tested in many ways (Alderborn, 2007). The method most used in pharmaceutical technology is the diametral compression test (Davies et al., 2007). Testing the mechanical strength of tablets with a conventional indirect diametral hardness-testing apparatus is an invasive and laborious method that breaks up the tablet. Recently, new nondestructive methods such as vibrational spectroscopic techniques have been introduced in the field of pharmaceutical powder technology.

### **2.5.2 Surface properties of tablets**

The scanning electron microscope (SEM) and non-contact laser profilometry (LP) can be used to investigate surface properties of granules and tablets. Riippi and coworkers (1998) examined the effect of compression force on surface structure and tablet

parameters, such as crushing strength and friability. They discovered that the surface roughness parameters characterise the tablet surface quite well and noted that the crushing strength of the tablets, as well as the surface smoothness, increased with compression force. In addition, Seitavuopio and coworkers (2003) came to the same conclusion that higher compression pressure leads to smoother tablet surfaces. Podczeck and others (1999) investigated tablets of five different compression formulations for their surface roughness, using SEM and LP. They found that the composition of a formulation not only influenced the tableting properties of the powder mixtures, but also the surface properties of the final product. An increase in tableting pressure reduced the tablet surface roughness.

### **2.5.3 Weight variation of tablets**

The weight variation of tablets is an important factor because if the weight changes also the content uniformity changes. The weight variation in tablets decreases with decrease in granule size according to Marks and Sciarra (1968). They suggested that when the size of the granules became smaller there was a greater loss of weight due to the friability of the granules. Laitinen and coworkers (2004) concluded that granules which size fraction was 0.25-0.50  $\mu\text{m}$  filled the tableting die efficiently and had small weight variation in tablets. Fan and coworkers (2005) noted that blends with good flowability have low tablet weight variation and good content uniformity. Spring (1977) noticed that the variation was greatest at the beginning and end of tableting process and it decreased with decreasing granule size. In general, issues that influence bulk density can affect tablet weight, because the weight of tablets is dependent on the packing conditions in the die (Ridgway and Williams, 1977).

## **2.6 Colour analysis**

The colour can be measured quantitatively either by a spectrophotometer or a colorimeter. The tristimulus method measures the light reflected from the object using three sensors filtered to have the same sensitivity as the human eye (Ohno, 2000). Tristimulus values are amounts of the three main colour stimulus. According to the Commission Internationale de l'Eclairage, International Commission on Illumination (CIE) 1931 standard tristimulus values are called X, Y and Z values. Tristimulus colorimeter directly measures these tristimulus values and they can be used to calculate values in  $L^*a^*b^*$  colour space.  $L^*a^*b^*$  colour space is a colour-opponent space based on

nonlinearly-compressed CIE XYZ colour space coordinates (CIELAB). The image is divided into three components:  $L^*$ ,  $a^*$  and  $b^*$ .  $L^*$  component describes the lightness and it is similar to black-and-white images,  $a^*$  component describes colour tones from green to red and  $b^*$  component colour tones from blue to yellow.  $L^*a^*b^*$  colour space is displayed as a figure in study **IV**.

In addition to  $L^*a^*b^*$  colour space also RGB (red, green, blue) and CMYK (cyan, magenta, yellow, key black) colour spaces are widely used. The main purpose of the RGB colour model is to display images in electronic systems, such as televisions and computers. The CMYK colour model, referred to as process colour, is used in colour printing.

### **2.6.1 Colorimetric studies**

Some colorimetric studies have been made in the field of pharmaceutical technology. Siddiqui and Nazzal (2007) conclude that there is a correlation between the surface colour and tensile strength of tablets and colour measurement could be in use to detect deviations in tablet hardness. Chan and coworkers (2001) measured colour distribution on the film coat using tristimulus colorimeter. Surface colour of tablets has also been studied by Bogdansky (1975) with tristimulus colorimeter. Oram and Strine (2006) identified key process parameters of a drug using colour measurement. Berberich and coworkers (2002) studied the whiteness of uncoated tablets during storage. Also the surface coverage of coarse particles which were coated with coloured or uncoloured stearic acid has been studied (Gren and Nyström, 1991).

### **2.6.2 Heat indicator materials**

The heat indicator materials are thermochromic which means that they change their colour at the specific temperature. The indicators used in this thesis were ChromaZone<sup>®</sup> indicators that are coloured until the specific temperature where they change into colourless or light (ChromaZone, 2010). The colour change is reversible because the colour returns when the temperature is decreased. More specific description of the indicator materials is introduced in study **IV**.

ChromaZone<sup>®</sup> materials have been used for example in labels, packaging and textile. They can also be used in coatings on plastics, ceramics or glassware. Thermochromic indicators have not formerly been used as a thermal indicator in pharmaceutical unit

processes. However these kinds of indicators could create new possibilities for visualising process at real-time. The indicator could be mixed into processed mass and the colour change of the mass could be observed during the operation. The colour change would indicate that the conditions are too hot for the heat sensitive API.

## **2.7 Vibrational spectroscopy**

Currently, the quality tests related to the unit processes mostly are performed *off line*, i.e. removing the sample from manufacturing site, after preparing collected samples for analysis. During sample preparation, other valuable information pertaining to the formulation matrix is often lost (US Food and Drug Administration (FDA), 2004). Several new technologies are now available that can acquire information with minimal or no sample preparation. Thus the process analytical technology (PAT) initiative of the FDA encourages the use of NIRS or similar analytical techniques for reducing production cycle times (FDA, 2004). With NIR and Raman spectroscopy it is possible to noninvasively and simultaneously analyse multiple attributes present in matrix, obtain quantitative and qualitative information on both the chemical and physical properties of sample. This eliminates the waiting period for laboratory results at the end of each unit operation (Gupta et al., 2005). It also provides the continuous real-time quality assurance as suggested by the FDA in the PAT initiative. In addition, spectroscopic methods may provide significant advances as a future process analytical tool, since spectra can be measured directly on the surfaces of nondestructed samples (i.e. tablets) without any pretreatment (Otsuka and Yamane, 2006). In addition, they can be used almost everywhere and the spectroscopic devices can be portable. The methods are easy to use and the measurements are repeatable.

### **2.7.1 Near infrared spectroscopy**

#### Theory

NIRS is a spectroscopic method utilising the near infrared region of the electromagnetic spectrum (780—2500 nm or 12821—4000  $\text{cm}^{-1}$ ) (Burns and Ciurczak, 2001). The NIR spectra consist of overtones and combination bands of the fundamental molecular absorptions of polar groups such as O-H, N-H, S-H and C=O bonds (Siesler et al., 2002). The important molecules for NIR measurements have most often been water (O-H stretch), proteins, carbohydrates, fats, and hydrocarbon classes including pharmaceuticals. The molecular overtone and combination bands seen in the NIR are

typically very broad, leading to complex spectra; it can be difficult to assign specific features to specific chemical components. Multivariate analysis techniques are usually needed to extract the desired chemical information. Careful development of a set of calibration samples and application of multivariate calibration techniques is essential for NIR analytical methods.

NIRS follows the Lambert-Beer law:

$$\text{Log} \frac{I_0}{I} = A = abc, \quad (\text{Eq. 1})$$

where

$I_0$  is the intensity of the incident light

$I$  is the intensity measured after passing through the sample

$A$  is absorbance

$a$  is the absorption coefficient or the molar absorptivity

$b$  is the path length

$c$  is the concentration of the absorbing material.

Since there is a direct and linear relationship between sample concentration, path length and the absorbance of light at a particular wavelength, the measuring set-up is crucial for accurate measurements.

Instrumentation for NIRS includes a light source, a detector, and a dispersive element (a prism, or more commonly a diffraction grating) to allow the intensity at different wavelengths to be recorded. The type of detector used depends primarily on the range of wavelengths to be measured. Silicon-based CCDs are suitable for the shorter end of the NIR range, but are not sufficiently sensitive over most of the range. InGaAs and PbS devices are more suitable. Depending on the sample, the spectrum can be measured in transmission, transfection or reflection mode.

### Pharmaceutical applications

One advantage is that NIRS can typically penetrate much deeper into a sample compared to mid infrared radiation. NIRS is therefore not a sensitive technique, but it can be very useful in measuring bulk material with little or no sample preparation. Physical properties

of the sample can also affect the reflected light and interfere with the chemical information of the spectra. This complicates especially quantitative measurements. However, the phenomenon can be utilised to determine physical properties, such as particle size, and density or crushing strength of the sample. However, physical measurement requires well-established measurement methods.

The most important benefits of NIRS are that the samples require no preprocessing and real-time information is gained from the process. Unlike conventional methods of analysis, NIRS is very fast, noninvasive, provides information about physical and chemical properties of the sample and it can be used *in line*, *at line* and *on line* measurements. NIRS can be used for the qualitative analysis as well as for the quantitative analysis of powders (Siesler et al., 2002). It is very sensitive for water, which enables the determination of the water content.

Typical applications for NIRS include pharmaceutical, medical diagnostics, food and agrochemical quality control. The basic uses for NIRS have been process control, quality assessment, identification of raw materials and process byproducts, and chemical quantitative analysis of complex mixtures. NIRS is a valuable measurement technique for use in continuous or real-time process monitoring. NIRS is described in the European Pharmacopoeia (chapter 2.2.40) and in the US Pharmacopoeia general chapter (1119). NIRS have been used in pharmaceutical field in moisture, polymorph, crystallinity, and API content determination (Roggo et al., 2007). The crushing strength of tablets has also been investigated with NIRS (Morisseau, 1996; Morisseau and Rhodes, 1997; Ebube et al., 1999; Kirsch and Drennen, 1999; Chen et al., 2001; Donoso et al., 2003; Otsuka and Yamane, 2006). In addition it has been utilised in monitoring of freeze drying, granulation, drying, coating and mixing processes. Ciurczak (1991) investigated the homogeneity of mixtures *off line*. Sekulic et al. (1996) and El-Hagrasy et al. (2001) studied powder blend homogeneity. Blanco et al. (2004) and Filho et al. (2004) acquainted themselves with strategies for constructing a calibration set for quantitative NIRS measurements. Berntsson et al. (2002) monitored *in line* powder blending by near infrared reflection spectroscopy and Patel et al. (2000) quantified polymorphs in mixtures. Rantanen et al. (2005a) used chemometrics in order to specify the factors influencing the quantification of anhydrate/hydrate powder mixtures. Chemometrics has also been used in a study conducted by Li and Worosila (2005) when the quantification

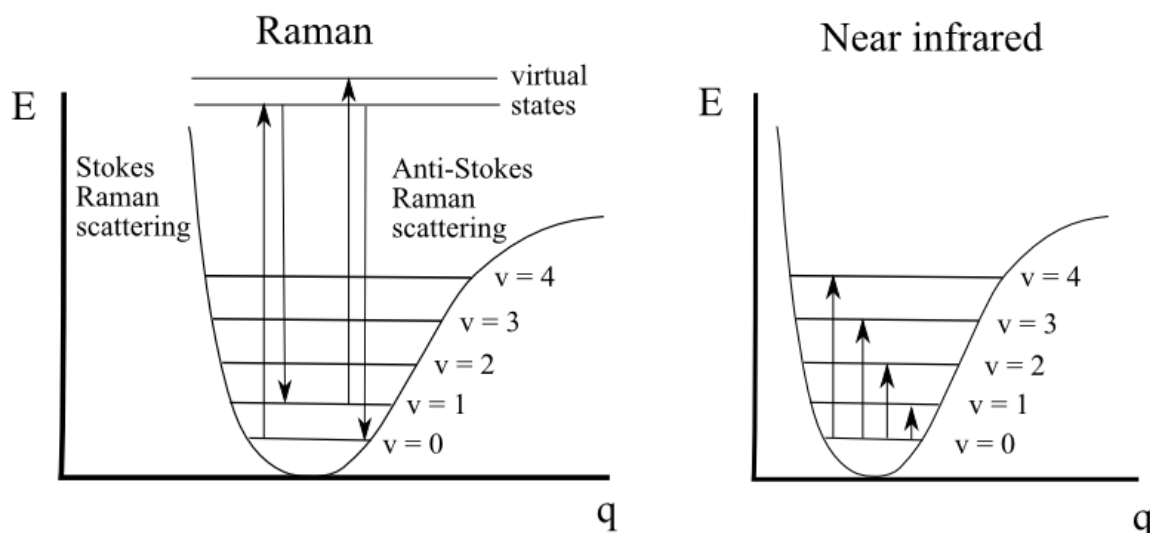
of powder mixtures using *at line* NIRS was performed. Other studies have used NIRS with a fibre-optic probe. The first reported study on powder mixtures with a fibre-optic probe was conducted by Kaye et al. (1969). More recently, Li et al. (2006) studied the mass-balanced blend uniformity of pharmaceutical powders with a fibre-optic probe as well as Storme-Paris with coworkers (2009) and Wu and Khan (2009). Benedetti's study concerning powder flow characterisation with *in line* NIRS also used a probe (Benedetti et al., 2007). Finally, NIRS has also been attached to the mixer by Liew and coworkers (2010). They quantified cohesive powders in a bin blender and used PLS as analysis method.

### **2.7.2 Raman spectroscopy**

#### Theory

The Raman effect occurs when light interacts with the electron cloud of the bonds (i.e. the electric dipole) of the molecule (McCreery, 2000). When light is scattered from a molecule most photons are elastically scattered. These scattered photons have the same energy and, therefore, wavelength, as the incident photons. However, a small fraction of light, approximately one of the million photons, is scattered at optical frequencies different from the frequency of the incident photons (Vankeirsbilck et al., 2002). The process leading to this inelastic scatter is termed the Raman effect. Sir Chandrasekhara Venkata Raman received a Nobel Prize in Physics concerning Raman effect in 1930.

The incident photon excites one of the electrons into a virtual state. For the spontaneous Raman effect, the molecule will be excited from the ground state to a virtual energy state, and relax into a vibrational excited state, and which generates Stokes Raman scattering (McCreery, 2000). However, a small fraction of the molecules are in vibrationally excited states and they are relaxed back to the ground state. The scattered photon appears at higher energy, as shown in Figure 5. This anti-Stokes Raman spectrum is always weaker than the Stokes-shifted spectrum. The Stokes and anti-Stokes spectra contain the same frequency information.



**Figure 5.** Vibrational energy state diagram for Raman and NIR spectroscopy. (Adapted from Siesler et al., 2002.) E is excitation energy, v is vibrational quantum number, q is vibrational coordinate, v = 0 is ground state, v = 1, v = 2, etc. are excited states.

Raman scattering occurs because a molecular vibration can change the polarisability of the molecule (McCreery, 2000). The polarisability measures the ease with which the electron cloud around a molecule can be distorted. A molecular polarisability change is required for the molecule to exhibit the Raman effect. In other words symmetric vibrations of non-polar groups are Raman active. The vibrations of a highly polar moiety, such as the O-H bond, are usually weak. Typical strong Raman scatterers are moieties with distributed electron clouds, such as carbon-carbon double bonds. Bending or stretching the bond changes the distribution of electron density substantially, and causes a large change in induced dipole moment.

Typically, a sample is illuminated with a laser beam. Light from the illuminated spot is collected with a lens and sent through a monochromator. Wavelengths close to the laser line (due to elastic Rayleigh scattering) are filtered out and those in a certain spectral window away from the laser line are dispersed onto a detector, usually a CCD camera.

#### Pharmaceutical applications

Raman spectroscopy is commonly used in chemistry, since vibrational information is very specific for the chemical bonds in molecules. It therefore provides a fingerprint by which the molecule can be identified. Vibrational Raman spectroscopy is not limited to intramolecular vibrations. Crystal lattice vibrations and other motions of extended solids are Raman-active. In addition to chemical applications Raman spectroscopy can also be used for physical measurements. The disadvantages of Raman spectroscopy are the



weakness of the signal, warming of the sample caused by the laser and the fluorescence phenomenon. However, the weakness of the signal can also be used as an advantage, since it enables measurement directly from the sample with no preprocessing. The fluorescence can be problematic, even when the measurement conditions are in order. Fortunately, fluorescence is not a problem for most APIs.

Quantitative measurement with Raman spectroscopy is possible because signal intensity is directly proportional with the concentration. Correlation between signal and concentration enables straightforward concentration measurements and explains why Raman spectroscopy has been used in many pharmaceutical processes, even in real-time applications (Rantanen, 2007). Nevertheless, the number of physical measurements, such as crushing strength of tablets, is limited in the literature. Some studies determined influence of particle size on Raman intensity (Pellow-Jarman et al., 1996; Fangxin et al., 1997; Wang et al., 2002; Williams et al., 2004; Hu et al., 2006). The results showed that the intensity of the signal changes with change in particle size. The particle shape and solid state form of the material measured, as well as the wavelength of the signal and finally temperature, also influence the signal intensity.

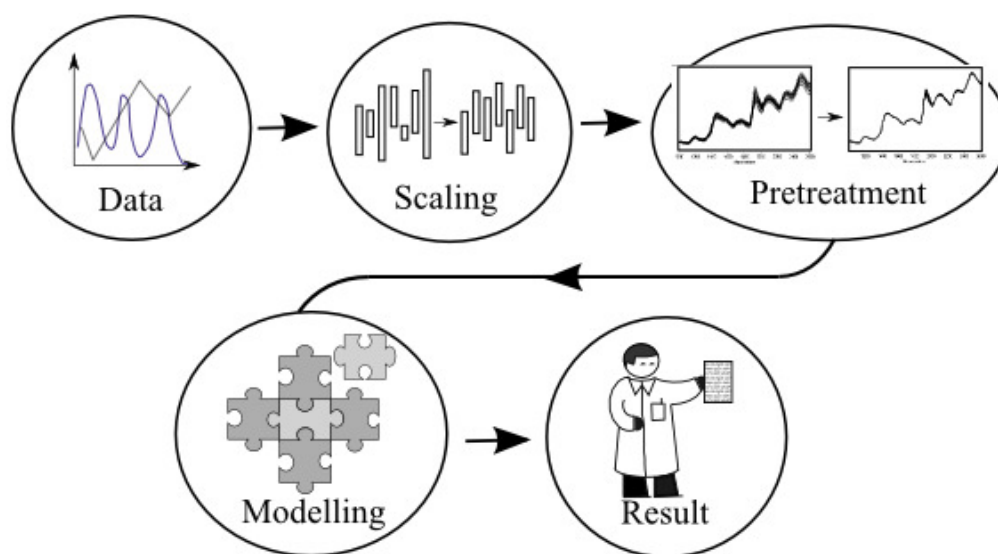
Few reports are available on the applicability of Raman spectroscopy for tablet hardness determination. Only Wang's (2002) and Johansson's (2005) groups studied intact tablets and Picker-Freyer and Schmidt (2004) studied broken tablets. Picker-Freyer and Schmidt observed differences in the Raman spectra that were due to structural changes in the tablet. The intensity of the spectra increased with increase in the hardness of the tablets. Johansson et al. (2005) compressed tablets with different compression forces and noted no significant effect of tablet density on the Raman signal. They also stressed that the results were based on measurements of a single type of tablet, so these results cannot be generalized for all types of tablets. Wang and coworkers (2002) investigated the effects of compression force during tableting on the Raman signal. They studied the effect of the tablet thickness by comparing the Raman signals for tablets of the same particle-size powder. In their measurement the Raman intensity decreased with increasing compression force until a constant density was achieved.

Raman and NIR spectroscopy are complimentary methods. They both can be utilised in the same processes and they can give information from the same phenomena but from

different point of view. In general NIRS can be faster and more water-sensitive than Raman spectroscopy. However, Raman has sharper peaks and it can be utilised measurements from aqueous systems, because water does not disturb it. The selection of method has to be done according to the attribute studied based on previous knowledge. Sometimes both of the methods can give the same information but most of the time one or the other is more convenient.

## 2.8 Data analysis and modelling

Extracting useful information from massive amount of data is a challenge when using spectroscopic methods. This procedure can involve multiple phases before actual analysis (Fig. 6.) and it demands knowledge and carefulness to succeed. In the next chapter scaling, spectra pretreatment and modelling are discussed. In addition spectral region used in the analysis can have significant affect to results.



**Figure 6.** Preprocessing of the data illustrated as a flow chart.

### 2.8.1 Scaling

Variables can have substantially different numerical values. Typically, a variable with a large range has a large variance and variable with a small range has a small variance. Thus, some kind of data scaling is mandatory when variables are of different type and their values are at different scales and units. There is always a risk present when scaling the data. Thus scaling, and other pretreatments, has to be performed with careful manner (Gabrielsson et al., 2006). The correct pretreatment methods have to be chosen according

to prior knowledge of the variables. Only if scaling is performed correctly it can lead to reliable results.

In general, if variables are all on the same scale such as spectroscopic data in chemical analysis then centering is usually recommended scaling method. If the variables are on different scales (for instance weight and length) the unit variance (UV) scaling is recommended.

#### Unit variance scaling

UV scaling is used to emphasise small variations in the data by giving all values equal weighting. The standard deviation (SD) is calculated for each variable and the scaling weight as the inverse SD is obtained. Subsequently, each variable is multiplied by inverse SD. Each scaled variable then has equal (unit) variance. UV scaling does not change the mean values of the variables (Eriksson et al., 2001). However, UV scaling has a risk of scaling up noisy variables.

#### Mean centering

In mean centering the average value of each variable is calculated and then subtracted from the data. This leads to the fact that the mean value for every variable is zero. By removing the average from the data, the differences between the samples are substantially enhanced in terms of both concentration and spectral response. This usually leads to calibration models that give more accurate predictions. Mean centering removes constant background contributions, which usually are of no interest for data variance interpretation.

Mean centering is often used for spectroscopic data when analysing chemical properties such as content uniformity. When applying mean centering there is a risk of losing relevant information which is hidden in the noise (Gabrielsson et al, 2006).

### **2.8.2 Pretreatments**

Spectra of powders typically display a scattering variation, due to the physical properties, such as particle size of the sample. This can induce variations of the optical path length. Sometimes the scattering can even be a superior contributor to the spectrum, accounting for most of the variance in the data. The scattering is not uniform throughout the spectrum. Typically, this appears as a baseline shift, tilt and sometimes curvature, where

the degree of influence is more pronounced at the longer wavelength end of the spectrum. That is why a well defined sample analysis preparation protocol is required.

The aim of the spectroscopic data preprocessing is to remove these unwanted systematic variations, such as baseline shift. The most current data pretreatments are the normalisation methods like standard normal variate (SNV) and multiplicative scatter correction (MSC), the derivative methods (for example the Savitzky-Golay method) and the orthogonal signal correction (Roggo et al., 2007).

SNV correction is designed to remove the large amount of variability that may be caused by scattering effects from reflectance spectra (Fearn et al, 2009). It corrects for differences in spectroscopic path lengths or multiplicative variations induced by scattering effect. SNV correction centres each spectrum to zero intensity by subtracting the average of all the spectral responses in the vector from each of the original values. Finally, each spectrum is divided by its SD (Barnes et al., 1989). The SNV method is performed on one spectrum at a time, and does not require the use of a reference spectrum. It has been used successfully with NIRS data (Fearn et al, 2009). However, the use of SNV for some quantitative measurements is questionable because the correction can alter the peak intensities.

The preprocessing of spectra to determinate amorphous content of lactose has been studied by Savolainen and coworkers (2007). They compared the effect of scaling and pretreatment methods. In addition Candolfi and coworkers (1999) and Blanco and others (1997) studied the effect of preprocessing to NIR spectra.

### **2.8.3 Modelling**

#### Principal component analysis

Principal component analysis (PCA) is a multivariate projection method designed to extract and display the systematic variation in a data matrix. Hence PCA is used for over viewing and classifying data and detecting trends (Wold et al., 1987). It can also be used to detect outliers.

The starting point for PCA is a matrix of data with N rows (observations) and K columns (variables). The observations can be process time points, batches from a process etc. In

order to characterise the properties of the observations variables are measured. These variables can be for instance of spectral origin (NIR, Raman) or measurements from sensors such as temperature. PCA can uncover the relationships between observation and variables, and among variables themselves. PCA derives a model that fits the data as well as possible in the least squares sense. It can be said that PCA displays systematic variation in the data matrix describing the variation with minimum amount of variables (Gabrielsson et al., 2002).

PCA creates score and loading plots. Scores provide information about similarities and differences in the spectra. Loadings explain the origin of scores, so they have a relationship to the original data (Eriksson et al., 2001). Prior to PCA, data is often pretreated in order to transform the data into a form suitable for analysis. Preprocessing can make the difference between useful model and no model at all (Eriksson et al., 2001).

#### Partial least squares regression

Partial least squares (PLS) regression (Wold, 1966; Wold et al., 1983) combines features of PCA and multiple linear regression in order to create a model between variables (X, for instance spectra) and property of interests (Y, for instance concentration) (Eriksson et al., 2001; Roy and Roy, 2008). It provides a reduced solution, which is statistically more robust than multiple linear regression and is useful when a large number of cross-correlated and/or noisy predictor variables are present (Beebe et al., 1998; Roy and Roy, 2008). PLS compresses the size of the spectra and removes insignificant information.

PLS creates latent variables and weights that provide information about the correlation between the variables and similarities/dissimilarities among the compounds. In other words PLS reveals how the spectra and for instance concentration are related. In its general form, PLS maximises the covariance between different sets of variables. PLS modelling can be used to obtain qualitative and quantitative information from spectra that are usually difficult to obtain using traditional univariate methods. It has become a standard tool for processing a wide spectrum of chemical data problems.

## **2.9 Process analytical technology**

The concept of PAT has been introduced to improve our understanding of the pharmaceutical process and to monitor and control critical process parameters (FDA,

2004). It was originally based on process analytical chemistry which is a multidisciplinary field that encompasses a combination of analytical chemistry, process engineering, process chemistry, and multivariate data analysis. Nowadays the view of FDA is that the quality cannot be tested into products; it should be designed beforehand. Thus PAT has emphasised the importance of evaluating not only the final product but the whole production process. In addition, the aim is real-time quality assurance and a capability of process control.

Product and process development on a small scale and *on* or *in line* process monitoring to collect data in real-time can provide increased understanding for process development, and control. A process is well understood when all critical sources of variability are identified and explained, and variability is managed in the process. Process monitoring and control strategies are intended to monitor the state of a process and actively manipulate it to maintain a desired state. Optimisation of manufacturing processes includes designing a process measurement system which allow real-time or near real-time monitoring of critical attributes.

## **2.10 Real-time monitoring**

The physical state of a process is derived from measured variables, for instance temperature and pressure. When monitoring these variables using traditional approaches usually only one variable can be observed at the time. However, the state of process is usually determined by several factors. There can be interactions between the variables, but they are not detected when using a univariate approach (Kourti and MacGregor, 1995). Nowadays chemometric methods enable multivariate approach to data analysis. This is really needed because the amount of data generated is increasing due to new process analysing techniques, such as spectroscopic methods.

Spectroscopic methods provide nondestructive measurements that contain information related to physical and chemical attributes of the materials. These measurements can be performed: 1) *at line*: Measurement where the sample is removed, isolated from, and analysed in close proximity to the process stream. 2) *on line*: Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream. 3) *in line*: Measurement where the sample is not removed from the process stream and can be invasive or noninvasive.

These techniques make real-time control and quality assurance during manufacturing possible. Simultaneous monitoring of both chemical and physical properties can lead to learning the important process variables and improved process understanding. This leads to possibility to control the process.

### **2.10.1 Near infrared spectroscopy as real-time monitoring tool**

NIRS has been widely studied as real-time monitoring tool in pharmaceutical powder technology (Bakeev, 2006). NIRS has been used as a PAT tool (Cogdill et al., 2004). Cogdill and coworkers (2005a, b, c) developed and validated a PAT method using NIRS for the *on line* prediction of intact tablet hardness and active pharmaceutical ingredient (API) content. In addition, real-time NIR monitoring of moisture in fluidised bed drying has been studied (Rantanen et al., 1998; Rantanen et al., 2000ab; Morris et al., 2000; Wildfong et al., 2002; Jørgensen et al., 2002; Rantanen et al., 2005a). Harris and Walker (2000) studied also drying and Rantanen and others (2005b) investigated the high shear granulation. In addition tensile strength measurements using NIRS during roller compaction has also been reported (Gupta et al, 2004). Also intact paracetamol tablets have been assayed using NIRS (Trafford et al., 1999). Mixing operation has been broadly studied using NIRS for years (Sekulic et al., 1996; Hailey et al., 1996; Lai et al., 2001; El-Hagrasy et al., 2005a,b,c) as well as flowability and segregation of powders (Barajas et al., 2007). The versatility and rapidness of NIRS enables increased process understanding, better process control and improved quality of drug products (Räsänen and Sandler, 2007).

### **2.10.2 Raman spectroscopy as real-time monitoring tool**

Raman spectroscopy has become established in pharmaceutical field. There are numerous of applications for Raman and they extend from screening in early phase discovery to final product testing in manufacturing (Rantanen, 2007). Raman spectroscopy has been used for example to monitor crystallisation (Starbuck et al., 2002), polymorph screening (Campbell Roberts et al, 2002), hydrate forming (Wikström et al., 2005) and dehydration (Aaltonen et al., 2007; Kogermann et al., 2007ab; Kogermann et al., 2008), drying (Aaltonen et al., 2007), content uniformity measurements (Vergote et al., 2004), granulation (Wikström et al., 2005), homogenisation of suspensions (De Beer et al., 2006), mixing (Vergote et al., 2004; Hausman et al., 2005) and coating (Romero-

Torres et al., 2006). In addition it has been successfully used as a quality control tool (Niemczyk et al., 1998) and it can differentiate the crystalline and amorphous samples (Langkilde et al., 1997; Taylor and Zografi, 1998; Savolainen et al., 2007). Nevertheless, the number of, especially real-time physical measurements have been limited in the literature. Few reports are available on the applicability of Raman spectroscopy for tablet hardness determination, (Wang et al., 2002; Picker-Freyer and Schmidt, 2004; Williams et al., 2004; Johansson et al., 2005) and particle size determination, (Wang et al., 2002; Williams et al., 2004; Hu et al., 2006) but these were not real-time measurements. However, Raman can also be utilised in real-time. Raman spectroscopy is a suitable PAT tool to control the pharmaceutical unit processes. Raman spectroscopy not only allows real-time measurements, but it also helps to understand the process.



### **3. Aims of the study**

The overall aim of this thesis was to study pharmaceutical powder technology processes at real-time in order to gain deeper understanding from the process.

The specific aims of this study were:

1. to study whether NIRS is suitable for measuring the degree of mixing in poorly miscible powder mixtures **(I)**
2. to create a coloured heat indicator and to present a new practical way to visualise the progress of the heat in the mass during fluidisation **(IV)**
3. to evaluate the particle size of granules during the tableting process in order to examine segregation phenomenon during compression **(III)**
4. to evaluate how different granule size distributions affect the tablet compression process. The emphasis was to develop new analysis methods for compression data for entire batches. **(V)**
5. to find out is there a correlation between tablet weights and compression force **(III)**
6. to determine the applicability of Raman spectroscopy for rapid crushing strength determination of intact tablets **(II)**

## 4. Materials and methods

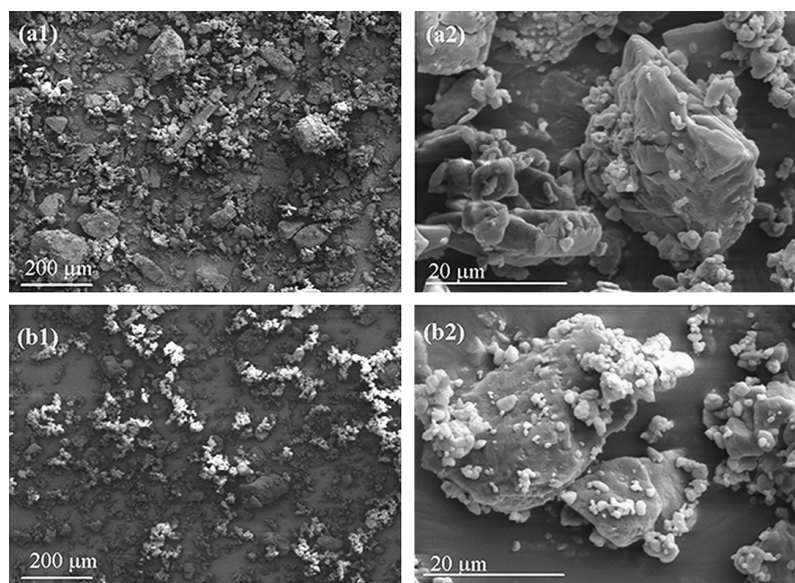
### 4.1 Materials

Carbamazepine (CBZ, Hawkins, inc. Pharmaceutical group, Minneapolis, USA (**I**)) and theophylline anhydrate (TP, BASF Corporation, Bishop, USA (**III**, **V**); BASF Corporation, Ludwigshafen, Germany (**V**)) and were used as model drugs. The commercial ChromaZone<sup>®</sup> (CZ, ChromaZone, Flintshire, Great Britain (**IV**)) powders were used as heat indicators and microcrystalline spheres (cellets, neutral pellets of Syntapharm GmbH, Mülheim an der Ruhr, Germany (**III**, **V**)) were used as a model granules. Polyvinylpyrrolidone (PVP, Kollidon K25 (**II**), Kollidon K30 (**III**, **IV**, **V**) BASF, Ludwigshafen, Germany),  $\alpha$ -lactose monohydrate (LMH, DMV International GmbH, Veghel, The Netherlands (**I**, **III**, **IV**, **V**)), hydroxypropyl methylcellulose (HPMC, Methocel E5, The Dow Chemical Company, Midland, USA (**IV**)) and magnesium stearate (MS, Orion Pharma, Espoo, Finland (**II-V**)) were used as excipients.

### 4.2 Methods

#### 4.2.1 Characterisation of materials

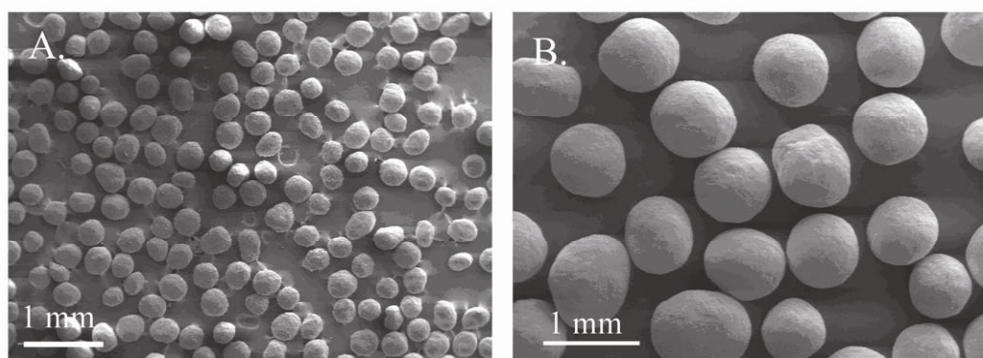
In study **I** CBZ was identified as a polymorph **III** by NIRS and X-ray powder diffraction (XRPD). CBZ was micronised and its particle size was around 300 nm measured with Zetasizer 3000 HAS (Malvern Instruments, Worcestershire, UK) based on intensity measurement. The particle shape seemed spherical. The particle size and shape appear in the SEM images (Fig. 7). In addition to the 300 nm particles, the powder also contained larger particles. The small particles aggregate in the CBZ powder. The particle size of used LMH was, according to the manufacturer, 200  $\mu$ m (i.e. 75  $\mu$ m). According to the SEM image the LMH powder also contained smaller particles. The CBZ particles were about 250 times smaller than LMH particles.



**Figure 7.** SEM micrographs of CBZ (a1, a2) and LHM (b1, b2).

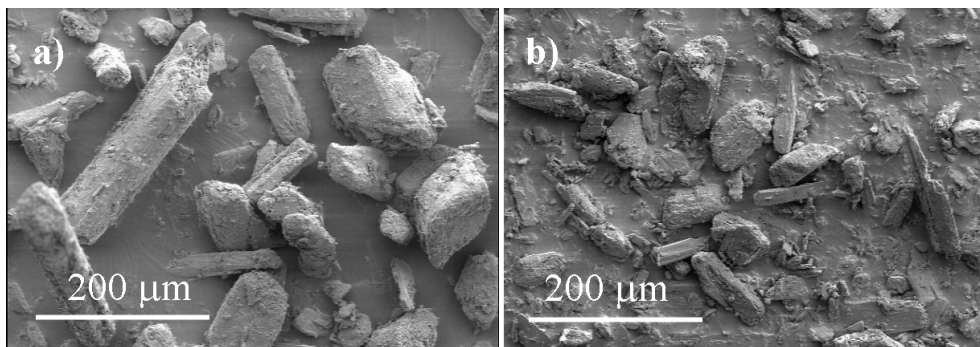
CZ is a microencapsulated thermochromic pigment which changes from coloured to colourless as the temperature rises. With decreasing temperature the colour returns. CZ pigments were used in study **IV**. The microcapsules are individual droplets of chromogenic material with an impervious polymeric wall. The particle size of the CZ powders was 6  $\mu\text{m}$ . The microcapsule wall can withstand most standard mixing and application procedures (ChromaZone, 2010). In this study, powders which activation temperatures were 31 (green; CZ31), 35 (pink; CZ35) and 40°C (blue; CZ40) were used.

Pellets prepared from MCC in the other words cellets with a particle size fraction of 200  $\mu\text{m}$  (cel200) and 700  $\mu\text{m}$  (cel700) were used as model (**III** and **V**). SEM micrographs of cel200 and cel700 are presented in Figure 8. In addition cellets with particle size 1000  $\mu\text{m}$  were used in study **IV**.



**Figure 8.** SEM micrographs of cellets. A. cel200, B. cel700.

The model drug in the studies **II**, **III** and **V** was TP. Its initial particle size was 100 M and 200 M in the study **II** and 200 M in the studies **III** and **V**. SEM micrographs of TP are presented in Figure 9.



**Figure 9.** SEM micrographs of TP. A. 100M, B. 200M.

#### 4.2.2 Mixing (I-V)

The batch size was 25.0 g and the filling rate was approximately 80% (v/v) in the CBZ mixing study (**I**). The dominant substance was first weighed directly in the jar, followed by the residual substance. The CBZ percentages for the calibration model were 0, 1, 5, 10, 15, 20, 25, 30, 40, 45, 50, 60, 70, 75, 80, 85, 90 and 100%. The powders for the calibration model were mixed in a Turbula mixer (Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland) until the mixtures were mixed homogeneously according to the UV-Vis analysis. The experimental batches were mixed at varying speeds and concentrations, and the experiment included nine replicates according to the experiment chart. The mixing time was 14 min for all of the experimental batches. The experiment chart was created with MODDE software (Umetrics, Umeå, Sweden). All of the powders were stored in 45% RH to reduce the electrostatic charges at least 72 h before the mixing.

Binary mixture of cel200 (50% w/w) and cel700 (50% w/w) was mixed using a Turbula blender at mixing speed of 46 rpm and mixing time of 3 min (**III** and **V**). The batch size was 800 g and a 2.0 l mixing jar was used. After mixing, the lubricant (0.5%, w/w) was added to the middle of the mass and mixed for an additional 3 min.

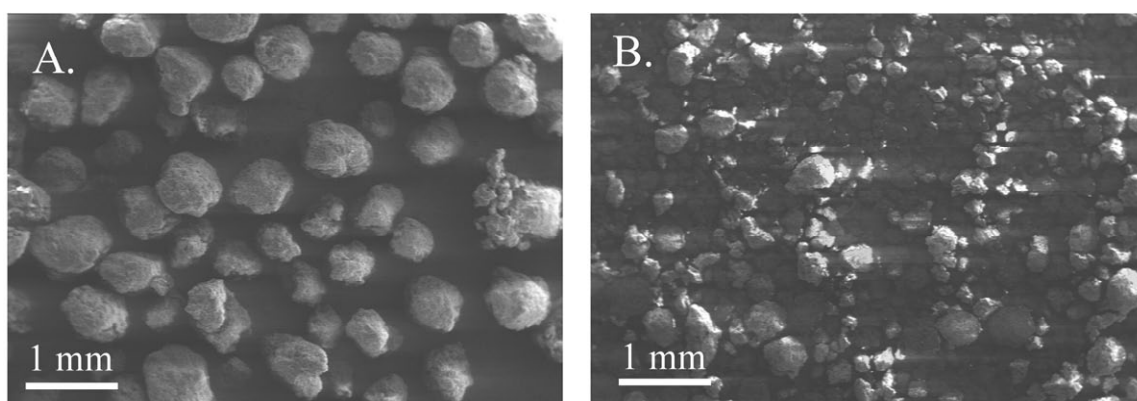
The granules were mixed with MS in a Turbula blender at a mixing speed of 46 rpm and mixing time of 3 min (**II-V**). The batch size was 250 g (**III**, **V**) and the materials were loaded into a glass jar in a systemic fashion, with MS in the middle of the jar (49.5%

granules – 1% MS – 49.5% granules) (**II**, **III**, **V**). The concentration of MS was 1% (w/w) (**III**, **V**), 0.5% (w/w) (**II**) or 0.1% (**IV**).

#### 4.2.3 Granulation (**II** -**V**)

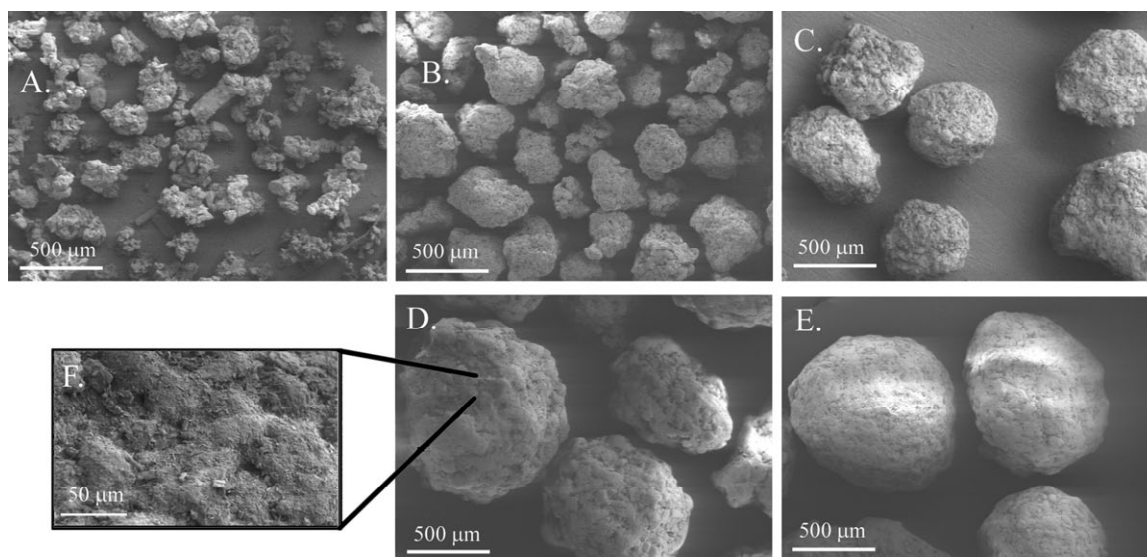
The TP and LMH were granulated with a 7.5% aqueous solution of PVP in an automated bench-scale fluid bed granulator (Glatt WSG5, Glatt Process technology GmbH, Binzen, Germany) (**II**, **III**, **V**). The instrumentation system is described by Rantanen and coworkers (2000c). The batch size for granulation was 4.0 kg and the amount of both solid materials was 2.0 kg. In addition, the amount of the PVP solution was 2.0 kg (**III**, **V**).

In study **III** two granulation batches were produced: G1 and G2. SEM micrographs from G1 and G2 are presented in Figure 10. The RH of the inlet air was 55% during the G1 granulation and 49% for G2 granulation. In addition, the flow rate of the granulation liquid was 84 g/min and 70 g/min, respectively. Other parameters such as atomisation pressure and nozzle height were held constant.



**Figure 10.** SEM micrographs from TP granules. A. Batch G1 and B. Batch G2.

In study **V** 18 batches of granules including three centre point triplicates were granulated. SEM micrographs of the granules from five chosen batches are presented in Figure 11. The design of experiments and the variables for granulation process have been specified by Närvänen and coworkers (2008). According to the model by Närvänen and coworkers the granulation liquid feed rate was altered in function of RH of inlet air. The inlet air temperature was fixed to 40°C for the granulation and 60°C for the drying phase. Other parameters such as atomisation pressure and nozzle height were held constant.



**Figure 11.** SEM micrographs of TP granules manufactured in the study V. A. Batch 2, B. Batch 5, C. Batch 9, D. Batch 13, E. Batch 17, F. Close-up image from batch 13. Magnification is 50x for A to E and 500x for F.

After granulation the granules were poured through a 3.15 mm sieve to remove any clumps (III, V). The granules were thereafter distributed, using a sample divider (Fritsch Sample Divider Laborette 27; Fritsch GmbH, Idar-Oberstein, Germany) for tableting.

CZ powders were manually granulated with LMH (IV). Granulation liquid was 20% polyvinylpyrrolidone-water liquid. Used CZ concentration was 5% (w/w). The moist mass was pushed through 1 mm sieve and the granules were dried 2 h in room temperature. After drying the granules were sieved first through 1.0 mm sieve and then the granules which penetrated the 1.0 mm sieve were sieved through 0.5 mm sieve. Resulting three particle size groups which were small (S) (< 0.5 mm), medium (M) (0.5 mm – 1.0 mm) and large (L) (> 1.0 mm). In addition fourth group was also granulated. It contained 15% (w/w) of CZ31 powder and it was used to study how the indicator content affected colour values.

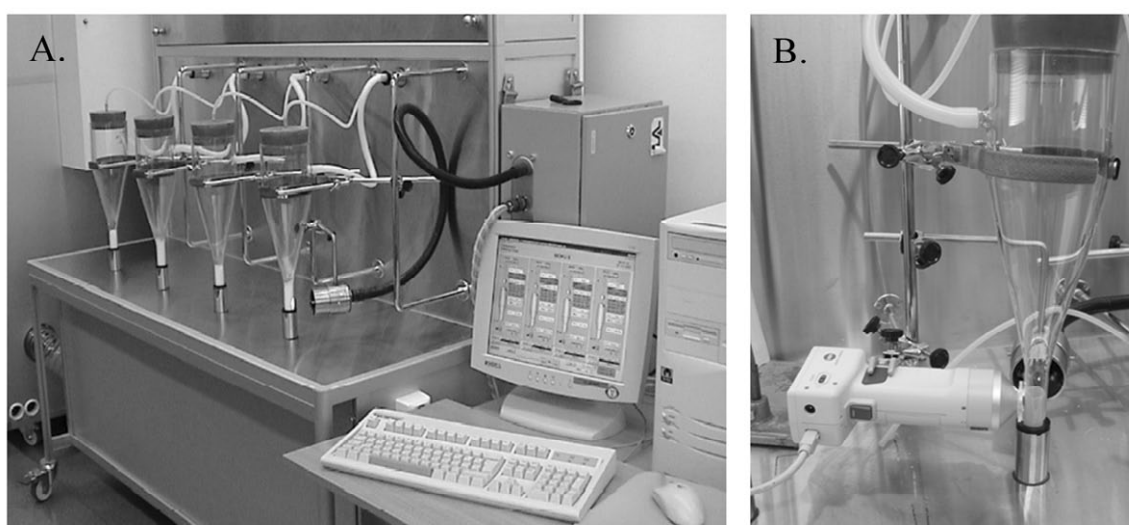
#### 4.2.4 Coating (IV)

Cell1000 were coated with CZ powders using Caleva top-spray coating equipment (Caleva Mini Coater, Caleva Process Solutions, Dorset, Great Britain) (IV). The coating liquid contained 1% (w/w) CZ powder, and 5% (w/w) HPMC. The batch size was 40 g and the average consumption of coating liquid was about 25 ml per coating process. The pellets were fluidised with mechanical vibration and air flow during the coating process. The frequency of the vibration was 17 Hz and amplitude 5 mm. The air flow rate was

4 m/s and the temperature of air was 50°C. Spray pressure was 0.5 bar and the nozzle height was 140 mm. The flow rate of the coating liquid was 35 ml/h. The pellets were coated first for 15 min and then they were dried in the air flow for 10 min without the liquid feed. This procedure was repeated three times.

### 4.2.5 Fluidisation (IV)

The granules and the coated pellets were fluidised to observe the progress of the heat flow in the material and to study the heat indicator properties of the CZ materials (IV). The used equipment was a multichamber microscale fluid bed device (MMFD), (Ariacon Oy, Turku, Finland). The apparatus involves four individual glass chambers which inlet air rate and temperature can be controlled individually in each chamber. Though, in this study only one chamber was used. The equipment is attached to a process air control unit (Ilmasäätö Oy, Turku, Finland). The control unit is used to control the humidity and the temperature of the inlet air. The set-up for colour monitoring is presented in Figure 12.



**Figure 12.** Set-up for colour monitoring during fluidisation. A. Multichamber microscale fluid bed device and its control unit. B. Fluid bed chamber and the colorimeter.

All of the samples were fluidised with three temperatures and with three inlet air speeds. If the particles were fluidised with even higher air flow rates than the highest used air flow rate the movement of granules was so intensive that the colorimeter “saw” through the fluidised material. In this case the colorimeter did not measure the granules in the chamber but background behind the chamber. When measuring powders, the  $L^*a^*b^*$  values can vary depending on the density of the powder and the surface conditions. To avoid errors, usually a fixed amount of powder is placed into a container of a fixed shape

and size and maintaining the surface quality. In fluid bed dryer the mass was moving continuously. The temperature was chosen according to the activation temperatures of the CZ-materials. The temperature was increased until the  $L^*a^*b^*$  value was not changing notably. This ensured that the temperature was steady in the entire mass, not just near the sensor. The colour values were measured before the fluidisation, various times during the fluidisation and after the fluidisation during the cooling period with some samples. The batch size during the fluidisations was 5 g. In study **IV** the fluid bed drying was an expedient for study the changes in the colour of the indicators not the target of investigation as such.

#### 4.2.6 Tableting (**II**, **III**, **V**)

After lubricant mixing the granules were tableted using an instrumented eccentric tableting machine (Korsch EK-0, Erweka Apparatebau, Heusenstamm, Germany) (**II**, **III** and **V**). The machine was equipped with strain gauges and a feed shoe. Flat-faced 9 mm punches were used in all of the tableting studies (**II**, **III**, **V**). The rotating speed was 30, 61 and 60 rpm, in the studies **II**, **III** and **V**, respectively.

The tablets were compressed so that their crushing strengths were between 30 N and 200 N and the tablet weight was adjusted to 250 mg (**II**). There were five groups of crushing strengths. Each tablet was treated individually so that the response (crushing strength) could be linked to the corresponding spectra measured from the same tablet.

In study **V** the weight of the tablets was adjusted to 250 mg and the crushing strength to 60 N. In study **III** the crushing strength of the tablets was set to 65 N. During tablet compression  $F_{up}$ ,  $F_{lp}$  and  $F_e$  were recorded (**III**, **V**).

$F_{eff}$  was also calculated as an additional tableting parameter (Eq. 2)

$$F_{eff} = \sqrt{F_{up} \cdot F_{lp}} \quad (\text{Eq. 2})$$

The  $F_{eff}$  is used because it explains the compression behaviour more accurate than for instance the average of the upper and lower punch force (Yliruusi and Antikainen, 1997).  $F_{eff}$  assumably minimises the effects of the inhomogeneous structure of compressed tablets such as die wall friction, particle rearrangement, partial melting, recrystallisation



and different types of deformation (Marshal, 1986; Yliruusi and Antikainen, 1997). The SD of the relative error ( $s_{rel}$ ) was also calculated (**III**).

In the studies **III** and **V** the cellet mixture was tableted, using the same instrumented eccentric tableting machine (Korsch EK-0). The tablet mass was set to 530 mg. No tablets were formed, when  $F_{up}$  was over 13 500 N. Even though no tablets were formed, the compression force data of the  $F_{up}$  and  $F_{lp}$  and  $F_e$  were recorded for further investigation.

In the study **III** the granule samples from the die, corresponding to the tablets, were also collected for particle size determination. The sampling points for particle size measurements were determined according to the  $F_{up}$  behaviour. The sampling method is described more closely in publication **III**.

Various methods were used to analyze tableting data in order to define both short and long-time-scale undulation in the study **V**. All of the analyses were performed using Matlab software (v 7.0, The MathWorks Inc., Natick, USA). The description of the analysis methods can be found in publication **V**.

### 4.2.7 Tablet properties (**II**, **III**, **V**)

In study **III** approximately with 100 tablets intervals, 10 tablets were collected during tableting. Tablets were collected manually in order to link each individual tablet with the corresponding punch force.

Before analysis the tablets were collected in the plastic tubes in the same order in which they were compressed in study **V**. This procedure ensured that each tablet was analysed individually. Hence, the results were not averaged as prevailing method normally does. A novel feeding apparatus was used for weighing of the tablets. The machine dropped tablets from the plastic tube one at the time and dropping time interval was kept the same. The tablets were dropped in the Multitester apparatus (Erweka GmbH, Heusenstamm, Germany). Multitester measured the weight, diameters and crushing strength of the tablet. Only weights of the tablets were further analysed in study **V**. Finally, the crushing strengths were measured with an indirect Multicheck diametral hardness apparatus in study **II**.

#### 4.2.8 Moisture content (III, IV)

The moisture content of the granules was measured using moisture analyser (Sartorius, MA100, Göttingen, Germany) (III and IV). A continuous heating was used until 105°C and the measurement ended when the weight loss was decreased to 1 mg/24 sec. The samples were measured after granulation, after being in the desiccator (0% RH) for 24 h and after fluidisation (IV). In addition, the water activity ( $a_w$ ) of the granules was determined, using a dew point hygrometer (Aqualab Series 3 TE; ADAB Analytical Devices Ab, Stockholm, Sweden) (III).

The moisture equalises electric charges on the particle surfaces (Antikainen, 2003) and therefore increases the flowability (Zhuikova et al., 2009). In addition water can act as lubricant during tableting and even be a part of bonding (hydrogen bonding and liquid bridges) during compression (Antikainen, 2003). On that account the moisture content of material to be compressed has to be standardised. Thus, the cellet mixture was stored at 50% RH and ambient temperature for 1 month (III and V).

#### 4.2.9 Particle size (III, V)

The particle size was measured using Parsum<sup>®</sup> equipment (IPP 70; Gesellschaft für Partikel-, Strömungs- und Umweltsmesstechnik mbH, Chemnitz, Germany) (III, V). The Parsum<sup>®</sup> method is accurate even with small sample size (Närvänen et al., 2008). The SFT determines the chord length of each particle passing through the laser light beam (Petraik, 2002; Närvänen et al., 2008). The apparatus was installed on a laboratory table and the sample was poured through the orifice (diameter 4 mm), using a funnel. The particles were dispersed by pressurised air. The particle size (chord length) distribution was converted to volume particle size distribution.

The particle size was also measured using sieves as a comparison for Parsum method (V). For sieve analysis, a 50 g sample was vibrated using an automatic sieve shaker (Fritsch analysette, Idar-Oberstein, Germany) for 5 min. The sieve analysis (range 71–2000  $\mu\text{m}$  with  $\sqrt{2}$  increment) was performed in triplicate and the mean value for the median granule size was determined.

#### 4.2.10 Surface properties (I, II, III, V)

Visual images of the particles corresponding to the tablets were measured, using a prototype 3D surface roughness instrument (iPharmaceutics Ltd., Helsinki, Finland)

(III). Its operational principle is described by Laitinen and coworkers (2004). The roughness parameter was calculated for each 3D image using equation adapted from publication by Krogars and coworkers (2002).

#### Scanning electron microscopy (I, II, III, V)

SEM images were measured with Zeiss DSM 962 scanning electron microscope (Oberkochen, Germany) and they were used to visually characterise the powder mixtures (I), the surface of the tablets (II) and the morphology of the cellets and granules (III, V).

#### Non-contact laser profilometry (II)

The surface profile of the tablets, i.e. roughness, was determined with non-contact LP (UBM Microfocus Optical Measuring system, UBM Messtechnik GmbH, Ettlingen, Germany), using three 100 M TP tablets from each crushing strength group (II). The image size was 2 mm x 2 mm and the measuring range was  $\pm 50 \mu\text{m}$ . The laser spot size was  $1 \mu\text{m}$  and the resolution 200 points per mm. The laser input was 0.2 mW and the wavelength 780 nm. After data collection, the image was levelled to remove slope caused by tilting of the tablet surface, using Usoft software (v 2.8 DOS, UBM Messtechnik GmbH, Ettlingen, Germany). The roughness parameters were calculated from these corrected images. The most important of these were average roughness (Ra) and root-mean-square roughness (Rq). These parameters were standardised and are presented in full detail in British Standard (1972) and in the UBM System Reference Guide (1995). The parameters described the tablet surface, using comparable numerical values which gave better results than other methods. The surface characteristics of the tablets were examined with contriving micrographs using Mathematica software (v 5.1, Wolfram Research Inc., Champaign, USA).

#### **4.2.11 Analytical methods**

##### UV-Vis assay for CBZ (I)

The calibration curve for the UV-Vis assay was prepared for the CBZ solutions in the study I. In the 100% CBZ sample there was 60.0 mg of CBZ which was dissolved with 25.0 ml of ethanol (96%). An assay for CBZ powder mixtures was made for the calibration set batches in concentrations of 1, 10, 30, 60, 70 and 100%. CBZ concentrations were determined with a UV/Vis spectrophotometer (Ultrospec II, LKB Biochrom Ltd., Cambridge, UK) at 285 nm.

### Colour measurement (IV)

Konica-Minolta CR-400 tristimulus colorimeter with 8 mm aperture was used to measure the  $L^*a^*b^*$  values in study IV. The colorimeter was attached in contact with fluidisation chamber. The measurement was controlled with the Värítőtori (Mitaten Oy, Kauniainen, Finland) software.

### Near infrared spectroscopy (I)

NIRS was used to measure the concentration of CBZ mixtures in study I. The NIRS setup consisted of a NIRS spectrometer with an InGaAs diode array detector, tungsten light source, and six 400- $\mu\text{m}$  collecting optical fibres around one collection fibre (Control Development, Inc., South Bend, IN). The white teflon served as a reference (99% reflective Spectralon, Labsphere Inc., North Sutton, USA). Spec32 software (v 4.0, Control Development, Inc., South Bend, USA) was used to control the NIR spectrometer. The batches were measured at the spectral region from 1100 to 2200 nm in the same jars they were mixed using the fibre-optic probe. Consequently, removal of the sample was unnecessary. Measurements were performed at three different depths in the batch: at the surface, in the middle and at the bottom. The data were filtered during the measurement. The procedure is described more closely in publication I.

### Raman spectroscopy (II)

Raman spectroscopy was used to measure the crushing strength of tablets in study II. The Raman spectra were collected using a Raman spectrometer (Control Development Inc., South Bend, USA) equipped with a thermoelectrically cooled CCD detector and a fibre-optic probe (RamanProbe, InPhotonics, Norwood, USA). A 500 mW laser source at 785 nm was used (Starbright 785S, Torsana Laser Technologies, Skodsborg, Denmark). The spectral range recorded was between 100 and 2200  $\text{cm}^{-1}$  with a 2 s integration time and by averaging three scans. At least 20 parallel tablets from each crushing strength group were measured using Raman spectroscopy from the lower side of the tablets. During Raman measurement the tablet was rotated and the distance between the tablet surface and the probe was fixed to 8 mm.

#### **4.2.12 Data analysis**

##### Principal component analysis (I, V)

The PCA plot provided a graphical presentation of the spectra in the calibration set in study **I**. Granule size distributions of the batches were analysed using PCA in the study **V**. PCA categorised data so that the similar distributions are plotted at the same area in the scatter plot. Analysis was performed using SIMCA-P (v 10.5, Umetrics, Umeå, Sweden) software.

##### Partial least squares regression (I, II)

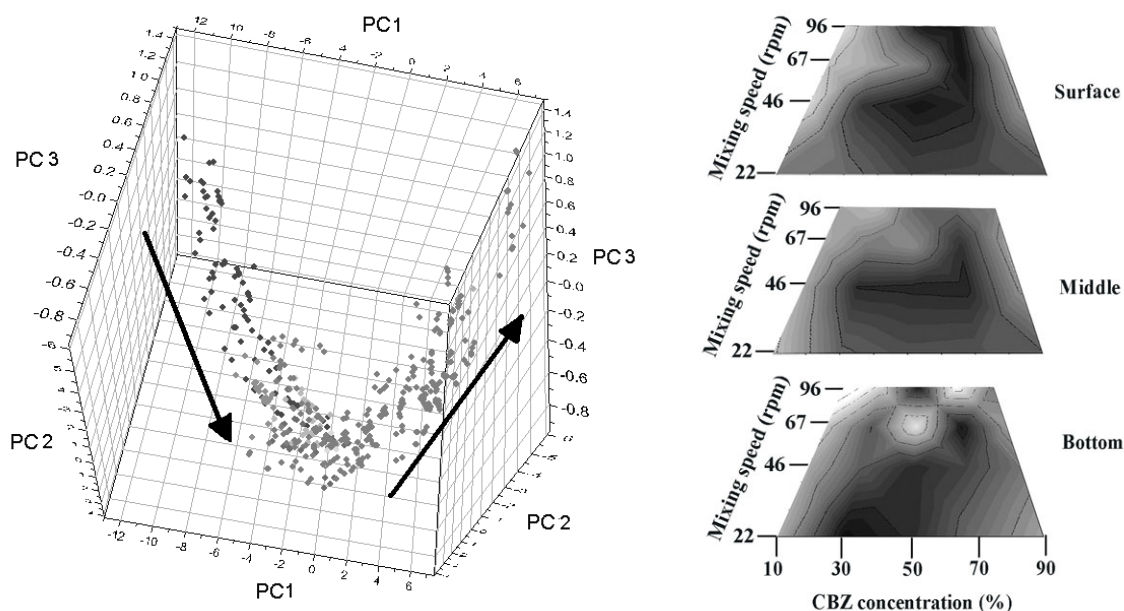
The PLS regression was used to define the degree of mixing in study **I**. The PLS modelling was performed with SIMCA-P software. Before modelling, the data were SNV corrected and mean centered. Such matrix normalisation is usually recommended to improve the predictability and interpretation of the PLS regression model (Eriksson et al., 2001). The batches of the calibration model were used to create a PLS model. The actual measurements were fitted to this calibration model with SIMCA-P software.

A PLS model was also used in study **II** to define the correlation between the spectra and the crushing strength of the tablets. The spectral region between 400 and 1730  $\text{cm}^{-1}$  was used in the data analysis. PLS modelling was performed with SIMCA-P software. Every third spectrum was used to create the PLS model and the rest two thirds served as the test set. Hence, the spectra were collected and the model was tested equally for each crushing strength group. The parameters used to test the model performance were  $R^2$  and  $Q^2$ . The spectra gained were standardised using UV correction before PLS modelling.

## 5. Results and discussion

### 5.1 Mixing of poorly-miscible powders (I)

Firstly, a calibration set samples were prepared and then measured and analysed. The mixing degree was measured from three different locations: a) on the surface, b) in the middle and c) at the bottom. Obtained results were used to create contour plots which expressed the degree of mixing in the experimental domain (Fig. 13). The determination of mixing degree is described in publication I. Differences in the degree of mixing were large. Most of the batches were mixed well or moderately well, but some of the batches hardly mixed at all. This was desirable because one purpose of this study was to measure differences in mixing degrees of the batches to enable analysis of the degree of mixing.



**Figure 13.** On the left hand side PCA score scatter 3D plot. The PCA plot provides a graphical presentation of the spectra in the calibration set. The arrows point towards increasing CBZ concentration. On the right hand side the concentration difference in the different layers described with the help of mixing degree values. The mixing degree value increases when the concentration difference (heterogeneity of the batch) increases. The darker colour indicates a higher degree of mixing.

CBZ was difficult to mix because of its electrostatic nature and small particle size. Moreover, the size difference between CBZ and LMH presented a problem in mixing and in the NIR measurement. Increasing the RH of the air decreased, but did not eliminate, the problem. CBZ particles adsorbed to the surface of LMH particles which affected to the mixing behaviour of the mixtures (Bell et al., 1971, Malcolmson and Embleton,

1998). Mixing of cohesive powders can inflict significant problems in pharmaceutical powder processing. If the mixing parameters and environmental circumstances are not carefully selected the mixing can be ineffective even if the mixing time is substantially increased.

## **5.2 Fluidisation of heat indicator materials (II)**

### **5.2.1 Colour change of heat indicator granules**

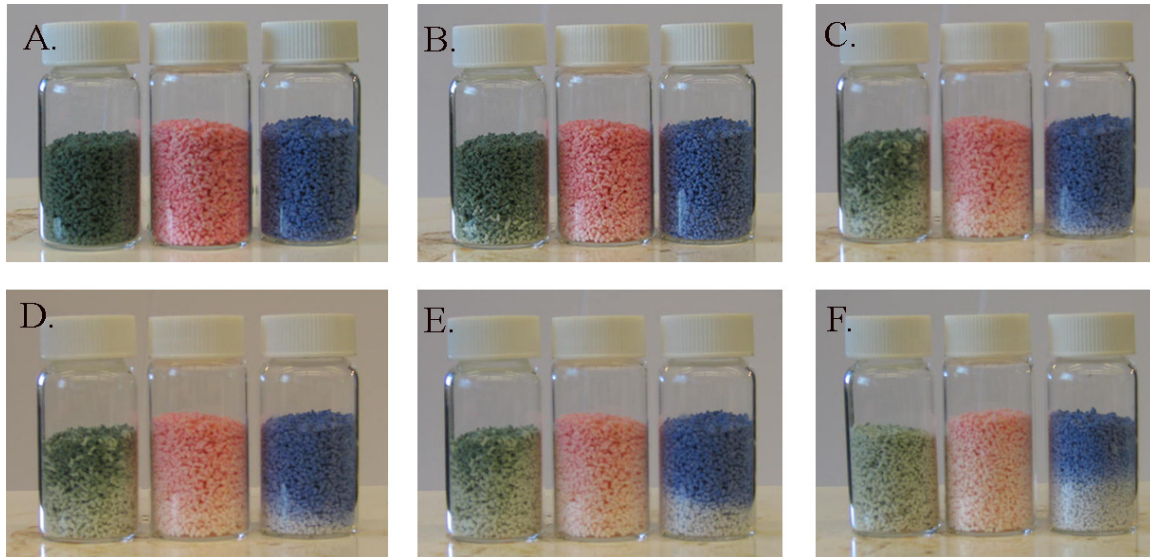
At first, the colour change of the granules was studied as visual demonstration. The granules were heated on the hot plate and they were cooled down afterwards (Fig. 14). The colour started to return from the edges where the temperature decreased at first. The CZ40 changed the colour most reliable, at first from blue to white and when cooling down from white to blue. Also CZ31 worked quite well. The colour change for CZ35 was not as clearly detectable.

After visual characterisation granules and pellets were fluidised. The CZ40 group worked the best during the fluidisation. All the particle size groups changed their colour at 40-41°C. The colour of the CZ31 and the CZ40 groups was recovered very fast after the fluidisation and their colour after the fluidisation was as bright as before fluidisation. However, the colour of the granules from CZ35 group did not recover totally and the return was slower. It was also noticed that the colour values altered depending the particle size of the granules: smaller particles were lighter than the larger ones.

### **5.2.2 Fluidisation behaviour**

The CZ granules and pellets were fluidised in the MMFD. Following observations were made during fluidisation process.

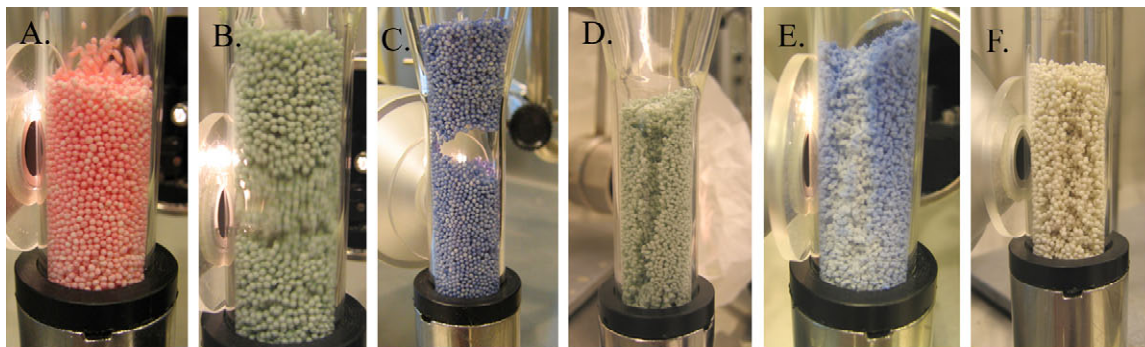
The temperature in the chamber was lower than in the spot where the temperature sensor was located. The temperature difference was larger immediately after the elevation of the temperature but the difference was balanced when the temperature was kept constant for a while. The temperature decreased when going up in the chamber. The change rate of the temperature had an effect on colour change of the indicators. If the temperature of the air was increased too fast the temperature in the chamber did not have time to change to the value that the sensor was showing.



**Figure 14.** The colour change of the granules (from the right 31L, 35L, 40L) at the hot plate. Temperature was A. 25°C, B. 30°C, C. 35°C, D. 40°C, E. 45°C, F. 50°C measured from the bottom plate.

The air flow rate affected the rate of colour change. The higher the speed, the faster the colour change. When air could flow through the mass it transferred the heat to the whole mass. In addition, the thickness of the fluidised bed had an effect on the heat behaviour of the mass. The thicker bed hindered the air flow more efficient than the thinner bed and that is why the heat was also transferred slower to the upper parts of the bed.

Usually the edges of the chamber were cooler than the centre part. Therefore the colour in the centre parts became lighter faster. The temperature changed at first in the lower parts of the chamber and after that it raised upwards.



**Figure 15.** Fluidisation of CZ samples. A. Only the surface of the pellet35 mass is fluidised (temperature 33°C C and the air flow 270 ml/s). B. Pellet31 is slugging (31°C, 320 ml/s). C. Pellet40 is stuck at the bottom of the straight part of the chamber (38°C, 300 ml/s). D-F. The formation of the caverns of D. 31L (33°C, 240 ml/s), E. 40L (39°C, 180 ml/s) the mass warmed up first at the centre parts. F. 31 pellets (33°C, 325 ml/s).



The air flow in the chamber was different depending on the fluidised material and fluidisation parameters (Fig. 15.). Different fluidisation manners could be perceived. When the air flow was increased so that the mass started to move, a “crater flow” was developed especially with the smaller granules. In the crater flow the centre and lower particles were gushed through the centre to the surface. A problem occurred when measuring this kind of crater flow: the colorimeter measured only particles next to the chamber walls. The particles next to the chamber walls were usually cooler (and darker) than particles in the centre especially when the fluidisation was not sufficient. Different fluidisation manners of materials can inflict errors in measurements if they are not recognised when choosing fluidisation parameters.

The fluidisation properties of the granules with different indicator but same particle size were very similar with each other. The large granules fluidised better than small. The fluidisation could be adjusted easily with air flow rate. The heat behaviour of the granules was better with medium size granules than with small and large granules.

The pellets needed higher air flow rate than the granules mainly because they are denser. That is why they also kept the heat inside longer than granules and the colour return was slower. The pellets were electrified if they were fluidised in high air flow and/or in the high temperature. The triboelectricity inflicts the sticking of the pellets into the chamber walls. A typical behaviour for the pellets was that they stuck on each other and did not move in the air flow. However, even if the air flow was not altered the pellets could suddenly start to flow again.

### **5.2.3 Utilisation of heat indicators**

Although the equipments for measuring colours are available, the colour analysis is rarely employed in pharmaceutical industry (Šubert and Čižmárik, 2008). Hayauchi (2005) presented reliable and precise equipment for colour analysis. It was stated that visual colour matching without any colour measuring device is very inaccurate and there is wide variability even with the same person and especially between persons. That is why it would be important to measure colours with colorimeters.

When using these kinds of colour indicators one must remember that their colour change is reversible contrary to physical changes in APIs which are irreversible. This can lead to

the fact that some extreme temperatures can be missed if the operator is not accurate and if the chamber is not totally transparent.

The coloured heat indicators could be utilised for example with scaling up research when studying the changes at the heat flow in fluidisation chamber. When the scale of fluidisation chamber is increased also the amount of sensors should be increased. The placement of the sensors should be chosen so that they cover all temperature regions inside the chamber. The most important location is in the lower region where the incoming air is coming into the chamber. It is usually the hottest region where the temperature can change fast and possible physical changes can happen.

In addition, heat sensitive colour indicators can be used for detecting conditions that would alter the crystal structure of active pharmaceutical ingredients or process induced transformation (PITs). Various APIs can possess multiple polymorphs or amorphous state when conditions (temperature and humidity) are changed. If these conditions are known, can indicators which change their colour at these specific conditions be used to visualise in which part of the chamber the changes are happening during fluidisation.

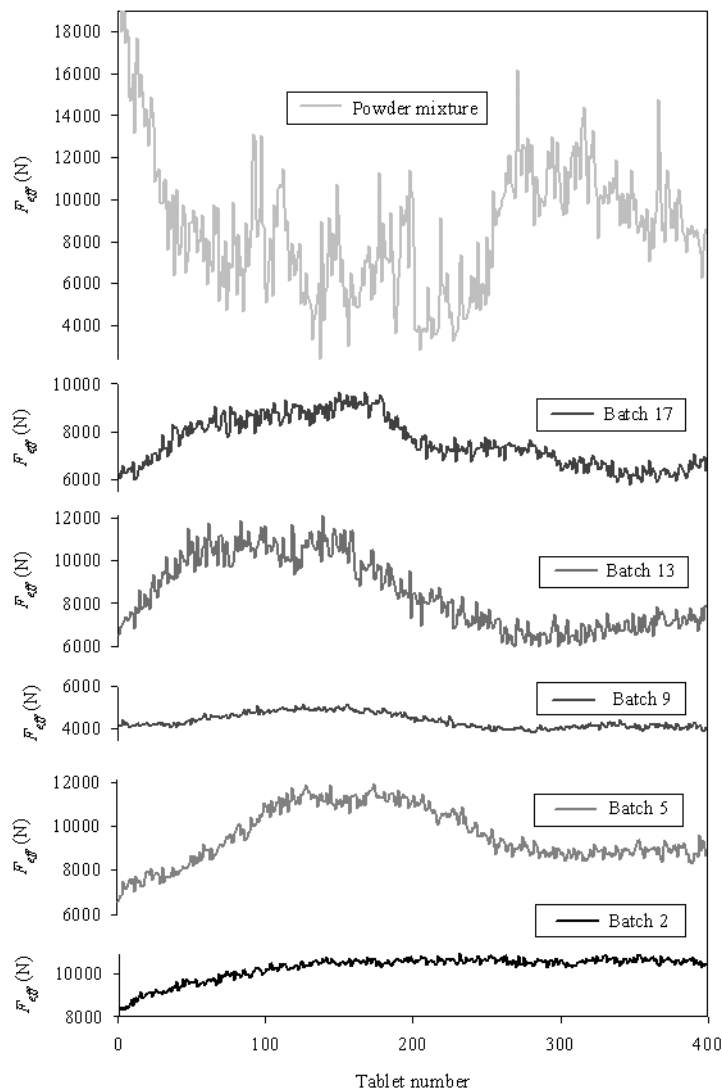
The coloured heat indicators give an opportunity to visualise the process at real-time. The visual monitoring of colour is natural for humans and it can be very informative. In addition real-time quantitative colour analysis is possible with colorimeters. Finally at the best case even process understanding can be gained.

### **5.3 Tableting (II, III, V)**

#### **5.3.1 The effect of particle size on tablettability (II, III, V)**

The effect of particle size to crushing strength of tablet was studied using two different sized TP particles, 200M and 100M, in the study **II**. The smaller particles endure higher crushing force than larger ones. This may be the result of increased interactions among the smaller particles during compression. Their surface area versus weight is higher than with the larger particles. TP is known to be a plastic material (Suihko et al., 2001), which supports this suggestion.

The batches could be divided according to their tablettability in the study V. Tablettability in this context is defined as general ability to form tablets with low variation in the compression data (or low weight variation of tablets). When these results were compared to the median particle size smaller particles gave usually better results in other words their tablettability was better. However there was a minimum particle size for adequate flowability. In order to find out the smallest acceptable particle size additional study was performed. The starting materials (TP, LMH, and PVP) were mixed with no granulation. This mixture faced difficulties upon tableting because it did not flow from the hopper into the tableting table. The mixture had the worst tableting properties and there was a great fluctuation in  $F_{eff}$  (Fig. 16). For these materials adequate  $d_{50}$  particle size for tableting was found to be approximately  $200\ \mu\text{m}$ .



**Figure 16.** The  $F_{eff}$  forces of powder mixture, and five batches prepared in the study V.

In addition PCA was established based on particle size distributions measured with Parsum<sup>®</sup> equipment in study V. Similar size distributions were plotted to the same area in the scatter plot so the data can be divided according to the particle size distribution. The behaviour of the batches could not be explained only with the particle size, because above-mentioned groups were not consistent in the certain sector in the PCA scatter plot. This was due to the fact that also other things than particle size distribution affects the results.

### **5.3.2 Effect of other factors on tablettability (III, V)**

The particle size and particle size distribution cannot alone explain the tablettability. Other factors influencing tablettability are flowability and surface texture of the granules. Also porosity, density, and particle shape could have an effect. In addition the better tablettability of smaller granules can be partly contributed by the behaviour of MS and humidity of air. Flowability of the smaller granules could be reduced by triboelectricity because the moisture in the larger granules equalises electric charges on the particle surfaces (Antikainen, 2006). The humidity decreased triboelectricity clearly deriving to substantially better flowability (Pingali et al., 2009). MS on the other hand lubricated the granule mass and the flowability increased.

The shape and surface characteristics of the granules could have an influence on tablettability through flowability. Good flowability of the powder mixture assists to achieve favourable content uniformity and low weight variation of tablets (Fan et al., 2005). It has been noticed that particle shape has an influence on filling of the tableting die (Ridgway and Scotton, 1970) and packing density of particles (Pitkin and Carstensen, 1990).

Although the smaller particle seemed to pose the best properties for tableting, the situation is not this clear in real life. When using the eccentric tableting machine the mass is tabletted more easily than with rotational tableting machines which have higher tableting speed, larger masses, longer dwell time, and both punches are moving (Palmieri et al., 2005). In addition gained results cannot be generalised for other sized or shaped punches than flat-faced 9 mm. In general, the shape and size of the punch affect the filling of the die. A larger die can be filled more efficiently when the particle size of compressed material stays unaltered. Particles pack differently near die walls than in the

middle of the mass. For instance oval shaped die has more wall surface and more “wall-effect” than round-shaped die.

In discussing particle size and its enlargement or decrease, one must consider the original particle size and other particle properties. For instance, it has been stated that particle size reduction improves flowability, but when the particle size was reduced under a certain limit the flowability became poorer (Marks and Sciarra, 1968). With decreasing particle size, interparticulate forces such as electrostatic and van der Waals forces can become more predominant (Harnby, 2000). In addition, tablet strength is not a simple function of particle size (Hersey et al., 1967). If particles form, via fragmenting or aggregation, the breakdown into smaller particles, can result in stronger tablets than the initial particle size predicts. The original particle size and size distribution should be always mentioned when presenting the results in which an alteration in the particle size will produce change in some phenomenon such as flowability.

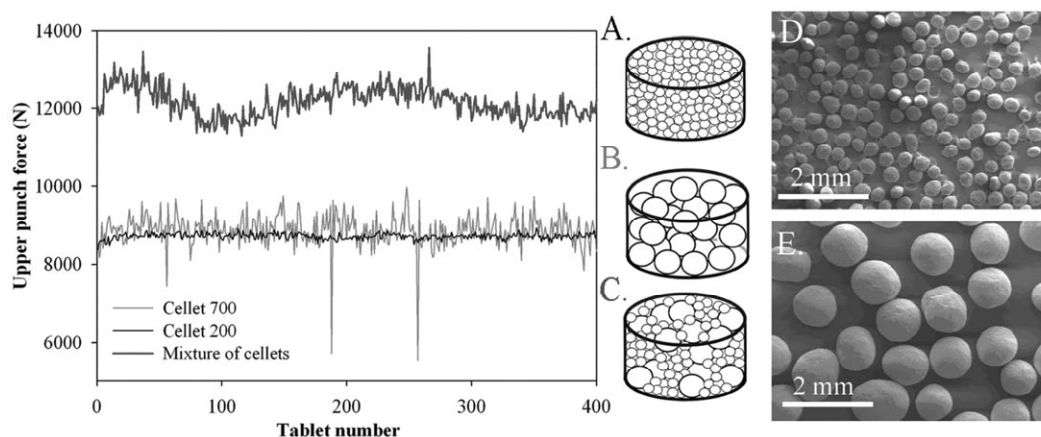
### **5.3.3 Segregation during tableting (III, V)**

Segregation of powders can occur as a result of differences in the physical (i.e. particle size, surface area, particle shape) and mechanical (i.e. strength, elasticity, plasticity, brittleness) properties of the particles. It can eventually cause weight variation in tablets and therefore quality problems for the final dosage form. The effect of particle size on segregation during the tableting process was studied using different sized cellets and granules with various properties.

The segregation was studied by compressing cellets, which particle size was homogenous in the studies **III** and **V**. At first, cel200 and cel700 were compressed using eccentric tableting machine. The particle size distribution was very narrow for both the 200  $\mu\text{m}$  and 700  $\mu\text{m}$  cellets. The particle size of cellets had an effect on compression force during tableting (Fig. 17). The force curve for cel200 was steady and there were not much differences between consecutive forces. The force curve for cel700 was steady for long-time-scale examination but there was a substantially larger difference between consecutive forces compared to cel200 consecutive forces. This could be explained with the larger particle size of cel700. When the particles were larger the packing into the die varied more compared to smaller particles. If the size of the pellets was small enough, the mass filled the die evenly every time. A schematic diagram of the die filling for both

smaller and larger particle size cellets is presented in Figure 17. In theory, the same sized free flowing spherical particles are packed equally tight, no matter what the particle size. However, in reality larger gaps remain with the larger particles in the tableting die because real granules are not freely flowing and the die walls disturb the packing. Even a single large particle can remarkably add the mass of a tablet. This phenomenon was also reported by Ridgway and Williams (1977) who concluded that the proportion of smaller particles had little effect on the bulk density of lactose granules. In addition, Laitinen and others (2004) stated that large particles did not fill the die completely, and varying amount of empty space was left between the granules. If the mass included several sized particles, like the pharmaceutical masses usually do, the smaller particles could fit to the gaps between the larger ones, leading to smaller undulation in the tableting data. The increase in the particle size distribution could also increase the undulation compared to compression on only small particles. Variation in the mass in the die increased and the die was filled differently every time. In practice every mass induces some short-time-scale variation or difference between consecutive forces in the compression data. In addition, the mass with broad particle size distribution has a obvious possibility of segregation. In this study segregation was established with as simple way as possible. The binary mixture (50/50) of the aforementioned cellets was also tabletted. The segregation phenomena can be seen in the level of  $F_{up}$  as a large-time-scale undulation which is typical for segregation. Fluctuation of  $F_{up}$  during tableting was found to be clearly smaller with cellets having a smaller particle size compared to that observed with cellets with a larger particle size. A broad particle size distribution induces segregation that influences tableting force and tablet weight. When the particle size distribution is narrower there is no significant segregation and the level of  $F_{up}$  is kept more constant, as can be seen in the cellet tableting.

In study **V** the changes which are present in compression data were divided to two different kinds of phenomenon: short-time-scale variation (tablet-to-tablet changes) and large-time-scale undulation. Long-time-scale undulation is defined as “waving” kind of undulation which happens during the tableting. Long-time-scale undulation can reveal for instance segregation or compaction of the mass in the hopper.



**Figure 17.** Effects of particle size of cellets on upper punch force during tableting. Red line represents the tableting behaviour of cel700 and black line represents the cel200. Blue line represents upper punch force during cellet mixture tableting. Mixture contains cel200 and cel700 (50/50). (A) Schematic diagram of the die filling of smaller cellets, (B) larger cellets, and (C) cellet mixture. D. SEM micrograph of cel200 and E. cel700.

### 5.3.4 Mathematical analysis of the compression data (V)

Various methods were used to analyse tableting data in study V. Short-time-scale variation was evaluated using amount of noise in the data. Long-time-scale undulation was studied describing linearity of the data, the quality of the fit for polynomial function into the data, and the relative quality of the fit. This mathematical processing is described more closely in publication V. In general if the data were smooth concerning with tablet-to-tablet analysis no significant segregation occurred.

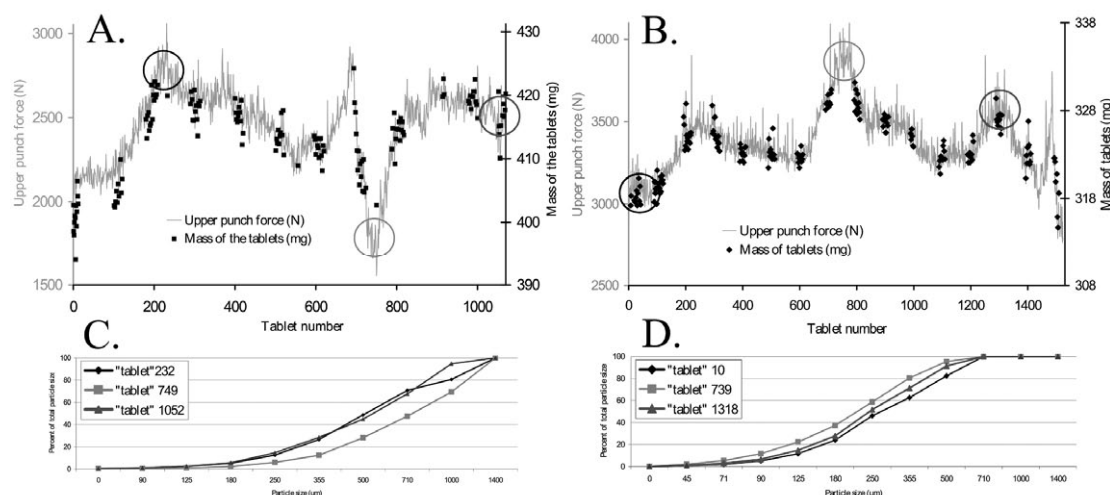
According to the results in study V it seems that short-time-scale variation with small granules ( $d_{50} < 300 \mu\text{m}$ ) is affected by flowability.  $d_{50}$  is the particle diameter at which 50% of the particles have diameters that are greater or smaller than the  $d_{50}$  value. If the granules have poor flowability they do not have time to flow into the die, which will induce short-time-scale variation to the compression data. With larger granules short-time-scale variation is due to uneven filling of the die. As mentioned before large granules fill the die in variable manner every time and establish different densities for the mass in the die. Large-time-scale undulation can be introduced if large granules have a broad size distribution. This is normally segregation. If the granule size distribution is narrow there is no large-time-scale undulation.

According to the FDA draft guidance, product and process specifications are based on understanding of how formulation and process factors affect product performance (FDA, 2004). In addition there is the capability of process control and the quality of

products can be ensured at real-time. Before-mentioned mathematical methods for analysing the compression data could be used for real-time monitoring. This would enable detection of segregation during tableting and required means could be used to prevent variations in the content uniformity of tablets. This prevents rejection of products, decreases waste and enables the real-time product release which are primary goals for utilisation of PAT.

### 5.3.5 Correlation between upper punch force and tablet weights (III)

A clear correlation between the level of  $F_{up}$  and tablet weights was detected in the study III (Fig. 18). According to the results the tablet weights were increased when the  $F_{up}$  was increased in both granule batches. This phenomenon was also described previously (Antikainen et al, 2006).



**Figure 18.** Upper punch force during tableting (gray lines) and mass variation (black points) in A. G1 tablets and B. G2 tablets. Cumulative particle size distribution of C. G1 granules and D. G2 granules during tableting. Sampling points for particle size measurement are marked with circles.

The granule size distributions change according to the compression force and tablet weight. The granule size was smaller when the force and tablet weight were larger and vice versa. Smaller particles can fill the die more efficiently than the larger particles, leading to a heavier tablet. The  $d_{50}$  values also support these observations.

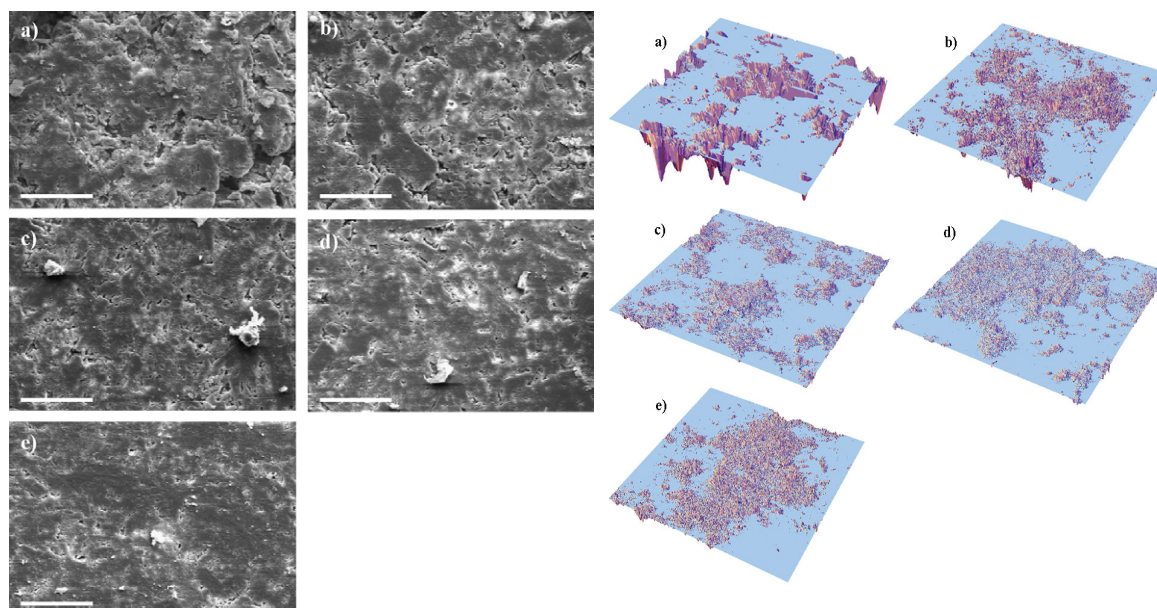
## 5.4 Mechanical strength of tablets (II)

### 5.4.1 Dependence of surface texture on mechanical strength of tablets (II)

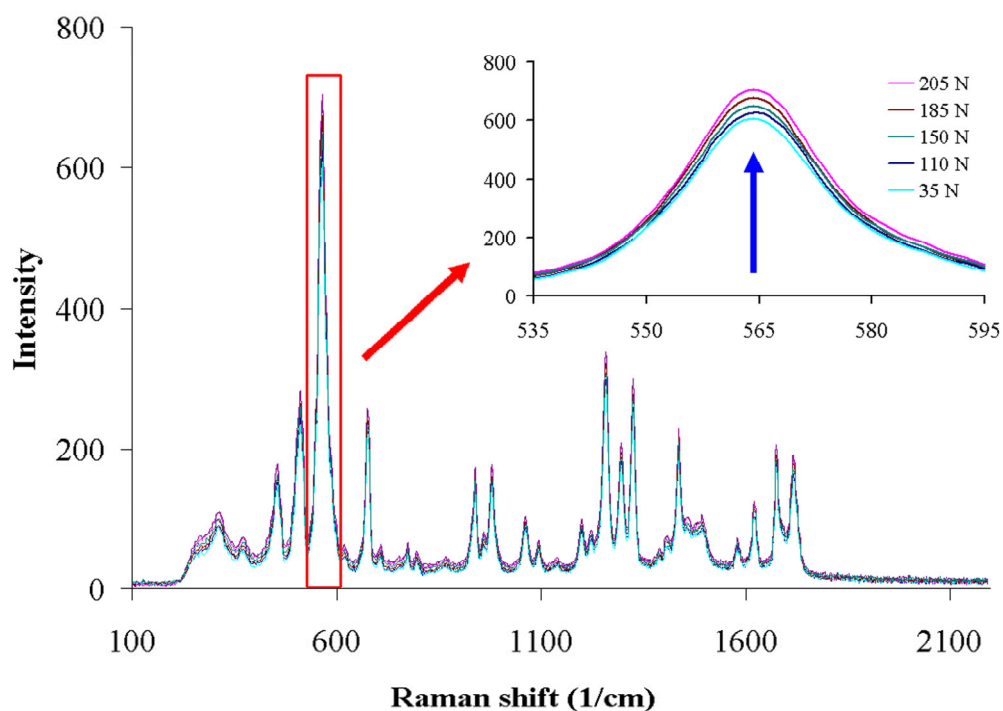
SEM and LP methods were used as additional methods to visually illustrate the tablet surface profile in study II. The surface morphology and texture were related to the



crushing strength of the tablets. This was seen in the SEM and LP micrographs from the surfaces of the TP containing tablets (Fig. 19).



**Figure 19.** On the left hand side the surface of TP tablets (200M) became smoother as the compression force was increased. SEM images on tablets with crushing strengths of (a) 35 N, (b) 110 N, (c) 150 N, (d) 185 N, and (e) 205 N. Scale bar 50  $\mu\text{m}$ . On the right hand side the surface profiles of the TP tablets (100M) measured using non-contact laser profilometry. (a) 35 N, (b) 110 N, (c) 150 N, (d) 185 N, and (e) 205 N.



**Figure 20.** Raman spectra of the TP tablets. The measured spectra (100–2200  $\text{cm}^{-1}$ ) and magnification from one peak to show the baseline shifting. The intensity increase, which correlates with increase in the crushing strength, is marked with blue arrow.

The LP method is in some cases more efficient because quantitative roughness parameters can also be calculated in contrast to SEM images. The SEM and LP micrographs representing the tablets indicate that clear differences exist within the surface textures of the tablets depending on their crushing strength (i.e. the compression force applied in tableting). As expected, the higher the crushing strengths of the tablets, the smoother were the surfaces of the tablets. Clear differences in the surface roughness properties of the tablets were observed in tablets compressed using lower compression forces. However, since the crushing strength of the tablets was 100 N or more, the differences in surface roughness properties within the tablets were no longer evident. Application of higher compression forces in tableting results in greater tendency for deformation and/or fragmentation of the individual powder particles and granules, thus making it more challenging to detect differences in the surface texture of the tablets. In most cases the smoother surface indicates larger crushing strength of the tablet. However, it cannot be generalized to all situations. For instance if the surface of the compressed material melts or if capping, sticking or picking happens during tableting the surface roughness does not implicate the crushing strength.

### **5.4.2 Crushing strength of tablets measured using Raman spectroscopy (II)**

Raman spectroscopy was used as an alternative vibrational spectroscopy technique to determine the mechanical strength of the TP tablets in study II. Raman spectroscopy detected increases in crushing strength mainly as a smoothing of the tablet surface. When the compression force was high, the surface of the tablet was smoother and there were fewer pores in the tablet. When the compression force was increased, the structure of the material condensed as the interfaces between air and the material decreased. In this case, the Raman radiation penetrated the material more easily because the interfaces were diminished, which decreased scattering from the surface.

No specific peaks in the spectra were sensitive enough to detect changes in the crushing strength values of the tablets, due to baseline shifting which occurred evenly throughout the spectra (Fig. 20). Since the crushing strength is a physical property, one must be careful that preprocessing of the spectra will not destroy the information. Typical preprocessing methods such as mean centering and corrections such as SNV, MSC, and the derivatives cannot be used because they lose the baseline-shifting information. The data can be modelled as such or after basic scaling.

The correlation between the crushing strengths measured with the Multicheck apparatus and with Raman spectrometry was studied, using multivariate modelling. The PLS model was established, using four principal components (PC) for both TP grades after UV scaling. All four components explained 82.7% of the X-variance for the 100 M grade and 98.8% of the X-variance for the 200 M grade. The  $Q^2$  value was higher than 0.8 and  $R^2$  value higher than 0.9. In addition, the loadings for the first principal component (PC 1) substantially resembled the Raman spectra.

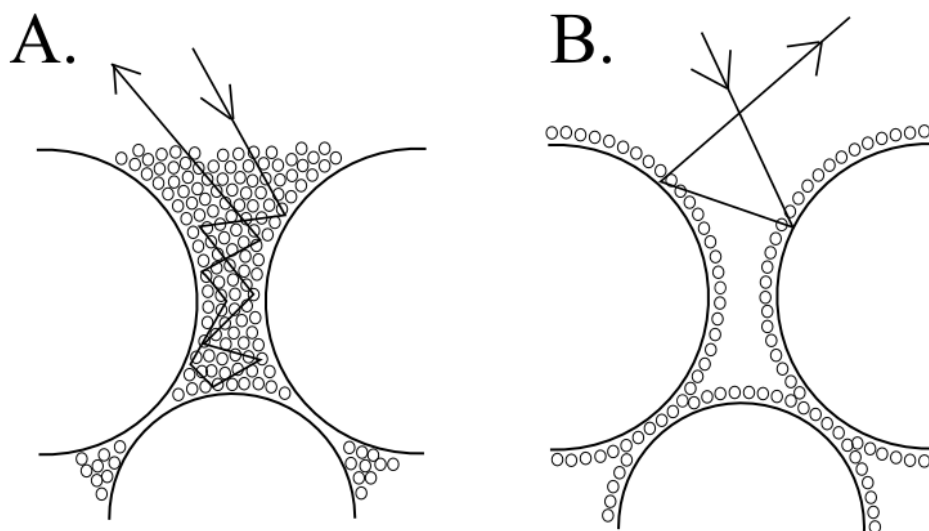
There was a correlation between the measured and predicted crushing strength values (Raman spectra) for TP tablets. The SDs of the measured and predicted crushing strength values were determined. The Raman spectra were obtained for both TP grades and were very similar. The results indicated that the correlation between the crushing strength data for the TP tablets and the Raman spectra applied was excellent.

To determine whether the Raman technique detects the crushing strength of the TP tablets as smoothness of the surface or whether it detects the structure and bonding in the tablet, in addition Raman spectra were measured from the plane of fracture of the tablets. The tablets were halved and the spectra measured from the plane of fracture, using a rotating sample. No correlation was found with either of the TP tablet grades. In conclusion Raman spectroscopy detected the crushing strength of the TP tablets as a smoothing of the tablet. In addition it can be concluded that if there is picking, sticking or capping happening during tableting, the Raman method does not reveal the accurate crushing strength values.

Raman spectroscopy, among other vibrational spectroscopy techniques, is applicable as a rapid and noninvasive method for predicting the crushing strength of tablets. However, the results indicate strongly that determination of the crushing strength of tablet using Raman spectroscopy, demands a well-established and accurate method.

### 5.5 Sources of error using spectroscopic methods (I, II)

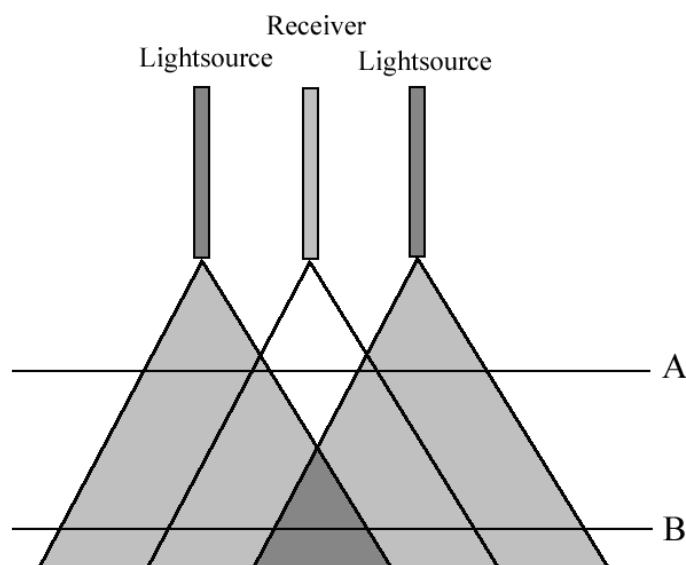
NIRS was used to study the mixing process of CBZ and LMH in study I. The coating of the LMH particles with the CBZ particles caused changes in the NIR signal when the mixing proceeded (Fig. 21). The small CBZ particles formed clusters between bigger LMH particles in the early phase of the mixing. The CBZ particles covered the LMH particles when the mixing proceeded. The NIRS detected the situation differently in these two circumstances. In the early stage of the mixing, NIR radiation reflected from one CBZ particle to another CBZ particle before it reflected back to the detector. In that case, NIRS detected more CBZ than the calibration mixture contained. When CBZ covered LMH, NIR radiation reflected straight from the LMH particles. The calibration had to be performed with completely homogeneous mixtures which why long mixing times were used. When the powders were mixed for a long time, the coating of the CBZ particles and the coating increased. The increase in homogeneity could also be seen as a decrease in the SD of the predicted CBZ concentrations with different concentration levels.



**Figure 21.** Behaviour of the NIR signal in the mixture. (A) The small CBZ particles form clusters between larger LMH particles in the early phase of the mixing. NIR light reflects from CBZ particle to CBZ particle before it reflects back to the detector in the early stage of the mixing. (B) The CBZ particles cover the LMH particles as the mixing proceeds. NIR radiation reflects from the LMH particles.

The densification of the batches can be a source of error because the geometry of measurement changes. In study I the intensity of the NIRS measurement increased with the predicted CBZ concentration when the powder was very tight. The distance of the batch from the probe was also crucial for the geometry of the measurement (Fig. 22).

The geometry of the measurement changed together with the distance from receiver. The intensity also changed if the distance between the batch and the probe was too high.



**Figure 22.** The influence of geometry on the NIRS measurement. Only very little reflection can reach the receiver if the sample is at distance A from the receiver. If the sample is moved further away from the receiver, to distance B the batch reflects more radiation that can reach the receiver and the intensity increases. The intensity also changed if the distance between the sample and the probe is too high.

In NIRS reflectance measurement, the bulk density (i.e. geometry changes in the NIR measurement) of the mass affects among other things the intensity of the reflected signal. Because of this phenomenon, the level of the measured absorption spectrum fluctuates during measurement. This variation in the intensity of the spectra results from the fact that the probe can densify the sample being in contact with the powder. The density of some batches is also higher at the edges of the batch jar due to centrifugal forces during the mixing process. A complete computational correction of the fluctuation phenomenon is impossible today.

The sources of variation in spectroscopy measurements lie at 1) the material used, 2) the measuring geometry (set-up), and 3) the distance between the probe and the sample. Analysis of the tablet with spectroscopic methods requires considerable experience. Due to spatial variations and inhomogeneities of the tablet spectroscopic assessment is a precise task that can give differing results, depending on how the measurement is performed. The wavelength and compression force can also affect the intensity of the signal. The importance of these factors is even more pronounced when

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measuring physical properties. For instance the results indicate strongly that determination of the crushing strength of tablets, using Raman spectroscopy, demands a very accurate method. Hence, every formulation demands its own model and production parameters have to be constant.

When using NIRS at least some of the samples must be analysed with a reference technique such as high performance liquid chromatography (HPLC) or UV-Vis spectrophotometry. The real concentrations can be determined with methods that can be used in a calibration model or validation process (Berntsson et al., 2000).

Raman spectroscopic measurement is critical, because the area measured is very small (scale of scrutiny), which explains that the sample must be moved, usually rotated. When the sample is rotated the measurement covers a larger area and warming of the sample can also be reduced. A rotating sample holder was used to achieve high repeatability (Szostak and Mazurek, 2002). When physical properties are measured the distance between the sample and the probe must be standardised (Lombardi et al., 1994). The change in distance causes the same alterations in the spectra as does the increase in the crushing strength of the tablet.

## 6. Summary and conclusions

There is a need for better understanding of the processes and new ideas to develop traditional manufacturing procedures. PAT has been developed to improve understanding of the pharmaceutical processes and establish methods to monitor and control processes. The real-time process monitoring demands tools, which enable fast and noninvasive measurements with sufficient accuracy. In this study three pharmaceutical processes were investigated: drying, mixing and tableting. In addition tablet properties were evaluated. Real-time monitoring was performed with NIR and Raman spectroscopies, colour analysis, particle size analysis and compression data during tableting was evaluated using mathematical modelling.

NIRS was used to analyse mixing of poorly-miscible powders. NIRS detected differences in the mixing degrees. However, the difference in particle size of the materials and the densification due to the electrostatic nature of CBZ caused problems in the NIR measurement.

Raman spectroscopy was employed to measure strength of the tablets. A correlation between measured and predicted crushing strength values for the tablets was achieved. With Raman spectroscopy, shifting of the baseline was observed as the crushing strengths of the tablets (and the smoothness of the tablet surface) were increased. Consequently, correlation between the crushing strength data on the tablets and Raman spectra was observed. Raman spectroscopy is a promising alternative for established real-time tablet-testing methods for some tablet formulations. Spectroscopic methods require accurate operation and method development.

Colour indicators for heat detection were developed to mimic the heat sensitive API in the pharmaceutical drying process. Indicators detected the progression of heat in the fluidisation chamber. In addition, the indicators enable real-time monitoring of other pharmaceutical unit processes. The visual monitoring of colour is natural for humans and it can be very informative. In addition quantitative colour measurements are possible.

The effect of particle size distribution on compression process was studied by collection of the samples during tableting and analysing compression force data. The particle size

distribution changed during the tableting, due to the segregation phenomenon. A granule batch with a broad particle size distribution causes more segregation problems during tableting than a granule batch with smaller size distribution. Since the die is filled differently due to the segregation, it can induce variation of tablet weights and therefore quality problems of tablets. Different kind of particle size distributions can also induce undulation in the compression data and these changes can be divided into two different phenomenon: short-time scale variation and large-time scale undulation. Short-time scale variation was due to tablet-to-tablet changes in the force data during tableting. Long-time scale undulation described the changes during the whole tableting process. The undulation phenomena can be analysed using mathematical methods.

The studied methods were suitable for real-time monitoring of pharmaceutical unit operations. They can improve our process understanding and therefore, finally, enhance the quality of final products.



## References

Aaltonen J., Kogermann K., Strachan C.J., Rantanen J., 2007. In-line monitoring of solid-state transitions during fluidization. *Chem. Eng. Sci.* 62, 408-415.

Adolfsson Å., Gustafsson C., Nyström C., 1999. Use of tablet tensile strength adjusted for surface area and mean interparticulate distance to evaluate dominating bonding mechanisms. *Drug Dev. Ind. Pharm.* 26(6), 753-764.

Alderborn G., Nyström C. *Pharmaceutical Powder Compaction Technology. Drugs and the pharmaceutical sciences* vol. 71, Marcel Dekker Inc. New York, 1996.

Alderborn G., *Tablets and compaction in Aulton's Pharmaceutics: the design and manufacture of medicines.* Ed. Aulton ME, 3<sup>rd</sup> edition, Churchill Livingstone Elsevier, 2007, 441-482.

Antikainen O., 2003. New methods to evaluate applicability of powders and granules for tablet compression. Ph. D. Thesis. Yliopistopaino, Helsinki, Finland.

Antikainen O., Tervakangas H., Pietiläinen J., Yliruusi J., Sandler N., 2006. Screening of particle size related segregation behavior of granules with surface image analysis. *AAPS Journal*, 8(S2).

Bakeev K.A. *Process Analytical Technology.* 2<sup>nd</sup> edition, Blackwell Publishing. Pondicherry, 2006.

Barajas M.J., Rodriguez Cassiani A. Vargas W., Conde C., Roperio J., Figueroa J., Romañach R.J., 2007. Near-infrared spectroscopic method for real-time monitoring of pharmaceutical powders during voiding. *Appl. Spectrosc.* 61(5), 490-496.

Barnes R.J, Dhano M.S., Lister S.J., 1989. Standard normal variate transformation and detrending of near-Infrared diffuse reflectance spectra. *Appl. Spectr.* 43(5), 772-777.

Beebe, K.R., Pell, R.J., Seasholtz, M.B. *Chemometrics: A Practical Guide*, John Wiley and Sons, New York, 1998.

Bell, J.H., Hartley, P.S., Cox, J.S.G., 1971. Dry powder aerosols. I. A new powder inhalation device. *J. Pharm. Sci.*, 60, 1559–1564.

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

Berberich J., Dee K.-H., Hayauchi Y., Pörtner C., 2002. A new method to determine discoloration kinetics of uncoated white tablets occurring during stability testing – an application of instrumental color measurement in the development pharmaceuticals. *Int. J. Pharm.* 234, 55-66.

Berntsson, O., Danielsson, L.-G., Johansson, M.O., Folestad, S., 2000. Quantitative determination of content in binary powder mixtures using diffuse reflectance near infrared spectrometry and multivariate analysis. *Anal. Chim. Acta* 419, 45-54.

Berntsson, O., Danielsson, L.-G., Lagerholm, B., Folestad, S., 2002. Quantitative in-line monitoring of powder blending by near infrared reflection spectroscopy. *Powder tech.* 123, 185-193.

## References

---

- Blanco M., Coello J., Iturriaga H., MasPOCH S., De La Pezuela C., 1997. Effect of data preprocessing methods in near-infrared diffuse reflectance spectroscopy for the determination of the active compound in a pharmaceutical preparation. *Appl. Spectrosc.* 51, 240-246.
- Blanco, M., Romero, M.A., Alcalà, M., 2004. Strategies for constructing the calibration set for a near infrared spectroscopic quantitation method. *Talanta*, 64(3), 597-602.
- Bogdansky F.M., 1975. Measurement of surface color and color difference of tablet colorants by tristimulus colorimetry. *J. Pharm. Sci.* 64(2), 323-328.
- British Standard 1134. Method for the assessment of surface texture. British Standard Institution, London, 1972.
- Burns D.A., E.W. Ciurczak E.W. (Eds.). *Handbook of Near-Infrared Analysis, Revised and Expanded*, 2<sup>nd</sup> edition, Marcel Dekker, Inc., New York, Basel, Hong Kong, 2001.
- Campbell Roberts S.N., Williams A.C., Grimsey I.M., Booth S.W., 2002. Quantitative analysis of mannitol polymorphs. FT-Raman spectroscopy. *J. Pharm. Biomed. Anal.* 28, 1135–1147.
- Candolfi A., De Maesschalck R., Jouan-Rimbaud D., Hailey P.A., Massart D.L., 1999. The influence of data pre-processing in the pattern recognition of excipients near-infrared spectra. *J. Pharm. Biomed. Anal.* 21, 115–132.
- Carless J.E., Sheak S., 1975. Changes in the particle size distribution during tableting of sulphathiazole powder. *J. Pharm. Pharmacol.* 28, 17-22.
- Carson J.W., 1988. Overcoming particle segregation in the pharmaceutical and cosmetic industries. *Drug Dev. Ind. Pharm.* 14(18), 2749-2758.
- Chan L.W., Chan W.Y., Heng P.W.S., 2001. Characterization of surface coverage of coarse particles coated with stearic acid. *Int. J. Pharm.* 213, 63-74.
- Chen, Y., Thosar, S.S., Forbess, R.A., Kemper, M.S., Rubinovitz, R.L., Shukla, A.J., 2001. Prediction of drug content and hardness of intact tablets using artificial neural network and near-infrared spectroscopy. *Drug Dev. Ind. Pharm.* 27, 623-631.
- ChromaZone<sup>®</sup> free flowing powder, <http://www.chromazone.co.uk/Powder.htm> (Accessed February 13<sup>th</sup> 2010).
- Ciurczak, E.W., 1991. Pharmaceutical mixing studies using near-infrared spectroscopy. *Pharm. Technol.* 15, 140–145.
- Cogdill R.P., Anderson C.A., Drennen J.K.III., 2004. Using NIR Spectroscopy as an Integrated PAT Tool. *Spectroscopy (Duluth, MN, United States)*, 19(12), 104-109.
- Cogdill R.P., Anderson C.A., Delgado-Lopez M., Molseed D., Chisholm R., Herkert T., Afán A.M., Drennen J.K.III., 2005a. Process analytical technology case study Part I: Feasibility studies for quantitative near-infrared method development. *AAPS PharmSciTech.* 6(2), E262-E272.
- Cogdill P., Anderson C.A., Delgado M., Chisholm R., Bolton R., Herkert T., Afan A.M., Drennen J.K.III., 2005b. Process analytical technology case study: Part II. Development and validation of quantitative near-infrared calibrations in support of a process analytical technology application for real-time release. *AAPS PharmSciTech.* 6(2), E273-E283.
-

## References

---

- Cogdill R.P., Anderson C.A., Drennen J.K.III., 2005c. Process analytical technology case study, Part III: Calibration monitoring and transfer. *AAPS PharmSciTech.* 6(2), E284-E297.
- Cooper A.R., Eaton L.R., (1962). Compaction behavior of some ceramic powders. *J. Am. Ceram. Soc.*, 45(3), 97-101.
- Davies P.N., Worthington H.E.C., Podczec F., Newton J.M., 2007. The determination of the mechanical strength of tablets of different shapes. *Eur. J. Pharm. Biopharm.* 67(1), 268-276.
- Deanne R., Etzler F.M. Particle size analysis and powder sampling. *Am. Pharm. Rev.* <http://www.americanpharmaceuticalreview.com/ViewArticle.aspx?ContentID=456>, (Accessed February 13<sup>th</sup> 2010)
- De Beer T.R.M., Baeyens W.R.G, Ouyang J., Vervae C., J. P. Remon J.P., 2006. Raman spectroscopy as a process analytical technology tool for the understanding and the quantitative in-line monitoring of the homogenization process of a pharmaceutical suspension. *Analyst* 131, 1137–1144.
- Donoso M., Kildsig D.O., Ghaly E.S., 2003. Prediction of tablet hardness and porosity using near-infrared diffuse reflectance spectroscopy as a nondestructive method. *Pharm. Dev. Tech.*, 8 (4), 357-366.
- Duberg M., Nyström C., 1986. Studies on direct compression of tablets XVII. Porosity-pressure curves for the characterization of volume reduction mechanism in powder compression. *Powder technol.* 46(1), 67-75.
- El-Hagrasy A.S., Morris H.R., D'amico F., Lodder R.A., Drennen J.K.III., 2001. Near-infrared spectroscopy and imaging for the monitoring of powder blend homogeneity. *J. Pharm. Sci.*, 90(9), 1298-1307.
- El-Hagrasy A.S, D'Amico F., Drennen J.K. III, 2005a. Process analytical technology approach to near-infrared process control of pharmaceutical powder blending. Part I: D-optimal design for characterization of powder mixing and preliminary spectral data evaluation. *J. Pharm. Sci.* 95(2), 392-406.
- El-Hagrasy A.S., Delgado-Lopez M., Drennen III J.K., 2005b. Process analytical technology approach to near-infrared process control of pharmaceutical powder blending: Part II: Qualitative near-infrared models for prediction of blend homogeneity. *J. Pharm. Sci.* 95(2), 407-421.
- El-Hagrasy A.S., Drennen III J.K., 2005c. Process analytical technology approach to near-infrared process control of pharmaceutical powder blending: Part III: Quantitative near-infrared calibration for prediction of blend homogeneity and characterization of powder mixing kinetics. *J. Pharm. Sci.* 95(2), 422-434.
- Ebube, N.K., Thosar, S.S., Roberts, R.A., Kemper, M.S., Rubnovitz, R., Martin, D.L., Reier, G.E., Wheatley, T.A., Shukala, A.J., 1999. Application of near-infrared spectroscopy for non-destructive analysis of Avicel powders and tablets. *Pharm. Dev. Tech.*, 4, 19-26.
- Eriksson M., Alderborn G., 1995. The effect of particle fragmentation and deformation on the interparticulate bond formation process during powder compaction. *Pharm. Res.* 12(7), 1031-1039.
- Eriksson L., Johansson E., Kettaneh-Wold N., Wold S. Multi- and megavariate data analysis: Part I. Basic principles and applications, Umetrics Academy, Umeå, 2001.
-

## References

---

- European Pharmacopoeia. 5<sup>th</sup> edition, Council of Europe, Strasbourg, 2005.
- Fan L.T., Chen S.J., Watson C.A., 1970. Solids mixing. *Ind. Eng. Chem.* 62(7), 53-69.
- Fan A., Parlerla S., Carlson G., Ladipo D., Dukich J., Capella R., Leung S., 2005. Effect of Particle size distribution and flow property of powder blend on tablet weight variation. *Am. Pharm. Rev.* 8(2), 73-78.
- Fangxin L, Jinlong Y, Tianpeng Z, 1997. Raman and Fourier infrared photoacoustic spectra of granular ZrO<sub>2</sub>. *Phys. Rev. B* 55, 8847-8851.
- Fearn T., Riccioli C., Garrido-Varo A., Guerrero-Ginel J.E., 2009. On the geometry of SNV and MSC. *Chemom. Intell. Lab. Syst.* 96, 22–26.
- Fichtner F., Rasmuson A., Alderborn G., 2005. Particle size distribution and evolution in tablet structure during and after compaction. *Int. J. Pharm.*, 292, 211-225.
- Fichtner F., Mahlin D., Welch K., Gaisford S., Alderborn G., 2008. Effect of surface energy on powder compactibility. *Pharm. Res.* 25(12), 2750-2759.
- Filho H.A.D., Galvão R.H.G., Araújo M.C.U., da Silva E.C, Saldanha T.C.B., José G.E., Pasquini C., Raimundo Jr. I.M., Rohwedder J.J.R., 2004. A strategy for selecting calibration samples for multivariate modeling. *Chemom. Intell. Lab. Syst.* 72, 83–91.
- Florence A.T., Attwood D. Drug stability. In *Physicochemical Principles of pharmacy*. A.T Florence, D. Attwood (eds.), 4<sup>th</sup> edition, Pharmaceutical Press, Great Britain, 2006, 94-138.
- Gabrielsson J., Lindberg N.O, Lundstedt T., 2002. Multivariate methods in pharmaceutical applications. *J. Chemom.* 16(3), 141-160.
- Gren T., Nyström C., 1991. Characterization of surface coverage of coarse particles coated with stearic acid. *Int. J. Pharm.* 74, 49-58.
- Gunsel W.C., Swartz C.J., Kanig J.L., *Tablets in The theory and Practice of Industrial Pharmacy*. Lachman L, Lieberman HA, Kanig JL (eds.). Lea & Febiger, Philadelphia, 1970, 305-345.
- Gupta A., Peck G.E., Miller R.W., Morris K.R., 2004. Nondestructive measurements of the compact strength and the particle-size distribution after milling of roller compacted powders by near-infrared spectroscopy. *J. Pharm. Sci.* 93(4), 1047–1053.
- Gupta A., Peck G.E., Miller R.W., Morris K.R., 2005. Real-time near-infrared monitoring of content uniformity, moisture content, compact density, tensile strength, and Young's modulus of roller compacted powder blends. *J. Pharm. Sci.* 94(7), 1589-1597.
- 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.
- Harnby N., 2000. An engineering view of pharmaceutical powder mixing. *Pharm. Sci. Technol. Today* 3(9), 303-309.
- Harris S.C., Walker D.S., 2000. Quantitative real-time monitoring of dryer effluent using fiber optic near-infrared spectroscopy. *J. Pharm. Sci.*, 89(9), 1180-1186.
-

## References

---

- 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(1), 80-90.
- Hayauchi Y., 2005. A precise colour determination method for tablets – an application of instrumental color measurement in the pharmaceutical development. *Pharmeur. Sci. Notes* 2005-1, 21-26.
- Heckel R.W., 1961. Density-pressure relationship in powder compaction. *Trans. Metal. Soc. AIME*, 221, 671-675.
- Heng P.W.S., Chan L.W., Easterbrook M.G., Li X., 2001. Investigation of the influence of mean HPMC particle size and number of polymer particles on the release of aspirin from swellable hydrophilic matrix tablets. *J. Control. Release* 76, 39-49.
- Hersey J.A., Bayraktar G., Shotton E., 1967. The effect of particle size on the strength of sodium chloride tablets. *J. Pharm. Pharmac.* 19, 24S-30S.
- Hoblitzell J.R., Rhodes C.T., 1990. Instrumented Tablet Press Studies on the Effect of Some Formulation and Processing Variables on the Compaction Process. *Drug Dev. Ind. Pharm.*, 16(3), 469-507.
- Hu Y, Wikström H, Byrn S R, Taylor L S, 2006. Analysis of the effect of particle size on polymorphic quantitation by Raman spectroscopy. *Appl. Spectrosc.* 60(9), 977-984.
- Jillavenkatesa A., Kelly J., Dapkunas S.J., 2002. Some issues in particle size and size distribution characterization of powders. *Am. Pharm. Rev.* 5, 98–105.
- Johansson J, Pettersson S, Folestad S, 2005. Characterization of different laser irradiation methods for quantitative Raman tablet assessment. *J. Pharm. Biomed. Anal.* 39, 510-516.
- Johnson, M.C.R., 1975. The effect of particle size upon mixture homogeneity. *Pharm. Acta Helv.* 50, 60-63.
- Jørgensen A., Rantanen J., Karjalainen M., Khriachtchev L., Räsänen E., Yliruusi J., 2002. Hydrate formation during wet granulation studied by spectroscopic methods and multivariate analysis. *Pharm. Res.* 19(9), 1285-1291.
- Kaye B.H., Brushenko A., Ohlhaber R.L., Pontarelli D.A., 1969. A fiber optics probe for investigating the internal structure of powder mixtures, *Powder Technol.*, 2(4), 243–245.
- Kawakita K., Lüdde K.H., 1970/1971. Some considerations on powder compression equations, *Powder Technol.*, 4, 61-68.
- Khan K.A., Rhodes C.T., 1975. Effect of compaction on particle size. *J. Pharm. Sci.* 64(3), 444-447.
- Kirsch J.D., Drennen J.K., 1999. Nondestructive tablet hardness testing by near-infrared spectroscopy: A new and robust spectral best-fit algorithm. *J. Pharm. Biomed. Anal.*, 19, 351–362.
- Kogermann K., Aaltonen J., Strachan C. J., Pöllänen K., Veski P., Heinämäki J., Yliruusi J., Rantanen J., 2007. Qualitative in situ analysis of multiple solid-state forms using spectroscopy and partial least squares discriminant modeling. *J. Pharm. Sci.* 96(7), 1802-1820.
-

## References

---

- Kogermann K., Zeitler J. A., Rantanen J., Rades T., Taday P. F., Pepper M., Heinämäki J., Strachan C. J., 2007. Investigating dehydration from compacts using terahertz pulsed, Raman and near-infrared spectroscopy. *Appl. Spectros.*, 61(12), 1265–1274.
- Kogermann K., Aaltonen J., Strachan C. J., Pöllänen K., Heinämäki J., Yliruusi J., Rantanen J., 2008. Establishing quantitative in-line analysis of multiple solid-state transformations during dehydration. *J. Pharm. Sci.* 97(11), 4983-4999.
- Kourti T., MacGregor J.F., 1995. Process analysis, monitoring and diagnosis, using multivariate projection methods. *Chemom. Intell. Lab. Syst.* 28(1), 3-21.
- Krogars K., Antikainen O., Heinämäki J., Laitinen N., Yliruusi J., 2002. Tablet film-coating with amylose-rich maize starch. *Eur. J. Pharm. Sci.* 17(1-2), 23-30.
- Krycer I., Pope D.G., 1982. The role of scanning electron microscopy in the study of crystal compaction mechanisms. *Int. J. Pharm. Technol. Prod. Manuf.* 3(4), 93-99.
- Lai C.-K., Holt D., Leung J.C., Cooney C.L., Raju G.K., Hansen P., 2001. Real time and noninvasive monitoring of dry powder blend homogeneity. *AIChE Journal.* 47(11), 2618-2622.
- Laitinen N., Antikainen O., Rantanen J., Yliruusi J., 2004. New perspectives for visual characterization of pharmaceutical solids. *Int. J. Pharm.* 93(1), 165-176.
- Langkilde F.W., Sjöblom J., Tekenbergs-Hjelte L., Mrak J., 1997 Quantitative FT-Raman analysis of two crystal forms of a pharmaceutical compound. *J. Pharm. Biomed. Anal.* 15(6), 687-696.
- Lanz M., 2006. Pharmaceutical powder technology: Toward science based understanding of the behavior of powder systems. Ph. D. Dissertation, Basel, 2006.
- Lee T., Kuo C.S., 2006. Effects of initial average particle size on tableting: Evaluating predictive tools for crystal engineers and formulators. *Pharm. Tech.* March 2.
- Li W., Worosila G.D., 2005. Quantitation of active pharmaceutical ingredients and excipients in powder blends using designed multivariate calibration models by near-infrared spectroscopy. *Int. J. Pharm.* 295, 213–219.
- Li W., Johnson M.C., Bruce R., Ulrich S., Rasmussen H., Worosila G.D., 2006. Mass-balanced blend uniformity analysis of pharmaceutical powders by at-line near-infrared spectroscopy with a fiber-optic probe. *Int. J. Pharm.* 326, 182–185.
- Li T., 2008. Materials Engineering of Solid-State Dosage Forms. *Pharm. Res.* 25(4), 949-952.
- Lieberman H., Lachman L., Schwartz J.B. *Pharmaceutical dosage forms: Tablets.* vol. 2. 2<sup>nd</sup> edition, H.H. Lieberman Associates, Inc., Informa Healthcare, Livingston, New Jersey, 1993
- Liew C.V., Karande A.D., Heng P.W.S., 2010. In-line quantification of drug and excipients in cohesive powder blends by near infrared spectroscopy. *Int. J. Pharm.* 386, 138-148.
- Lombardi D R, Wang C, Sun B, Fountain A W, Vickers T J, Mann C K, Reich F R, Douglas J G, Crawford B A, Kohlasch F L, 1994. Quantitative and qualitative analysis of some inorganic compounds by Raman spectroscopy. *Appl. Spectrosc.* 48(7), 875-883.
- Malcolmson R.J., Embleton J.K., 1998. Dry powder formulations for pulmonary delivery. *Pharm. Sci. Technol. Today* 1, 394– 398.
-

## References

---

- Marks A.M., Sciarra J.J., 1968. Effect of size on other physical properties of granules and their corresponding tablets. *J. Pharm. Sci.* 57(3), 497-504.
- Marshall K. Compression and consolidation of powdered solids. In *Theory and practice of industrial pharmacy*. Lachman L., Lieberman H.A., Kanig J.L. (eds.) .3<sup>rd</sup> edition, Lea & Febiger. Philadelphia, 1986, 66-99.
- Marshall K., 1989. Monitoring punch forces and punch movements as an aid to developing robust tablet formulations. *Drug Dev. Ind. Pharm.*, 15(13), 2153-2176.
- McCreery R.L. Raman Spectroscopy for chemical analysis. vol. 157. Wiley-Interscience, John Wiley & Sons. Inc. USA, 2000.
- Miroshnyk I., Khriachtchev L., Mirza S., Rantanen J., Heinämäki J., Yliruusi J., 2006. Insight into thermally induced phase transformations of erythromycin A dihydrate. *Cryst. Growth Des.* 6(2), 369-374.
- Morris K.R., Stowell J.G., Byrn S.R., Placette A.W., Davis T.D., Peck G.E., 2000. Accelerated fluid bed drying using NIR monitoring and phenomenological modelling. *Drug Dev. Ind. Pharm.* 26(9), 985-988.
- Morisseau, K.M., 1996. The effect of compression force on the near-infrared spectra of tablet dosage forms. Ph.D. Thesis. University of Rhode Island, U.S.A.
- Morisseau, K.M. and Rhodes, C.T., 1997. Near-infrared spectroscopy as a nondestructive alternative to conventional tablet hardness testing. *Pharm. Res.*, 14, 108-111.
- Muzzio F.J., Shinbrot T., Glasser, B.J. 2002. Powder technology in the pharmaceutical industry: The need to catch up fast. *Powder Technol.* 124(1-2), 1-7.
- Nicklasson F., Alderborn G., 2000. Analysis of the compression mechanics of pharmaceutical agglomerates of different porosity and composition using the Adams and Kawakita equations. *Pharm. Res* 17(8), 949-954.
- Niemczyk T.M., Delgado-Lopez M.M, Allen F.S., 1998. Quantitative determination of bucindolol concentration in intact gel capsules using Raman spectroscopy. *Anal. Chem.* 70, 2762-2765.
- Nyström C., Alderborn G., Duberg M., 1993. Bonding surface area and bonding mechanism – two important factors for the understanding of powder compactability. *Drug Dev. Ind. Pharm.* 19(17&18), 2143-2196.
- Närvänen T., Lipsanen T., Antikainen O., Rääkkönen H., Yliruusi J., 2008. Controlling granule size of granulation liquid feed pulsing. *Int. J. Pharm.* 357, 132-138.
- Ohno Y., 2000. CIE Fundamentals for color measurements. IS&T NIP 16 Conference, Vancouver, 16-20.
- Olsson H., Nyström C., 2001. Assessing tablet bond types from structural features that affect tablet tensile strength. *Pharm. Res.* 18(2), 203-210.
- Oram P.D., Strine J., 2006. Color measurement of a solid active pharmaceutical ingredient as an aid to identifying key process parameters. *J. Pharm. Biomed. Anal.* 40, 1021-1024.

## References

---

- Otsuka M., Yamane I., 2006. Prediction of tablet hardness based on near-infrared spectra of raw mixed powders by chemometrics. *J. Pharm. Sci.* 95(7), 1425-1433.
- Palmieri G.F., Joiris E., Bonacucina G., Cespi M., Mercuri A., 2005. Differences between eccentric and rotary tablet machines in the evaluation of powder densification behaviour. *Int. J. Pharm.* 298, 164-175.
- Patel, A.D., Luner, P.E., Kemper M.S., 2000. Quantitative analysis of polymorphs in binary and multi-component powder mixtures by near-infrared reflectance spectroscopy. *Int. J. Pharm.* 206, 63-74.
- Patel S., Kaushal A.D., Bansal A.K., 2006. Compression physics in the formulation development of tablets. *Crit. Rev. Ther. Drug Carrier Syst.* 23(1), 1-65.
- Patel S., Kaushal A.M., Bansal A.K., 2007. Effect of particle size and compression force on compaction behavior and derived mathematical parameters of compressibility. *Pharm. Res.* 24(1), 111-124.
- Pellow-Jarman M. V., Hendra P.J., Lehnert R. J., 1996. The dependence of Raman signal intensity on particle size for crystal powders. *Vibr. Spectrosc.* 12(2), 257-261.
- Petrak D., 2002. Simultaneous measurement of particle size and particle velocity by the spatial filtering technique. *Part. Part. Syst. Charact.* 19, 391-400.
- Picker-Freyer K, M, Schmidt A G, 2004. Does temperature increase induced by tableting contribute to tablet quality? *J. Therm. Anal. Cal.* 77, 531-539.
- Pingali K.C., Hammond S.V., Muzzio F.J., Shinbrot T., 2009. Use of a static eliminator to improve powder flow. *Int. J. Pharm.* 269, 2-4.
- Pitkin C., Carstensen J.T., 1990. Effect of particle shape on some bulk solids properties. *Drug Dev. Ind. Pharm.* 16(1), 1-12.
- Podczeczek F., Brown S., Newton M., 1999. The influence of powder properties and tableting conditions on the surface roughness of tablets. *Part. Part. Syst. Charact.* 16, 185-190.
- Poux M., Fayolle P., Bertrand J., 1991. Powder mixing: Some practical rules applied to agitated systems. *Powder Tech.* 68, 213-234.
- Prescott J.K., Hossfeld R.J., 1994. Maintaining product uniformity and uninterrupted flow to direct compression tablet presses. *Pharm. Tech.* 18(6), 99-114.
- Rankell A.S., Lieberman H.A., Schiffmann R.F. Drying. In *The Theory and Practice of Industrial Pharmacy*. L. Lachman, H.A. Lieberman, J.L Kanig (eds.), 3<sup>rd</sup> edition, Lea and Febiger, Philadelphia, 1986, 47-65.
- Rantanen J., Lehtola S., Rämetsä P., Mannermaa J-P., Yliruusi J., 1998. On-line monitoring of moisture content in an instrumented fluidized bed granulator with a multi-channel NIR moisture sensor, *Powder Technol.* 99, 163-170.
- Rantanen J., Antikainen O., Mannermaa J-P., Yliruusi J., 2000a. Use of nearinfrared reflectance method for measurement of moisture content during granulation, *Pharm. Dev. Technol.* 5, 209-217.
-



## References

---

- Rantanen J., Räsänen E., Mannermaa J-P and Yliruusi J., 2000b. In-line moisture measurement during granulation with a four wavelength near infrared sensor: an evaluation of particle size and binder effects. *Eur. J. Pharm. Biopharm.* 50, 271-276.
- Rantanen J., Käsäkoski M., Suhonen J., Tenhunen J. Lehtonen S., Rajalahti T., Mannermaa J-P., Yliruusi J., 2000c. Next generation fluidized bed granulator automation. *AAPS PharmSciTech*, 1(2) article 10.
- Rantanen, J., Wikström, H., Rhea, F.E., Taylor, L.S., 2005a. Improved understanding of factors contributing to quantification of anhydrate/hydrate powder mixtures. *Appl. Spectrosc.* 59(7), 942-951.
- Rantanen J., Wikström H., Turner R., Taylor L.S., 2005b. Use of in-line near-infrared spectroscopy in combination with chemometrics for improved understanding of pharmaceutical processes. *Anal. Chem.* 77, 556-563.
- Rantanen J., 2007. Process analytical applications of Raman spectroscopy. *J. Pharm. Pharmacol.* 59(2), 171-177.
- Ridgway K, Scotton JB. 1970. The effect of particle shape on the variation of fill of a tableting die. *J. Pharm. Pharmac.* 22, 24S-28S.
- Ridgway K., Williams I.E., 1977. The effect of particle shape and size distribution on granulation bulk density and tablet weight variation. *J. Pharm. Pharmacol.* 29, 57P.
- Riippi, M., Antikainen, O., Niskanen, T., Yliruusi, J., 1998. The effect of compression force on surface structure, crushing strength, friability and disintegration time of erythromycin acistrate tablets. *Eur. J. Pharm. Biopharm.* 46, 229-245.
- Rippie E. Mixing. In *The theory and Practice of Industrial Pharmacy*. Lachman L, Lieberman HA, Kanig JL (eds.). Lea & Febiger, Philadelphia, 1970, 82-99.
- Roggo Y., Chalus P., Maurer L., Lema-Martinez C., Edmond A., Jent N., 2007. A review of near infrared spectroscopy and chemometrics in pharmaceutical technologies. *J. Pharm. Biomed. Anal.* 44(3), 683-700.
- Rohrs B.R., Amidon G.E., Meury R.H., Seceast 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(5), 1049-1059.
- Romero-Torres S., Pérez-Ramos J.D., Morris K.R., Grant E.R., 2006. Raman spectroscopy for tablet coating thickness quantification and coating characterization in the presence of strong fluorescent interference. *J. Pharm. Biomed. Anal.* 41, 811-819.
- Roy P.P, Roy K., 2008. On some aspects of variable selection for partial least squares regression models. *QSAR Comb. Sci.* 27(3), 302 – 313.
- Räsänen E., Sandler N., 2007. Near infrared spectroscopy in the development of solid dosage forms. *J. Pharm. Pharmacol.* 59(2), 147-159.
- Savolainen M., Jouppila K., Pajamo O., Christiansen L., Strachan C., Karjalainen M., Rantanen J., 2007. Determination of amorphous content in the pharmaceutical process environment. *J. Pharm. Pharmacol.* 59(2), 161-170.
-

## References

---

- Schmidt C., Vogel P.J., 1994. Force-time-curves of a modern rotary tablet machine I. Evaluation techniques and behaviour of pharmaceutical substances characterization of deformation. *Drug Dev. Ind. Pharm.* 20(5), 921-934.
- Seitavuopio P., Rantanen J., Yliruusi J., 2003. Tablet surface characterisation by various imaging techniques. *Int. J. Pharm.* 254, 281–286.
- Sekulic S.S., Ward H.W., Brannegan D.R., Stanley E.D., Evans C.L., Sciavolino S.T., Hailey P.A., Aldridge P.K., 1996. On-line monitoring of powder blend homogeneity by near-infrared spectroscopy. *Anal. Chem.* 68, 509-513.
- Siesler H.W., Ozaki O., Kawata S., Heise H.M. *Near-Infrared Spectroscopy - Principles Instruments Applications*, 1<sup>st</sup> edition, Wiley-VCH, Weinheim, 2002.
- Siddiqui A., Nazzal S., 2007. Measurement of surface color as an expedient QC method for the detection of deviations in tablet hardness. *Int. J. Pharm.* 341, 173-180.
- Sindel U., Schweiger A., Zimmermann I., 1998. Determination of the optimum mixing time for a mixture of lactose and colloidal silicon dioxide. *J. Pharm. Sci.* 87 (4), 524-526.
- Speiser P., Tawashi R., 1962. The mixing action of pharmaceutically used powder mixers. *Pharm. Acta Helv.* 37, 529-543.
- Spring M.S., 1977. The segregation of granules during tableting. *J. Pharm. Pharmacol. Commun.* 29, 513-514.
- Staniforth J.N., Aulton M.E. *Powder flow* In Aulton's *Pharmaceutics: the design and manufacture of medicines*. Aulton M.E. (ed.), 3<sup>rd</sup> edition, Churchill Livingstone Elsevier, 2007, 168-179.
- Starbuck C., Spartalis A., Wai L., Wang J., Fernandez P., Lindemann C.M., Zhou G.X., Ge Z., 2002. Process optimization of a complex pharmaceutical polymorphic system via in situ Raman spectroscopy. *Cryst. Growth Des.* 2(6), 515-522.
- Storme-Paris I., Clarot L., Esposito S., Chaumeil J.C, Nicolas A., F. Brion F., Rieutord A., Chaminade P., 2009. Near infra red 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.
- Šubert J., Čižmárik J., 2008. Application of instrumental colour measurement in development and quality control of drugs and pharmaceutical excipients. *Pharmazie.* 63(5), 331-336.
- Suihko E., Lehto V.P., Ketolainen J., Laine E., Paronen P., 2001. Dynamic solid-state and tableting properties of four theophylline forms. *Int. J. Pharm.* 217, 225-236.
- Summers M.P. *Powders and granules* In Aulton's *Pharmaceutics: the design and manufacture of medicines*. Aulton M.E. (ed.), 3<sup>rd</sup> edition, Churchill Livingstone Elsevier, 2007, 406-409.
- Sun C., Grant D.J.W., 2001a. Effects of initial particle size on the tableting properties of L-lysine monohydrochloride dehydrate powder. *Int. J. Pharm.* 215, 221-228.
- Sun C., Grant D.J.W., 2001b. Influence of crystal structure on the tableting properties of Sulfamerazine polymorphs. *Pharm. Res.* 18(3), 274-280.
-

## References

---

- Sun C.C., Himmelspach M.W., 2006. Reduced tableability of roller compacted granules as a result of granule size enlargement. *J. Pharm. Sci.* 95(1), 200–206.
- Szostak R, Mazurek S, 2002. Quantitative determination of acetylsalicylic and acetaminophen in tablets by FT-Raman spectroscopy. *Analyst* 127, 144-148.
- Taylor L.S., Zografi G., 1998. The quantitative analysis of crystallinity using FT-Raman Spectroscopy. *Pharm. Res.* 15(5), 755-761.
- Trafford A.D., Jee R.D., Moffat A.C., Graham P., 1999. A rapid quantitative assay of intact paracetamol tablets by reflectance near-infrared spectroscopy. *Analyst* 124, 163–167.
- Train D., 1957. Transmission of forces through a powder mass during the process of pelleting. *Trans. Instn. Chem. Engrs.* 35, 258- 266.
- UBM Messtechnik GmbH, Microfocus non-contacting measurements (brochure). UBM Messtechnik GmbH, Ettlingen, 1995.
- United States Food and Drug Administration, 2004. Guidance for industry; PAT—a framework for innovative pharmaceutical development, manufacturing and quality assurance.
- The United States Pharmacopeia XXII, United States Pharmacopeial Convention, Rockville, 1990.
- Vankeirsbilck T., Vercauteren A., Baeyens W., van der Weken G., Verpoort F., Vergote G., Remon J.P. 2002. Applications of Raman spectroscopy in pharmaceutical analysis. *TrAC trends in analytical chemistry*, 21(12), 869-877.
- Vergote G.J, De Beer T.R.M, Vervaet C., Remona J.P, Baeyens W.R.G., Diericx N., Verpoort F., 2004. In-line monitoring of a pharmaceutical blending process using FT-Raman spectroscopy. *Eur. J. Pharm. Sci.* 21, 479–485.
- Wang H., Mann C.K., Vickers T.J., 2002. Effect of powder properties on the intensity of Raman scattering by crystalline solids. *Appl. Spectrosc.* 56(12), 1538-1544.
- Wargo, D.J., Drennen, J.K., 1996. Near-infrared spectroscopic characterization of pharmaceutical powder blends. *J. Pharm. Biomed. Anal.* 14, 1415-1423.
- Wells J.I., Aulton M.E. Pharmaceutical preformulation In Aulton's *Pharmaceutics: the design and manufacture of medicines*. Aulton M.E. (ed.), 3<sup>rd</sup> edition, Churchill Livingstone Elsevier, 2007, 336-360.
- Wikström H., Marsac P.J, Taylor L.S., 2005. In-line monitoring of hydrate formation during wet granulation using Raman spectroscopy. *J. Pharm. Sci.* 94(1), 209-219.
- Wildfong P.L.D., Samy A.S., Corfa J., Peck G.E., Morris K.R., 2002. Accelerated fluid bed drying using NIR monitoring and phenomenological modeling: Method assessment and formulation suitability. *J. Pharm. Sci.* 91(3), 631–639.
- Williams A C, Cooper V B, Thoman L, Griffith L J, Petts C R, Booth S W, 2004. Evaluation of drug physical form during granulation, tableting and storage. *Int. J. Pharm.* 275, 29-39.
- Wold S., Esbensen K., Geladi P., 1987. Principal component analysis. *Chemom. Intell. Lab. Syst.* 2(1-3), 37-52.
-

## References

---

- Wu H., Khan M.A., 2009. Quality-By-Design (QbD): An Integrated approach for evaluation of powder blending process kinetics and determination of powder blending end-point. *J. Pharm. Sci.* 98(8), 2784-2798.
- Xie L., Wu. H., Shen M., Augsburger L.L., Lyon R.C., Khan M.A., Hussain A.S., Hoag S.W., 2008. Quality-by-Design (QbD): Effects of testing parameters and formulation variables on the segregation tendency of pharmaceutical powders measured by the ASTM D 6940-04 segregation tester. *J. Pharm. Sci.* 97(10), 4485-4497.
- Yajima T., Itai S., Hayashi H., Takayama K., Nagai T., 1996. Optimization of size distribution of granules for tablet compression. *Chem. Pharm. Bull.* 44(5), 1056-1060.
- Yalkowsky S.H., Bolton S., 1990. Particle size and content uniformity. *Pharm. Res.* 7(9), 962-966.
- Yliruusi J., Merkkü P., Hellen L., Antikainen O., 1997. A new method to evaluate the elastic behavior of tablets during compression. *Drug Dev. Ind. Pharm.* 23(1), 63-68.
- Yliruusi J.K., Antikainen O.K., 1997. New parameters derived from tablet compression curves. Part I. Force-time curve. *Drug Dev. Ind. Pharm.* 23(1), 69-79.
- Yu L.X., 2008. Pharmaceutical Quality by Design: Product and process development, understanding, and control. *Pharm. Res.* 25(4), 781- 791.
- Zhuikova N.N., Sablina O.S., Gavrilov A.S., 2009. Effects of moisture on the pressing of pharmaceutical powders. *Pharm. Chem. J.* 43(1), 62-64.