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Interfacial Phenomena in Pharmaceutical Low Moisture Content Powder Processing

by

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ACADEMIC DISSERTATION

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Abstract

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Powders are essential materials in the pharmaceutical industry, being involved in majority of all drug manufacturing. Powder flow and particle size are central particle properties addressed by means of particle engineering. The aim of the thesis was to gain knowledge on powder processing with restricted liquid addition, with a primary focus on particle coating and early granule growth. Furthermore, characterisation of this kind of processes was performed.

A thin coating layer of hydroxypropyl methylcellulose was applied on individual particles of ibuprofen in a fluidised bed top-spray process. The polymeric coating improved the flow properties of the powder. The improvement was strongly related to relative humidity, which can be seen as an indicator of a change in surface hydrophilicity caused by the coating. The ibuprofen used in the present study had a d_{50} of 40 μm and thus belongs to the Geldart group C powders, which can be considered as challenging materials in top-spray coating processes.

Ibuprofen was similarly coated using a novel ultrasound-assisted coating method. The results were in line with those obtained from powders coated in the fluidised bed process mentioned above. It was found that the ultrasound-assisted method was capable of coating single particles with a simple and robust setup.

Granule growth in a fluidised bed process was inhibited by feeding the liquid in pulses. The results showed that the length of the pulsing cycles is of importance, and can be used to adjust granule growth. Moreover, pulsed liquid feed was found to be of greater significance to granule growth in high inlet air relative humidity. Liquid feed pulsing can thus be used as a tool in particle size targeting in fluidised bed processes and in compensating for changes in relative humidity of the inlet air.

The nozzle function of a two-fluid external mixing pneumatic nozzle, typical for small scale pharmaceutical fluidised bed processes, was studied *in situ* in an ongoing fluidised bed process with particle tracking velocimetry. It was found that the liquid droplets undergo coalescence as they proceed away from the nozzle head. The coalescence was expected to increase droplet speed, which was confirmed in the study. The spray turbulence was studied, and the results showed turbulence caused by the event of atomisation and by the oppositely directed fluidising air. It was concluded that particle tracking velocimetry is a suitable tool for *in situ* spray characterisation.

The light transmission through dense particulate systems was found to carry information on particle size and packing density as expected based on the theory of light scattering by solids. It was possible to differentiate binary blends consisting of components with differences in optical properties. Light transmission showed potential as a rapid, simple and inexpensive tool in characterisation of particulate systems giving information on changes in particle systems, which could be utilised in basic process diagnostics.

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Yours sincerely,



Henrik Ehlers

To Pauliina

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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** **Ehlers H.V.**, Räikkönen H., Antikainen O., Heinämäki J., Yliruusi J., 2009. Improving flow properties of ibuprofen by fluidised bed particle thin-coating. *Int. J. Pharm.* 368: 165-170.
- II** Genina N., Räikkönen H., **Ehlers H.**, Heinämäki J., Veski P., Yliruusi J., 2010. Thin-coating as an alternative approach to improve flow properties of ibuprofen powder. *Int. J. Pharm.* 387: 65-70.
- III** **Ehlers H.**, Liu A., Räikkönen H., Hatara J., Antikainen O., Airaksinen S., Heinämäki J., Lou H., Yliruusi J., 2009. Granule size control and targeting in pulsed spray fluid bed granulation. *Int. J. Pharm.* 377: 9-15.
- IV** **Ehlers H.**, Larjo J., Antikainen O., Räikkönen H., Heinämäki J., Yliruusi J., 2010. *In situ* droplet size and speed determination in a fluid bed granulator. *Int. J. Pharm.* 391: 148-154.
- V** **Ehlers H.**, Heinämäki J., Yliruusi J., 2011. Particle size and packing characterisation by diffuse light permeation. *Particuology*, Submitted.

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Abbreviations and symbols

AFM	Atomic force microscopy
DC	Duty cycle
DLS	Diode laser stroboscopy
HPMC	Hydroxypropyl methylcellulose
MCC	Microcrystalline cellulose
NIR	Near-infrared spectroscopy
PTV	Particle tracking velocimetry
R^2	Goodness of fit
RH	Relative humidity
RH_0	Critical RH for deliquescence
Q^2	Predictive power
SEM	Scanning electron microscopy
SFV	Spatial filtering velocimetry
A	Surface area
a	Droplet trajectory angle
a_w	Water activity
d_e	Equivalence sphere diameter
d	Diameter
g	Gravitational acceleration
ΔH	Latent heat of evaporation
h_p	Planck constant
h_t	Heat transfer coefficient
k	Boltzmann constant
M	Circularity
P	Perimeter
$\Delta p/H$	Pressure drop over a distance in the chamber
r	Distance between interacting atoms or molecules
S	Spreading coefficient
T	Temperature
u	Electric dipole moment
v	Droplet velocity
ν_a	Electric adsorption frequency
dW/dt	Change in mass of evaporated water over time
W_A	Work of adhesion
W_C	Work of cohesion
$w(r)$	Interaction energy
x	Ratio of true area and the projection area of a solid surface
α	Electric polarizability
γ	Interfacial energy or tension
ϵ_0	Dielectric permittivity of vacuum
ϵ_{mf}	Void fraction of the bed
θ	Contact angle
λ	Spreading coefficient
ρ_g	Density of gas
ρ_s	Density of solids
φ_s	Solid fraction in contact with a droplet

1 Introduction

In manufacturing pharmaceutical dosage forms the concepts Quality by Design and Process Understanding have recently gained attention (Yu 2008). Both of these embrace the idea of being able to produce high quality solid dosage forms by thoroughly knowing the demands of processes, material properties and the interconnection between these, replacing earlier empirical and heuristic approaches (Muzzio *et al.* 2002). The design of solid dosage forms and their manufacturing processes are initiated from the particle level (Muzzio *et al.* 2002; Hamad *et al.* 2011). All of the following steps concern modifying particles by different means to form an acceptable final product (Muzzio *et al.* 2002). To understand the behaviour of a particle system, such as a powder, further down in the production chain, the basic physicochemical properties of the particles need to be known and if necessary modified to fit the requirements of the product or process. Consequently, good particle level engineering is a prerequisite for efficient production of high quality solid dosage forms.

The traditional approach in manufacturing solid dosage forms is to enlarge the particle size by granulation prior to tableting, to ensure sufficient flow and tablettability (Bolhuis and Armstrong 2006; Yu 2008). As the industry currently has a more pronounced focus on cost efficiency, direct compression has gained popularity subsequently increasing the demand for powders with good flow and compression properties. Smaller particles have been shown to give stronger tablets (Sun and Grant 2001), but also experience more pronounced cohesion (Kendall and Stainton 2001). Modifying the particle characteristics to comply with process and other demands is called particle engineering (Davies *et al.* 1998; Caruso 2001). Particle properties addressed by means of particle engineering have been dusting, powder flow, compressibility, segregation, dissolution, taste and smell, drug release, size, shape, density and instability (Guignon *et al.* 2002; Hémati *et al.* 2003; Desai and Park 2005). Traditionally solvents have been used in modifying the above mentioned properties (Bose and Bogner 2007). The use of organic solvents is, however, not problem free due to *e.g.* toxicity, flammability and environmental reasons. In many cases water can be used to replace organic solvents.

The free moisture within a particle system is the difference between added and removed moisture (Abberger 2001). Moisture removal occurs through evaporation or by absorption into the particles. The amount of free moisture greatly affects the process behaviour in terms of *e.g.* particle size and cohesion, and thus also affects final product quality. Water has a high latent heat of evaporation resulting in longer processing times and higher processing temperatures, which is not favourable when processing heat or moisture sensitive compounds or when aiming for cost efficiency (Bose and Bogner 2007). In addition, atmospheric moisture and moisture sorption have a major effect on particle system behaviour (Kontny and Zografi 1995). Taken together, there is a clearly defined need for increased knowledge on low moisture particle systems modification, in order to be able to produce powders with desirable attributes for direct compression. Currently new drug molecules discovered within the pharmaceutical industry tend to be more potent, small in particle size and poorly soluble, which further increases the demand for understanding of particle level phenomena (Muzzio *et al.* 2002).

Particle systems modification can be performed with dry and wet methods (Stanley-Wood 1990). Wet methods are *e.g.* fluidised bed coating and granulation and high-shear granulation, and dry methods are *e.g.* hot melt extrusion, roller compaction and die compaction. As modest amounts of water can be used in dry methods, wet methods with restricted amounts of liquid additions can be distinguished from dry methods by referring to them as low moisture content processes.

An interface is the boundary that separates different states of substance (Buckton 2000). These states are solid, liquid and vapour. The boundary between two like but immiscible states (*e.g.* oil and water) is also defined as an interface. Physical and chemical phenomena that occur on or at an interface are interfacial phenomena.

This thesis focuses on studying restriction of the use of moisture in wet coating and agglomeration processes. In addition, characterisation of this kind of low moisture content processes is discussed. The aim is to bring insight into the borderline between coating and granule formation and taking advantage of interfacial phenomena on the particle surfaces in order to produce particles with desired behaviour and size. Furthermore, the aim was to gain knowledge on methods intended for increasing process understanding and process monitoring.

2 Literature overview

2.1 Particle systems

2.1.1 Definitions

A particle is a single, coherent unit of solid matter with a defined and limited interface to the media in which it exists (Hawkins 1990). The particle can be a single unit, such as one crystal or particle, or consist of several primary particles adhered to each other forming an aggregate or agglomerate. An aggregate is defined as several particles with faces tightly adhered to each other, while agglomerates consist of more loosely adhered particles. The size of particles can vary from only a few nanometres to several millimetres (Shekunov *et al.* 2007).

A particle system can be defined as a population of single particles confined within a restricted volume or otherwise in close interaction with each other (Menon and Durian 1997), of which powders are a typical example. Powders are by definition solids, although they can show both fluid-like and gas-like properties, such as the ability to flow and become compressed, respectively (Geldart 1990; Menon and Durian 1997). This versatility in behaviour is essential in processing particular material into suitable dosage forms such as tablets.

2.1.2 Particle size and morphology

Particle size affects numerous properties of pharmaceutical dosage forms, such as flow, solubility and drug release (Shekunov *et al.* 2007). Particle size is dependent on which measures are reported, *e.g.* **Feret's diameter, Martin's diameter or different kinds of equivalent sphere diameters** (Hawkins 1990; Svarovski 1990; Kaye 1997; Shekunov *et al.* 2007). The choice of measure needs to be based on the desired functionality (Kaye 1997). The particle size of a particle system is a combination of all individual particle sizes combined to form a particle size distribution, giving information on particle size as a bulk property (Svarovski 1990). In particle size distributions compromises need to be made due to the heterogeneity of particle systems. Particle size analysis methods can be based on measuring particle size as a bulk property, measuring anonymous particles as a part of a population or measuring individual particles (Hawkins 1990).

There are several methods for particle size analysis (Svarovski 1990; Shekunov *et al.* 2007), of which image analysis, sieve analysis and methods based on light scattering are the

most common ones (Heng and Chan 1997). Microscopy with subsequent image analysis is thought of as a suitable reference method (Shekunov *et al.* 2007). The number of particles needed in image analysis is dependent on particle size distribution width (Anares *et al.* 1996). Recently more automated photometric image analysis methods have been developed (Sandler 2010).

Spatial filtering velocimetry (SFV) yields higher results than laser diffractometry, but up to 100 μm lower results than sieve analysis (Närvänen *et al.* 2008; 2009). Still, the results of SFV have been found to be reliable and logical. Image analysis has been reported to give larger particle sizes than laser diffraction in air or liquid (Anares *et al.* 1996). These differences rise from particle dispersion (Adi *et al.* 2007). Dispersion decreases particle size, and the dispersion medium also affects the result. Dispersion is of more crucial importance with cohesive powders.

Particle shape affects *e.g.* powder flow, packing (Hawkins 1990; Sandler and Wilson 2010) and distribution of surface charge (Führer 1996). Particle shape can be described verbally or numerically with *e.g.* with particle form factor or elongation ratios (Hawkins 1990; Heng and Chan 1997). Particle shape analysis is done from individual particles with suitable optical methods, which can be considered to be labour intensive and time consuming (Heng and Chan 1997).

2.1.3 Particle-particle interactions

Particle-particle interactions are present in all particle systems (Führer 1996). These interactions determine particle system behaviour and properties to a large extent. Forces of interaction between particles can be divided into permanent and fluctuating forces. Permanent forces of interaction consist of gravitational and van der Waals forces (Israelachvili 1992; Führer 1996). In addition, there are electrostatic and molecular interactions. These can be either attractive or repulsive. Attraction between similar and dissimilar surfaces is called cohesion and adhesion, respectively. Van der Waals interaction is described briefly in section 2.2.1.

Cohesion describes the force required to separate two particles and is proportional to particle diameter (Kendall and Stainton 2001). Cohesion originates from gravitational or electrostatic forces, but most commonly from van der Waals interaction. Cohesion causes aggregation. Aggregate formation and cohesion is of importance in all particle systems, including *e.g.* powders and granules. Aggregate strength increases with stronger cohesion, but packing, aggregate structure and particle size also affects the strength.

As particles are in contact, there is an exchange of electrons between the surfaces (Führer 1996). This gives rise to temporary triboelectric charging of the surfaces. The charge is not uniformly distributed; asperities have higher local values of charge. Surfaces can also have permanent charges, which are independent of triboelectrification. Electric charges are formed and charge transfer can occur as a result of triboelectrification whenever powder is handled and there is interparticle interaction between dissimilar surfaces (Bailey 1984). Small particles become charged more easily and charge transfer occurs easier from large particles to small particles. Electrostatic interactions are dependent on the electrostatic charges of the participating particles and the distance separating them (Führer 1996). The electrostatic force decreases with the second power of the distance of separation.

Triboelectrical charging can be used as a tool for improving the quality and stability of ordered mixtures, as oppositely charged particles attract (Staniforth and Rees 1982). Close contact caused by triboelectric charging can also enhance the strength of van der Waals interaction. Usually, though, electric charges need to be reduced to avoid spark formation

and explosions (Bailey 1984; Guardiola *et al.* 1996). In addition, electric charges are reduced to minimise adhesion, in order to facilitate or even enable processing.

Increased relative humidity (RH) can dissipate charges or change their polarity (Bailey 1984). Moisture sorption isotherms can thus be used in predicting triboelectrification behaviour, as electric charge has been found to correspond well with absorbed moisture (Nomura *et al.* 2003; Rowley and Mackin 2003). Under a certain threshold, RH does not affect charge (Guardiola *et al.* 1996). When a certain RH is exceeded electrification is strongly reduced, and above a certain threshold no changes are to be obtained by further increases in RH (Guardiola *et al.* 1996; Nomura *et al.* 2003; Räsänen *et al.* 2004). Interestingly, it has been suggested that electric charging itself is not affected by RH, but more so the rate of charge dissipation (Boland and Geldart 1972; Visser 1989).

Water on particle surfaces causes both molecular and capillary interaction. The molecular interaction between the water molecules and particle surface and the water molecules themselves are by hydrogen bonding (Israelachvili 1992; Führer 1996). When a powder is wetted and two particles are in close contact, the free moisture forms liquid bridges between the particles (Rumpf 1975; Führer 1996). The capillary pressure of the liquid bridge is inversely dependent on the radii of the curvatures of interface and directly dependent on the surface tension of the participating liquid, as described by the Laplace equation (Rumpf 1975).

Surface roughness of particles can both increase and decrease interparticle attraction (Führer 1996). The mechanism of decreased interaction is governed by increasing distance of separation between particles. If the surface roughness separates particles more than 1 micron from each other van der Waals interaction can be neglected (Visser 1989). Surface roughness might with certain geometries cause mechanical interlocking of particles resulting in increased attraction (Führer *et al.* 1996).

The effective distance of all interparticle attraction forces mentioned above varies (Führer 1996). Van der Waals forces range from 0.2 nm to 10 nm, and decrease to the sixth power of the separating distance. Formation of liquid bridges demands close interaction, but after formation the bridges can be stretched. Electrostatic interaction has the longest range of effect of the forces mentioned.

2.1.4 Powder flow

Sufficient powder flow is demanded in order to be able to produce high-quality solid dosage forms (Staniforth 2002b; Sinka *et al.* 2004). Powders have a natural tendency to resist motion rising from electrostatic, van der Waals and moisture-related cohesive and adhesive forces of interaction (Davies 2001). Other factors influencing powder flow are particle size and size distribution, particle shape and surface texture (Geldart *et al.* 1984; Staniforth 2002b; Genina *et al.* 2009; Sandler and Wilson 2010). Common approaches to overcome poor flow properties are particle size enlargement by granulation or spray drying as well as modifying particle surface and shape. Furthermore, RH can be used to alter electrostatic interactions favouring particle flow. Flow properties can be quantified by measuring shear or tensile strength, angle of repose, funnel discharge, avalanching behaviour and flow through an orifice (Davies 2001; Staniforth 2002b; Schwedes 2003; European Pharmacopoeia (Ph. Eur.) 2005; Faqih *et al.* 2006; Seppälä *et al.* 2010). The flow properties can also be estimated by comparing bulk and tapped densities with Hausner indices and **Carr's compressibility indices** (Davies 2001).

RH affects powder flow properties, depending on the vapour sorption characteristics of the powder (Faqih *et al.* 2007; Seppälä *et al.* 2010). Also interstitial air has been found to

impair powder flow (Sinka *et al.* 2004). Flow properties can also be affected by formulation design; for instance increasing the amount of active pharmaceutical ingredient with poor flow properties in a blend with cellulose impairs the flow properties of the blend (Soppela *et al.* 2010) and adding magnesium stearate has been reported to improve powder flow by increasing hydrophobicity and reducing van der Waals interaction (Faqih *et al.* 2007). Also polymer coatings have been used to improve powder flow (Fernández-Arévalo *et al.* 1990; Holgado *et al.* 1996).

2.2 Interfacial phenomena

2.2.1 Van der Waals interaction

Van der Waals forces are present in all particulate and molecular systems, and participate in all phenomena related to these (Israelachvili 1992). The interaction can be divided into dipole-dipole or Keesom-interaction (Equation 1), dipole - non-polar or Debye interaction (Equation 2) and non-polar interaction or London-dispersion interaction energies (Equation 3)

$$w(r) = -u_1^2 u_2^2 / 3(4\pi\epsilon_0)^2 kT r^6 \quad (1)$$

$$w(r) = -u_1^2 \alpha / (4\pi\epsilon_0)^2 r^6 \quad (2)$$

$$w(r) = -\frac{4}{3} \frac{h_p \nu \alpha^2}{(4\pi\epsilon_0)^2 r^6} \quad (3)$$

in which T stands for temperature (K), \mathbf{u} is the electric dipole moment, α is electric polarizability, \mathbf{r} is the distance between interacting atoms or molecules, \mathbf{k} is the Boltzmann constant, h_p is the Planck constant, ν is the electric adsorption frequency and ϵ_0 is the dielectric permittivity of vacuum.

The interaction of non-polar species is a result of random electron positioning causing the formation of a temporary dipole, which induces a dipole moment in a neighbouring molecule (Visser 1989; Israelachvili 1992). Van der Waals interaction extends to distances of separation from 0.2 nm to 10 nm and it can be attractive or repulsive. If particle diameter is less than 100 microns and the distance of separation is in the range of a few nanometers van der Waals interaction will dominate over gravitational forces (Visser 1989). For flat or very porous particles this holds true even for particle diameters over 100 μm . In liquid environment van der Waals interaction is suppressed. It must be kept in mind, that on an atomic and molecular level van der Waals interaction is relatively weak, but gains significance in the interaction between surfaces.

2.2.2 Hydrogen bonding

Hydrogen atoms are very small, and when they are covalently bound to highly electronegative atoms such as oxygen, nitrogen, fluoride or chloride, formation of hydrogen bonds becomes possible (Israelachvili 1992). The hydrogen bond has features of both ionic or covalent bonds and van der Waals interaction regarding the length and strength of the bond. Hydrogen bonding is a typical interaction for systems containing any amount of water. The

bond can be formed inter- or intramolecularly, one-, two- or three-dimensionally and linearly or in an angle.

2.2.3 Hydrophobicity and hydrophilicity

Hydrophobicity and hydrophilicity are molecular characteristics affecting solid/liquid interfaces originating from hydrogen bonds (Israelachvili 1992). Hydrogen bonds are present in water connecting water molecules to each other according to the polarity of the molecule. When a non-polar molecule is introduced into an aqueous environment, there will be a loss of hydrogen bonds unless the water molecules rearrange themselves to a more regular structure. This would thermodynamically unfavourably decrease the entropy of the system, giving rise to hydrophobicity. Hydrophilicity, on the other hand, is thought of as the ability of a substance to associate itself with the hydrogen bond network of an aqueous environment. The association disrupts the hydrogen bond network, increasing the entropy of the system. Hydrophobic substances typically have high and hydrophilic substances have low contact angles (θ) of water.

2.2.4 Surface free energy and surface tension

Molecules in a bulk substance are attracted to each other in all directions (Lambros and Nicolaou 2003). Molecules on the surface are drawn to the sides and inwards towards the bulk. This gives rise to surface or interfacial tension or energy, γ . The interfacial energy consists of a polar (γ^p) and non-polar (γ^d , dispersion) component expressed by Wu (1973) as

$$\gamma = \gamma^d + \gamma^p \quad (4)$$

Surface tension resists mixing with other surfaces and aims to minimize the surface area. Surface tension can be defined as the work demanded to create an area (Buckton 2000). Surface free energy is the work demanded to expand the surface area (Israelachvili 1992: Buckton 2000). The unit of surface tension is mNm^{-1} and the unit of surface free energy is mJm^{-2} , which in essence are equal. Work of cohesion and adhesion are defined as the work needed to separate to like and un-like surfaces, respectively (Israelachvili 1992: Lambros and Nicolau 2003). The work of cohesion and adhesion are given in Equations 5 and 6

$$W_C = \gamma_1 + \gamma_1 = 2\gamma_1 \quad (5)$$

$$W_A = \gamma_1 + \gamma_2 - \gamma_{12} \quad (6)$$

in which subscripts 1 and 2 are two different substances (Lambros and Nicolaou 2003). In the case of solid/liquid contacts (Buckton 2000) the work of adhesion is given as

$$W_A = \gamma_{SL} - (\gamma_{SV} + \gamma_{LV}) \quad (7)$$

From these the interfacial energy between two unlike substances is derived in the Dupré-equation (Israelachvili 1992).

$$\gamma_{12} = \gamma_1 + \gamma_2 - W_{A12} = \gamma_1 + \gamma_2 - W_{A12}^d - W_{A12}^p \quad (8)$$

in which W_{A12}^d and W_{A12}^p are non-polar and polar components of the work of adhesion, respectively (Rowe 1989). The overall work of adhesion is determined as

$$W_{OA} = W_A \times S \quad (9)$$

in which S is the contact surface area (Saleh and Guignon 2007).

2.2.5 Contact angle, wetting and spreading

When a droplet of a liquid is placed on a flat levelled surface, the interfacial tensions of the liquid/vapour- (γ_{LV}), solid/liquid- (γ_{SL}) and solid/vapour-interfaces (γ_{SV}) determine the nature of interaction between the liquid and the solid, as shown schematically in Figure 1 (Lambros and Nicolaou 2003). The relation between θ and the interfacial tensions are given in Young's equation (10) and in the Young-Dupré equation (11) (Israelachvili 1992; Buckton 2000; Lambros and Nicolaou 2003).

$$\cos \theta = \frac{\gamma_{SV} - \gamma_{SL}}{\gamma_{LV}} \quad (10)$$

$$\gamma_L(1 + \cos\theta) = W_{ASL} \quad (11)$$

Wetting is complete when $\theta=0$ or $\cos \theta=1$ (Lambros and Nicolaou 2003). θ is a good descriptor of wettability, but with hydrophilic surfaces pore penetration can cause inaccuracies in θ (Zhang *et al.* 2002).

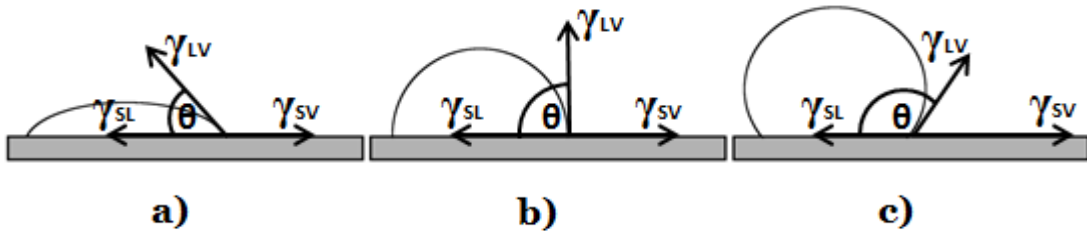


Figure 1. Contact angles (θ) of a liquid droplet on a solid surface. a) $\theta < 90^\circ$; b) $\theta = 90^\circ$; c) $\theta > 90^\circ$. (Modified from Buckton 2000)

The above mentioned holds true for flat surfaces. Solid surfaces are often processed or prepared in a way which results in the surface texture being uneven in addition to chemically and physically heterogeneous (Kontny and Zografis 1995; Buckton 2000). The surface will have high surface energy asperities and crystalline regions coexisting with lower energy amorphous and flat regions. When a droplet of liquid is placed on a rough surface, θ can be given according to the Wenzel model (θ^W ; equation 12) and the Cassie-Baxter model (θ^{CB} ; equation 13)

$$\cos\theta^W = x \cdot \cos\theta \quad (12)$$

$$\cos\theta^{CB} = \varphi_s \cos\theta - (1 - \varphi_s) \quad (13)$$

in which x is the ratio of true area and the projection area of the solid surface and φ_s is the solid fraction in contact with the droplet (McHale *et al.* 2004). For completely flat surfaces $x = 1$, for uneven surfaces $x > 1$. Heterogeneous or tilted surfaces give rise to two θ , the advancing θ and the receding θ (Buckton 2000). The aforementioned gives an estimate of the hydrophobic θ and the latter of the hydrophilic θ . When a droplet of a liquid (1) is placed onto the surface of another substance (2), the droplet can spread to form a thin film, remain on the surface in the shape of a lens or a combination of both of these (Lambros and Nicolaou 2003). Forming a thin layer is called spreading. Spreading is governed by the surface tensions of the substances, and can be described by the spreading factor S (Lambros and Nicolaou 2003) or λ (Rowe 1989) as

$$S = \gamma_2 - \gamma_1 - \gamma_{12} \quad (14)$$

or

$$\lambda_{12} = W_{A12} - W_{C1} \quad (15)$$

When $S > 0$, $W_A > W_C$ or $\lambda > 0$ spreading occurs (Rowe 1989; Zajic and Buckton 1990; Iveson *et al.* 2001a, Lambros and Nicolaou 2003).

2.2.6 Vapour sorption

Adsorption is defined as uptake of one material onto the surface of another material (Buckton 2000). In adsorption water molecules interact with the solid surface by hydrogen bonding. Absorption refers to uptake of one material into the bulk of another material. Absorption by liquid migration into pores is based on physical interactions between the solid and the liquid (Denesuk *et al.* 1993; Iveson *et al.* 2001a). The term sorption denotes uptake in general, including both adsorption and absorption (Buckton 2000).

Vapour sorption is the uptake of water from the atmosphere, which can be described by adsorption-desorption isotherms (Kontny and Zografí 1995). In these the amount of water is expressed as a function of water activity (w_a). w_a is the ratio of the vapour pressure of the measured system and pure water. RH is defined as $100 \times w_a$. Vapour sorption isotherms give information on the surface characteristics of the solid and on the nature of the solid/liquid-interface. There are different models describing vapour sorption. The Langmuir adsorption isotherm describes the volume of gas necessary to cover a solid surface with a monolayer of adsorbent (Newman 1995). This model, however, has certain restrictions, based on which Brunauer, Emmett and Teller (1938) derived their model for adsorption called the BET-model, further developed by Guggenheim, Anderson and deBoer to extend over a wider range of vapour pressures (Kontny and Zografí 1995).

Regarding crystalline solids, when the RH of the atmosphere is increased, vapour is adsorbed on the surface of the solid (Kontny and Zografí 1995). With non-hydrates the adsorption is dependent in surface polarity and area, and conversion to a corresponding hydrate form can occur. When the critical RH is reached (RH_0), the surface of the solid begins to dissolve into the adsorbed liquid. As the RH is further increased, water vapour condensates onto the liquid film diluting it and allowing further dissolution of solid. This phenomenon is called deliquescence.

Hygroscopicity is a term describing substance ability to uptake moisture from the atmosphere (Kontny and Zografí 1995; Byrn *et al.* 1999). Due to the relative nature of the term hygroscopicity, RH_0 is suggested as a more exact descriptor of the vapour sorption behaviour (Byrn *et al.* 1999). Amorphous substances generally absorb more vapour than non-hydrating crystalline solids, and exhibit more pronounced desorption hysteresis (Kontny and Zografí 1995; Airaksinen *et al.* 2005). Vapour sorption causes variability in both chemical and physical characteristics of powders.

2.2.7 Capillary condensation

Vapour sorption into curved surfaces and pores occurs already below vapour pressures at which condensation occurs for flat surfaces (Israelachvili 1992; Kontny and Zografí 1995). This is due to higher attraction between adsorbent molecules derived from surface curvature. Capillary condensation increases with decreasing pore size. All phenomena that are affected by RH are also affected by the amount of capillary condensation, and the effect of capillary condensation is more pronounced with porous materials. Capillary condensation has been shown to affect fluidisation **behaviour and granule growth** (D'Amore *et al.* 1979; Visser 1989).

2.3 The heterogeneous nature of pharmaceutical surfaces

Pharmaceutical surfaces are in general heterogeneous due to variations in chemical and physical properties (Israelachvili 1992; Kontny and Zografi 1995; Buckton 2000). These variations are due to the processing history of the solid, including crystallisation (Buckton 2000). Considering the distribution of electrical charges within a particle, charge is accumulated in crystalline regions (Füher 1996). When a particle is fully amorphous, electric surface charges are evenly distributed. Surface roughness affects the surface properties to a great extent. Asperities are often of a more crystalline nature (Buckton 2000), and electric surface charges are accumulated in asperities. Even the particle shape affects the way electric charges are distributed; irregularly shaped particles have an uneven distribution of charge (Führer 1996). When a liquid droplet is placed on a solid surface, the θ might vary due to surface heterogeneity (Israelachvili 2002). Examples of such are shown schematically in Figure 2.

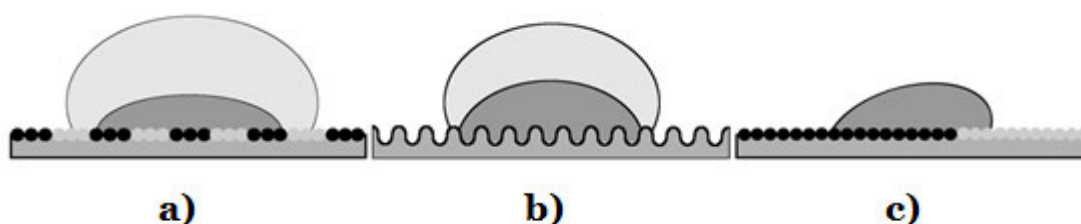


Figure 2. Variation in contact angle due to surface heterogeneity. a) Difference in contact angle of two droplets on a solid surface caused by chemical or physical heterogeneity; b) Difference in contact angle of two droplets with a contact angle $\theta = 90^\circ$ on a solid surface caused by surface roughness; c) Advancing and receding contact angles due to surface heterogeneity. (Modified from Israelachvili 2002).

Processing also affects the degree of crystallinity (Buckton 2000). Amorphous regions usually occur at the particle surfaces as a result of processing, which results in surface heterogeneity. It must also be kept in mind that in crystalline materials the chemical properties of each crystal face will differ from each other. The properties of a surface are not fixed; *e.g.* when a droplet of water is placed on a surface the surface molecules might rearrange themselves to a more favourable configuration for solid/liquid-contact. This is typical for amorphous materials.

2.4 Particle systems modification

2.4.1 Particle surface engineering

Particle engineering can be seen as controlling or modifying particle size and surface to achieve a desired functionality of the particle (Davies *et al.* 1998; Caruso 2001). Particle surface engineering is designing a particle surface with tailor-made properties (Davies *et al.* 1998). Coating is a simple example of surface engineering. Nanoengineering of surfaces can be done by surface polymerization to achieve one or more thin polymeric layers, layer-by-layer coating with cations, and anions, adhering bio-molecules onto surfaces or precipitation of chemical reactions on surfaces (Caruso 2001). Crystallisation is a method of particle surface engineering (Davies *et al.* 1998). Crystal habit can be modified by crystallisation in presence of disrupting and blocking molecules or surfactants. Particles can also be designed to have certain properties by co-crystallisation techniques with excipients, by spherical crystallisation techniques (Remenar *et al.* 2003; Nokhodchi *et al.* 2007; Maghsoodi *et al.*

2008) or simply by adjusting crystallisation supersaturation (Price *et al.* 2002). As an example, improved flow, tablettability and dissolution of ibuprofen was achieved by crystallisation with additives (Rasenack and Müller 2002a, b). Surface roughness has a noticeable influence on interparticle interaction (Führer 1996). Surface roughness has been modified with coating (Iida *et al.* 2005), mechanical processing in the presence of solvents (Iida *et al.* 2003; Ferrari *et al.* 2004) and by treatment with fine mist (Genina *et al.* 2009). By such treatments powder inhalation properties and powder flow can be improved (Kawashima *et al.* 1998; Price *et al.* 2002; Young *et al.* 2002; Iida *et al.* 2004; Genina *et al.* 2009).

2.4.2 Wet coating

Particle coating, or microencapsulation, can be achieved by adding coating material in liquid form to a particle system in small enough amounts to avoid agglomeration (Saleh *et al.* 1999). There are several methods for wet coating, such as spray drying, spray cooling, fluidised bed processing, liposome formation or coacervation (Gibbs *et al.* 1999; Desai and Park 2005). Microencapsulation can be performed by single-layer, multi-layer, multicore, matrix and irregular shaped coating, as presented in Figure 3. Smaller particles can also be attached to larger ones by means of wet coating (Beck *et al.* 2004). Microencapsulation by spray drying is the most widely used microencapsulation method in the food industry due to the ability to produce good quality particles (Desai and Park 2005). Microencapsulation by spray-cooling is done with melted coating, and particle formation is performed through droplet solidification instead of droplet evaporation, producing regular spheres with good flow properties. Wet coating does not have to be restricted to individual particles; ordered mixes can be stabilized into particle systems with good flow properties by coating in a fluidised bed (Thiel and Nguyen 1984).

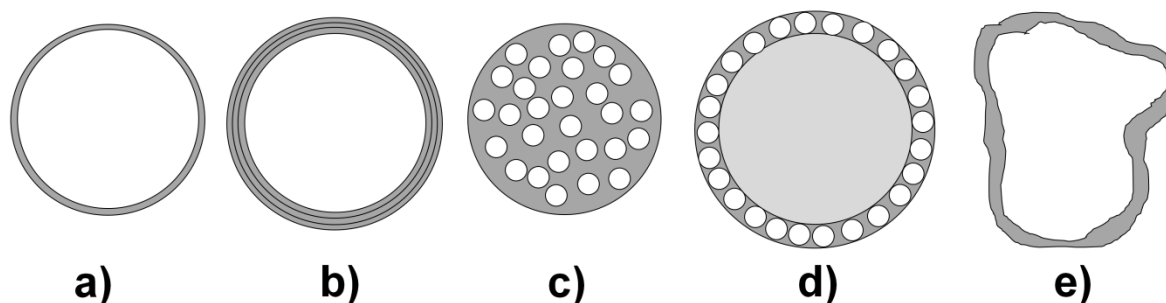


Figure 3. Schematics of types of microencapsulation. a) single-layer; b) multilayer; c) multicore; d) stabilized ordered mix; e) irregular particle coating. White colour indicates core, dark gray coating and light gray carrier particle.

2.4.3 Dry coating

Surface engineering by dry coating aims for forming a protective barrier around the particle and adding functional properties to the surface without the use of solvents (Davies *et al.* 1998; Pfeffer *et al.* 2001; Bose and Bogner 2007). Different methods of dry coating are reviewed by Bose and Bogner (2007). Coating can be performed by compressing dry powder around a suitable core, by precipitating coating material onto the cores from a supercritical fluid, by adding melted coating material onto particle surfaces or by attracting smaller guest particles onto the surface of host particles aiming to form a uniform layer of smaller particles on the surface of larger host particles (Pfeffer *et al.* 2001; Bose and Bogner 2007). The

difference between dry particle coating and formation of ordered mixtures is the stronger interaction between host and guest in dry coating (Pfeffer *et al.* 2001). Dry coatings can be used to enhance flow, to modify drug release or change wettability. There are several reports on dry coating to improve flow and fluidisation properties by *e.g.* coating with hydrophilic or hydrophobic nanosized silica (*e.g.* Räsänen *et al.* 2004; Linsenbühler and Wirth 2005; Yang *et al.* 2005).

2.4.4 Particle size enlargement

Particle size enlargement is a common way to improve handling characteristics of particle systems (Stanley-Wood 1990). To increase particle size, smaller particles are adhered to each other by inducing different kind of bonds between them. Size enlargement processes can be divided into wet and dry methods. Particle size enlargement in wet methods is based on mixing, liquid spraying, evaporation from particle surface, agglomeration, abrasion and fragmentation (Hémati *et al.* 2003). Fluidised bed granulation, high-shear granulation and spray drying are examples of wet size enlargement methods (Stanley-Wood 1990). In dry methods the particles are adjoined by compressing them to form coherent structures with subsequent breakage to suitable particle size. Dry methods might include the use of water in modest amounts. Roller compaction, hot melt extrusion and die compaction are examples of dry size enlargement methods.

2.4.5 Particle size reduction

Particle size reduction is performed to *e.g.* improve dissolution rate, alveolar drug deposition or the physicochemical stability of drug preparations (Shekunov *et al.* 2007). To reduce particle size, energy is demanded to break the structure of the particles (Staniforth 2002a). Only a small fraction of the energy directed to the system is responsible for the actual size reduction; the majority of the energy is lost during the process. In size reduction mechanic energy is directed to the particle to cause a fracture and propagate it through the particle until particle structure failure occurs (Prior *et al.* 1990; Staniforth 2002a). This is continued until the desired particle size distribution is obtained. There are numerous methods of particle size reduction. Comprehensive knowledge on the demands of the process and on the material behaviour under stress is needed for successful processing (Prior *et al.* 1990).

2.5 Fluidised bed powder processing

2.5.1 Principle of action

In fluidised bed processing particulate material is brought to a fluid-like state by directing a stream of air through the powder bed from below, which causes mixing of the powder (Parikh *et al.* 1997). When the powder is mixed liquid is sprayed onto the particles usually with a pneumatic nozzle. Based on nozzle position fluidised bed processes can be divided into top-spray, bottom-spray and tangential-spray processes. In bottom-spray processes draft tubes can be used to direct the particle circulation. Such processes are called Wurster spouted beds. When the particulate material has obtained the appropriate amount of liquid the spray is terminated, after which the granules are dried in the fluidising air. Taken together, mixing, spraying and drying are all performed in the same vessel with no intermediate treatment or process interruptions.

Granule formation depends on binder addition rate, degree of atomisation, temperature of fluidising air and nozzle position which affect wetting, liquid penetration and evaporation (Davies and Gloor 1971). Variables affecting fluidised bed coating are equipment design variables (chamber, nozzle, nozzle position, distributor plate), process variables (inlet air temperature, velocity and RH, binder spray rate, atomisation pressure, batch size) and product variables (solvent choice, coating material, coating solution, particle properties), of which all affect particle circulation rates within the chamber (Cheng and Turton 2000a). These all also determine the size of the wetting active, isothermal and heat transfer zones (Jiménez *et al.* 2006). Wetting and agglomeration occurs in the wetting zone, in which the temperature is low and moisture high. Wurster souted beds and top-spray fluidised beds share certain features and can to some extent be compared to each other (Christensen and Bertelsen 1997). The major difference between these is that Wurster spouted beds have a pronounced, regular circulatory pattern and clearly defined bed regions.

2.5.2 Fluidisation

When gas is directed through a powder bed at low velocities, the air percolates through the bed (Seville 2007). When increasing the velocity of the gas the powder bed expands and the pressure drop over the bed decreases. At a certain point the particles are set into subtle motion, as the pressure drop over the bed equals the weight of the bed as expressed in

$$\Delta p/H = (1 - \epsilon_{mf})(\rho_s - \rho_g)g \quad (16)$$

in which $\Delta p/H$ is the pressure drop over a distance in the chamber, ϵ_{mf} is the void fraction of the bed, g is gravitational acceleration and ρ_s and ρ_g are the densities of the particles and the gas, respectively. The point where the pressure drop over the bed equals the mass of the particle is called incipient fluidisation, and the gas velocity at which it occurs is called minimum fluidisation velocity. The pressure drop does not increase when exceeding the minimum fluidisation velocity. As the gas velocity is increased further, the bed shows bubbling behaviour.

Fluidisation behaviour of powders has been classified into four categories by Geldart (1973). Powders of Geldart group A are small, low density particles which are fluidisable, and group B powders are slightly larger and dense. The behaviour characteristics which determine to which of these a powder belongs is the velocity difference between incipient fluidisation and bubbling bed. In group A the difference is large, during which the bed expands. In group B the velocity difference between incipient fluidisation and bubbling bed is small. Group D powders are large and dense and fluidise only with difficulty. Group C powders are small and very low density particles experiencing strong cohesion. They react to air by lifting as a plug or by passing the air through the powder bed in channels. They do not fluidise easily without external assistance.

The particle motion caused by the fluidising air induces mixing and participates in binder spreading. Mixing of powders in fluidised beds is not problem-free, as segregation has been reported with a wide range of fluidising velocities (Hoffmann and Romp 1991; Bancelos *et al.* 2007; Närvänen *et al.* 2009). When there is an increase in fluidising air velocity the granule growth rate decreases due to more pronounced attrition and drying (Saleh *et al.* 1999). In addition, fast particle circulation rates favour mechanical distribution of the liquid and reduce residual moisture in the final product (Litster 2003; Behzadi *et al.* 2005).

2.5.3 Spraying

A binder liquid is added to the powder to induce appropriate changes in particle characteristics (Saleh *et al.* 1999). Binder spray rate needs to be determined based on the evaporative capacity of the inlet air, coating tackiness and the particle circulation rate (Dewettinck and Huyghebaert 1999). An increase in binder spray rate results in an increase in agglomeration tendency when a critical threshold is passed and an uneven binder distribution pronounces the agglomeration tendency (Becher and Schlünder 1998). With low spray rates the droplet size distribution is more uniform (Chen *et al.* 2009). Increasing binder spray rate results in an increase in granule size and decreased friability and porosity (Davies and Gloor 1971). This is due to enhanced wetting and penetration and partly due to increased droplet size (Davies and Gloor 1971; Chen *et al.* 2009). Increasing the amount of binder added results in larger granules with higher residual moisture (Behzadi *et al.* 2005). It has to be kept in mind that too low a spray rate results in spray drying of the liquid droplets (Guignon *et al.* 2002).

2.5.4 Drying

There are two kinds of moisture in particles: free unbound water and pore water (Abberger 2001; Wang *et al.* 2007). Drying of granules proceeds in stages (Hlinak and Saleki-Gerhardt 2000; Wang *et al.* 2007). First the granules are heated followed by a period of constant drying rate of free water (Wang *et al.* 2007). In these stages the drying is controlled partly by heat and mass transfer between particle and the fluidising medium and heat transfer from particle to liquid and partly by the differences in vapour pressure between air and liquid (Guignon *et al.* 2002; Wang *et al.* 2007). The drying proceeds with liquid migrating to the granule surface by means of diffusion to evaporate, during which the drying rate is falling (Hlinak and Saleki-Gerhardt 2000; Wang *et al.* 2007). Finally the moisture content reaches an equilibrium, which depends on process conditions, RH of the drying air and vapour sorption properties of the granules (Hlinak and Saleki-Gerhardt 2000). The drying rate can be expressed as

$$\frac{dW}{dt} = \frac{h_t A}{\Delta H} \cdot \Delta T \quad (17)$$

in which dW/dt is the change in mass of evaporated water over time, h_t is the heat transfer coefficient, A is the surface area of the particle, ΔH is the latent heat of evaporation and ΔT is the temperature difference between the drying air and product surface (Schæfer and Wørts 1978a). Taken together, inlet air RH, temperature and velocity affect drying (Guignon *et al.* 2002).

Bed temperature and outlet air humidity are indicators of granule moisture content (Schæfer and Wørts 1977a; Schæfer and Wørts 1978a; Rantanen *et al.* 1998; Rantanen *et al.* 2001; Lipsanen *et al.* 2008). In addition, near-infrared (NIR) spectrometry can be used in moisture content analysis in fluid bed drying (Frake *et al.* 1997; Rantanen *et al.* 2001). Different drying end-point criteria have been used, such as fixed outlet air moisture content, fixed drying time and specific outlet air temperature (Lipsanen 2008). A fixed bed temperature difference between the onset and completion of drying has been implemented and found superior to the above mentioned, especially with varying moisture content of the inlet air (Schæfer and Wørts 1978a; Lipsanen *et al.* 2008).

More recently NIR-spectrometry has been used as a tool in granulation end point determination (Frake *et al.* 1997; Rantanen *et al.* 2001). High inlet air humidity leads to a

higher bed temperature (Lipsanen *et al.* 2007; Wang *et al.* 2007), but also prolongs the drying time (Wang *et al.* 2007). The particle size distribution of the dried mass affects drying (Guignon *et al.* 2002). Large granules usually contain more water (Nieuwmeyer *et al.* 2008), and drying time has been found to increase with increasing particle size (Wang *et al.* 2007). During drying, the particle size decreases and the amount of fines increases, which is more pronounced with high inlet air velocities (Nieuwmeyer *et al.* 2008). Granule moisture content and formation of fines during drying correlate.

2.6 Moisture in fluidised bed processes

2.6.1 Atomisation and droplet formation

The typical nozzle in a fluidised bed process is a pneumatic two-fluid or binary nozzle (Dewettinck and Huyghebaert 1999; Hede *et al.* 2008). Two-fluid nozzles can be divided in external and internal mixing nozzles (Hede *et al.* 2008). In internal mixing nozzles the air and liquid are mixed in a mixing chamber within the nozzle head, while in external mixing nozzles the mixing occurs outside of the nozzle head, as shown in Figure 4. External mixing nozzles offer more exact control of atomisation due to the possibility to independently control of the liquid and air flow rates.

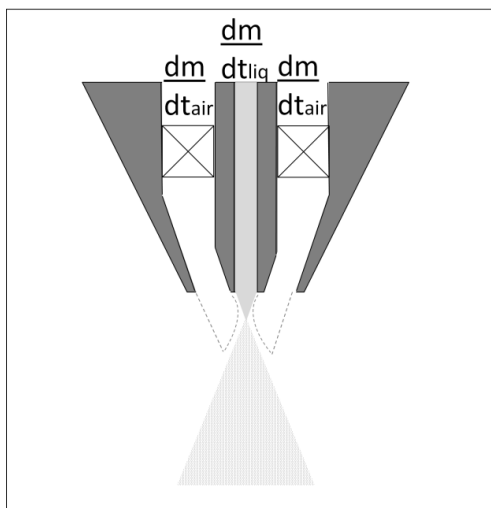


Figure 4. Schematics of the principle of operation of a two-fluid external mixing pneumatic nozzle with swirl inserts. Modified from Hede *et al.* 2008.

In pneumatic nozzles the atomisation is a result of low velocity liquid being in contact with high velocity gas (Hede *et al.* 2008). The atomisation proceeds in two steps; first the liquid is dispersed into filaments or larger droplets, after which these are further atomised to small droplets. Atomisation is affected by surface tension, viscosity and density of both gas and liquid. The level of atomisation is dependent on the mass flow ratio of gas and liquid (Kim and Marshall 1971). Technically this is modified by adjusting the atomisation pressure or liquid feed rate. Droplet size decreases with increasing gas and liquid mass flow ratio. As the ratio increases, the droplet size approaches a plateau level, after which it is no longer affected by a further increase in mass flow ratio. It has to be kept in mind that atomisation air also affects droplet evaporation (Dewettinck and Huyghebaert 1999) and droplet velocity (Hede *et al.* 2008). Other factors affecting droplet size are gas flow rate, liquid flow rate, gas pressure, the density and viscosity of both gas and liquid and the liquid surface tension (Kim

and Marshall 1971). Increased spray rate results in a more dense spray consisting of larger droplets with wider and less uniform size distributions (Juslin *et al.* 1995a; Wan *et al.* 1995; Müller and Kleinebudde 2007; Chen *et al.* 2009). Increased binder concentration, and thus increased viscosity, leads to larger droplets with wider droplet size distribution (Kim and Marshall 1971; Schæfer and Wörts 1977b; Juslin *et al.* 1995a,b; Müller and Kleinebudde 2007; Chen *et al.* 2009).

2.6.2 Spray characterisation

Knowledge on nozzle function is an advantage in fluidised bed coating and agglomeration (Hede *et al.* 2008), as nozzle height and spray width determines the wetted area (Schæfer and Wörts 1977a) and droplet size has been found to correlate with granule size by numerous authors (*e.g.* Schæfer and Wörts 1978b; Schaafsma *et al.* 1998; Schaafsma *et al.* 2000). There has been several approaches to study the spray characteristics of nozzles, such as laser diffractometry (Juslin *et al.* 1995a,b), laser Doppler anemometry (Müller and Kleinebudde 2006,2007), particle tracking velocimetry (PTV; Rantanen *et al.* 1999) and droplet collection into oil (Schæfer and Wörts 1977b) or cups (Schaafsma *et al.* 2006). Most of the studies have been performed with the nozzle separated from the equipment in which it functions; only a few studies have been performed *in situ* (*e.g.* Yuasa *et al.* 1999; Leclère *et al.* 2004).

Droplet formation is heterogeneous as a process, which results in a droplet size distribution (Hede *et al.* 2008). There have been reports on both unimodal and bimodal droplet size distributions (Juslin *et al.* 1995a; Yuasa *et al.* 1999), and usually the droplet size with two-fluid nozzles lies between 10 and 100 μm (Guignon *et al.* 2002). Small droplets with narrow size distribution promote uniform coating. It has to be kept in mind that all droplets measured in spray characterisation do not participate in coating or granulation; it has been suggested that only a small percentage (2-6%) of particles present in the spraying zone **receive coating due to “sheltering” by other particles (Cheng and Turton 2000b)**, and some droplets undergo premature evaporation before droplet particle impact (Guignon *et al.* 2002).

2.6.3 Droplet-particle impact and adhesion

For granulation or coating to be possible, droplet particle impact with subsequent droplet adhesion needs to occur (Link and Schlünder 1997). Particle droplet impact occurs in the spray zone by four mechanisms: inertia, interception, diffusion, and field forces (Link and Schlünder 1997; Guignon *et al.* 2002). Not all droplets undergo impact; some droplets are prematurely dried before impact and in addition to this the particle circulation rate and spray characteristics determine the probability of impact (Guignon *et al.* 2002). Impingement efficiency can be described by the ratio of critical impact area to particle projection area, which is dependent on particle and droplet size and velocity as well as solid-liquid interfacial interaction (Link and Schlünder 1997; Panda *et al.* 2001). Upon impact the droplet can become deposited, reflected, re-atomised, or it can coalesce or spread (Link and Schlünder 1997; Hardalupas *et al.* 1999). If both the solid and the liquid have high work of cohesion, the contact area of the two is minimized (Iveson *et al.* 2001a).

Droplet adhesion is described by adhesion probability (Link and Schlünder 1997). Adhesion probability is determined by the droplet momentum and liquid/solid-interfacial phenomena (Link and Schlünder 1997; Guignon *et al.* 2002). There are different mechanisms for adhesion after impact (Guignon *et al.* 2002). The mechanisms of adhesion are bond formation (ionic or covalent), melting and resolidification, diffusion between droplet and

particle and chemical reactions. When $\gamma_{SL} < \gamma_{SV}$ the surface energies are more favourable for solid-liquid contact than solid-vapour contact (Denesuk *et al.* 1993). Reducing liquid viscosity improves spreading, but reduces the critical velocity for reflection and counteracts droplet coalescence (Guignon *et al.* 2002; Werner *et al.* 2007). Reducing surface tension reduces the tendency to droplet reflection (Werner *et al.* 2007). The moisture content of the surface and the bed temperature affects droplet adhesion by altering *e.g.* pore penetration (Link and Schlünder 1997). Only the first coating layer has a liquid-particle interface, and subsequent layer deposition is determined by liquid-dry film interface characteristics (Donida *et al.* 2005).

2.6.4 Liquid spreading and absorption

In coating and granulation, good wettability and water entering pores are of fundamental importance (Donida *et al.* 2005). If the powder does not absorb water the process becomes more sensitive to process conditions (Schæfer and Wørts 1977a). After the impact, droplet coalescence and spreading occurs (Guignon *et al.* 2002). When $\lambda_{12} > 0$, there is formation of liquid bridges and subsequently strong and dense granules with low friability (Planinšek *et al.* 2000; Iveson *et al.* 2001a; Bouffard *et al.* 2005). When $\lambda_{21} > 0$, the resulting granules are weak and porous (Iveson *et al.* 2001a), or the solids might spread over the liquid causing liquid filled hollow structures (Hapgood and Khanmohammadi 2009).

Liquid migrates into pores based on pore geometry, surface energies and liquid viscosity (Denesuk *et al.* 1993; Iveson *et al.* 2001a). The droplet contact radius is more largely determined by pore penetration than spreading, with the amount of pores participating being the rate determining factor (Denesuk *et al.* 1993). Short penetration times are favoured by small droplets, low viscosity, high porosity, large pores, low θ and high surface tension (Hapgood *et al.* 2002). In addition, liquid penetration with a constant droplet radius and decreasing θ favours rapid pore penetration (Denesuk *et al.* 1993).

Wettability assessment can be performed with single particles or bulk solids, which give different information, as the wettability of bulk solids is affected by packing in addition to the single particle properties (Hapgood *et al.* 2002; Lazghab *et al.* 2005). Changing a single component in a powder mixture to a substance with better wettability even if present only in a modest percentage leads to stronger granules (Jaiqeoba and Spring 1980). By studying the liquid-solid interface phenomena, it is possible to predict the behaviour of the liquid in the process (Zhang *et al.* 2002). Adding polymer to a solution decreases surface tension and increases θ and binder viscosity (Schæfer and Wørts 1978b; Pont *et al.* 2001; Rajniak *et al.* 2007). Increased θ and lower surface tension decreases the granule size, granule growth rate and coating efficiency (Iveson *et al.* 2001a; Pont 2001; Saleh and Guignon 2007). If the liquid θ is very high, other wetting parameters can be neglected (Saleh and Guignon 2007).

Increased binder concentration has been found to increase granule size, growth rate and porosity, and decrease final product density (Schæfer and Wørts 1978b,c; Rajniak *et al.* 2007). Increased polymer concentration also enlarges the droplet size, partly explaining the gain in size (Rajniak *et al.* 2007). Liquid bridge strength decreases with decreasing surface tension (Iveson *et al.* 2001a). Regarding the final product, increased binder concentration leads to decreased granule friability and flow in addition to increased granule size, porosity and tablet disintegration time (Davies and Gloor 1972). The increased tablet disintegration time is due to increased porosity and impaired flow, causing problems in dye filling.

2.6.5 Coating and nucleation

Coating, nucleation, growth, and over-wetting are determined by maximum pore saturation and deformation upon granule impact (Iveson and Litster 1998; Iveson *et al.* 2001b; Litster 2003). If there is large amounts of excess liquid in the process, or if the droplets are much larger than the particles, an agglomeration will occur (Saleh *et al.* 1999). If the droplet size is smaller than the particle or if there is rapid drying after droplet-particle impact, the result is coating. Low bed temperatures favour granule growth and coating efficiency (Schæfer and Wörts 1978a; Dewettinck and Huyghebaert 1998). Coating uniformity is impaired in polydisperse systems as smaller particles receive more coating and larger particles have faster rate of growth (Maronga and Wnukowski 2001).

If wet particles collide and the dispersive forces are not sufficient, agglomeration occurs (Saleh *et al.* 1999). Several forces participate in the formation of granules, such as liquid bridges, solid bridges, van der Waals forces, electrostatic forces and mechanic interlocking (Reynolds *et al.* 2005). Nucleation is the formation of initial agglomerates (Iveson *et al.* 2001b). Nucleation is controlled by nucleation thermodynamics and efficient binder distribution, and when the conditions for nucleation are beneficial, formation of nuclei occurs rapidly (Schaafsma *et al.* 1998; Iveson *et al.* 2001b). Nucleation kinetics is determined by liquid penetration into the bed (Hapgood *et al.* 2002). If pore saturation is kept low enough, there will only be nucleation without further growth (Iveson *et al.* 1998, Litster 2003).

For nucleation the θ and spreading coefficients are of importance, as good binder distribution leads to even nucleation (Iveson *et al.* 2001a). Poor wetting or liquid penetration into the powder bed results in uneven binder distribution, broadening the nuclei size distribution (Hapgood *et al.* 2002). In fluidised bed processes the size of the nuclei is dependent on droplet size (Iveson *et al.* 2001a). Drop controlled nucleation is the event of one liquid droplet leading to one nucleus (Hapgood *et al.* 2002). Drop-controlled nucleation demands rapid penetration of the droplet into the bed or effective mechanical dispersion of the liquid (Litster 2003). Drop-controlled nucleation can be adjusted by adjusting droplet penetration into the bed by formulation design or by modifying the process parameters controlling droplet evaporation (Hapgood *et al.* 2002). Drop controlled nucleation leads to a uniform size distribution of nuclei.

Several approaches to restrict granule growth in fluidised bed coating have been reported. Increasing atomising gas velocity and lowering liquid flow rate reduces agglomeration tendency (Becher and Schlünder 1997). Higher nozzle air velocity leads to more uniform liquid deposition and thus more uniform granule growth. Wide particle size distributions favour agglomeration tendency and by reducing attrition agglomeration tendency can be suppressed (Guignon *et al.* 2002).

2.6.6 Granule growth

After nucleation the voids of the nuclei are saturated with water (Schaafsma *et al.* 1998). Particle growth is dependent on plastic deformation during particle coalescence caused by this local pore saturation (Schaafsma *et al.* 1998; Abberger 2001; Hapgood *et al.* 2003). When pore saturation is complete there is free liquid on the surface to bind other particles (Schaafsma *et al.* 1998). The process air evaporation efficiency depends on temperature of the inlet air and absolute humidity of the inlet and outlet air (Dewettinck *et al.* 1998).

Agglomeration occurs when a critical evaporation efficiency is exceeded and there is particle-particle interaction between wet particles (Dewettinck *et al.* 1998; Guignon *et al.*

2002). Granules are formed from one droplet, coalesced droplets or coalesced particles (Schaafsma *et al.* 2000). Coalescence of droplets, nuclei and droplet-nuclei coalescence occurs in the spray zone (Schaafsma *et al.* 2006). Following coalescence, water migrates to the pores of the newly adhered particle driven by capillary pressure differences (Schaafsma *et al.* 1998). The water migration is the rate limiting step in granule growth which is initially slow followed by a gradual increase (Schaafsma *et al.* 1998; Jiménez *et al.* 2006).

Liquid feed rate and binder concentration affect granule growth rate (Jiménez *et al.* 2006; Hu *et al.* 2008). High amount of binder results in faster granule growth and larger final granule size, although the increased viscosity reduces the amount of liquid penetration (Bouffard *et al.* 2005). Binder available at the surface is of greater influence on granule growth. Higher nozzle air velocity leads to more uniform liquid deposition and thus more uniform granule growth (Becher and Schlünder 1997). Increased particle size decreases particle growth rate (Saleh *et al.* 2003).

2.6.7 Interparticle forces in fluidisation

The interparticle forces causing cohesion mentioned in section 2.1.3 all affect the fluidisation characteristics of particle systems (Visser 1989). In addition, sintering impairs the quality of fluidisation (Seville *et al.* 2000). These are important to consider as improper fluidisation might lead to impaired product quality. Adding liquid to a fluidised bed impairs the fluidisation behaviour by forming liquid bridges and thus increasing particle cohesion (Seville and Clift 1984; McLaughlin and Rhodes 2001; Forsyth *et al.* 2002, Bachelos *et al.* 2007). Increased amounts added and high liquid viscosity pronounces the fluidisation impairment (McLaughlin and Rhodes 2001). Wider particle size distributions are more affected by liquid content increase than monodisperse systems (Bachelos *et al.* 2007). Porous materials are suggested to be able to retain more water without losing their fluidizability (D'Amore *et al.* 1979). Electrostatic interactions are more pronounced with elevated fluidising air velocity due to increased particle motion (Guardiola *et al.* 1996). Loss of electric charges occurs due to conduction through the chamber wall or through moisture dissipating the charge. Thus, fluidisation can be improved by increasing the inlet air RH. Still, in certain cases increased RH impairs the fluidisation behaviour, as in the case of lactose in RH over 50% (Schaafsma *et al.* 1999).

There have been different approaches to overcome the problems caused by high levels of cohesion, such as using higher fluidising gas velocities (Zhou *et al.* 1999), aid of a magnetic field (Guo *et al.* 2005), vibration or by large inert particles into the bed (Chen *et al.* 2008) and adding fines, such as nanoparticles (Chen *et al.* 2008).

3 Aims of the study

The aim of this thesis was to study coating and granulation of powders, and to characterise the borderline between these by restricting the addition of moisture into the particulate systems. In addition, the aim was to develop tools for characterising particle systems modification processes.

More specifically, the aims of the present study were to:

- improve the flow properties of poorly flowing ibuprofen by fluidised bed particle thin-coating.
- investigate the possibilities of using a novel ultrasound-assisted method for particle thin-coating to achieve improved flow properties of ibuprofen.
- control and restrict particle growth in a fluidised bed process by regulating atomisation pressure and applying a pulsed liquid feed.
- characterise the droplet and spray properties *in situ* in a fluidised bed process using PTV coupled with diode laser stroboscopy (DLS).
- study whether diffuse visible light transmitted through a dense powder bed carries enough information on particle size and packing density of the sample for basic process diagnostics.

4 Experimental

4.1 Materials (I-V)

The materials used in the studies were ibuprofen (Ibuprofen 50, Boots Pharmaceuticals, Nottingham, the United Kingdom), 2910-substituted hydroxypropyl methylcellulose (HPMC; Methocel E5 Premium EV LP, Dow Chemical Company, Midland, USA), α -lactose monohydrate (Pharmatose 200M, DMV, Veghel, The Netherlands), micronized anhydrous caffeine (supplied by Orion Pharma, Espoo, Finland), anhydrous theophylline (supplied by Orion Pharma, Espoo, Finland), polyvinylpyrrolidone (Kollidon® K25, BASF, Ludwigshafen, Germany), Eudragit NE (Röhm GmbH & Co, KG, Pharma Polymers, Darmstadt, Germany), microcrystalline cellulose (MCC) pellets (Cellets®, Syntapharm GmbH, Muelheim an der Ruhr, Germany) and glass ballotini (Assistant Glasswarefabrik, Karl Hecht GmbH & Co KG, Sondheim, Germany and Jencons Ltd., Bedfordshire, England).

4.2 Methods

4.2.1 Fluid bed powder processor (I,III,IV)

In studies I, III and IV the powder processing equipment used was an Aeromatic STREA-1 laboratory scale fluidised bed powder processor (Aeromatic AG, Muttenz, Switzerland) with a top-spray nozzle setup. The nozzle was a Schlick 970/7-1 pneumatic external mixing two fluid nozzle (Düsen-Schlick GmbH, Untersiemau, Germany). The spray angle width was set at position 3 on a scale of 1-5. The nozzle was mounted on an aluminium-brass-tripod placed between the top of the chamber and the oscillating upper sieve. The distance between the nozzle head and the perforated bottom plate was 340 mm. The powder processor with instrumentation was connected to a PC and operated via InTouch–software (Wonderware, Lake Forest, USA).

4.2.2 Fluid bed coating (I)

The coating liquid used was a 0.15 % (m/V) solution of HPMC. The ibuprofen powder to be coated was sieved with a 1-mm sieve. The batch size was 300 g. The atomising pressure was set to 0.5 bar and the air flow rate to 3.5 l/s, both empirically determined in preliminary experiments.

All batches were processed in an ambient inlet air RH of 28 ± 5 % measured with a Vaisala HUMICAP® HMT100 humidity and temperature probe (Vaisala Oyj, Helsinki, Finland). Before every experiment, the chamber was dried empty for 5 minutes with an inlet air flow rate of 5 l/s and an inlet air temperature of 35 °C. The ibuprofen was mixed for six minutes before initiating the spraying phase. During the mixing phase the inlet air flow rate was increased from 2 l/s to 3.5 l/s by 0.5 l/s-increments every two minutes. To avoid temperature peaks, the inlet air temperature was increased stepwise to the target temperature.

The liquid feed rate and inlet air temperatures were varied between 0.42 g/min and 0.98 g/min and 20.9 °C and 49.1 °C, respectively, according to the experimental design presented in section 4.2.16. The endpoint of the spraying phase was determined as the point where a theoretical mass increase of 0.025 % was reached. The end point of the drying phase was when the difference in RH between the inlet and outlet air was constant.

4.2.3 Fluid bed granulation (III)

Prior to the granulations 100 g of anhydrous caffeine and 400 g lactose monohydrate were sieved with a 1-mm sieve. Consequently, the batch size was 500 g. The binder liquid was a 20 % (w/w) aqueous solution of polyvinyl pyrrolidone (Kollidon K-25). The duration of the mixing phase was 2.5 minutes, during which the inlet air temperature was increased from ambient room temperature to 40 °C, at which the spraying phase was performed. Controlling the level of fluidisation was performed by keeping the pressure difference between below and above the fluidisation chamber between 600 and 800 Pa. To achieve this, the air flow rates were varied from 2 l/s to 12 l/s.

The spraying phase was performed by sequentially interrupted, i.e. pulsed, spray. The spray was turned on and off in duty cycles (DC) consisting of equal parts of spray and lag time. During the sequences with absence of spray the atomising pressure was kept constant to avoid fluidisation irregularities. The liquid feed rate during the spray sequences was kept at 2.5 g/min. As the target liquid consumption was 100 g, the spraying phase duration was 80 minutes, after which the drying phase was initiated and the inlet air temperature was increased to 50 °C. The drying end-point criterion was a difference of 1 % in RH between inlet and outlet air continuously for a full minute measured with a Vaisala HUMICAP® HMT100 humidity and temperature probe (Vaisala Oyj, Helsinki, Finland). The theophylline granules were prepared in a fluidised bed granulator (Glatt WSG 5, Glatt GmbH, Binzen, Germany).

4.2.4 In situ fluid bed spray characterisation (IV)

To characterise the spray in a fluidised bed process *in situ*, process parameters mimicking an actual process were chosen. Glass ballotini with a diameter of 10 mm were placed in the chamber to function as an immobile heat reserving inlet air flow diffuser. Purified water was used as spraying liquid. The inlet air temperature was set to 50 °C, the inlet air flow was set at 6 l/s and the spray rate was kept at 2.5 g/min. As inlet air velocity and temperature have been shown to affect droplet size, they were kept constant to isolate the effect of atomisation pressure (Yuasa *et al.* 1996). The liquid temperature was at an ambient 21.6 ± 0.4 °C. The images used in the spray characterisation were obtained through an extension piece fitted into orifices drilled on the side of the chamber to avoid droplet deposition on the imaging window. All orifices were air-insulated during measurement.

4.2.5 Ultrasound assisted powder coating (II)

120 g of ibuprofen powder was coated in an ultrasound assisted process with an aqueous solution consisting of 0.15 % (m/V) HPMC. The coating solution was atomised with a ultrasound nebulizer (Ultrasonic Nebulizer NE-U17, Ultra Air, Omron, Hoofddorp, The Netherlands). The powder was transported to the ultrasonic mist by a vibratory feeder (Fritch Laborette 24, Idar-Oberstein, Germany), and gravitationally deposited in a collector vessel. This procedure was repeated to a total of 30 exposures to the ultrasonic mist. The powder in the collector vessel was mixed at intervals by a stirrer (IKA®-Werke, RW 11 Basic, Staufen, Germany) in order to prevent agglomeration. 20g samples were removed with an interval of five full cycles. The setup is described in detail in Genina *et al.* 2009.

4.2.6 Measurement of flow properties (I,II)

The flow properties of ibuprofen in studies **I** and **II** were measured using an in-house developed powder flow testing method especially designed for small amounts of poorly

flowing powders. The method is based on flow through an orifice assisted by abruptly interrupted oscillatory vertical motion. The powder is discharged onto an analytical scale, and the scale readings are recorded by a computer and converted into flow rates of mg/s and $\mu\text{l/s}$. The method is presented in detail by Seppälä *et al.* (2010). The measured powders were acclimatised in low, intermediate and high RH for a minimum of 24 hours (**I**) and 72 hours (**II**). The measurements were performed five times.

4.2.7 Moisture content analysis (I-III)

The moisture content of the ibuprofen in study **II** was measured with an AquaLab water activity meter (AquaLab 3 TE, Decagon Devices, Inc., Washington USA). The moisture content of the thin-coated ibuprofen in study **I** and granules in study **III** were measured with a Sartorius MA 100 moisture analyser (Sartorius AG, Göttingen, Germany).

4.2.8 Microscopy and image analysis (I)

Optical microscopy with subsequent image analysis using Matlab (Matlab 7.5.0 (R2007B), Mathworks Inc., USA) was used in study **I** to determine particle size and circularity. The magnification was 2.5 \times . The particle size data obtained was volume weighed. Equivalent sphere diameter was used as particle size descriptor according to

$$d_e = 2 \cdot \sqrt{\frac{A \cdot (\text{pix})^2}{\pi}} \quad (18)$$

in which **A** is the area of the particle projection in square pixels and **pix** the pixel-micron-convexion coefficient 3 $\mu\text{m}/\text{pixel}$. The value of **pix** was determined by measuring and relating a known distance of 100 μm to the number of pixels covered by the distance. The circularity **M** was derived according to

$$M = \frac{4\pi A}{P^2} \quad (19)$$

in which **A** represents the particle area and **P** the perimeter (Heng and Chan 1997).

4.2.9 Photometric particle size analysis (V)

Particle size measurements of theophylline granules, glass ballotini and MCC pellets were made with Flash Sizer (Intelligent Pharmaceuticals Ltd., Helsinki, Finland). The method is presented in detail by Sandler 2010.

4.2.10 Spatial Filtering Velocimetry (II,III)

The particle size of the coated ibuprofen in study **II** and the granule size of the granules in study **III** were studied using SFV. The used piece of equipment was a Parsum Probe (Parsum® PII 70-Se, Gesellschaft für Partikel-, Strömungs- und Umweltmesstechnik GmbH, Chemnitz, Germany). Prior to analysis, the granules in study **III** were divided into suitable samples using a vibratory feeder (Fritch Laborette 24, Idar-Oberstein, Germany) coupled with a rotary sample divider (Fritch Laborette 27, Idar-Oberstein, Germany) to produce a sample size of 13 ± 0.7 g.

4.2.11 Particle tracking velocimetry and droplet size analysis (IV)

Spray characteristics were measured using PTV and image analysis. Images were obtained using a charge coupled device (CCD) (Lumenera, Ottawa, Canada) with an image area of 9.3×6.95 mm (IV) and (V). The camera was positioned 170 mm from the vertical central line of the spray. Each frame was exposed in triplicate by DLS (HiWatch, Oseir Ltd., Tampere, Finland). The DLS pulse duration was 100-200 and delay between pulses 50-80 μ s. The time-related parameters were chosen based on observed droplet speed.

PTV was performed using Osirec-software (Oseir Ltd., Tampere, Finland). Droplet size data was obtained from the same images based on droplet diameter. Every measurement consisted of 100 images. The lower limit of accurate measurement of the present setup was 18 μ m. The method is presented more thoroughly by Larjo (2005).

4.2.12 X-ray powder diffractometry (I,II)

In studies **I** and **II** X-ray powder diffractometry was used (D8 Advance, Bruker AXS GmbH, Karlsruhe, Germany) to exclude process induced changes in the studied material. **CuK α radiation and symmetric reflection mode ($\lambda=1.54\text{\AA}$) with Göbel mirror optics was used. The 2θ range was 5-40 ° with 0.05 °/s increments.**

4.2.13 Scanning electron microscopy (I-III)

Scanning electron microscopy (SEM; Zeiss DSM 962, Carl Zeiss, Oberkochen, Germany) was used to visualise particle size, morphology and surface morphology. The samples were platinum coated by vacuum evaporation. Accelerated voltages of 8 kV (**I** and **II**) and 10 kV (**III**) and magnifications of 200 \times , 2000 \times (**I** and **II**) and 500 \times (**III**) were used.

4.2.14 Atomic force microscopy (II)

An atomic force microscope (AFM; Autoprobe CP, Thermomicroscopes, Sunnivale, California, USA) was used to study surface topography on an area of 5 \times 5 μ m. The AFM measurements were performed in contact mode with a scanning rate of 0.5 Hz with a cantilever with the spring constant 0.35 N/m. The measurements were performed in ambient conditions. Based on the obtained data (n=6) the surface roughness parameter was calculated.

4.2.15 Light transmission analysis (V)

Light transmission analysis was performed with a sample cuvette (15 \times 15 \times 100 mm) placed between two diffusive lenses. The sample was illuminated with a light emitting diode through a diffusive lens on the emitting side and the transmitted light was detected on the opposite side of the sample through another diffusive lens. A phototransistor was used to convert light to voltage proportionally to the intensity of the received light. The chamber was slowly moved vertically between the illuminating and measuring heads and the light intensity was recorded every 330 μ m with tailor-made software (Hatara Consulting, Helsinki, Finland). The apparatus for measuring the light transmission is shown schematically in Figure 5.

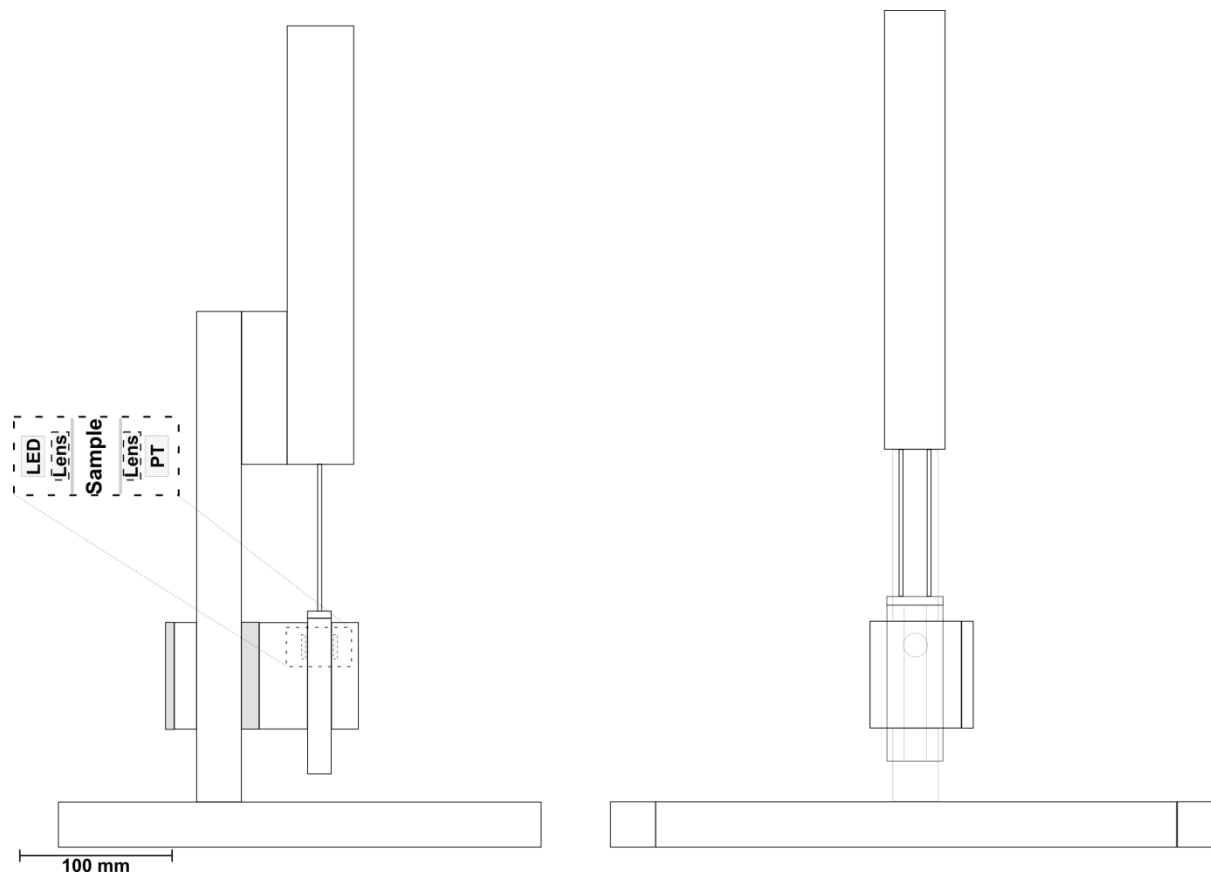


Figure 5. Schematics of the apparatus for light transmission analysis. Side view on the left and front view on the right side. LED = light emitting diode, Lens = diffusing lens, PT = phototransistor.

The repeatability was determined by measuring a 6.0 g sample of theophylline granules of size fraction 500-710 μm 50 consecutive times. The resolution of the measuring system was determined by measuring the signal received from a sample consisting of a layer of theophylline granules of sieve fraction 1000-1400 μm with varying height (h) placed between two 20 mm thick layers of theophylline granules of sieve fraction 250-355 μm . The values of h used were 1, 2, 3, 4, 5, 7.5, 10, 12.5 and 15 mm.

To determine the effect of packing of theophylline granules, a sample of 6.0 g of size fraction 355-500 μm were placed in the sample cuvette and the light transmission was measured. The sample was vibrated in six sequences with different settings and the light transmission and powder bed height was measured after every vibration sequence. The four first vibration sequences had a frequency of 10 Hz, amplitude of 2.5 mm and a duration of 2, 5, 15 and 15 seconds. The two last vibration sequences had a frequency of 30 Hz, amplitude of 0.6 mm and the durations 1 and 5 seconds, respectively. The average phototransistor voltage of each measurement was plotted against powder bed density.

Size correlation of the signal was measured with sample sizes of 20 g for glass ballotini, 10 g for MCC standard pellets and 5 g for theophylline granules. Three theophylline blends (A, B and C) were also measured (Table I). The light transmission of these was measured five times, and the results were averaged. Light transmission of binary blends consisting MCC pellets with a particle size of $d_{50} = 220 \mu\text{m}$ and glass ballotini with a particle size of 230-320 μm with volume ratios $V_{\text{MCC}}/V_{\text{Glass}}$ of 0.1 – 0.9 were measured five times and the results were averaged. All samples were acclimatised for at least 24 hours before measuring and the RH

(ambient) in the laboratory facilities during all measurements was 54 ± 4 % RH. The obtained light intensity curves were refined further using MATLAB R2008a (Mathworks, Inc., Natick, MA, USA).

Table I. Compositions of three artificial distributions (A-C) of theophylline granules expressed in grams (g). The percentage of fraction 180-250 μm for blends A, B and C are 8.3 %, 4.2 % and 0 %, respectively.

Blend	180-250 μm	250-355μm	355-500μm	500-710μm
A	0.5	1.0	2.5	1.0
B	0.25	1.0	2.5	1.0
C	0	1.0	2.5	1.0

4.2.16 Experimental design (I,III,IV)

The experimental design in studies **I**, **III**, and **IV** was a full central composite design constructed with MODDE 7 software (Umetrics Ab, Umeå, Sweden). The studied variables and their ranges are presented in table II. The variable in study **IV** “**distance from nozzle**” described in table II is shown in Figure 6 to alleviate visualisation of the chamber geometry.

Table II. The variables studied with full central composite design.

Study	Variable	Unit	$-\alpha$	-1	0	+1	$+\alpha$	Explanation
I	Inlet air temperature	$^{\circ}\text{C}$	21	25	35	45	49	
	Spray rate	g/min	0.42	0.50	0.70	0.90	0.98	
III	Duty cycle length	s	21	50	120	190	219	
	Atomisation pressure	bar	0.42	0.50	0.70	0.90	0.98	
	Relative humidity	%	N/A	N/A	N/A	N/A	N/A	Uncontrolled, added retrospectively
IV	Distance from nozzle	mm	0	34	116	198	232	See Figure 6 for schematics
	Atomisation pressure	bar	0.42	0.50	0.70	0.90	0.98	
	Relative humidity	%	N/A	N/A	N/A	N/A	N/A	Uncontrolled, added retrospectively

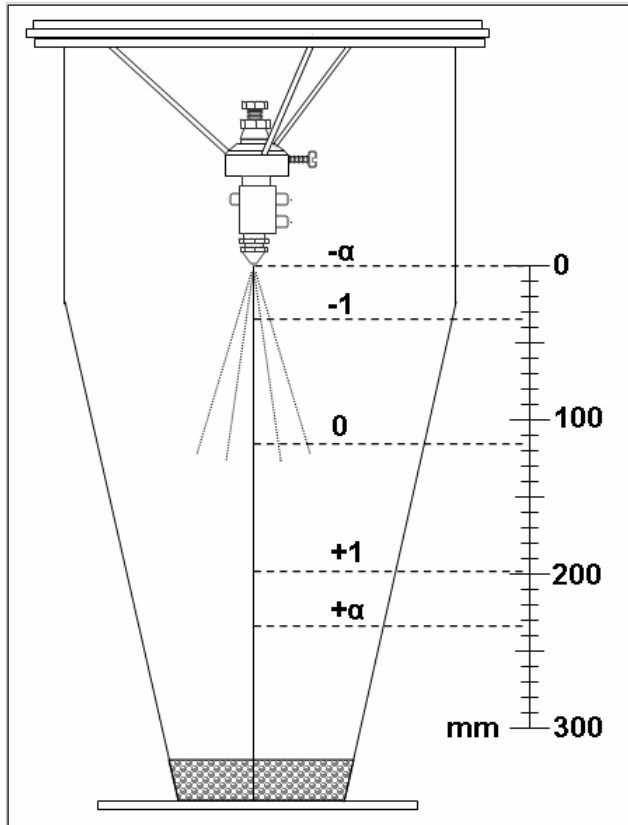


Figure 6. Schematic visualisation of the fluidised bed chamber geometry.

4.2.17 Data analysis and modelling (I,III,IV)

The results of studies **I**, **III** and **IV** were modelled with stepwise multilinear regression analysis using MODDE 7 software (Umetrics Ab, Umeå, Sweden). The normally distributed results were fitted into the second degree polynomial expression

$$z(A, B) = a_1 \cdot A + a_2 \cdot B + a_3 \cdot A^2 + a_4 \cdot B^2 + a_5 \cdot A \cdot B + a_6 \quad (20)$$

and log-normally distributed results were fitted into the expression

$$\log[z(A, B)] = a_1 \cdot A + a_2 \cdot B + a_3 \cdot A^2 + a_4 \cdot B^2 + a_5 \cdot A \cdot B + a_6 \quad (21)$$

in which z is the studied response and A and B are two independent studied variables. In the process of modelling the terms are eliminated stepwise in order of lowest statistical significance with a confidence level of $p=0.05$. The terms were eliminated until achieving maximum predictive power (Q^2) taking the statistical significance of the individual terms into consideration. In study **IV**, additional points not included in the design were measured and included in analysis. The modelled responses are presented in Table III.

Table III. The modelled responses in studies I, II and IV.

Study	Response	Unit	Explanation
I	flow rate	mg/s	
III	d ₅₀	μm	50 % -fractile of granule size distribution
IV	d ₁₀ , d ₅₀ , d ₉₀	μm	10, 50 and 90 % -fractiles of droplet size distribution
	V ₁₀ , V ₅₀ , V ₉₀	m/s	10, 50 and 90 % -fractiles of droplet speed distribution
	a ₁₀ , a ₅₀ , a ₉₀	degrees	10, 50 and 90 % -fractiles of droplet trajectory angle distribution
	n	N/A	Droplet count
	m	fg	sum of mass of droplets

The data obtained in the analysis of flow properties (**I**) was subjected to one-way analysis of variance (ANOVA) **with subsequent analysis by Tukey's Multiple Comparisons Test** using GraphPadPrism Software (GraphPad Software Inc., California, USA).

5 Results and discussion

5.1 General remarks

This research clearly shows the possibilities of taking advantage of interfacial phenomena in both processing of powders and also characterising these processes to achieve thin coatings or restrict granule growth to nucleation. In addition to this, the research shows that coating can be done with top-spray systems with small particles in contradiction to previous reports in the literature (Dewettinck and Huyghebaert 1998). The research brings new insight into the effects of pulsed liquid feed on granule growth, and shows that increased inlet air RH does not always result in larger granules, as previously stated by *e.g.* Närvänen *et al.* (2008).

The present thesis also applied the latest advanced technologies in spray characterisation *in situ* in a fluidised bed process, and showed that in a process environment droplet coalescence occurs. Droplet speed data was in contradiction to what has previously been reported (Mueller and Kleinebudde 2007), but direct comparison to previous findings is not possible as the present study is the first of its kind performed *in situ*. Light transmitted through dense packed powder beds was found to be a promising tool in basic particle systems characterisation, which has previously only been presented by implication.

5.2 Fluid bed powder thin-coating (I)

5.2.1 General remarks

The moisture content of all batches was ~0.1 % (m/m) measured immediately after the process. The ibuprofen can be characterised as a **class C powder in Geldart's powder classification system** (Geldart 1973). In all batches, between 20 and 30 minutes of processing time a clear improvement in fluidisation was observed indicating a change in cohesion (Seville *et al.* 2000).

Successful fluidised bed coating has previously been reported with as small particles as 100 μm (Dewettinck and Huyghebaert 1998), but there are no previous reports on successful top-spray coating of powder with a particle size as small as in the present study. Particles as small as 10 μm have successfully been agglomerated to 50-60 μm in a Wurster-process (Ichikawa and Fukumori 1999) and coating of particles as small as 7-14 μm has been possible after coating with fumed silica nanoparticles (Chen *et al.* 2009). The present study shows that top-spray coating of small Geldart group C-powders can be performed without using fluidisation aids.

5.2.2 Flow properties

The flow rate of the thin-coated powders differed from untreated ibuprofen statistically significantly ($p < 0.001$) in all batches except one (batch N4; $p = 0.08$) in comparison to untreated ibuprofen. The difference in flow rate can be attributed to changes in surface roughness and in interaction with atmospheric moisture. The RH during measurements was 52 ± 5 %. Batch N3 showed the largest improvement in flow properties with a 2.5-fold increase in flow rate. Batch N5 could be considered as equally much improved, as it did not statistically significantly differ from batch N3. The reproducibility of the process was found to be sufficient, as the triplicate centre point batches did not show a statistically significant difference in flow rate.

The flow rate data was fitted into a second order polynomial expression, resulting in the equation

$$z = z(S, T) = 0.35 \cdot T + 31.92 \cdot S - 0.812 \cdot T \cdot S - 4.126 \quad (22)$$

in which z represents powder flow rate (mg/s), T inlet temperature ($^{\circ}\text{C}$) and S spray rate (g/min). The model showed acceptable goodness of fit (R^2) and Q^2 ($R^2 = 0.949$, $Q^2 = 0.826$).

The results show that an increase in spray rate and decrease in temperature increase the flow rate of the powder (Figure 7). The beneficial effects of decreased inlet air temperature and increased liquid feed rate on coating efficiency are supported by previous findings by other authors (Becher and Schlünder 1998; Dewettinck and Huyghebaert 1998; Cheng and Turton 2000a; Jiménez *et al.* 2006). The results are in line with previous studies on improving rheological properties of particle systems by polymer coating (Fernández-Arévalo *et al.* 1990; Holgado *et al.* 1996). In these studies the coating polymer was Eudragit E, L, R and S and the percentage of coating was between 2 and 12%, which is clearly higher than in the present study. The coating was performed with coacervation and subsequent agglomerate grinding. As a whole, improvements in rheological properties were achieved, but the changes were modest and the method very different to the one in the present study.

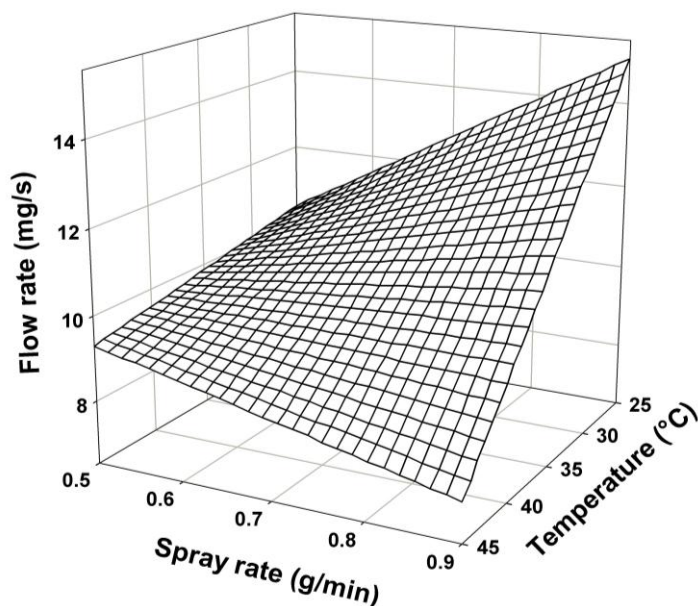


Figure 7. Effect of spray rate (g/min) and inlet air temperature ($^{\circ}\text{C}$) on the flow rate of ibuprofen powder coated with hydroxypropyl methylcellulose in a fluid bed powder processor.

The present study presents a method to improve flow properties maintaining a small particle size. The results are applicable in *e.g.* direct compression, as smaller particles have been shown to give stronger tablets (Sun and Grant 2001). A polymer coating could be used to ensure sufficient flow despite of the small particle size. The method is labour intensive and difficult, and can thus not be considered as a first choice of method in an industrial context.

5.2.3 Particle morphology and solid state properties

Particle size of the batch with the highest and lowest improvement in flow properties (N3, N4) was compared to untreated ibuprofen to clarify whether the improvement in flow properties could be attributed to an increase in particle size. The particle size in the treated powders was slightly smaller (Table IV). Considering cohesion and process induced particle attrition this result seemed logical (Verkoeijen et al 2002; Ferrari *et al.* 2004). There were no apparent changes in particle shape in the chosen batches.

Table IV. Particle size characteristics for uncoated and coated (N3, N4) batches of ibuprofen.

	Ibuprofen	N3	N4
n	1092	1150	1052
d₁₀	25	21	21
d₅₀	42	39	37
d₉₀	72	65	72

SEM micrographs of untreated ibuprofen and treated batches N3 and N4 show no apparent changes in particle properties at a magnification of 200 \times . With a magnification of 2000 \times there are visible changes in surface characteristics indicating successful deposition of coating onto the particle surface (Figure 8). In high inlet air temperatures there might be changes in surface crystallinity of the particles (Panda *et al.* 2001). The X-ray powder diffraction patterns showed no process induced polymorphic changes in batches N3 and N4 compared to untreated ibuprofen.

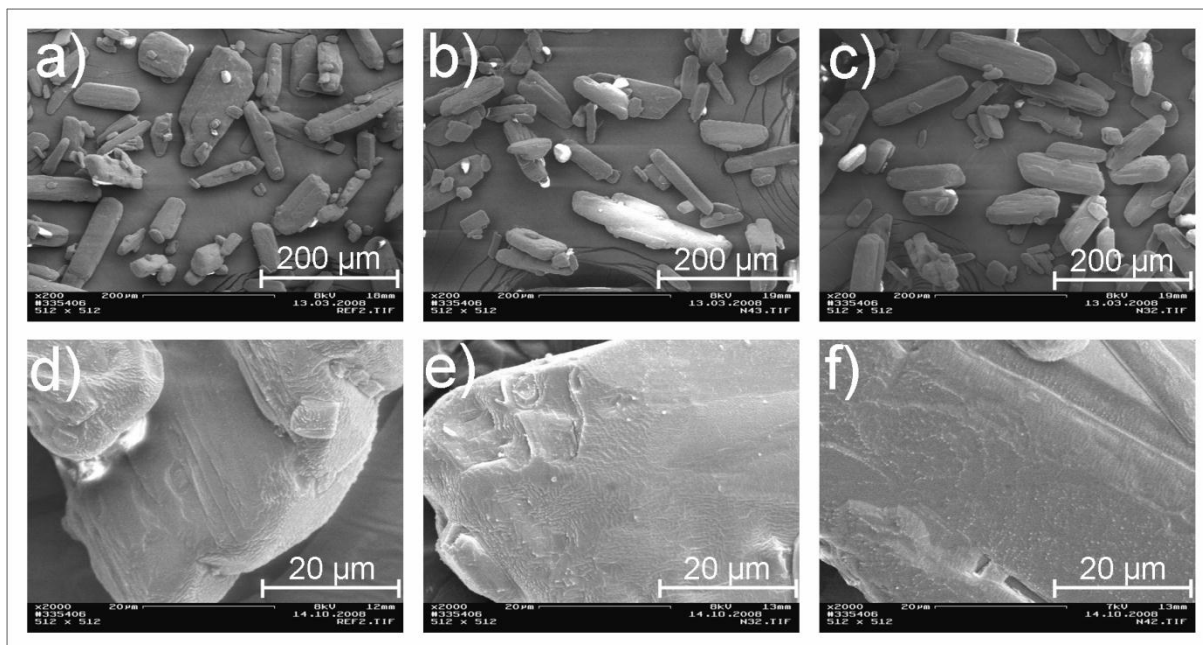


Figure 8. Scanning electron microscope micrographs of untreated ibuprofen (a,d) and two treated batches N3 (b,e) and N4 (c,f) with magnifications of 200 \times (a-c) and 2000 \times (d-f).

5.2.4 Effect of relative humidity on flow properties

The flow properties of uncoated ibuprofen, and batches N3, N5 and N4 were measured in low (25 \pm 1 %), intermediate (52 \pm 5 %) and high (70 \pm 10 %) RH. The flow properties in low and intermediate RH did not show any significant difference (Figure 9). In high RH batches N3 and N5, which gained the largest benefit from the treatment, showed a clearly larger decrease in flow rate. This is an indicator of a change in surface hydrophilicity caused by the coating of hydrophilic HPMC, causing adsorbed vapour to affect flow behaviour (Faqih *et al.* 2007; Seppälä *et al.* 2010). This can be interpreted as a sign of differences in the extent of the coating.

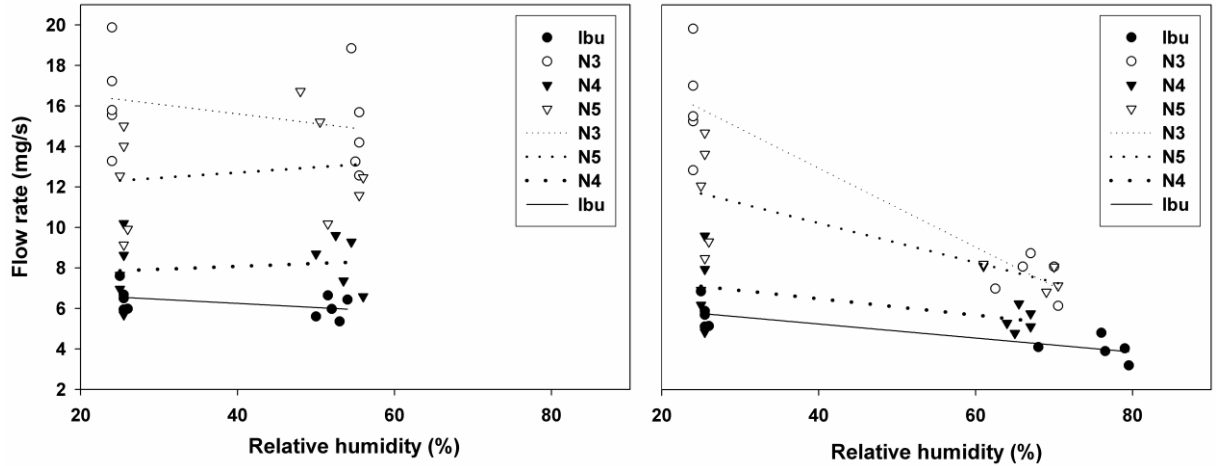


Figure 9. Flow rate of untreated (Ibu) and three batches of ibuprofen coated with hydroxypropyl methylcellulose (N3-N5) in different relative humidities.

5.3 Ultrasound assisted powder thin-coating (II)

5.3.1 Flow properties

The flow rate of treated ibuprofen powder improved with increasing amount or treatment cycles (Figure 10). The increase becomes more pronounced after 10 treatment cycles and ceases after 25 cycles. This can be seen as an indication of complete coverage by the coating polymer at 25 cycles.

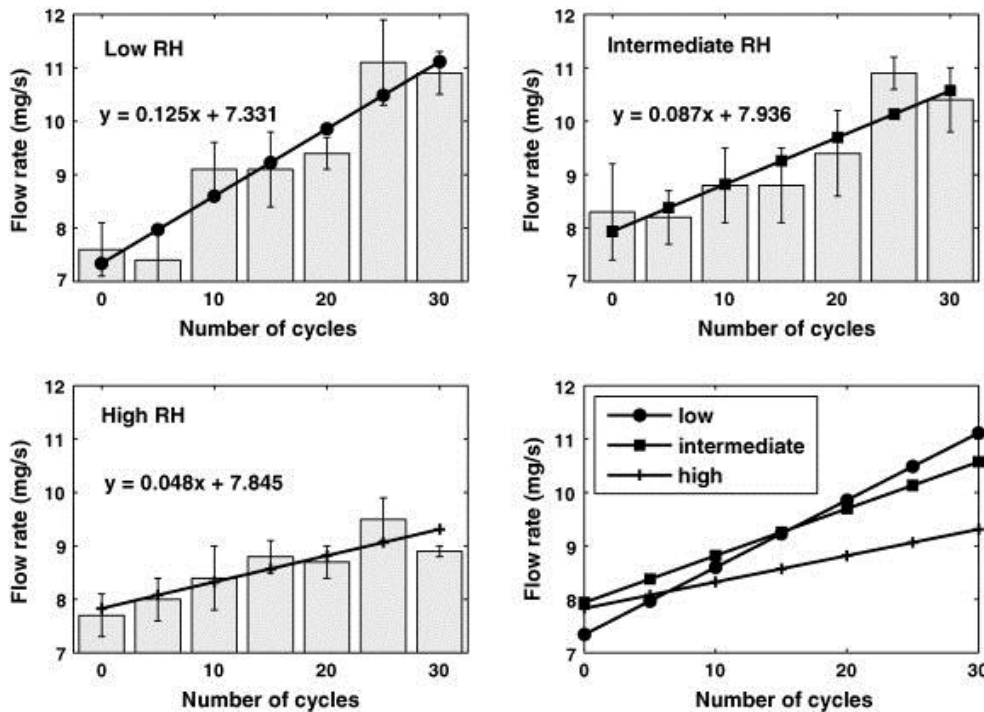


Figure 10. Flow rate (mg/s) of ibuprofen after 0-30 coating cycles with an ultrasound assisted coating technique. The measurements were performed in low, intermediate and high relative humidity.

The smoother surface results in less particle interlocking, which improves powder flow properties in addition to the changes in surface chemistry (Genina *et al.* 2009). The cycle dependent improvement in flow properties decreases with increasing RH, which can be interpreted as a result of change of vapour sorption characteristics caused by increased surface hydrophilicity due to the increase in extent of coating (Faqih *et al.* 2007; Seppälä *et al.* 2010). As stated in section 5.1.3 the results are applicable in *e.g.* direct compression of tablets.

5.3.2 Particle morphology and solid state properties

The processing did not have a major effect on the particle size distribution of ibuprofen powder. The slightly smaller particle size values obtained for the treated ibuprofen can be explained by reduced cohesiveness of the powder resulting in better dispersion when measuring with SFV (Adi *et al.* 2001; Ferrari *et al.* 2004). The surface roughness parameter derived from the results of AFM of the treated powder decreased clearly, which could be visually confirmed in SEM micrographs (Figure 11).

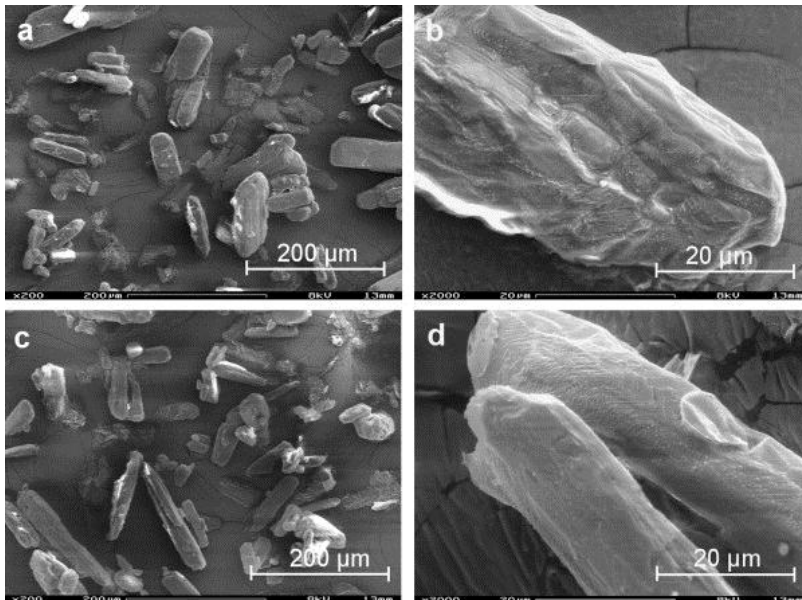


Figure 11. Scanning electron microscope micrographs of uncoated (a, b) ibuprofen and ibuprofen coated with hydroxypropyl methylcellulose (c, d) with magnifications 200x (a, c) and 2000x (b, d).

5.4 Pulsed liquid feed fluidised bed processing (III)

5.4.1 Data-analysis and modelling

The d_{50} -values of the granulated batches were fitted in to a second order polynomial expression with $R^2=0.997$ and $Q^2=0.909$, respectively (Table V).

Table V. Scaled factor coefficients and statistical significance (p). A=atomisation pressure [bar], D=duty cycle length [s] and RH = relative humidity [%]. **Statistical significances (p):** † > 0.05; * ≤ 0.05; ** < 0.01; *** < 0.001; N/S = not significant in the model

Factor	Scaled coefficients	p
Constant	$1.16 \cdot 10^2$	***
A	$-1.36 \cdot 10^1$	***
D	$-3.79 \cdot 10^0$	*
RH	$3.15 \cdot 10^0$	† ($5.19 \cdot 10^{-2}$)
A×A	N/S	N/S
D×D	$2.00 \cdot 10^1$	***
RH×RH	N/S	N/S
A×D	$-6.32 \cdot 10^0$	† ($5.10 \cdot 10^{-2}$)
A×R	$-5.26 \cdot 10^0$	† ($5.96 \cdot 10^{-2}$)
D×RH	$-1.03 \cdot 10^1$	**

As inlet air RH was included in the model, three response surfaces were constructed to illustrate the effect of RH on granule size (Figure 12). Process repeatability was found sufficient by comparing the triplicate centre point batches (9, 10 and 11). Batch 11 was slightly smaller than batches 9 and 10, which can be explained by the smaller RH during processing.

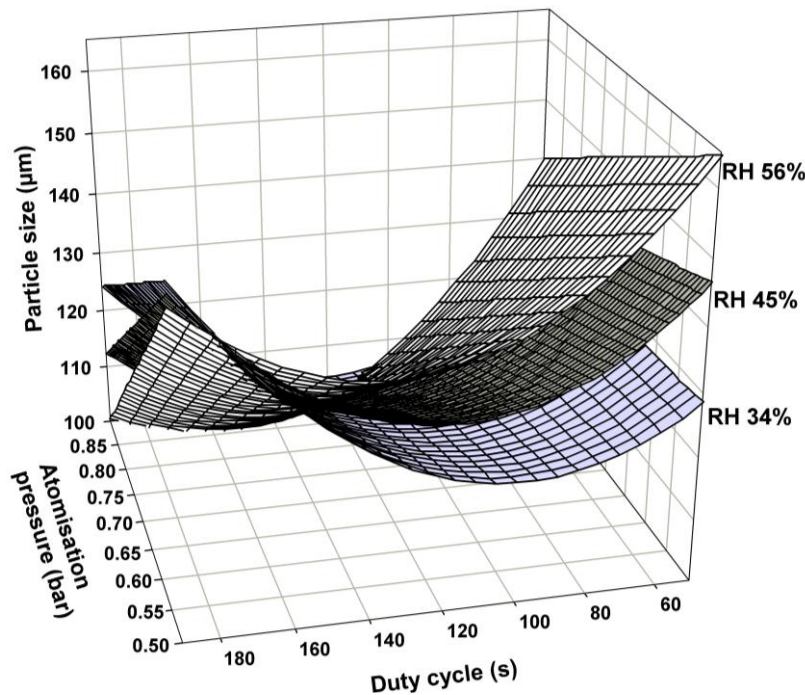


Figure 12. Effect of atomisation pressure (bar), duty cycle length (s) and relative humidity (RH) on particle size (μm) of granules granulated with pulsed liquid feed.

5.4.2 Effect of atomisation pressure on granule size

In the present study atomisation pressure affected granule size linearly (Figure 12), *i.e.* pulsed spray did not affect droplet formation or droplet particle interaction. Increased atomisation pressure has been found to result in decreased particle size (Davies and Gloor 1971; Schæfer and Wørts 1977a; Saleh *et al.* 1999). An increase in atomisation pressure decreases droplet size (Kim and Marshall 1971; Juslin *et al.* 1995b; Dewettinck and Huyghebaert 1999; Müller and Kleinebudde 2007), and decreased droplet size results in smaller granules (Schæfer and Wørts 1978b; Schaafsma *et al.* 1998, 2000) due to reduced wetting caused by the inferior ability of small droplets to penetrate compared to large droplets (Bouffard *et al.* 2005). In addition, increased atomisation pressure results in increased attrition (Saleh *et al.* 1999).

5.4.3 Effect duty cycle on granule size

The granule size as a function of DC duration forms a second order expression (Table V, Figure 12). This gives rise to a granule size minimum at certain DC durations. With a DC duration shorter than the minimum the wet granule mass can be assumed to not dry extensively enough to restrict growth, and with a DC duration longer than the minimum the granules are more thoroughly wetted promoting granule growth. Liquid feed pulsing facilitates evaporation and drying by elevating the bed temperature and can thus be used to control particle size without affecting granule density or flow properties (Närvänen *et al.* 2008).

The shear forces caused by the pressurised atomisation air were of importance in the present study, as the liquid feed was repeatedly interrupted exposing the granules to shear without wetting. This shear might cause granule attrition and granule breakage. All collisions cause attrition, which widens the size distribution resulting in higher agglomeration tendency (Guignon *et al.* 2002). Breakage occurs for both wet and dry granules (Iveson *et al.* 2001a; Verkoeijen *et al.* 2002). Liquid feed pulsing has been found to widen the granule size distribution, which is due to attrition and breakage (Närvänen *et al.* 2008). In the present study the drying time of the different batches did not vary in a systematic manner, partly due to fact, that the spraying phase end point, 100g of liquid consumption, was achieved in various stages into a DC. Taken together, the effect of DC length on granule size is a sum of wetting, drying, attrition and growth of the processed material.

5.4.4 Effect of inlet air relative humidity on granule size

Ambient air conditions affect fluidised bed process outcome (Dewettinck and Huyghebaert 1999). Increased RH leads to formation of liquid bridges between particles (Visser 1989) and thus leads to increased final product particle size and moisture content (Schæfer and Wørts 1978a; Lipsanen *et al.* 2007, 2008; Närvänen *et al.* 2008). In the present study the effect of atomisation pressure on granule size was pronounced in case of increased RH (Figure 13). The heat transfer coefficient in moist air is higher than that of dry air, which offers an explanation to this observation. In contrast to previous reports by other authors (Schæfer and Wørts 1978a; Lipsanen *et al.* 2007, 2008; Närvänen *et al.* 2008), both smaller and larger granules could be obtained in higher RH. The formation of smaller granules in higher RH can be explained by the higher heat transfer coefficient of moist air in comparison to dry air. The higher heat transfer coefficient allows the temperature of the granulate mass to increase faster, resulting in more efficient drying. In the literature this approach is supported both by experimental and computational studies (Lipsanen *et al.* 2007;

Wang *et al.* 2007). The pulsed liquid feed is essential in the presented approach, as increased RH has been proven to increase drying time in more conventional processes (Wang *et al.* 2007). Higher RH is also known to decrease the amount of electrostatic interaction (Bailey 1984; Guardiola *et al.* 1996), which also contributes to regulating particle growth. Taken together, the present study confirms that liquid feed pulsing can be used to regulate granule growth and to compensate for changes in inlet air RH (Närvänen *et al.* 2008). In addition, it strengthens the knowledge of the effects of RH on granule growth and brings further insight into the possibilities of pulsed liquid feed in granule growth regulation.

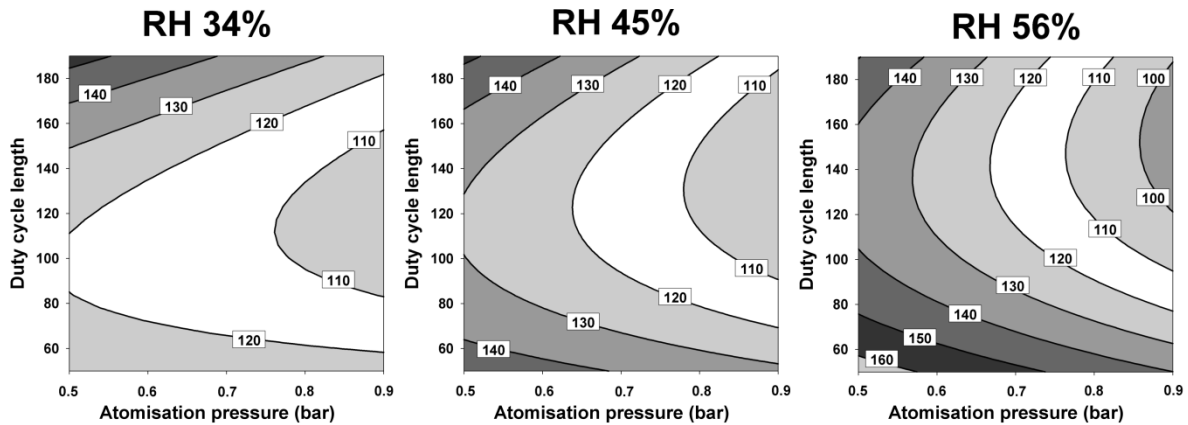


Figure 13. Effect of atomisation pressure (bar), duty cycle length (s) and relative humidity (RH) on particle size (μm) of granules granulated with pulsed liquid feed.

5.5 *In situ* characterisation (IV)

5.5.1 Modelling

The results were fitted in a second order polynomial expression. Droplet size and trajectory angle characteristics were normally distributed and droplet speed, droplet count and sum of droplet mass were log-normally distributed. The results show that DLS coupled with PTV is a suitable tool for measuring spray characteristics. Droplet velocity was not modelled, but droplet speed, as the obtained images contain data only on droplet dislocation, not direction of movement. For the same reason, droplet turbulence was modelled as trajectory angle, *i.e.* the difference in direction of movement in comparison to the vertical central axis of the spray.

5.5.2 Sum of mass and droplet count

The mass of the droplets was calculated and summed to give an estimate of the moisture profile along the vertical central axis of the spray. The mass of the droplets gave models with a $R^2=0.954$ and $Q^2=0.919$. The sum of masses decreases with increasing atomisation pressure and distance from the nozzle (Figure 14), which is in accordance with the literature (Mueller and Kleinebudde 2007). Implications of this has been found in granule properties; when decreasing the nozzle height the granule size has been reported to increase as friability decreases (Davies and Gloor 1971).

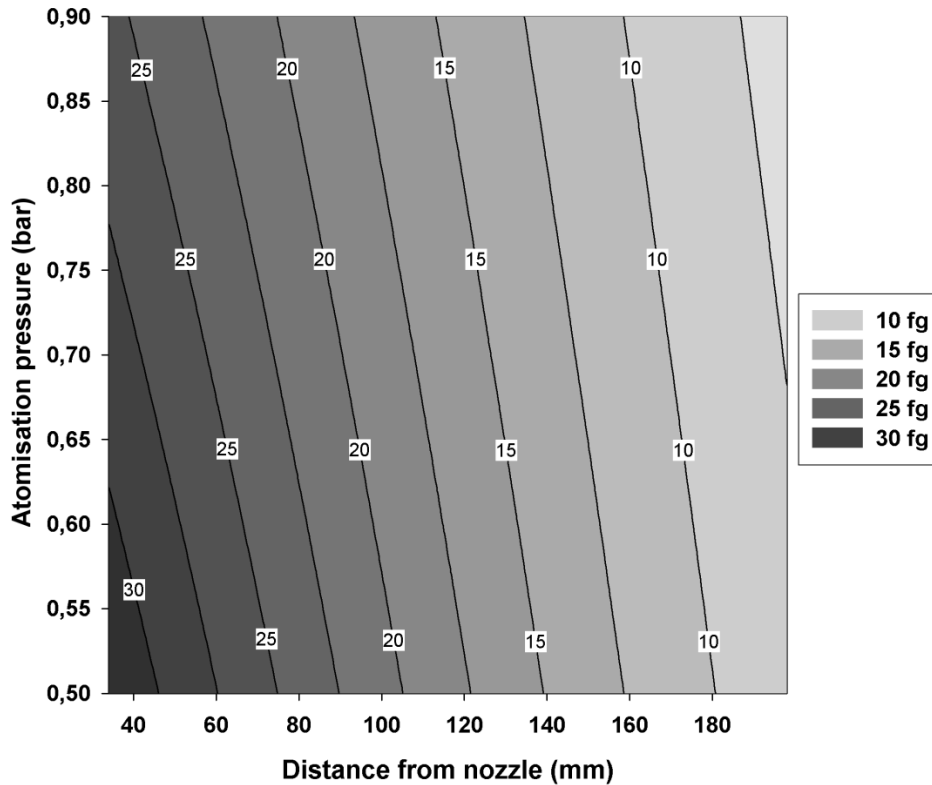


Figure 14. Effect of atomisation pressure and distance from nozzle on sum of masses of droplets measured with particle tracking velocimetry *in situ* in a fluidised bed granulator.

The amount of droplets detected was found to be independent of atomisation with $R^2=0.948$ and $Q^2=0.933$. The amount of droplets decreased with increasing distance from the nozzle, with a more pronounced decrease closer to the nozzle. This can be interpreted as a result of pronounced droplet coalescence followed by subtle evaporation. Droplet coalescence has previously been discussed as a phenomenon occurring in the spraying zone (Schaafsma *et al.* 2006), of which there are experimental implications the present study.

5.5.3 Droplet size

The results of the present study confirmed what is widely presented in the literature; an increase in atomisation pressure, or air to liquid mass ratio, results in decreased droplet size (Kim and Marshall 1971; Schæfer and Wørts 1977b; Juslin *et al.* 1995b; Bouffard *et al.* 2005; Mueller and Kleinebudde 2006, 2007) with an emphasis on d_{90} (Juslin *et al.* 1995b; Bouffard *et al.* 2005) as seen in Figure 15. With high atomisation pressures a plateau is reached after which droplet size is indifferent to further reductions in atomisation pressure (Kim and Marshall 1971; Wan *et al.* 1995; Mueller and Kleinebudde 2007). This behaviour is reflected in granule properties such as residual moisture and granule size (Behzadi *et al.* 2005; Saleh *et al.* 1999). The studied range of pressures in the present study was not wide enough to reach this plateau. An increase in atomisation pressure leads to increased spray width according to Mueller and Kleinebudde (2006) and decreases spray width according to Juslin *et al.* (1995a). As the present study focused on the vertical central axis of the spray, the effect of spray angle on the results cannot be confirmed.

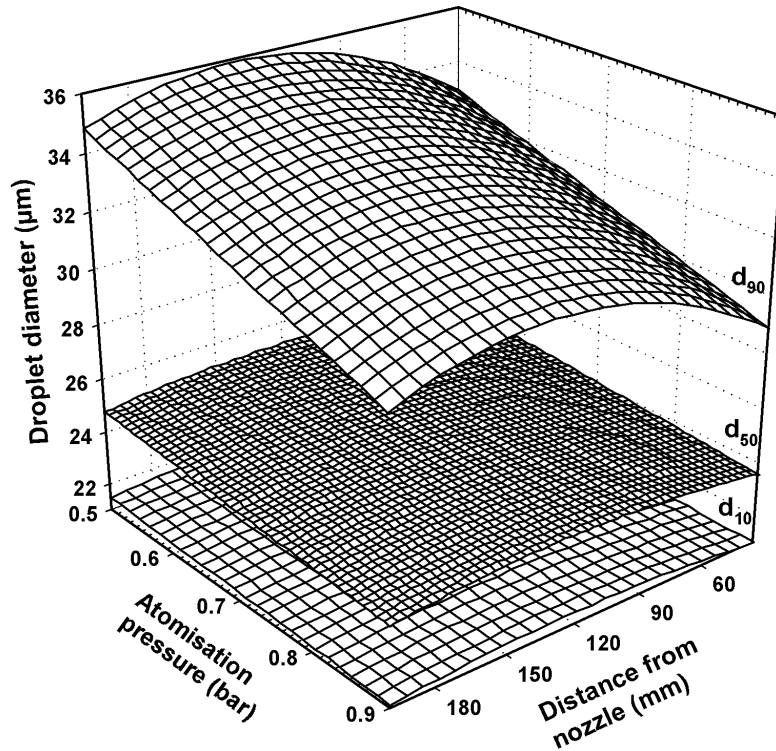


Figure 15. Droplet size characteristics (d_{10} , d_{50} and d_{90}) of droplets measured *in situ* in a fluidised bed granulator using particle tracking velocimetry.

The droplet size characteristics gave clearly weaker models than speed and trajectory angle characteristics. This might be due to noise caused by surface tension-related droplet pulsating and stretching as a result of atomisation. The d_{10} -value is close to the detection limit, which might cause inaccuracies in the results. Previously both bimodal and unimodal droplet size distributions have been reported by Juslin *et al.* (1995a) and Yuasa *et al.* (1996), respectively. In the present study no bimodality of the droplet size distribution was observed. The data on droplet size distribution width and relative width ($d_{90}-d_{10}$) ($d_{50}/(d_{90}-d_{10})$) could not be modelled, indicating a lack of systematic differences in these.

When moving down the chamber, the spray showed an initial increase in droplet size until 136 mm from the nozzle, after which there was a clear decrease in droplet size. This confirms the finding of droplet coalescence presented by Yuasa *et al.* (1996). In an ex-situ study an increasing gun-to-bed distance resulted in a subtle increase of droplet size (Müller and Kleinebudde 2007). Droplet size has been found to correlate with granule size (Schäfer and Wörts 1978b; Schaafsma *et al.* 1998; Schaafsma *et al.* 2000). Schaefer and Wörts (1977a) found that at short nozzle-to-bed distances granule size was clearly smaller than with intermediate distances. They further reported that granule size decreased at long distances. This confirms the droplet size findings of the present study. The increase in size can be explained by droplet coalescence and the oppositely directed air flow removing small droplets, which has previously been found in the *in situ* -study by Yuasa *et al.* (1996). The d_{50} values in the chamber have been found to be smaller than outside of the chamber by Yuasa *et al.* (1996). Inlet air temperature affects coating efficiency mainly by affecting premature droplet evaporation (Dewettinck and Huyghebaert 1998). Droplet drying has been suggested to consist of four steps: droplet heating without significant evaporation, evaporation without further change in temperature, formation of solid crust and heating of the dried particle

formed (Farid 2003). No evidence of dried solid droplets was found in the present study. Taken together, the present study shows that there is significant coalescence of droplets and that evaporation does not occur to a large extent.

5.5.4 Droplet speed

Droplet speed characteristics gave models with satisfactory R^2 and Q^2 . The droplet speed at the event of atomisation was independent of atomisation pressure (Figure 16). The differences in speed further down the vertical central axis of the spray were linear in relation to atomising pressure. The most significant changes were observed in the v_{90} -values. The result was logical in comparison to previous reports found in the literature (Saleh *et al.* 1999; Mueller and Kleinebudde 2007). The radial effects of the spray were not studied, but in previous studies by other authors droplet velocity has been found to be higher along the central axis of the spray than at the rim (Müller and Kleinebudde 2007).

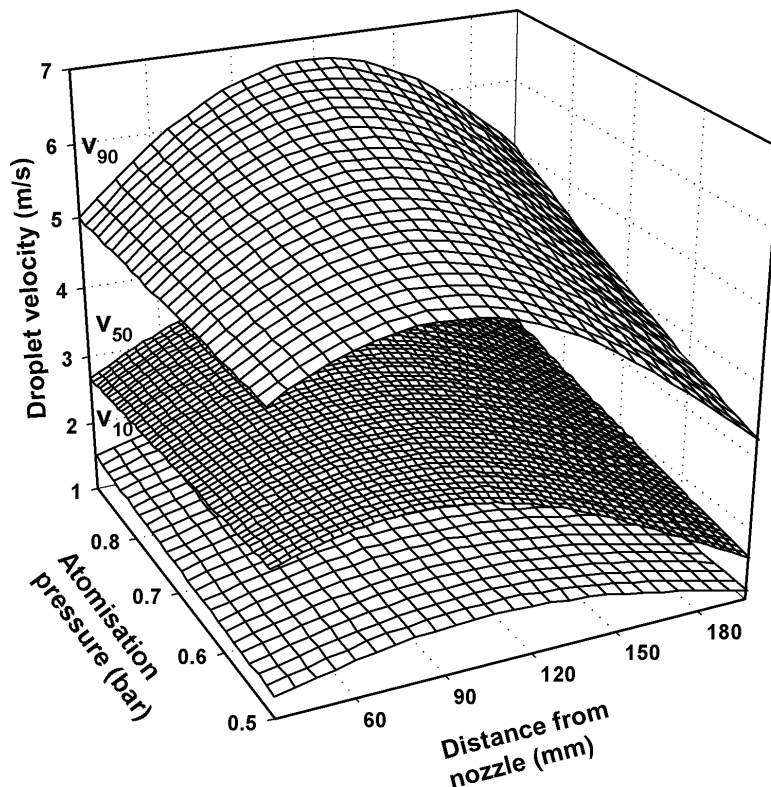


Figure 16. Droplet speed characteristics (v_{10} , v_{50} and v_{90}) measured from droplets *in situ* in a fluidised bed granulator using particle tracking velocimetry.

The droplet speed increased when proceeding down the vertical central axis of the spray (Figure 17). The increase occurred until 79-123 mm for atomisation pressures 0.42-0.98 bar. The initial increase in droplet speed can be interpreted as a result of droplet coalescence, and the extent to which the acceleration occurred can be seen as an indicator of the extent to which the atomising air reaches down the chamber. The increase in droplet speed is contradictory to the findings by Mueller and Kleinebudde (2007), but as their study was performed *ex situ* direct comparisons are difficult. After the initial acceleration, the droplet speed decreased with increasing distance from the nozzle. This was expected, as the increasingly narrow chamber diameter increases the velocity of the oppositely directed

fluidising air and evaporation reduces droplet mass and thus momentum. Droplet momentum has been described to increase with increasing atomisation pressure (Dewettinck and Huyghebaert 1998; Saleh et al. 1999). Droplet velocity affects impingement efficiency, droplet adhesion, coating efficiency and granule growth rate (Link and Schlünder 1997; Dewettinck and Huyghebaert 1998; Saleh et al. 1999; Guignon *et al.* 2002). Still, the effect of droplet velocity on process outcome is scarcely studied. The present study shows a correlation between droplet size and speed as a function of distance from the nozzle.

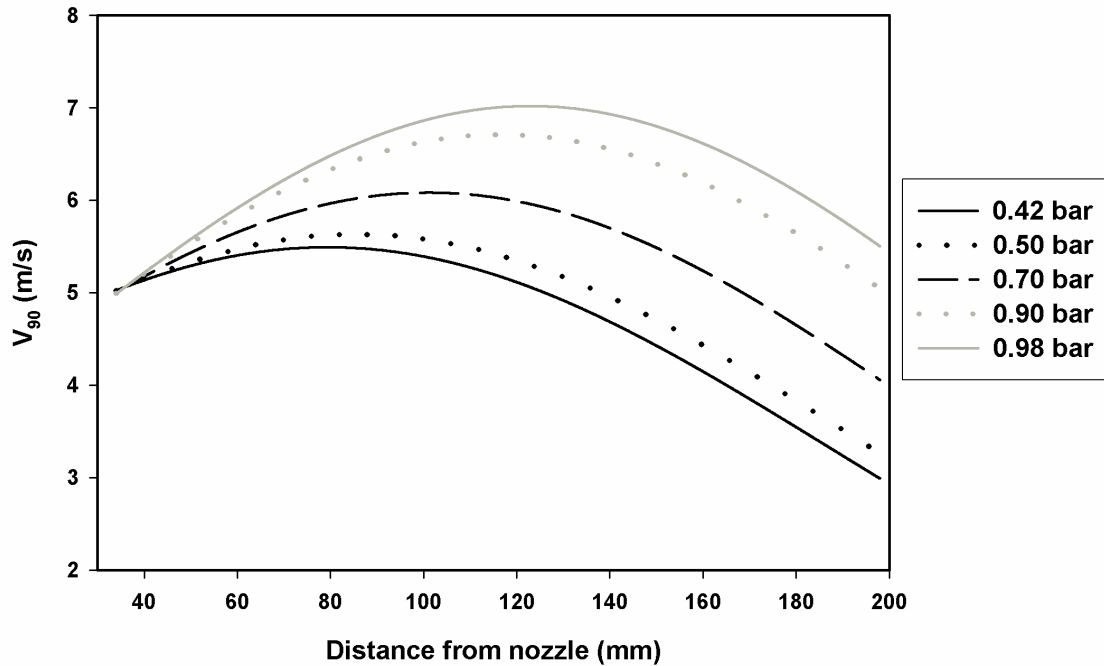


Figure 17. The 90%-fractile (v_{90} [m/s]) of the velocity distribution of droplets measured *in situ* in a fluidised bed granulator as a function of distance from the nozzle (mm) with varying atomisation pressure (bar).

5.5.5 Turbulence

The obtained models for droplet trajectory angle were of satisfactory Q^2 and R^2 . The turbulence was very high at the event of atomisation, as expected. The turbulence decreased with increasing distance from the nozzle until reaching a minimum at 122-155 mm for atomising pressures 0.42-0.98 bar, respectively (Figure 18). Further down the central axis of the spray turbulence expectedly increases. The turbulence increased linearly with increasing atomisation pressure. The droplets are expected to mainly move parallel to the vertical axis (Müller and Kleinebudde 2007), which holds true at the minimum turbulence values.

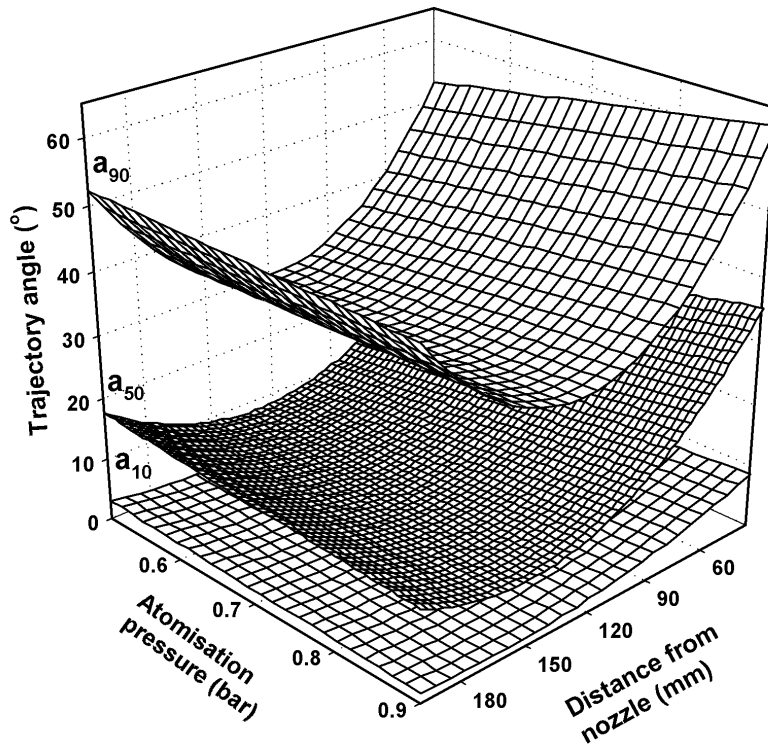


Figure 18. Droplet turbulence characteristics (a_{10} , a_{50} and a_{90}) measured from droplets *in situ* in a fluidised bed granulator using particle tracking velocimetry.

5.6 Light transmission (V)

5.6.1 Resolution and the effect of powder bed packing

In the repeatability measurements relative standard deviations of 0.6 % for the treated signal and 1.0 % and 0.2 % for the sum of the measuring points of the treated and untreated signals, respectively, were obtained. The average light transmission decreased as the number of measurements increased due to rapid changes in chamber movement at the outer limits of the chamber motion range. With theophylline granule size fraction 355-500 μm increased powder bed density caused the light transmission to decrease (Figure 19), indications of which have been reported by Rafaat *et al.* (1996), Djaoui and Crassous (2005) and Zivkovic *et al.* (2009).

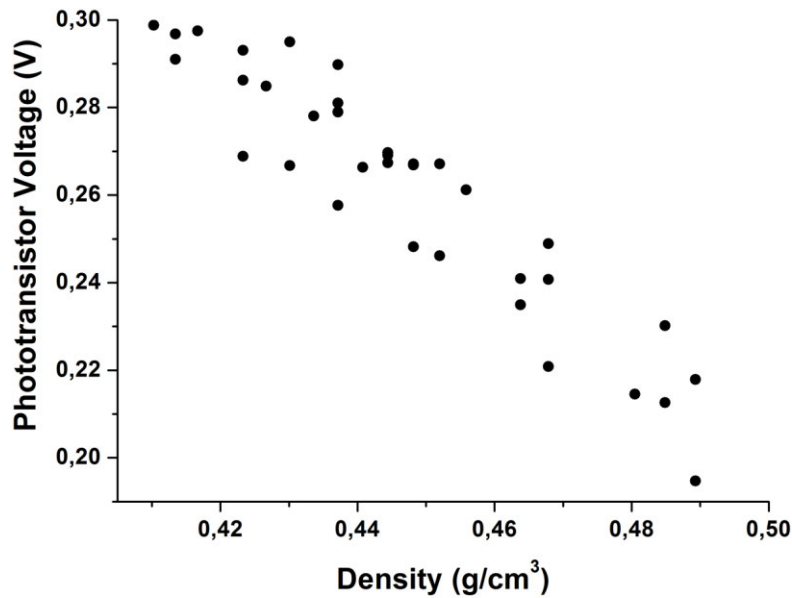


Figure 19. Effect of powder bed density on light transmission of theophylline granules of sieve fraction 355-500 μm .

The resolution measurements showed that, with the studied material, powder at the measuring height ± 4 mm contributes to the signal, giving a sample volume of 1.8 cm³.

5.6.2 Correlation between particle size, composition and light transmission

With glass ballotini, the particle size clearly affected the amount of light transmission (Figure 20). Still, no clear relation could be determined. The findings can be explained by the different colour tones exhibited by the samples, in addition to spherical glass particles acting as lenses. MCC pellets gave reasonable linear correlation, and theophylline granules gave a clear linear behaviour (Figure 20). There were slight deviations from the linear trend in very small particle size and at roughly 700 μm . When it comes to the small theophylline granules the deviations can be attributed to interparticle interactions, such as electrostatic and van der Waals interactions. The deviation at 700 μm could be due to wall effects extending far enough into the sample to affect the packing behaviour.

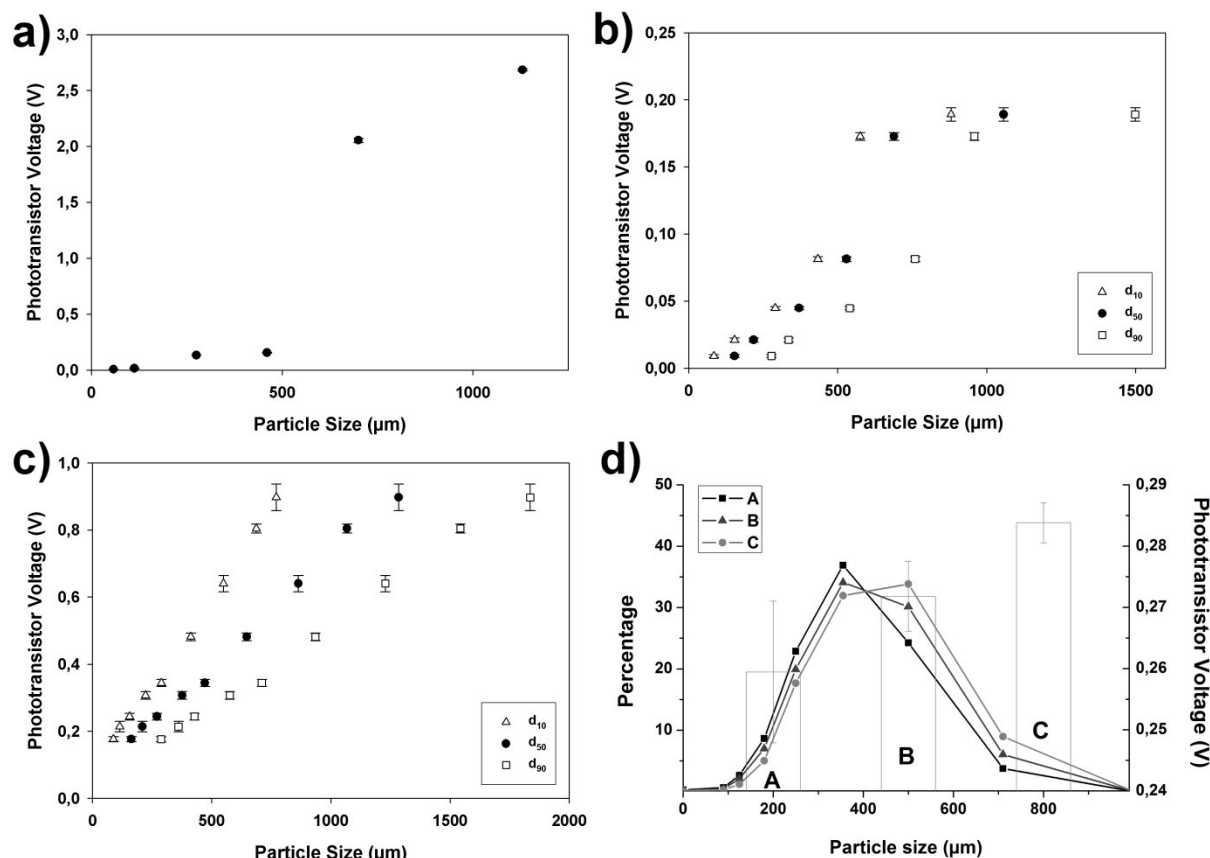


Figure 20. Correlation between light transmission and particle size with a) glass ballotini, b) microcrystalline cellulose pellets, c) theophylline granules and d) three blends of theophylline granules. For details on d), see Table III.

Light transmission was found to be able to differentiate samples of different size, as indicated by Mercado-Uribe & Ruiz-Suárez *et al.* (2009) in a previous study. Glass ballotini behaved irregularly due to the spherical shape and clarity causing lens-like behaviour. In addition, absence of colour in glass could not be verified. The results from the analysis of MCC pellets were more consistent. The second largest size fraction showed a deviation from the trend of the other fractions, to which no obvious explanation could be found. Theophylline granules showed a systematic behaviour. The measurements in the lower end of the particle size range showed positive deviations, possibly due to agglomeration caused by cohesion (Laitinen and Juppo 2003; Shekunov *et al.* 2007). Due to the erratic particle size results obtained with glass ballotini, the particle size data used in Figure 20 was the median of the sieve fractions reported by the supplier. The standard deviation of the measurements with glass ballotini was smaller than with MCC pellets and theophylline granules in all size fractions due to better flow properties and thus consistent packing of the sample. With all sample materials there was a discontinuity in the light transmission at the d_{50} -value of approximately 700-800 μm , which could be an indication of wall effects (Sederman *et al.* 2001)

The light transmissions of polydisperse theophylline granule blends A, B and C (Table II) were found to increase with increased particle size, although the polydispersity of the samples make the changes more subtle (Figure 20). Light transmission of binary blends of glass ballotini and MCC pellets decayed exponentially with increasing relative amounts of

MCC pellets (Figure 21). This is due to the differences in reflection and refraction affecting the scattering and transmission of light (Crassous 2007).

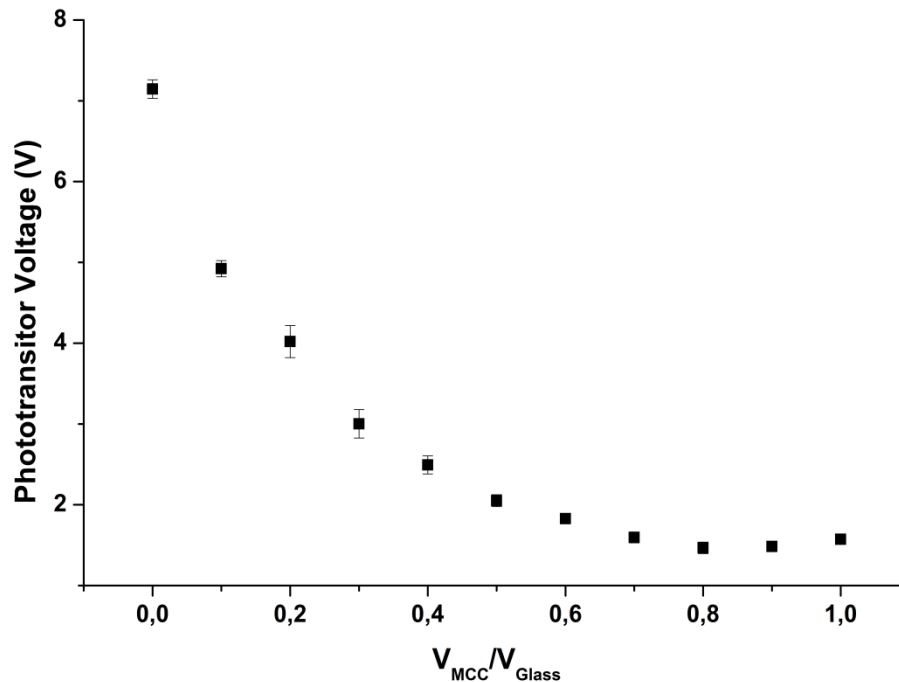


Figure 21. Light transmission of 11 blends of microcrystalline cellulose (MCC; $d_{50} = 220 \mu\text{m}$) and glass ballotini with a particle size of 230-320 μm (Table I) with volume ratios V_{MCC}/V_{Glass} of 0.0 – 1.0.

5.6.3 Advantages of light transmission analysis

Light transmission shows potential as a rapid, simple and inexpensive process analytical tool, which has been indicated by other authors in previous studies (Rafaat *et al.* 1996; Menon & Durian 1997). The technique is easily set up and requires minimal sample preparation. The result can be linked to suitable reference methods with no underlying assumptions in the data pre-treatment. The method is best suited for detecting changes in a process, showing potential to give enough information for elementary process diagnostics. There is a need for such in *e.g.* continuous blending, granulation and pneumatic conveying (Tenou and Poncelet 2002; Fokeer *et al.* 2004; Plumb *et al.* 2005; Vervaet & Remon 2005; Pernenkil & Cooney 2006; Bridgwater 2010).

5.6.4 Limitations of light transmission analysis

The limitations of the presented technique are mostly related to the powder bed density and measuring motionless non-dispersed particles. As the amount of particles within the light path changes, the light transmission varies accordingly (Weiner 1984; Jones 1999). All factors affecting packing behaviour, such as powder flow properties, particle shape, RH, electrostatic interactions *etc.* affect the light transmission. Furthermore, loose agglomerates are not detected correctly due to irregularities in particle packing and lack of dispersion. The method is not global. The obtained result does not contain absolute information on any particle characteristics. The light transmission needs to be linked to a suitable reference method. The method is highly dependent on pre-tests and knowledge on the process, sample variability and process environment.

6 Conclusions

This research clearly showed that by taking advantage of knowledge on interfacial phenomena in pharmaceutical particle modification processes the versatility of these processes and the knowledge on them can be improved.

The present study showed that ibuprofen powder with a median diameter of 40 μm belonging to the Geldart group C powders can successfully be coated in a fluidised bed with a top-spray setup without using fluidisation aids, in contradiction to previous reports found in the literature. The results also showed that the HPMC coating applied in a fluidised bed process and with a novel ultrasound assisted coating process was able to change the surface properties of the particles enabling statistically significantly improved powder flow. The response to change in RH correlated with the improvement in flow properties, indicating changes in surface hydrophilicity. Taken together, fluidised bed thin coating with HPMC can be used as a flow enhancer of ibuprofen powder.

Granule growth in a fluidised bed process was restricted by applying pulsed liquid feed. Previous studies with pulsed liquid feed have not concentrated on restriction of granule growth to nucleation, but this study shows that with pulsed liquid feed the size enlargement proceeded from formation of ordered mix to nucleation and early growth without undergoing further granule growth. In high RH the effect of pulsed liquid feed increased. In partial contradiction to previous studies, both smaller and larger granules were formed in high RH. This can be explained by higher heat capacity of moist air, which enables a higher bed temperature favouring liquid evaporation. Consequently, pulsed liquid feed can be used to compensate for changes in RH of the inlet air.

PTV coupled with DLS was found to give process relevant information on spray characteristics measured *in situ* in a fluidised bed process. The results show droplet coalescence as the droplets proceed away from the nozzle head. Contradictory to previous findings, the droplet speed initially increased with increasing distance to the nozzle. This can be seen as further evidence of droplet coalescence. The measured droplet trajectory angles showed where the droplet trajectories are most favourable for droplet particle impact in addition to which extent the fluidising air reaches down the chamber.

In the present study diffuse visible light transmitted through a motionless powder bed showed to carry information on the characteristics of the powder sample. Light transmission showed to be a suitable method for basic particle systems characterisation in terms of particle size, packing density and blend composition.

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