Division of Pharmaceutical Technology
Faculty of Pharmacy
University of Helsinki
Finland

Process Analytical Technology Approach on Fluid Bed Granulation and Drying

Identifying Critical Relationships and Constructing the Design Space

Tanja Lipsanen

ACADEMIC DISSERTATION

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Supervisors: Professor Jouko Yliruusi
Division of Pharmaceutical Technology
Faculty of Pharmacy
University of Helsinki
Finland

Dr. Osmo Antikainen
Division of Pharmaceutical Technology
Faculty of Pharmacy
University of Helsinki
Finland

Dr. Sari Airaksinen
Division of Pharmaceutical Technology
Faculty of Pharmacy
University of Helsinki
Finland

Reviewers: Professor Jukka Rantanen
Department of Pharmaceutics and Analytical Chemistry
Faculty of Pharmaceutical Sciences
University of Copenhagen
Denmark

Docent Eetu Räsänen
Central Hospital of South Karelia, Pharmacy
Lappeenranta
Finland

Opponent: Docent Jukka-Pekka Mannermaa
Oy Verman Ab
Kerava
Finland

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Abstract

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Fluid bed granulation is a key pharmaceutical process which improves many of the powder properties for tablet compression. Granules of high quality can be obtained by understanding and controlling the critical process parameters by timely measurements. Physical process measurements and particle size data of a fluid bed granulator that are analysed in an integrated manner are included in process analytical technologies (PAT). Recent regulatory guidelines strongly encourage the pharmaceutical industry to apply scientific and risk management approaches to the development of a product and its manufacturing process. The aim of this study was to utilise PAT tools to increase the process understanding of fluid bed granulation and drying.

Inlet air humidity levels and granulation liquid feed affect powder moisture during fluid bed granulation. Moisture influences on many process, granule and tablet qualities. The effect of inlet air humidity and granulation liquid feed on the temperature measurements at different locations of a fluid bed granulator system were determined. This revealed dynamic changes in the measurements and enabled finding the most optimal sites for process control. The moisture originating from the granulation liquid and inlet air affected the temperature of the mass and pressure difference over granules. Moreover, the effects of inlet air humidity and granulation liquid feed rate on granule size were evaluated and compensatory techniques used to optimize particle size. Various end-point indication techniques of drying were compared. The ΔT method, which is based on thermodynamic principles, eliminated the effects of humidity variations and resulted in the most precise estimation of the drying end-point. The influence of fluidisation behaviour on drying end-point detection was determined. The feasibility of the ΔT method and thus the similarities of end-point moisture contents were found to be dependent on the variation in fluidisation between manufacturing batches.

A novel parameter that describes behaviour of material in a fluid bed was developed. Flow rate of the process air and turbine fan speed were used to calculate this parameter and it was compared to the fluidisation behaviour and the particle size results. The design space process trajectories for smooth fluidisation based on the fluidisation parameters were determined. With this design space it is possible to avoid excessive fluidisation and improper fluidisation and bed collapse. Furthermore, various process phenomena and failure modes were observed with the in-line particle size analyser. Both rapid increase and a decrease in granule size could be monitored in a timely manner. The fluidisation parameter and the pressure difference over filters were also discovered to express particle size when the granules had been formed. The various physical parameters evaluated in this thesis give valuable information of fluid bed process performance.

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Helsinki, October 2008

Tanja Lipsanen

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List of original publications

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals (I-V).

I Lipsanen, T., Antikainen, O., Räikkönen, H., Airaksinen, S., Yliruusi, J., 2007. Novel description of a design space for fluidised bed granulation. Int. J. Pharm. 345, 101-107.

II Lipsanen, T., Antikainen, O., Räikkönen, H., Airaksinen, S., Yliruusi, J., 2008. Effect of fluidisation activity on end-point detection of a fluid bed drying process. Int. J. Pharm. 357, 37-43.

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

IV Närvänen, T., Lipsanen, T., Antikainen, O., Räikkönen, H., Heinämäki, J., Yliruusi, J., 2008. Gaining fluid bed process understanding by in-line particle size analysis. J. Pharm. Sci. DOI: 10.1002/jps.21486. In Press.

V Lipsanen, T., Närvänen, T., Räikkönen, H., Antikainen, O., Yliruusi, J., 2008. Particle size, moisture, and fluidization variations described by indirect in-line physical measurements of fluid bed granulation. AAPS PharmSciTech. DOI: 10.1208/s12249-008-9147-4. In Press.

Abbreviations

API	active pharmaceutical ingredient
ASTM	Americal Society for Testing of Materials
CCC	central composite circumscribed
CCF	central composite face-centered
CCP	critical control point
CPP	critical process parameter
cGMP	current good manufacturing practices
CPAC	Center for Process Analytical Chemistry
CPACT	Center for Process Analytics and Control
CTD	common technical document
CQA	critical quality attribute
ΔT	deltaT
Dev.	development
DoE	design of experiments
EFPIA	European Federation of Pharmaceutical Industries Associations
FDA	Food and Drug Administration
FMEA	failure mode effects analysis
FMECA	failure mode, effects and criticality analysis
FTA	fault tree analysis
HACCP	hazard analysis and critical control points
HAZOP	hazard operability analysis
ICH	International Conference on Harmonisation
IR	infrared
ISPE	International Society for Pharmaceutical Engineering
LOD	loss on drying
MCEC	Measurement and Control Engineering Center
Mgmt.	management
NIRS	near infrared spectroscopy
PAC	process analytical chemistry
PAT	process analytical technology
PHA	preliminary hazard analysis
PLS	partial least squares
QbD	quality by design
R&D	research and development
RH	relative humidity
RSM	response surface modelling
SFT	spatial filtering technique
T/temp.	temperature
U_{mb}	minimum bubbling velocity
U_{mf}	minimum fluidisation velocity

1. Introduction

The pharmaceutical industry is encouraged to use the latest scientific achievements to improve the quality and efficiency of the manufacturing processes (FDA, 2004; ICH Q8, 2005; ICH Q9, 2005). Protection of the patient is the ultimate goal. Compared to conventional approaches, the use of quality by design (QbD) principles during product development provides opportunities to facilitate innovation and continual improvement throughout a product's lifecycle (Garcia *et al.*, 2008). Process analytical technologies (PAT) are utilised to ensure final product quality by designing, analysing, and controlling manufacturing through timely measurements of critical quality and performance attributes of materials and processes.

Scientific understanding facilitates the establishment of a design space. This is defined as 'multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality' (ICH Q8, 2005). Operating within a design space will result in a product meeting the quality attributes designed. There are many scientifically justifiable approaches towards achieving a design space (Lepore and Spavins, 2008). Measuring and analysing the solid state properties during processing can be remarkable in determining the performance of a final product. Formal experimental designs can be used to identify critical and interacting variables that might be important for constructing the design space and ensuring the quality of the drug product. The ICH Q8 guideline (2005) states that the unexpected results of pharmaceutical development studies can be useful in constructing the design space. The pharmaceutical industry is advised to determine the design space initially during the product development through an iterative process (Fig. 1).

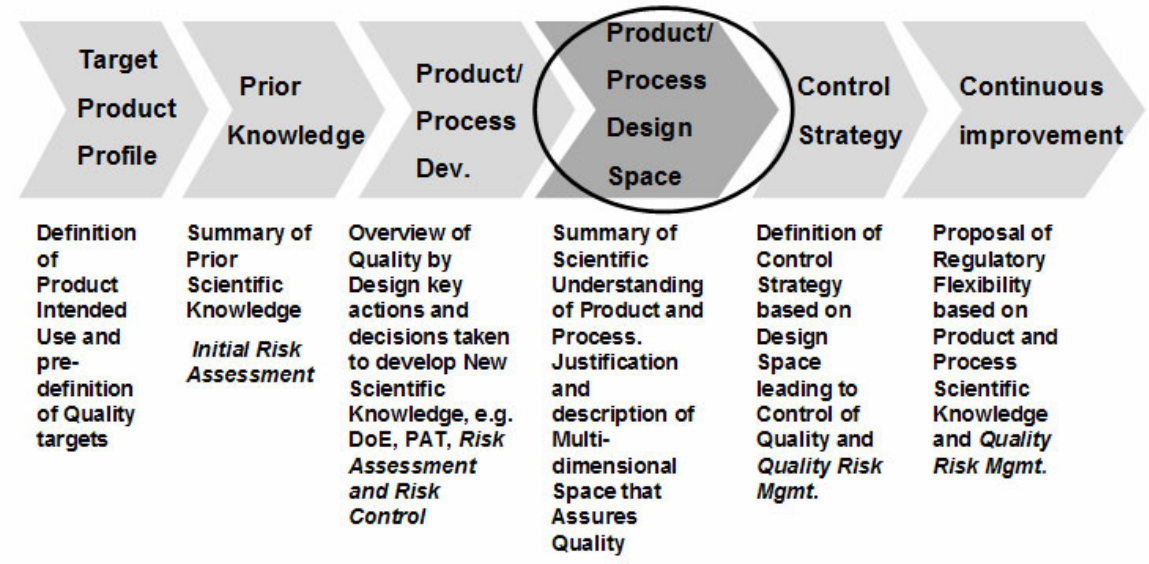

Fig. 1. Design space in the flow of development (represents the view of EFPIA PAT working group), modified from Lepore and Spavins (2008).

Methods such as chemical, physical, microbiological, mathematical, and risk analyses performed in an integrated manner are included in PAT tools (FDA, 2004). These tools include process analysers, process control tools, multivariate methods and knowledge management systems. Ideally, PAT principles and tools should be introduced during the development phase of a drug product. The level of relevant scientific knowledge determines the degree of regulatory flexibility (ICH Q8, 2005), i.e. reduction of post-approval submissions and reduction of end-product release testing. Benefits, such as reduced operating costs and quality improvements, directly impact on an organization's profits (Scott and Wilcock, 2006).

Gaining a deep and fundamental understanding of the manufacturing processes is at the heart of PAT (Davies and Ellis, 2005). Identifying and explaining all critical sources of variability, managing variability by the process, and predicting product quality attributes over the design space are indications that a process is well understood (FDA, 2004). The process understanding enables process control, optimisation and end-point control and improves efficiency. PAT tools help to identify process variables that may be critical to product quality and performance. These tools may also identify potential failure modes and quantify their effects on product quality. Process signatures provided by sensors may also be linked to product and process quality and thereby can be used to monitor and control the process and determine the end-point. A process end-point is the achievement of the desired material attribute within the PAT framework.

Most solid products in the pharmaceutical industry are manufactured using the wet granulation process. Fluidised (fluid) bed granulation is an established choice for improving the processing properties of pharmaceutical powders, such as flow characteristics and tablet compaction (Kristensen and Schaefer, 1987). As many other pharmaceutical processes, fluid bed granulation is a complex multi-factorial system. The effects of the critical parameters on the fluid bed process and on its critical quality attributes including moisture and particle size are important to identify and control. Physical process measurements of a fluid bed granulator analysed in an integrated manner are essential in process understanding, implementing PAT principles and constructing the design space. Monitoring the material behaviour in a fluidised bed has traditionally relied on the observational ability and experience of an operator. There has been a lack of good criteria for characterising material behaviour during spraying and drying phases, even though the entire performance of a process and end product quality are dependent on it.

The approach in this thesis was to identify sources of variation that are mainly related to moisture. The aim was to determine correlations and relationships, and utilise the PAT and design space concepts for the fluid bed granulation and drying. Physical in-line measurements (i.e. temperature, air flow rate) and various particle size determinations were used to increase process understanding. This approach is consistent with recent guidelines for highlighting continuous improvement in manufacturing processes.

2. Literature review

2.1 Design of fluidised bed systems

Fluid bed granulation (incl. mixing, wetting and drying), and wet massing in a high shear mixer with subsequent fluid bed drying, are the two most important methods to produce granules for pharmaceutical manufacturing (Schæfer, 1988; Wørts, 1998). Fluid bed granulating and drying operations use the same mechanical principle by which air is drawn through the machine (Olsen, 1989). The airflow generally is created by turbine fan suction located at the exhaust end (Fig. 2). First air enters through the air handler, where it is conditioned for the process and then it is drawn into the product processing area. The design of the gas distributor plate is essential for the optimum behaviour of the material in a fluidising process (Geldart and Baeyens, 1985). Filter bags separate the product from the process air before the air exits into the atmosphere through an outlet air duct. The ideal filter material should retain all of the product particles in the container while allowing process air to pass through (Parikh, 1991).

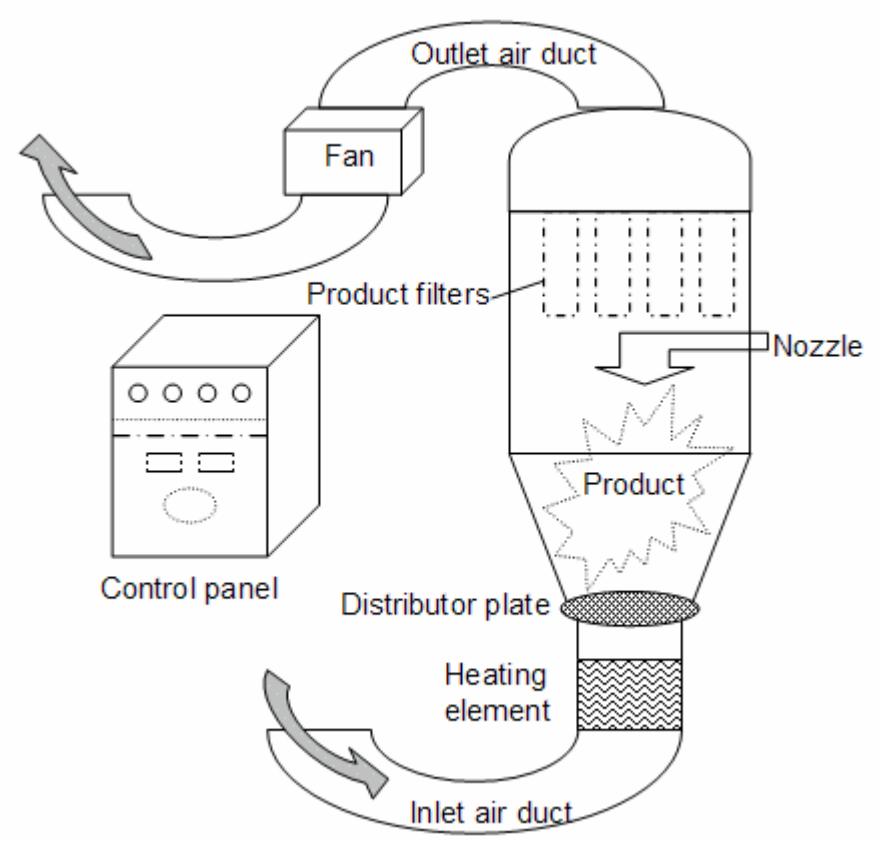

Fig. 2. Diagram of a traditional fluid bed processing system.

A high-shear mixer can be placed in-line with a fluid bed processor. After the mixture is granulated in a high-shear mixer, the dense material is transported to the fluid-bed dryer to dry. These two unit operations and the transfer between them can be controlled by a single controller (Parikh, 1996).

The current objective is to have an air-handling unit, which can produce air of consistent quality with the desired dew point throughout the year (Parikh, 1996). In general, a high degree of control over the temperature and humidity of the process airstream results in fewer problems with batch-to-batch reproducibility (Westrup, 1996). In the most sophisticated systems the process air can be heated, cooled, humidified, dehumidified and filtered as it enters the fluid bed unit's air-handling system.

It is also becoming common to monitor and control fluid bed process with such systems that utilise near infrared spectroscopy (NIRS) (Frake *et al.*, 1997; Rantanen *et al.*, 1998 a,b; Rantanen *et al.* 2000 a,b; Findlay *et al.*, 2005; Green *et al.*, 2005). Moisture, particle size and polymorphic changes have especially been monitored in fluid bed system with NIRS.

2.2 Fluidisation behaviour

The mixing effect of a fluid bed process is considered to be generally good for particles between 50 and 2000 μm (Law and Mujumbar, 2007). For fluidised bed operations, good particle mixing is essential and therefore knowledge on particle fluidisation characteristics is required to ensure good performance of fluid bed process. Fluidisation behaviour is a summation of various interactions and interparticle forces (Visser, 1989). The van der Waals forces have been established to be dominant during powder handling and fluidisation, but the electrostatic forces also have a great influence on the behaviour of the process. Other potential forces are liquid and solid bridges. The interactions, in which the interparticle forces may appear, are particle-particle, particle-chamber, and particle-gas interactions. Two approaches, minimum fluidisation velocity U_{mf} and Geldart classification, are generally accepted as having the capability to predict and characterise the fluidisation behaviour of the solids (Kunii and Levenspiel, 1991).

U_{mf} is used in quantifying one of the particle properties in a fluid bed (Pell and Dunson, 1999; Räsänen *et al.*, 2003, 2004; Sobrino *et al.*, 2008; Formisani *et al.*, 2008). This term refers to a stage, at a certain velocity, the elevating force of upward moving gas counterbalances the weight of the bed (Kunii and Levenspiel, 1991). At this point, the pressure drop across the bed equals the weight of the bed. The flow required to maintain a complete homogeneous bed of solids in which coarse or heavy particles will not segregate from the fluidised portion, is very different from the minimum fluidising velocity. After the bed has been fluidised and the velocity of air increased, the pressure drop across the bed stays constant but the height of the bed continues to increase. The design of distributor plate and the optimal pressure drop over it, are the most important factors in fluid bed

design in relation to fluidisation (Whitehead, 1981; Geldart and Baeyens, 1985). Räsänen *et al.* (2003, 2004) found that the pressure difference over the granules as a function of velocity of the process air was a parameter expressing fluidisation behaviour.

Geldart classification consists of four groups that are characterised by the density difference between solid and gas, and the mean particle size of the solid phase (Geldart, 1973). From the smallest to largest particle, they are as follows: C, A, B, D. Geldart class C materials are cohesive and very fine powders. The inter-particle forces in this group are stronger than those resulting from the gas flow and that leads via channelling to turbulent fluidisation. Aeratable Geldart class A materials fluidise easily and the beds of powders in this group expand considerably before bubbling takes place. Fluid beds of 'A' powders that are operated at gas velocities above the U_{mf} but below the minimum bubbling velocity (U_{mb}) are said to be particulately fluidised (Kunii and Levenspiel, 1991). As the gas velocity is increased above U_{mf}, the bed further expands. The bed is fully particulately fluidised at some point, usually at high pressure. Class B powders expand only a little before bubbling takes place and these solids fluidise easily. Bubbling occurs slightly above the minimum fluidisation velocity U_{mf}. The bubbles are small and they coalesce as they rise through the bed. Class D particles are large and the gas velocity in the dense phase is high, which results in poor mixing of these solids. Moreover, an enormous amount of fluidised gas is needed to fluidise these solids. Bubbles in the bed coalesce rapidly and grow to large size. The behaviour of bed is often described as spouting with these particles.

The most important variable, when considering fluidisation during the spraying phase, is the gas velocity i.e. the inlet airflow (Whitehead, 1981). The inter-particle forces required to cause de-fluidisation are very small and, when operated at velocities only slightly in excess of incipient, the bed collapses or 'freezes' due to over-wetting and uncontrollable granule growth (Rambali *et al.*, 2001a, 2003). Under certain circumstances, static charges may result in freezing even when high air velocities are used. Mechanical agitation in a rotary fluid bed granulator enables the fluidization of materials with poor fluidisation characteristics and to increase the moisture content of the bed (Jones, 1985; Kristensen and Schaefer, 1987; Türkoğlu *et al.*, 1995).

2.3 Principles of fluid bed granulation

The first pharmaceutical experiments of fluid bed granulation were made by Wurster (1959, 1960) and ever since much effort has been focused on developing, studying and utilising this method. (Davies and Gloor Jr., 1971, 1972; Ormós, 1973; Schæfer and Wørts, 1977, 1978a,b; Record, 1980; Schwartz, J.B., 1988; Banks and Aulton, 1991; Merkku *et al.*, 1992; Abbaerger *et al.*, 1996a; Juslin and Yliruusi, 1996a,b; Kristensen and Schaefer, 1987; Rantanen *et al.*, 2000c; Räsänen *et al.*, 2004; Bouffard *et al.*, 2005).

The basic reasons for wet granulation are to:

(1) render material free-flowing
(2) densify materials
(3) prepare uniform mixes which do not segregate
(4) improve the compression characteristics of a drug
(5) control the rate of drug release
(6) facilitate volume dispensing
(7) reduce dust
(8) improve the appearance of a product
(9) reduce variations in different batches of raw materials.

The wet granulation process can generally be viewed as a combination of three rate processes (Iveson *et al.*, 2001):
(1) wetting and nucleation
(2) consolidation and growth
(3) attrition and breakage.
Each of the above is affected by the process parameters. Consequently, fluid bed granulation is considered a fairly complex process.

The volume of granulating liquid needed depends mainly on the solubility of the drug and/or excipients. Insoluble drugs require larger volumes of granulating liquid than soluble drug preparations (Abdel-Alim *et al.*, 1986). It is usually assumed that satisfactory granulation requires 100% liquid saturation, but there is considerable variation (Kristensen and Schaefer, 1987). Particle size distribution, particle shape, surface roughness, and liquid, equipment and process characteristics all affect the amount of liquid required.

Binder is an essential part of a granulating liquid. Most binding agents used for wet granulations are hydrophilic in nature. In normal circumstances, spreading of fluids on hydrophobic surfaces is limited, but in the granulation process spreading is promoted by the efficient mixing action and the (normally) low surface tension of the binder fluids (Cutt *et al.,* 1986). It is generally recognized that hydrophobic drug surfaces can be changed towards a more hydrophilic character by granulation with water-soluble binders. Binder quality and quantity affect average granule size, granule friability, interparticulate porosity, and granule flowability (Davies and Gloor Jr., 1972; Alkan and Yuksel, 1986). While binders increase the bulk density of material and reduce porosity of powder, they also diminish the effective surface for area for evaporation and thereby increase the time needed for drying (Bhutani and Bhatia, 1975). The distribution of the binding agent within the granule controls both the intra-granular particulate adhesion, and the inter-granular compression: hence the resultant tablet properties.

Average particle size and size distribution are the two of the principal factors involved in the agglomeration of moist particles (Newitt and Conwey-Jones, 1958). Liquid binder can spread on the granule surface, evaporate, or be absorbed into the porous powder structure. It can also migrate to the surface upon collision with other granules, and that greatly affects the granulation mechanism and the granule growth profile (Bouffard *et al.*, 2005). As a result of collisions and coalescence between the surface-wetted powder particles,

liquid bridges are formed and nucleation of particles occurs leading to the growth of granules (Iveson *et al*., 2001). The granule growth stages are categorized as nucleation, transition, steady state and ball growth (Wørts, 1998; Summers and Aulton, 2002). Moreover, all these processes might occur simultaneously (Iveson *et al*., 2001). A low growth rate in the transition region is advantageous from a product point of view, resulting in good reproducibility. On the other hand, ball growth is usually undesirable. After evaporation of liquid in the drying phase, the particles are held together by solid bridges resulting from the hardening of binders, crystallization of dissolved substances or deposition of suspended particles (Schæfer and Wørts, 1978c).

The theoretical prediction of average particle size and size distribution is difficult since the exact mechanism by which the size enlargement occurs is not fully understood. Therefore the monitoring of granule size during the fluid bed processing is justified (Cooper and Clough, 1985; Hu *et al.*, 2008). Particle size of a granulation is an important attribute to analyse, because particle size affects physical properties such as powder flow, dissolution rate, compression, and tablet hardness. It is important to be aware that various particle size instruments yield significanly different particle size distributions for the same material (Etzler and Sanderson, 1995).

2.4 Fluid bed drying process

2.4.1 Reasons for fluid bed drying

The aim of the pharmaceutical drying process is to remove part of the water contained in a granulation to obtain the moisture level best suited to the subsequent process of compression (Terrier de la Chaise and LePerdriel, 1972).

O'Reilly (1997) has listed general reasons for drying:
(1) prevent the degradation of moisture sensitive drugs, e.g. ascorbic acid
(2) improve flowing properties of powders
(3) facilitate handling
(4) eliminate microbiological contamination.

The fluid bed dryer provides significant advantages over the conventional tray dryer traditionally used in the pharmaceutical industry (Scott *et al.*, 1963). These advantages include:
(1) increased rates of drying and product throughput, accompanied by significant improvements in thermal efficiency
(2) increased drying capacities per unit of floor space
(3) increased ability to control product temperature during drying and the facilitation of the handling of heat sensitive materials
(4) decreased handling costs resulting from simplified loading and unloading operations

(5) simplification of tablet manufacturing procedures by possible elimination of grinding steps.

High heat transfer, mass transfer and drying rates are thus obtainable in fluid bed systems. Heat transfer is at least 28 times more effective in a fluid bed dryer than in a tray dryer (Scott *et al.*, 1963). Thereby fluid bed drying of tablet granulations is estimated to be at least 15 times faster than tray drying procedures. In addition, turbulent systems of fluid bed give rise to good mixing, and as a consequence, uniform bed temperature verifies that local areas of overheating can be completely eliminated.

2.4.2 State of water in granular material

Free moisture exists in the bed of bulk solids in three different forms: capillary, funicular and pendular (Newitt and Conwey-Jones, 1958). The water contained in the granular material before the drying phase originates from the three sources (Terrier de la Chaise, 1972):
(1) constitutive (hydrate) water
(2) adsorption water
(3) added water.
Water distribution in the granules is described in terms of four different modes (Terrier de la Chaise, 1972):
(1) surface water
(2) capillary water
(3) swelling water
(4) crystalline (hydrate) water.

Bound moisture in a solid is a liquid that exerts a vapour pressure less than that of the pure liquid at a given temperature (Moyers and Baldwin, 1999). Liquid may become bound by retention in small capillaries, by solution in cell or fiber walls, by its homogeneous solution throughout the solid, or by chemical or physical adsorption onto solid surfaces. Unbound moisture in a hygroscopic material is that moisture in excess of the equilibrium moisture content corresponding to saturation humidity. Practically all water in a nonhygroscopic material is unbound water. Free moisture content is that liquid which is removable at a given temperature and humidity. It may include bound and unbound moisture. Both the active pharmaceutical ingredients (APIs) and excipients in the formulation have different moisture sorption properties. The more amorphous excipient is used in the formulation the more water is absorbed into the structure of the material.

Crystalline solids can exist in the form of polymorphs, solvates or hydrates (Vippagunta *et al.*, 2001). Water is able to interact with crystalline solids in three major ways: adsorption of water vapour onto solid at the solid-air interface, crystal hydrate formation, and deliquescence (Ahlneck and Zografi, 1990). Capillary condensation to microvoid spaces that leads to occluded water is also possible at fairly low relative humidity levels. Water interacts with various crystalline solids at the surface primarily through its ability to

hydrogen bond (Zografi, 1988). A hydrate typically forms when water molecules penetrate the crystalline lattice most often in a well-defined molecular position and hydrogen bonds are formed (Ahlneck and Zografi, 1990; Zhu *et al.*, 1996). The change in the thermodynamic activity of the drug due to hydrate formation alters its pharmaceutically important properties such as solubility, physical stability and chemical stability.

The uptake of water into amorphous solids decreases the glass transition temperature, Tg, of the solid and acts as an efficient plasticizer (Zografi, 1988). As the solid is plasticized, it undergoes a significant increase in free volume, which greatly increases the mobility of molecules or segments of molecules in the system. This increase in mobility by the addition of water is reflected in a decrease in the viscosity of the solid which is particularly significant if the solid is made to change from the 'glassy' state to the 'rubbery' state. Such changes are reflected in a number of physical measurements of water that have been interpreted to be changes in its thermodynamic state. This has led to the conclusion that water in amorphous solids can exist in both 'bound' and 'solvent-like' combinations. Moreover, there are perhaps two types of 'bound' states.

The two fundamental forces that can affect powder flow are cohesion and friction. Moisture may influence the force of interaction between solid particles in at least three ways (Nokhodchi, 2005):
(1) it may adsorb onto the surface and influence the surface energy
(2) it may alter the surface conductivity and, therefore, the electrostatic intensity of the particles
(3) it may condense in the capillary regions contiguous to the true area of contact.

2.4.3 Kinetics of drying

Drying of solids contains two fundamental and simultaneous processes (Cooper *et al.*, 1961; Maroulis *et al.*, 1995; Moyers and Baldwin, 1999; Mujumbar, 2007):
(1) heat is transferred to evaporate a liquid
(2) mass is transferred as a liquid or vapour within the solid and as a vapour from the surface.
The heat capacity is defined as the heat required to raise the temperature of a unit mass of substance by a unit of temperature. Heat transfer is convective from the air to a solid's surface and conductive within the solid mass. The removal of water as vapour from the material surface depends on the external conditions of air including temperature, humidity and flow, and in addition area of exposed surface and pressure. The moisture movements internally within the solid occurs as a function of the physical nature of the solid, its temperature, and its moisture content.

The factors governing the rates of heat and mass transfer determine the drying rate. Wet-bulb temperature is the dynamic equilibrium temperature attained by a water surface when the rate of heat transfer to the surface by convection equals the rate of mass transfer away from the surface (Fig. 3).

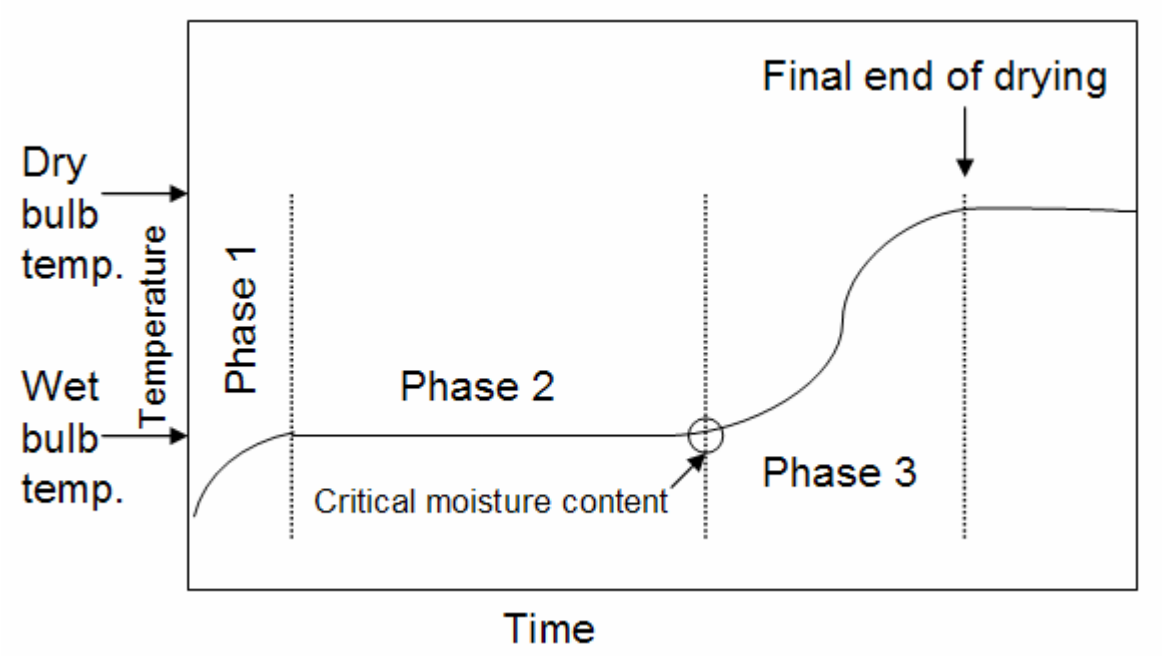

Fig. 3. Temperature phases in the drying process, modified from Parikh (1991).

Temperature phases of the drying material are best described by a three phase system (Newman, 1931). At the beginning of the process (phase I), the material heats up from the ambient temperature to approximately that of the wet-bulb temperature of the air in the dryer. In the second phase, the heat-transfer limited stage, the bed temperature remains constant, as all of the excess energy is used to evaporate the water. The rate of evaporation is essentially independent of the solid since the rate approaches the condition existing within a layer of liquid with no solid present (Cooper *et al.*, 1961). Thus suspended particles in a concurrent air stream are kept relatively cool by evaporation. This protective cooling effect prevents physical changes in the active ingredient, even when inlet air temperatures close to the melting point are used (Wildfong *et al.*, 2002). This constant temperature is maintained until the material's moisture content is reduced to the critical level. At this point, the material contains no free surface water, and the temperature starts to rise further. Thereby heat-labile formulations become susceptible to the influence of inlet air heat. The third phase of drying is the diffusion limited stage. In this phase the remaining water within the granules diffuses out before it is evaporated. Therefore this stage relies to a great extent on particle geometry. The third phase is usually divided into two zones: the zone of unsaturated surface drying and the zone where internal moisture movement dominates (Cooper *et al.*, 1961).

Consequently, the wet solid loses moisture first by evaporation from a saturated surface on the solid. This is followed in turn by a period of evaporation from a saturated surface of gradually decreasing area. Finally, moisture diffuses through the interior of the solid and subsequently evaporates. Periods of drying can also be illustrated by rate curves (Fig. 4).

Typical sections in drying rate curves are a rising warming-up period (A-B), smooth constant-rate period (B-C) and curved falling-rate period (C-D).

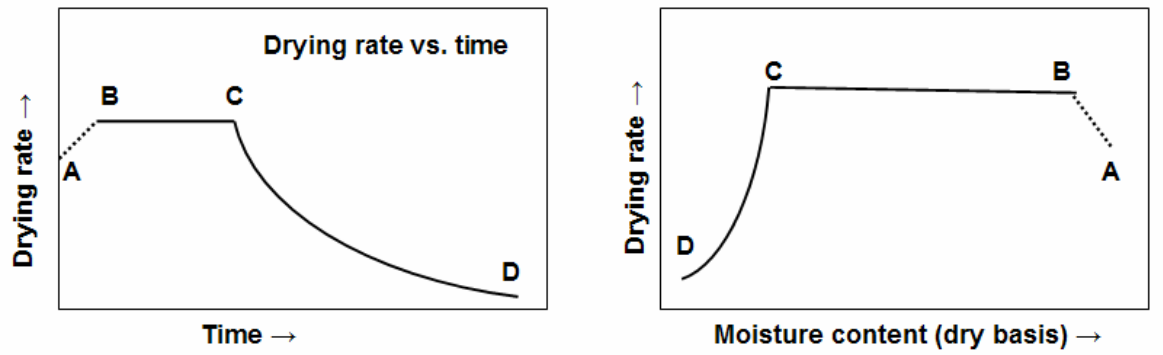

Fig. 4. The periods of drying, modified from Cooper *et al.* (1961).

A solid to be dried may be porous or nonporous, hygroscopic or non-hygroscopic. The rate of movement of liquid from the interior of the solid is dependent on the rate of surface evaporation, the temperature of the material, its texture and structure, its water content, and the way in which the moisture occurs throughout the material (Cooper *et al.*, 1961). The structure of the solid determines the mechanism by which internal liquid flow may occur (Cooper *et al.*, 1961; Moyers and Baldwin, 1999; Wang and Chen, 2000). These mechanisms can include:

(1) diffusion within continuous, homogeneous solids
(2) capillary flow within granular and porous solids
(3) flow caused by shrinkage and pressure gradient
(4) flow caused by gravity
(5) flow caused by vaporization-condensation sequence.

The first two mechanisms predominate during the drying of pharmaceutical granulations. In general, one mechanism predominates at any given time in a solid during drying. Moreover, it is not uncommon to find different mechanisms predominating at different times during the whole drying cycle. The distribution of saturation, temperature, and gas pressure play different roles in the heat and mass transfer in the particle throughout different drying periods (Wang and Chen, 2000). The forces acting to remove water from the crystalline solids are mainly gravitation and capillary. Their drying curves are characterised by constant rate. Internal water transfer is slower in amorphous solids. The liquid diffuses through structural obstacles caused by the molecular configuration. The drying rate curves of these amorphous materials are characterised by a short constant rate period followed by extended falling-rate period. Thus their drying is not a rapid process and they retain high residual humidity (Terrier de la Chaise, 1972). Although fluid bed drying is a very efficient method for drying, most pharmaceutical solids have poor thermal conductivity and thereby slow terminal diffusional rates add drying costs when very small amounts of moisture in the end product are a target (Syahrul *et al.*, 2002).

2.4.4 Equilibrium moisture content and sorption properties

The vapour pressure of water in the atmosphere is quantified as the percentage relative humidity (% RH). The absolute water content in air (for example g/kg dry air) can be calculated by using temperature information and psychrometric chart. The moisture content at which a solid material produces a water vapour pressure equal to that of the surrounding environment is defined as the equilibrium moisture content. Consequently, the equilibrium moisture content is the limiting moisture to which a given material can be dried under specific conditions of air temperature and humidity. The amount of water associated with a solid at a particular RH and temperature depends on its chemical affinity for the solid. It also depends on the available sites of interaction, surface area, and nature of material (Moyers and Baldwin, 1999).

Sorption isotherms measured experimentally under isothermal conditions are used to describe the hygroscopic properties of a product (Mujumbar, 2007). Moisture sorption isotherms characterise the amount of vapour adsorbed or desorbed at different equilibrium concentrations in the gas phase. A sorption isotherm is a graph of moisture content as a function of water activity (a_w). Moisture sorption isotherms of excipients are useful in predicting solid-state stability, interactions at early stages of formulation development, and the effects of moisture on the physicochemical properties of the final dosage forms (Airaksinen *et al.*, 2005a,b). For many materials the value of the equilibrium moisture content depends on the direction in which equilibrium is approached. The desorption values are preferred for drying calculations. The equilibrium moisture content reached by losing moisture is usually higher than that reached by adsorbing it (Strictland, 1962). This difference between adsorption and desorption isotherms is termed hysteresis, which occurs in the capillary condensation region of the sorption isotherms over ranges of different adsorbate-adsorbent pairs.

2.4.5 End-point indication of drying, the ΔT method and NIRS

Specified residual moisture content for tablet compression is usually expected of the finished granules. Capping of tablets may occur at moisture contents that are too low whereas picking of tablets occurs when moisture contents are too high (Sucker, 1982). Under optimal conditions the moisture content of granules is in equilibrium with the surrounding air so that sorption changes are small during storage (Schæfer and Wørts, 1978a). However, water activities over the range of 0.35-0.5 may be needed to obtain the required hardness and crushing strength of the tablets (Hyland and Naunapper, 1986). Chemical, physical and microbiological stability problems may result, if the moisture content of the granules remains too high.

Various end-point criteria for drying have been used. A fixed time criterion is not adequate for controlling the end-point of drying because all other process variables are ignored (Alden *et al.*, 1988). The temperature measurements of the inlet and outlet air and the granulation mass are important determinations for describing both heat transfer during

the fluid bed process and for indicating the drying end-point. The specific temperature value of the outlet air or mass is a widely used method for detecting the end-point (Davies and Gloor Jr., 1971). However, the 'weather effect' is a confounding factor in this method (Jones, 1985). This kind of criterion may be repeatable only if the humidity level of the inlet air does not vary. This is because the temperatures of the drying mass and that of the outlet air are influenced by the humidity content of the inlet air (Schæfer and Wørts, 1978a). The humidity level of the outlet air was used in some granulation studies as an indication to finalise drying (Niskanen *et al.*, 1990; Merkku *et al.*, 1992). Continuous measurement of the humidity of the air surrounding the substance was also examined (Hyland and Naunapper, 1988).

The temperature difference (ΔT) end-point indication technique has been used in many investigations (Harbert, 1972, 1973, 1974; Ehrhardt, 1977; Schæfer and Wørts, 1978a; Gore *et al.*, 1985; Leuenberger and Imadidis, 1986; Alden *et al.*, 1988). The ΔT technique exploits the relationship of temperature increase of a material from that of the wet-bulb temperature and the simultaneous depletion of the moisture content of that material. When air passes through a moist material its temperature drops towards the evaporative (wet-bulb) temperature value as the vapour pressure and dew point of the air rise. The wet-bulb temperature of the processed material is maintained as long as it is saturated with liquid and until the critical moisture content is reached (Fig. 3). One important principle behind the ΔT technique is that the latent heat of evaporation of water from moist materials is not significantly greater than that of evaporation from free water (Harbert, 1972). Therefore, the standard psychrometric chart establishes the foundation of this technique and it can easily be used for practical purposes.

The effect of humidity variations on end-point detection can be diminished using the ΔT technique. The technique can be applied to a dryer by measuring and comparing the following two temperatures: the temperature of the drying material in the saturated state (wet-bulb temperature of the drying air) and the temperature during the falling rate drying phase after the critical moisture content. The basic principle of ΔT technique can be described by the simple formula (Leuenberger, 1982):

Eq. 1 $T_e = T_k + \Delta T$

T_e Temperature in which the drying is finished
T_k Saturation (wet-bulb) temperature, temperature in the beginning of drying
ΔT Constant value

In practice it has been found that the end-point drying temperature T_e established empirically for a specific composition provides adequate reproducibility of the final moisture content of granules (Leuenberger, 1982). A fluid bed dryer can be automated in order to automatically switch off the process when the constant temperature rise is obtained. A typical thermocouple has a high level of reliability. The results of a study by Harbert (1974) show that the final moisture content of powder leaving the dryer could be kept very near the target value (1 ± 0.16%). In another study (Ehrhardt, 1977) the final moisture content in dried powders was kept within the range of ± 0.1% if the inlet air

temperature was maintained between 45°C and 55°C and the relative humidity varied between 30% and 60%. Naturally, the sampling of granules and measuring technique of moisture involve inherent error. However, extensive comparison of different techniques by Ehrhardt (1977) confirms that compared to other conventional end-point indication techniques, the ΔT technique provides maximum control with minimum variations. In addition, the ΔT method is substantially independent of atmospheric pressure changes. This is because the wet-bulb temperature and the temperature of the material increase or decrease by the same amount in response to changes in atmospheric pressure; the difference is therefore unaffected.

Non-direct methods based on temperature and humidity measurements do not give exact information on the moisture content of the granules. A primary interest in near infrared spectroscopy (NIRS) is for the rapid and non-destructive determination of the concentration of certain constituents in a material. The growing attention to NIRS for the end-point indication of fluid bed drying has arisen from improvements in instrumentation and in data analysis. Optical fibers allow fast transmission of NIR energy and information. However, the pharmaceutical industry and regulatory bodies have been slow to adopt the NIR approach, most probably since it lacks the capability of mid-IR to identify samples by mere inspection of spectra and involves the calibration and sophisticated mathematical techniques (Reich, 2005). NIR instruments determine the components of a substance by measuring for example log(1/reflectance) values. These values, in turn, must be related to the amount of the component as determined by some other method called a reference or standard method. Establishing this relationship by using a set of samples of known quantity and composition is called calibration of the NIR method.

NIRS is an effective alternative to conventional analytical methods such as thermo-gravimetry (LOD) and Karl Fischer titration (Blanco *et al.*, 1998). The NIR spectrum of water exhibits five absorption maxima at 760, 970, 1190, 1450 and 1940 nm wavelength. The bands at 760, 970 and 1450 correspond to the first three overtones of –O-H stretching bands, whereas the other two arise from combinations of –O-H oscillations and stretching. The specific band to be used for determining water depends on the desired sensitivity and selectivity levels. On-line monitoring of moisture levels using NIR fiber-optic probes is a feasible option for optimising drying times since –O-H vibrations of water exhibit a large absorption in the NIR region (Reich, 2005). To date, only a few published examples exist of utilising in-line NIR for controlling the end-point of fluid bed drying especially on the industrial scale.

Several different sampling configurations were tested in various fluid bed processes in an effort to understand better and improve in-line NIRS method accuracy (Green *et al.*, 2005). Several probe insertion depths were evaluated for improving the signal-to-noise ratio of the spectra, and a separate study was performed to assess the impact of air flow rate on spectral reproducibility. A device was developed to allow for the collection of spectra of stationary material to overcome sample presentation issues. This device allows for collection of quality spectra in turbulent systems and eases method development as NIR and reference measurements are performed on the same samples. In contrast to the

65-300 litre scale measurements experiments, sample presentation and quality of spectra for flowing material could be optimised through varying the probe insertion depth on the 600 litre dryer. This strategy was permitted by different inlet air configuration which allowed smoother, cyclonic air flow compared to the smaller scale systems. There still seems to be major challenges with measuring and controlling the end-point of fluid bed drying with in-line NIRS and tailored configurations are needed for the industrial scale.

2.5 Quality factors of fluid bed granulation and drying

2.5.1 Critical process variables of fluid bed granulation and drying

The process variables affecting the quality of finished granules have been analysed in many studies (Gorodnichev *et al.*, 1981; Wan and Lim, 1991; Merkku *et al.*, 1993; Miyamoto *et al.*, 1995; Juslin and Yliruusi, 1996a,b; Menon *et al.*, 1996; Watano *et al.*, 1996a,b,c; Rambali *et al.*, 2001a,b; Rajniak *et al.*, 2007). Schæfer and Wørts (1977) and Aulton and Banks (1981) classified variables of fluid bed granulation by their potential to influence the quality of an end product (Table 1). Critical variation sources of fluid bed granulation can be considered from many different perspectives. The significance of various variables depends mainly on critical quality attributes (CQA, chosen response). Variation in process parameters and thereby in critical quality attributes can elicit critical variation to the end product. On the other hand, according to the PAT principles, it is beneficial to be able to adjust process parameters to compensate and optimise for changing conditions such as seasonal changes and raw material alternations. Variations in the physical properties of the powders to be granulated can give rise to processing problems. In addition to formulation factors and process adjustments, it is important to understand the possible solid state transitions induced by processing conditions.

Table 1. Classification of fluid bed granulation parameters, modified from Schæfer and Wørts (1977) and Aulton and Banks (1981)

Apparatus parameters	Process parameters	Product parameters
Air distributor plate	Bed load	Type of binder
Shape of granulator bowl	Inlet air flow rate	Quantity of binder
Nozzle height	Inlet air temperature	Binder solvent
Positive or negative pressure operation	Inlet air humidity	Concentration of granulating solution
Scale-up	Atomization	Temperature of granulating solution
	- Nozzle type	Starting materials
	- Spray angle	- Fluidisation
	- Spraying regime	- Powder hydrophobicity
	- Liquid flow rate	
	- Atomizing air flow rate	
	- Atomizing air pressure	
	- Droplet size	

The most important properties of starting materials seem to be the size of the particles and size distribution within a mass (Kristensen and Schaefer, 1987). Inevitable variations in particle size from batch to batch of the same material can complicate the granulation process. A larger surface area of raw materials results in a smaller granule size. Therefore decreasing particle size of raw material results in a smaller granule size at a constant amount of liquid (Ormós and Pataki, 1979a; Georgakopoulos *et al.*, 1983). Larger amounts of liquid have to be used in order to keep granule size constant when raw material particle size decreases (Schæfer and Wørts, 1977; Leuenberger, 1983).

The spray rate of the binder solution and the atomization air pressure are the most important factors affecting granule size distribution (Schæfer and Wørts, 1978b; Gao *et al.*, 2002). When using water absorbing materials, such as starches or microcrystalline cellulose, absorption results in the incomplete wetting of the surface and therefore the amount of liquid has to be increased (Leuenberger *et al.*, 1979). Solubility, wettability, shape, and density of starting materials affect granule growth too (Ormós and Pataki, 1979a). The highest growth rate is seen, when the material is soluble in the binder solution. The lowest growth is found in insoluble and poorly wettable materials (Ormós and Pataki, 1979b).

The important quality attributes of a solid pharmaceutical product include stability, dissolution, bioavailability, appearance, ease of manufacture, density, hardness, etc. All of these may be influenced by phase transformations (Herman *et al.*, 1988; Fitzpatrick *et al.*, 2002; Debnath and Suryanarayanan, 2004; Zhang *et al.*, 2004). Although versatile, wet granulation is especially likely to induce phase transitions (Morris *et al.*, 2001; Table 2). In addition to the properties of the API, the granulating and drying conditions and the methods determine whether solution or solution-mediated phase transformations will occur. Such transformations include polymorphic conversion, hydration/dehydration or vitrification (converting a material amorphous solid)/crystallization. In certain cases it is advisable to monitor the crystal form of all incoming raw materials and the physical form(s) present in the final dosage unit, even after the solid form and the preferred processes are defined.

Table 2. Solid state properties and potential processing stresses during identified procedures used in solid state manufacturing, modified from York (1983)

Solid state properties	**Processing stresses**
Crystal structure	Temperature
Crystal hardness	Pressure
Crystal habit	Mechanical
Polymorphism and solvate forms	Radiation
Surface polarity	Exposure to liquids
Wettability and moisture sorption	Exposure to gases and liquid vapors

Variations in solid state properties, such as those originating from batch differences of the same material or alternative powder treatment procedures, can modify formulation requirements in addition to processing and product performance (York, 1983). Adsorbed

moisture is particularly important with respect to the physical and chemical stability of drugs. In addition, the equilibrium moisture content is likely to influence the flow and compression characteristics of powders and consequently the hardness of granules and tablets. Changes in ambient humidity can result in different moisture contents in sensitive materials which cause deleterious phenomena with respect to formulation and processing such as caking, solution formation and re-crystallization.

Moisture content of the fluidising mass is the most significant process variable of fluid bed granulation agglomeration (Kristensen and Schaefer, 1987). If the moisture content is too high, the bed becomes over-wetted and de-fluidises rapidly. In contrast when the moisture content is too low, no agglomeration will occur. The possible range of variation in moisture content is narrow, therefore it is necessary to accurately control the process variables affecting the moisture content. At any given time, the moisture content of the granules depends on wetting and evaporation. These are controlled by liquid flow rate and inlet air temperature, humidity and flow rate.

In addition to moisture content, specific particle size of finished granules is vital for further processing. Granule size is directly proportional to liquid flow rate and inversely proportional to air temperature (Schæfer and Wørts, 1978b). Provided that an optimum balance between liquid addition and evaporation is established, droplet size of the atomized binder solution is the most important process variable (Schæfer and Wørts, 1978b). Increase in atomizing air flow rate or air pressure result in decreases in droplet size and thereby result in smaller granule size (Schæfer and Wørts, 1978b,c; Juslin and Yliruusi, 1996b; Bouffard *et al.*, 2005). Granule size can be varied in a reproducible way by varying the air flow rate to the nozzle (Kristensen and Schaefer, 1987). However, granules made using higher atomizing air pressures are typically more friable. Binder concentration and drying rate also affect granule porosity and thereby friability (Berggren and Alderborn 2001; Rajniak, 2007; Ansari and Stepanek, 2008). Porous granules may be advantageous in some formulations resulting in better dissolution and compression characteristics (Aulton and Banks, 1981). An increased fragmentation can increase the surface area that takes part in inter-granular attraction. This in turn, will improve tablet strength. Generally, granules obtained from a fluid bed granulator are found to be more porous than those obtained from high shear mixers (Gore *et al.*, 1985, Kristensen and Schaefer, 1987).

2.5.2 Influence of granulation on further processing and end product

The production of tablets of high quality in large scale production requires a tablet mass with excellent properties regarding mixing homogeneity and flowability, both of which are improved by wet granulation. Bulk density, moisture content and granule size distribution can also be considered as very important granule properties for optimum tablet compression. The usual measurements of granules are moisture, bulk- and tapped density (Carr's or Hausner index), true density, friability, particle size, angle of repose, and flow rate (Kristl *et al.*, 1994, Rambali *et al.*, 2001a). Tablet properties are a natural choice as a

dependent variable. Examples of possible independent and dependent variables are found in Table 3. One categorisation presented by Sucker (1982) is to divide granule properties into physical (non-dynamic) characteristics (such as agglomerate densities, residual moisture content, size and shape measurements) and to behavioural (dynamic) characteristics (such as flow properties, friability and compressibility). The connections between these two groups are challenging.

Table 3. Example of system variables and responses in a typical wet massed tablet formulation, modified from Gould (1984)

System variables	Responses
• excipient levels	• dissolution
• compression force	• disintegration
• disintegrant level	• crushing strength
• binder level	• friability
• lubricant level	• weight uniformity

Water interacts with pharmaceutical solids at virtually all stages of manufacture. The powder properties are influenced greatly by moisture content and the final moisture content of the granules can be considered as a significant quality attribute of fluid bed drying (Amidon and Houghton, 1995). Therefore, water-powder interaction is a major factor in the formulation, processing, and performance of solid dosage forms (Nokhodchi 2005). A variety of physical and chemical properties of solid dosage forms are affected by residual water associated with drugs: chemical degradation, dissolution rate, flowability and compactibility (Ahlneck and Zografi, 1990). Furthermore, the moisture distribution patterns (i.e. surface or internally held) can have significant effects on powder packing and flowability, because the presence of surface moisture modifies inter-particle attractive forces (York, 1983).

Wet granulation improves homogeneity in the subsequent mixing process(es) and ultimately prevents segregation in the hopper. This also facilitates tablet weight and dose uniformity during tabletting. The flowability of a powder mass is primarily governed by the size and shape of its granules. At present, bulk density and tapped density measurements are much more widely used than angles of repose to assess powder cohesion and flow properties. The reduction in powder bulk density is attributed to the presence of inter-particle liquid bridges. These keep particles further apart and produce a more open structure than when the particles are non-cohesive (Nokhodchi, 2005). It is also observed that when water content of a powder mass is high enough to cover much of the particle surface, advantageous lubrication by the liquid occur. This promotes the flow of the particulate material with significantly reduced frictional forces.

One main reason to granulate the powder is to improve the compactability of the powder mass. Distribution of binder and the fragmentation property of the granules in addition to the granule size of the starting material and final material are important determiners for compression of granules (Alderborn, 1988). Compactability can be defined as the ability of a powder to give tablets of high mechanical strength without capping tendencies. Plastic

deformation and especially fragmentation of particles are considered to be strength producing volume reduction mechanisms. It is common knowledge that the physical manufacturing characteristics of tablets (particularly hardness and friability) are strictly related to those of the starting granules. The mechanical strength of tablets compressed from a granulated material is affected by their formulation parameters, primarily type and amount of binder, and process conditions during granulation.

Water content of the granulation can markedly affect the tablet strength in that there is a tendency that increasing amounts of water increases the tablet strength. Moisture increases the compact strength by increasing the tensile strength of the powder bed. This increases the contact area among particles for bonding, by decreasing the variation of density within the tablet and by the recrystallization effect (Dawoodbhai and Rhodes, 1989). The importance of the water content of the granulation for removing capping tendencies of a powder mass has also been demonstrated. The reduction in tablet density variation is ascribed to the lubrication of the die wall. This allows more of the applied force to be transmitted through the compacting material onto the lower punch (R value). A lack of moisture can be responsible for tablet lamination because the yield force and elastic recovery increases. A decrease in tensile strength can also be the result of the formation of water multilayers or the presence of free water at the surfaces (Nokhodchi 2005). Such water may then disturb or reduce intermolecular attraction forces and thereby reduce tablet strength.

2.5.3 Instrumentation system for measuring critical process parameters

Fluid bed processing requires accurate and reliable control of all the process parameters. Important parameters that must be sensed for wet granulation are product temperature, atomising air pressure, air dew point or humidity, and spray rate of the binder solution (Parikh, 1996). Other important variables are product-bed and filter pressure drop. Low values of pressure difference over granules indicate loss of granules or dead zones, whereas the pressure difference over the upper filter bags is known to indicate blocking of filters (Rantanen *et al.*, 2001). Monitoring these variables by sensors provides constant feedback of the information to the operator and the control system (Rantanen *et al.*, 2000c). In addition, historical data storage is important for data integration and further analyses. Instrumentation is necessary in studying the simultaneous effects of various variables in the fluid bed granulator. Automated processes guarantee higher and more repeatable product quality. Understanding of various phenomena results in better control of the process, reduced number of batch failures, and improved success rate in process scale-up and technology transfer (Merkku *et al.*, 1992; Li *et al.*, 2007). In addition, troubleshooting and optimisation of the process is possible with analysed process data.

The instrumentation system is also important for the control of the drying phase. How a solid dries depends upon the effects of external conditions and the mechanism of fluid flow. When a material to be dried has a linear falling-rate period, it indicates that surface evaporation is the controlling factor in the process and that the rate of drying can be varied

by changing such external conditions as air velocity, humidity and temperature. These external conditions (temperature, humidity and air flow rate) are all easily measured factors, and thus drying rates are usually based on these values (Cooper *et al.*, 1961). Parikh (1996) reported that important sensors for controlling of the drying process are those sensors that measure inlet and outlet air temperature and humidity. In addition to these an airflow sensor located in the air transport system is also considered important. Furthermore, temperature of the fluidising mass and humidity measurements can be considered critical for end-point indication of drying. Changes in the external drying conditions with materials, in which the internal resistance to moisture movement controls the drying, will not change the rate of evaporation from the surface. Rather, the rate of drying will be increased by reducing the thickness of the material, or by increasing the temperature within the granule, and/or reducing the external pressure.

2.5.4 Principles and benefits of PAT

Conventional pharmaceutical manufacturing generally uses batch processing with laboratory testing performed on collected samples to evaluate quality. Traditional quality systems in the pharmaceutical industry include process/method/equipment validation, process controls according to standard operating procedures (SOPs), process instructions/master recipes, and off-line testing of samples at the end of each batch. This kind of system does not inherently encourage to improvements in manufacturing processes. Process analytical chemistry (PAC) has been performed in the petrochemical industry for several decades (Drakulich, 2008). Many of the process analytical instruments currently in use were originally developed by the oil and petrochemical companies and then adopted by other industries. More recently, the term process analytical technology (PAT) has been used to describe this approach, which utilises analytical and process chemistry along with multivariate tools. These tools are used to ensure that quality is built into the products while improving the understanding of processes, increasing efficiency, and decreasing costs (Scott and Wilcock, 2006).

In 2002, the Food and Drug Administration (FDA) announced a new initiative, Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century, to enhance and modernise the regulation of pharmaceutical manufacturing and product quality. This initiative included an idea of the early adoption of new technological advances by the pharmaceutical industry. The cGMPs initiative was followed by more detailed PAT guidance for the industry (FDA, 2004). Similar elements of risk analysis, real-time quality control and continuous improvement were later included in the guidelines of the International Conference on Harmonisation (ICH Q8, 2005; ICH Q9, 2005). The latest initiative ICH Q10 ‘Quality Systems’ achieved recently (5th June, 2008) the final stage of the harmonisation process. The outcome was that all parties to ICH (US, Europe, and Japan) reached a scientific consensus on the guideline’s text and agreed to implement fully the guideline through their individual regulatory bodies (Drakulich, 2008). ICH Q10 incorporates the concepts behind ICH Q8 ‘Pharmaceutical Development’

and ICH Q9 ‘Quality Risk Management’ by providing a model for a pharmaceutical quality system that can be implemented throughout a product life cycle.

The FDA (2004) has defined PAT to be ‘system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring product quality’. An extended definition of PAT includes following items (Guenard and Thurau, 2005):
(1) development of the process, namely the identification of critical-to-quality attributes and their relationship to the quality of the product
(2) design of a robust process to control the critical-to-quality attributes
(3) simple sensors and more complex process analysers
(4) a system approach to use and correlate all significant process information
(5) data mining approaches to detect long-term trends and interactions
(6) potent data management systems to process the large amounts of data generated.

The benefits of implementing PAT are summarized in Table 4. Compared to conventional laboratory analyses, speed of analysis and elimination of manual sample handling are clear benefits. Integrity of the sample is more likely to be retained when it is not removed from the process. Measurements can be made to give a direct indication of reaction progress or the composition of a mixture at a given time. Additional advantages of process analysers are the possibility to automate all or the most parts of the analysis. Moreover, PAT based real-time monitoring of fluid bed granulation or any other pharmaceutical process can decrease product variability, reduce the number of batch failures and waste material, and increase batch-to-batch consistency. Thus PAT can not only lead to better manufacturing processes but also speed up the R&D process itself. This especially includes formulation development, scale up, clinical trial manufacture and the technology transfer into manufacturing facilities (Davies and Ellis, 2005).

Many academic-industrial consortia have worked on PAT related topics. The three consortia that have been the longest in existence are: Center for Process Analytical Chemistry (CPAC), Measurement and Control Engineering Center (MCEC), and the Center for Process Analytics and Control (CPACT). The International Society for Pharmaceutical Engineering (ISPE) has arranged training and evolved practical strategies for PAT implementation in collaboration with other parties. The European Federation of Pharmaceutical Industries Associations (EFPIA) represents 32 national pharmaceutical industry associations and 43 leading pharmaceutical companies operating in Europe. EFPIA has been involved in the development of the PAT approach. The American Society for Testing of Materials (ASTM) has been active in the area of PAT in the development of standards for the use PAT internationally in their standard committee E55. Different Pharmacopeas (US, Europe, Japan) have detailed procedures to test the quality of pharmaceuticals in which PAT based methods are also included.

Table 4. Benefits of implementing PAT in the pharmaceutical industry, modified from Scott and Wilcock (2006)

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

2.5.5 Risk analysis

An inverse relationship between the level of process understanding and the risk of producing a poor quality product is obvious. A focus on process understanding can facilitate risk-based regulatory decisions (FDA, 2004). Information from pharmaceutical development studies can be the basis for quality risk management (ICH Q8, 2005). The appropriate quality management principles can be helpful in prioritising pharmaceutical development studies in order to collect knowledge of the process performance. Quality risk management is ‘a systematic process for the assessment, control, communication and

review of risks to the quality of the drug (medicinal) product across the product lifecycle' (ICH Q9, 2005). Quality risk management supports a scientific and practical approach to decision-making. The primary principles of quality risk management are:
(1) The evaluation of the risk to quality should be based on scientific knowledge and ultimately linked to the protection of the patient.
(2) The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

Risk assessment is typically performed early in the pharmaceutical development and completed when any further relevant knowledge is gained. Systematic risk analysis contributes to the estimation of risk associated with the identified hazards (ICH Q9, 2005). It includes qualitative or quantitative processes that link the likelihood of occurrence and severity of harm. The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. Risk assessment tools can be used to identify and rank parameters (e.g. operational, equipment, input material) with potential to have an impact on product quality based on prior knowledge and initial experimental data (ICH Annex to ICH Q8, 2007; ICH Q9, 2005):
(1) basic risk management facilitation methods (flowcharts, check sheets etc.)
(2) failure mode effects analysis (FMEA)
(3) failure mode, effects and criticality analysis (FMECA)
(4) fault tree analysis (FTA)
(5) hazard analysis and critical control points (HACCP)
(6) hazard operability analysis (HAZOP)
(7) preliminary hazard analysis (PHA)
(8) risk ranking and filtering
(9) supporting statistical tools.

When considering risk assessment of fluid bed processing, the list in Table 1 is a good starting point for a risk evaluation. At the beginning of this work, an initial assessment of these parameters for the Glatt WSG 5 granulator was made. Only inlet air humidity presented a critical variable, which could not be kept constant or fully controlled. Therefore it was intentionally varied in a systematic experimental design (studies I and II). Moreover, other parameters (granulation liquid feed and regime) were thoroughly studied to increase process understanding (studies III, IV and V). The goal was to find measurements that express process changes and failure modes in order to identify and control them better. Moisture and particle size of granules were chosen as critical quality attributes (CQAs) based on prior published studies. A risk assessment and formal experimental designs of these kinds can lead to an understanding of the linkage and effect of process inputs on product CQAs and also help to identify the variables and their ranges within which consistent quality can be achieved.

2.5.6 Design of experiments

Information from formal experimental designs can be useful in identifying critical or interacting variables that might be important in assuring the quality of the drug product (ICH Q8, 2005). In addition to the PAT techniques and scientific (prior) knowledge, formal experimental designs can demonstrate enhanced knowledge of product performance over a wide range for material attributes, processing options and processing parameters. These experiments can lead to more flexible regulatory processes for a drug product. Formal experimental design, or Design of Experiments, DoE, is defined as a 'structured, organized method for determining the relationship between factors affecting a process and the output of that process'. For a start it is important to identify factors, i.e. parameters that can be changed to influence responses. These responses are variables that describe the essential properties of the system (process). A risk assessment may yield this kind of information. Applications of DoE are screening and optimisation studies that ultimately can determine the optimal process region (design space), robustness testing and mechanistic modelling. The goal of optimisation studies is to find the factor combination at which the desired response profile is best fulfilled (Lewis *et al.*, 1999). This includes regression analysis and model interpretation. The result of appropriate response surface modelling (RSM) can be a response contour plot which can be used for the construction of a design space.

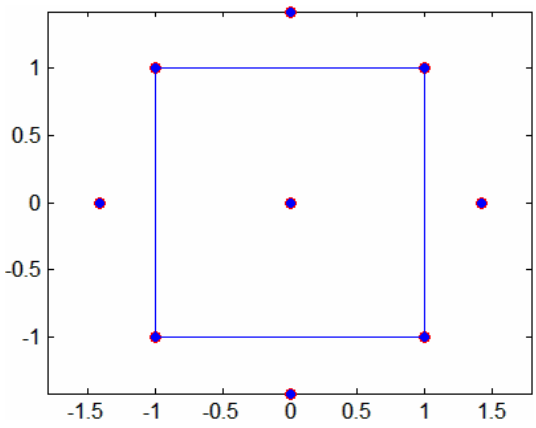

Fig. 5. Central composite circumscribed (CCC) design.

Full factorial, central composite and mixture designs are widely used in the pharmaceutical industry (Lewis *et al.*, 1999). Full factorial designs form the basis for classical experimental designs. They are regularly used with two to four factors and basically very simple. The composite designs are natural extensions of the two-level full and fractional factorial designs. The central composite circumscribed (CCC) design (Fig. 5) consists of three building blocks:
(1) regularly arranged corner experiments of a two-level factorial design
(2) symmetrically arrayed star points located on the factor axes
(3) repeatedly performed centre-points.
When it is desirable to maintain the low and high factor levels, and still perform an RSM design, the central composite face-centered (CCF) design is an appropriate alternative

(utilised in studies III, IV and V). CCF is the recommended design choice for pilot plant and full-scale investigations. A mixture design is a natural choice for formulation optimisation studies. Typically in this approach the total amount of components is constant but the proportions of these factors vary in relation to each other.

2.5.7 Design space in pharmaceutical industry

In 2005, ICH Q8 introduced officially the concept of design space, though this idea has been mentioned earlier (Westrup, 1996; FDA, 2004). Recently, the content of design space has been clarified (ICH Annex to ICH Q8, 2007; Garcia *et al.*, 2008; Lepore and Spavins, 2008). Design space is the region where acceptable product can be produced. An important step in defining the design space involves the differentiation between those product attributes and process parameters that are critical, from those that are not. The design space determines the relationship between critical quality attributes (CQAs) and critical process parameters (CPPs). Moreover, it identifies acceptable operating ranges for CPPs. One suggested approach to achieve such decisions is the use of risk assessment. The criticality determines what quality attributes and process parameters are defined in the design space. The control strategy ensures that operation of the process is maintained within the design space. It is intended to prevent operating in regions of limited process knowledge or other operations that are known to cause product failure (Garcia *et al.*, 2008). Understanding of a process comes from the ability to identify critical control points (CCPs). Full process understanding includes identification of key parameters that impact on a process, the product quality, and also key parameters that can be used to control the process (Baughman, 2005).

Use of the design space approach should enable more effective dialogue between industry and regulators during the application review process (Lepore and Spavins, 2008). Multivariate models based on chemistry, biotechnology, or engineering fundamentals can be used to build the design space. These models can be based on first principles, be empirical in nature, or a combination of both. The intent of the experimentation and modelling is to create an understanding of all variables that impact CQAs, and represent the linkage in the form of a design space. A design space can be defined in terms of input variables or parameters, or through more complex mathematical relationships (ICH Annex to ICH Q8, 2007). It is possible to define a design space as a time dependent function (e.g. temperature and pressure cycle of a lyophilisation cycle), or as a combination of variables such as principal components of a multivariate model. The design space can be established for one or more unit operations, or one design space can span multiple operations. Information regarding the site and scale of manufacture may also be included, depending on the quality of the process knowledge upon which the design space is based.

Design space, together with an appropriate control strategy, will reduce and focus end product testing, while increasing process performance and robustness (Garcia *et al.*, 2008). Increased development resources may be required to achieve knowledge based understanding of the process. However, this extra investment can be offset by more

efficient scale-up, more consistent manufacturing, and potential regulatory flexibility. The design space is dynamic and begins at the drug conceptualisation stage and continues to evolve over the entire lifecycle of the process. At the time of initial product commercialisation, the design space can be considered to represent the best overall process understanding. It will continue to evolve as additional information and knowledge is generated throughout the lifecycle of the product. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

At present there are many guidelines and tools available for pharmaceutical industry to increase process understanding and quality of finished products. PAT, risk analysis, systematic experiments (DoE) and design space will likely be important elements of R&D, production scale manufacturing and quality control in the future. Pharmaceutical companies are encouraged to plan and execute a system for the monitoring of process performance and product quality to ensure and maintain a state of control (ICH Q10, 2008). When efficient manufacturing processes and high quality of pharmaceuticals are targets, scientific knowledge of essential manufacturing processes becomes increasingly vital.

3. Aims of the study

The objective of this thesis was to utilise the PAT tools for identifying sources of variation and determine critical correlations and relationships of fluid bed granulation and drying. An integrated instrumentation system of a bench scale granulator with a total of 30 indirect physical measurements and various particle size measurement methods (including in-line SFT particle size measurement) were utilised for increasing the understanding of the process.

The specific aims were to:

1) determine the influence of inlet air humidity changes on temperature in different parts of a granulator system (study I)
2) study the effects of granulation liquid feed on temperature of fluidising mass (study V)
3) evaluate the effects of inlet air humidity and granulation liquid feed rate on particle size of the final granules (studies I and III)
4) determine a parameter describing fluidisation behaviour and to construct a design space for process performance (study I)
5) compare various drying end-point criteria based on temperature and humidity measurements (study II)
6) study the effect of inlet air humidity and fluidisation variations on fluid bed drying end-point detection (study II)
7) evaluate correlation between temperature and moisture of fluidising mass (study II)
8) increase process understanding by in-line particle size measurement (SFT) (study IV)
9) evaluate the instrumentation system for determining the measurements expressing the changing conditions during the spraying phase of a fluid bed process (study V).

4. Experimental

4.1 Materials

In studies I and II each batch consisted of 3.0 kg ibuprofen (USP/EP; BASF Corporation, Bishop, TX, USA) and 1.0 kg α-lactose monohydrate (200 mesh; DMV International GmbH, Veghel, The Netherlands) granulated with 2 kg of 15% aqueous solution of polyvinylpyrrolidone $(C_6H_9NO)_X$ (Kollidon K-30; BASF Corporation, Ludwigshafen, Germany).

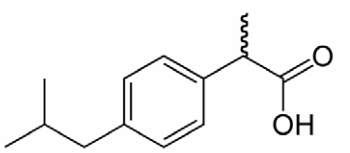

Fig. 6. Ibuprofen, 2-(4-isobutylphenyl)-propionic acid, is a non-steroidal drug that is widely used as an anti-inflammatory analgesic.

In studies III, IV and V each granulation batch consisted of 2.0 kg theophylline anhydrate (200 mesh, BASF Corporation, Ludwigshafen, Germany) and 2.0 kg α-lactose monohydrate (200 mesh, DMV International GmbH, Veghel, The Netherlands), granulated with 2 kg of 7.5% aqueous binder solution of polyvinylpyrrolidone (Kollidon K-30; BASF Corporation, Ludwigshafen, Germany).

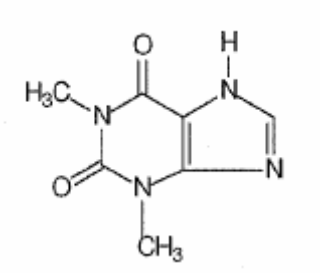

Fig. 7. Theophylline (3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione) is a common therapeutic agent for the treatment of asthma.

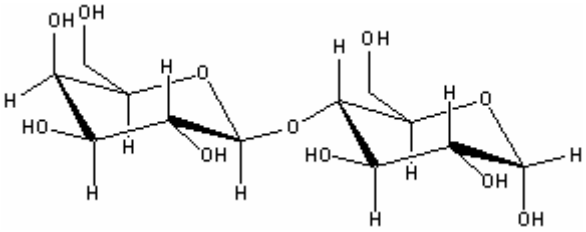

Fig. 8. Lactose monohydrate is a common pharmaceutical excipient.

4.2 Methods

4.2.1 Fluid bed granulation and drying

The granules were produced in an instrumented bench-scale fluid bed granulator (Glatt WSG 5; Glatt GmbH, Binzen, Germany). The instrumentation system is described in Rantanen *et al.* (2000) and in Table 5.

In studies I and II, the inlet air temperature, atomization pressure of the granulating liquid and nozzle height were constant. During the mixing, spraying and drying phase, a low inlet air temperature of 40°C was used, because the melting point of the model compound ibuprofen is low (75°C). The mixing phase lasted for about 6 minutes until the inlet air temperature (T3) had increased to 40°C. The atomization pressure was 0.1 MPa. The nozzle height was set at 45 cm above the distributor plate. The granulating liquid flow rate was 29 g/min during the first 10 min and 105 g/min thereafter. The inlet air volume was adjusted for smooth fluidisation and the flow rate of the inlet air varied between 0.040 and 0.100 m^3/s depending on the granulation phase.

In studies III, IV and V the atomization pressure of the granulating liquid and nozzle height were the same as in studies I and II. The inlet air temperature was 40ºC during the mixing and spraying phases and was subsequently raised to 60ºC during the drying phase. The inlet air flow rates were kept fixed by constant adjustments: 0.04 m^3/s during the preliminary mixing phase (2 min) and then 0.08 m^3/s throughout the wet granulation and drying phases.

The final moisture content of the granules varied between 0.5% and 1.2% (w/w) measured by loss on drying (LOD, see 4.2.3).

4.2.2 Humidifying system

The inlet air humidity of the process air was modified using a humidifying system (Defensor Mk4; Brautek Oy, Espoo, Finland). The system, which was connected to the fluid bed granulator, enabled granulation batches of high humidity (>13 g/m^3). The system is described in study I.

4.2.3 Moisture measurements

LOD in an infrared (IR) dryer (Sartorius Thermocontrol MA 100; Göttingen, Germany) was used for moisture measurements. In studies I and II the samples (about 3 g) were heated at 70°C until the rate of weight loss dropped to 0.1% in 50 s. At least two measurements were made of each sample. Karl Fischer titrations were performed on a

Mettler Karl Fischer titrator (model DL35; Mettler Toledo AG, Switzerland), using samples of 100 mg to confirm the validity of the IR dryer results. The result was a mean of three separate titrations. Hydranal solvent, formamide and hydranal titrant 5, purchased from Riedel-deHaën Laborchemikalien GmbH, Germany, were used as the reagents.

In studies III, IV and V samples (about 3 g) were heated at 105°C until the rate of weight loss dropped to 0.1% in 50 s.

4.2.4 Particle size measurements

The volume particle size distribution was determined by laser diffractometry (Laser Diffraction Particle Size Analyser LS13 320; Beckman Coulter Inc., Miami, FL, USA). The samples were measured using air as the medium and were prepared by dispersing powder in the unique Tornado Dry Powder System. The dispersion pressure was 4.7 kPa. The result was a mean of three measurements.

For sieve analysis, a 50 g sample was vibrated by an automatic sieve shaker (Fritsch analysette, Idar-Oberstein, Germany) for 5 min. The sieve analysis (range 71-2000 μm with √2 increment) was performed in triplicate and the mean value for mass median granule size was determined.

An in-line SFT (spatial filtering technique) probe (Parsum® IPP 70; Gesellschaft für Partikel-, Strömungs- und Umweltmesstechnik GmbH, Chemnitz, Germany) was installed in the granulator at a height of 45 cm. The particles passed through an aperture (diameter 4 mm). Pressurized air was used to disperse the particles. During the fluid bed process, an average number and volume of particle distribution data at 10 s intervals were saved. The sample was poured through an orifice of the SFT apparatus using a funnel and pressurized air in at-line and off-line applications.

Granules taken during the wet granulation by sampler were used for visual characterization and photographs of these samples were taken by an image system described in Laitinen *et al.* (2004). Images of the final granules were also recorded by scanning electron microscope (Zeiss DSM 962, Oberkochen, Germany).

4.2.5 Physical measurements

Direct and derived measurements and set values of Glatt WSG 5 are described in Table 5.

Table 5. Direct and derived measurements and set values of Glatt WSG 5

Measurement or derived parameter	Symbol	Unit
Direct:		
Temperature of process room	T1	ºC
Temperature after heater	T2	ºC
Temperature of air before granulator	T3	ºC
Temperature of air before granulator	T4	ºC
Temperature of mass	T5	ºC
Temperature of granulation chamber	T6	ºC
Temperature of granulation liquid	T7	ºC
Temperature after filters	T8	ºC
Temperature after filters	T9	ºC
Temperature in the outlet air duct	T10	ºC
Temperature in the outlet air duct	T11	ºC
Pressure difference over upper filters	dP1	kPa
Pressure difference over granules	dP2	kPa
Relative humidity of inlet air	U1	RH%
Relative humidity of outlet air	U2	RH%
Flow rate of inlet air	Fin	g/s
Flow rate of outlet air	Fout	g/s
Fan speed, value of frequency converter	Paw292	Hz, 1/s
Control current of heating element	Paw294	mA
Atomization pressure	Paw288	bar
Control current of granulation liquid pump	Paw500	mA
Pump rotation speed of granulating liquid	N1	rpm
Amount of granulation liquid sprayed (scale)	M1	g
Set value of inlet air flow rate	W1	g/s
Set value of inlet air temperature	W2	ºC
Derived:		
Absolute humidity of inlet air	AH1	g/m^3
Absolute humidity of outlet air	AH2	g/m^3
Flow rate of inlet air	F1	l/s
Flow rate of outlet air	F2	l/s
Fluidization parameter, Fin/PAW292	FlowInd	g/rev
Median particle size measured by in-line SFT	d50med	µm
Specific enthalpy of water vapour in inlet air	Latent_heat	kJ/kg
Average flow of granulating liquid from start	AveM	g
Water content of inlet air	Water_in	g/s
Water content of outlet air	Water_out	g/s
Cumulative water amount of inlet air	Water_in_cum	g
Cumulative water amount of outlet air	Water_out_cum	g
Cumulative water balance (Water_in_cum-Water_out_cum)	Water_bal_cum	g

5. Results and discussion

5.1 Effects of inlet air humidity and granulation liquid feed on temperature measurements and particle size

The influences of inlet air humidity and changing granulation liquid feed on the temperature measurements in the fluid bed granulator system were determined. Temperature measurements at different locations were compared considering dynamic changes and placement for process control. The effect of moisture changes, originating from inlet air humidity and liquid feed, on the particle size of the granulations were determined.

5.1.1 Effects of inlet air humidity on temperature measurements of the granulator system (I)

The influences of inlet air humidity on the temperature measurements at different locations in the fluid bed granulator system were determined (I). The heating property of humid versus dry air within and between granulation batches was shown. Controlled variations of high inlet air humidity resulted in fluctuations in temperature of the granulation mass (Fig. 3B, I). A rapid decrease of the high inlet air humidity content caused the temperature of the fluidising mass to decrease. These high and fluctuating air humidity conditions were clearly different to those of low ambient and constant inlet air humidity conditions, in which temperature fluctuations were absent (Fig. 3A, I)

Temperature measurements at different locations were compared considering how dynamically inlet air humidity variations were detected (Fig. 4, I). The temperature measurements of the granulation bowl (T5 and T6) were prone to change as the inlet air humidity decreased, which highlighted the dynamic nature of these measurements. In clear contrast, the temperature measurements upstream from the product processing area (T10 and T11) changed less because they were not as sensitive to the changes of the inlet air in general. Therefore it was concluded that the granulation bowl was a more optimal place than the outlet air duct to monitor and control the progression of wet granulation and drying. The effect of inlet air humidity on the granulation mass temperature was also clearly shown when different granulation batches were compared (Fig. 5, I). A clear linear temperature increase of 10°C was seen in the granulation mass during the spraying phase, when the absolute inlet air humidity (AH1) increased from 4.5 g/m^3 to 23.4 g/m^3.

The theory behind the presented air humidity phenomenon became evident from psychrometry and thermodynamic principles (Carrier, 1921; Moyers and Baldwin, 1999). Schæfer and Wørts (1978a) noted the heating property of humid process air in their fluid bed granulation studies. However, visual elucidation of this phenomenon in a fluid bed environment has been lacking. Moreover, this kind of humidity system and controlled

rapid changes in the humidity level have not been previously carried out in fluid bed studies. The dynamic changes of various temperature measurements were illustrated in this study. The distinct effect of inlet air humidity on the granulation mass temperature was also indicated between batches by correlation analysis.

5.1.2 Effects of granulation liquid feed on temperature of fluidising mass (V)

The effects of changes in granulation liquid feed could be seen in the temperature of fluidising mass. Low inlet air humidity, slow granulation liquid feed rate and continual pausing of granulation liquid feed every second minute resulted in very dry conditions for wet granulation and thus specific temperature changes. As soon as granulation liquid feed pausing began, the temperature of the mass began fluctuating (Fig. 7, V). This phenomenon was also seen in other batches involving liquid pulsing, however, the moister the conditions in these batches the smaller was the temperature level change and fluctuation. The same type of temperature rise was seen at the end of a typical drying phase: as soon as particle surface water diminished, the particulate material absorbed heat and a temperature rise was detected.

The temperature measurements, especially those of fluidising mass, indicate the moisture conditions of wet granulation. Unexpected temperature rises in the chamber can mean improper fluidisation (channelling) or interruption in granulation liquid feed. The effect of liquid feed pausing on the temperature of the granulating mass was shown in this study (V). When granulation liquid feed was stopped for a predetermined period, the temperature of mass began to rise, especially in batches with slow granulation liquid feed and low inlet air humidity. Unexpected interruption in granulation liquid feed, such as by blockage, could influence the properties of the finished granules. This risk is more pronounced, if temperature of the mass rises and the particle surfaces dry too early. It is evident due to the temperature level changes that pausing of granulation liquid feed could also confound the end-point indication based on temperature measurements, i.e. the ΔT criterion (Harbert, 1972). The effect of spray rate of the binder solution on the temperature of the outlet air was studied previously (Abberger *et al.*, 1996b). The spray rate of binder solution was classified as being either subcritical or supercritical according to the extent of saturation of the outlet air (Abberger and Egermann, 1994). Significant differences in humidity and temperature of outlet air were observed with these different spray rate modes. Although they used a different approach, their results are in accordance with the findings discovered in this study.

Accordingly there are two contrasting ways in which water in liquid and vapour forms affect the temperature of the granulation mass. The sprayed granulation liquid absorbs heat energy from the process air and the temperature of the mass as a whole falls. On the other hand, the water vapour in air has latent heat and this thermodynamic heating property of the humid process air was clearly seen in this study as a temperature increase in the wet mass.

5.1.3 Effects of inlet air humidity and liquid feed on particle size of granules (I, III)

The particle size of the granulations derived from either dry or humid air clearly differed (Fig. 6, I). In humid air the mean particle size of the granules increased by 280 μm when batches with low humidity (4-6 g/m^3) were compared with batches granulated in high humidity air (>13 g/m^3). Batches of dry air contained more small particles than granulations formed under high humidity conditions. This was because in dry inlet air conditions fewer liquid bridges and thereby fewer solid bridges are formed between particles. The steady ambient, comparatively high inlet air humidity unexpectedly caused more problems in fluidisation behaviour than the overall higher but fluctuating humidity levels. This resulted in a considerable larger granule size of batch 9 (I). Pulses of dry air (Fig. 3B, I) improved the fluidisation of batches with high overall humidity. There is a high probability that without these pulses there would have been more deviating batches with variable particle sizes resulting.

Granulation liquid feed also strongly influenced the median granule size (Fig. 4, III) in addition to inlet air humidity. When the inlet air humidity and/or liquid feed rate increased, larger granules were formed during granulation. It was found, that the liquid feed rate can be modified for adjusting particle size in changing air humidity conditions. For example, when a median granule size of 300 μm was targeted, the effect of inlet air RH increase from 20% to 70% could be compensated for by decreasing the liquid feed rate from 75 g/min to 60 g/min.

The larger particle size associated with increasing inlet air humidity and granulation liquid feed found in this study is in accordance with previous reports (Wurster, 1960; Schæfer and Wørts, 1978a,b; Bouffard *et al.*, 2005). Rambali *et al*. (2001) evaluated three inlet air humidity levels (6, 10 and 14 g/kg), but the real effect of inlet air humidity change on the particle size could not be fully determined, because the inlet air temperature, inlet airflow and spray rate also varied. Schaafsma *et al*. (1999) detected granule growth, when the relative humidity attained a critical value above 50% with a lactose formulation. Above 75% RH severe channelling was detected, which results from sub-optimal fluidisation. Hemati *et al*. (2003) noted a significant effect on particle growth when RH was above 40%. Generally, there seem to be a critical, formulation- and process-dependent humidity level above which the granulation is more vulnerable to particle enlargement and de-fluidisation, even to irreversible bed collapse. In study I a RH value of 50% was considered a risk level for excessive particle size enlargement and de-fluidisation. Identifying risks is essential in implementing PAT and QbD principles (ICH Q8, 2005; ICH Q9, 2005). Furthermore, gaining a repeatable end product in spite of varying conditions is very much in accordance with these concepts. In study III, moisture variation originating from inlet air conditions could be compensated by varying granulation liquid feed.

5.2 Evaluating fluidisation behaviour and constructing the design space (I)

The flow rate of the process air and correct fluidisation of the mass were for the most part determined by fan speed adjustment. The airflow was created by turbine fan suction located upstream from the product processing area, which is a common configuration (Olsen, 1989). Flow rate (g/s) was measured at the inlet air duct and fan speed (Hz, 1/s) at the turbine. Improper fluidisation of the mass caused the relationship of flow rate and fan speed to decrease because the de-fluidising mass partially blocked the upward-moving gas (I). Therefore, the following parameter was developed (Eq. 2).

Eq. 2
$$Fluidisation\ parameter = \frac{Airflow\ \ rate}{Fan\ \ speed}$$

Further comparison was made with the most humid batches (Fig. 7, I). The batch with the highest inlet air humidity (batch 14) had a deviating profile. Risk of improper fluidisation was identified, though the particle size results did not deviate. The fluidisation parameter progression of batch 9 (ambient intermediate humidity) was very low during wet granulation and drying. The over-wetting of the mass and subsequent improper fluidisation caused deviating high particle size of batch 9. Batch 15 (high humidity) collapsed unexpectedly after spraying 75% (1500 g) of granulation liquid. Improper fluidisation was the reason for the quality deviation in both batch 9 and 15. These batches had the very same progression of the fluidisation parameter initially and the further course of fluidisation parameter values described the fluidisation behaviour well.

Finally the process trajectories for the fluidisation parameter were developed (Fig. 8, I). The mode ‘smooth fluidisation’ was identified, which caused expected particle size results. Failure mode classification included ‘over fluidisation’, ‘improper fluidisation’ and ‘bed collapse’. The mode ‘risk of improper fluidisation’ was also identified. The risk factors for this model formulation and process were identified. These were occasionally insufficient airflow rate, the hydrophobic nature of the ibuprofen formulation, low temperature of the inlet air, relatively high spraying rate of the granulating liquid and relatively high binder content of granulating liquid. The flow rate of the inlet air at the beginning of spraying phase II (moisture increased) was especially critical when the humidity of inlet air was high, which was seen as over-wetting of the mass and as low fluidisation parameter values (Fig. 7, I).

Compensating adjustments should be evaluated to support further this design space: higher temperature of the inlet air, higher flow rate of the inlet air (if possible) and slower or pulse spraying of the granulating liquid (Schæfer and Wørts, 1978a; Schaafsma *et al*., 1999; Morris *et al*., 2000). The dehumidifying system is justified when handling hydrophobic material in varying humidity conditions. A humidifier and a dehumidifier together control the dew point of the process air (Olsen 1989; Greenhalgh and Westrup, 1997). Alternative approaches were found in this study: pulses of dry air may prevent over-wetting and bed collapse during the spraying phase. The fluidisation parameter can be used as a prognostic and control tool to prevent over-wetting and improper fluidisation.

It is possible to control the inlet airflow rate automatically, based on this fluidisation parameter. The fluidisation parameter and the design space together can achieve control over fluidisation process performance and it is possible to avoid failure modes during granulation.

5.3 Optimising fluid bed drying (II)

5.3.1 Comparing different end-point indication techniques of drying

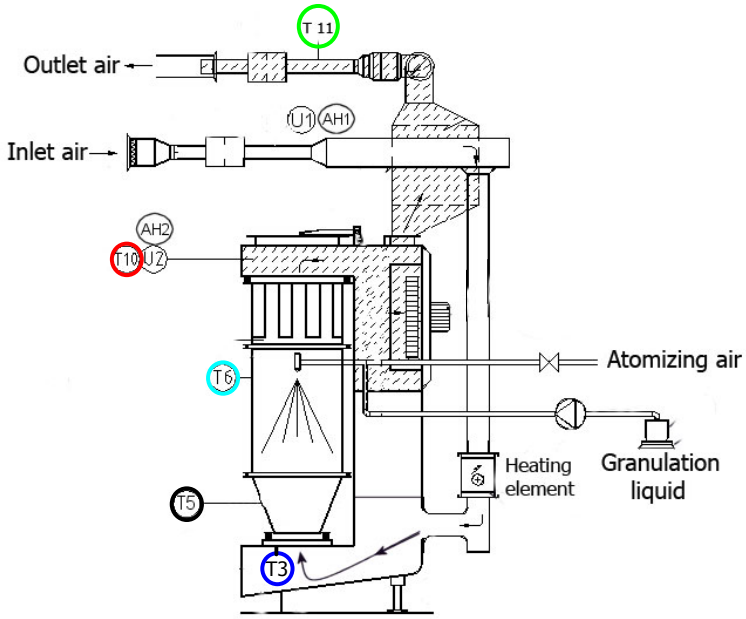

Fig. 9. Important measurements of this study are highlighted in the instrumented Glatt WSG 5 fluid bed granulator.
T3 = temperature of the inlet air below the distributor plate
T5 = temperature of the mass measured at the bottom of the granulator bowl
T6 = temperature of the process air in the middle of the granulator bowl
T10 = temperature on the top side of the filters
T11 = temperature in the outlet air duct
U1 = relative humidity of the inlet air
U2 = relative humidity of the outlet air
AH1= absolute humidity of the inlet air
AH2 = absolute humidity of the outlet air

The temperature of the process air was analysed from five different locations considering the end-point indication of drying (Fig. 8). It was obvious that the measurement became less effective and accurate and therefore less feasible for end-point detection the further from the distributor plate it was taken. The most effective location for detecting

granulation temperature was the bottom of the bowl (T5), where particles typically moved slowly and there was efficient heat exchange with the inlet air (Fig. 3, II). In addition, the upper part of the bowl (T6) where granules moved more freely was also an effective site. The top side of the filters (T10) was a less dynamic point of temperature control and the outlet air duct (T11) appeared to be unsuitable due to effective damping. Even so, the outlet air duct (T11) is the usual location for detecting the end-point of drying, though the temperature of the surroundings affects the measurement significantly. The measurement at the bottom of the chamber (T5) reflected the temperature of inlet air (T3) more than the upper locations (T6, T10, T11) did. Therefore T5 was more susceptible to temperature fluctuations in the inlet air than T6. However, temperature measurement in the middle of the chamber allowed a greater cooling effect of water evaporation. The T6 measurement was virtually as dynamic as T5 despite the heat being absorbed as the process air moved upwards. A temperature sensor in the middle of a chamber above the granulation mass is a preferable choice for drying end-point detection, if sticking of the mass on the surface of a sensor is a problem.

The inlet and outlet air humidity measurements are presented in Fig. 4 (II). The differences between AH2 and AH1 absolute humidity measurements provided another way to estimate the drying end-point, especially when inlet air humidity was low. When the AH1 increased, interpretation was difficult because the difference between AH2 and AH1 was not constant. In this setup the humidity measurements did not give reliable estimates of the moisture contents of the granules, especially when AH1 was high. As seen in Fig. 4 (II), the differences between relative humidity measurements U2 and U1 were not applicable because these values were temperature-dependent. In Fig. 5 (II) the absolute water content of the mass of the same batch during the drying phase is described. The fitted curve (Eq. 1, II) appeared to model the decrease in moisture content well. Later, these fitted moisture curves of different batches were correlated with the temperature measurements of the granules (Figs. 8 and 9, II).

Temperature measurements described the progression of drying better than humidity measurements. Therefore it is vital that temperature detection is made as dynamically as possible, in this case at locations T5 and T6 in the chamber.

5.3.2 Effects of inlet air humidity variations on fluid bed drying end-point detection

The influence of inlet air humidity (AH1) on temperature of the mass (T5) was clearly shown when different batches were compared at the beginning of the drying phase (Fig. 6, II). When the inlet air was dry, T5 was significantly lower than when the inlet air had high humidity, because the heat capacity of humid air is greater than that of dry air. When the humidity of the inlet air increased, more heat was transferred to the wet mass during fluidisation. Fig. 6 (II) also indicates the event in which the drying phase was finished when T5 reached 36 °C. The fulfilling of this criterion was used as the signal to finish the process. T5 of 36 °C was a favourable criterion when the inlet air was dry. However, when

the inlet air was humid, the final granules were clearly too moist at 36 °C. Fig. 6 (II) shows that T5 increased by 17.1 °C from wet-bulb temperature during the drying phase when the humidity was low. However, when the inlet air was humid T5 increased by only 8.3 °C from the wet-bulb temperature. These results show that a constant temperature criterion for the end-point of drying is not applicable when inlet air humidity changes on a large scale. However, a constant temperature increase ΔT from the wet-bulb temperature level should be used (Harbert, 1972). The ΔT is the difference between the end-point temperature of the granules and the temperature of the granules at the start of the drying phase (see 2.4.5). Fig. 7 (II) shows that there was a clear trend for the final moisture contents to increase when the humidity content of the air increased. The residual moisture contents of the finished granules varied between 0.46 and 1.22 w/w-% when the constant temperature criterion was used. This variation would have been smaller, if the ΔT technique was used as the end-point criterion.

The 'weather effect' is a confounding factor that often occurs in the widely used method of detecting drying end-point by specific temperature of the outlet air or the granules (Jones, 1985). Dynamic temperature measurements near the granulation mass depicted the drying end-point better than humidity measurements especially when inlet air humidity changed over a wide range. The effect of air humidity on temperature is crucial to take into account when temperature measurements are used to indicate the end-point of drying.

5.3.3 Relationships between temperature and moisture measurements during the fluid bed drying phase

The level of moisture in the fluidising mass cannot be directly predicted from the temperature measurements, as described in previous chapters. There is a clear interaction between the temperature and the moisture content of the granules during the drying phase. Therefore the variables influencing these parameters must be understood before clear relationships can be made. Fig. 8 (II) shows the absolute moisture level of the granules (w/w-%) as a function of T5. If the temperature and moisture of the mass were directly correlated, then the curves would be superimposed. Instead, the different humidity levels were clearly separated. Batch 9 deviated from the humidity pattern because the maximum inlet airflow was not high enough to maintain optimum fluidisation of the wet mass. The mass had relatively higher temperatures because it was partially collapsed and evaporative cooling was insufficient. When ΔT calculated with T5 was correlated with the absolute moisture level of the granules, most of the humidity level differences disappeared (Fig. 9, II). No further significant differences between the curves was observed, suggesting that ΔT is capable of predicting the moisture level of the mass better than T5. Even so, two batches (6 and 9) deviated from the general curve. These two batches were moister than other batches with the same ΔT value. Batch 9 deviated due to divergent fluidisation activity, whereas batch 6 also had a divergent profile. Short-term improper fluidisation during the wet granulation phase was suggested as a likely reason for this deviation. The effect of humidity fluctuations caused by the humidifying system was also seen at the end curve of batch 10.

The ΔT method for detecting the drying end-point eliminated the effects of the remarkably changing humidity levels of the process air. It is clear from these results that the ΔT criterion is valid only, if there are no fluidisation differences between batches. The effect of fluidisation on the ΔT technique has not been highlighted in previous studies (Harbert, 1972, 1973, 1974; Ehrhardt, 1977; Schæfer and Wørts 1978a; Gore *et al*., 1985; Leuenberger and Imadidis, 1986; Alden *et al*., 1988). De-fluidisation, even for short periods, can be considered a major source of deviation associated with the technique. This results from the granulation mass having a relatively higher temperature when fluidisation is low than when it is at optimum levels. Although the ΔT technique efficiently eliminates the effect of inlet air humidity variations, de-fluidisation caused by elevated humidity levels affects the criterion and thus the end-point moisture contents. The inlet air temperature and granulation liquid feed variations are also potential sources of error.

5.4 Increasing process understanding by in-line particle size measurements and physical measurements

5.4.1 Process phenomena described by in-line particle size analyser (IV)

The in-line particle size analyser (SFT) rapidly detected the actual granule size changes and these changes could be monitored in real time and analysed in greater detail afterwards. Various process phenomena and failure modes could be observed. Natural process related fluctuation of SFT particle size results could be utilised for increasing process understanding. Fluctuation was due to the fine material in the process, which returned to the fluidising mass when filter bags were regularly shaken. This information can be utilised for formulation and process development as one response. The target can be to minimise fine material already during processing, if such small particles impair the processability of the final granules.

Rapid increase in granule size could be observed (Fig. 4, IV) when the entrapment of fine particles in the filter bags caused a process deviation. As soon as the filter shaking mechanism was restored, the level of particle size results was normalised. Moreover, decreasing particle size could be monitored in a timely manner. Measured granule size and granule size fluctuation decreased at the end of the drying process in a few batches (Fig. 5, IV). This unexpected event was related to improper fluidisation due to the adhesion of fluidising material on the distributor plate. Pressure difference over the bed and inlet air flow rate measurements also suggested this. In addition, it was noticed after the process that the dry and fine material covered the chamber surfaces including distributor plate. It is likely that static electrical charges and van der Waals forces contributed to this adhesion.

The results of this study (IV) suggest that the novel SFT fluid bed in-line application can be used to increase process understanding both during the process itself and by analysing

the data afterwards. Various phenomena and process failure modes related to particle size could be identified.

5.4.2 Determining the changing conditions during the spraying phase (V)

The aim of the study V was to evaluate an instrumentation system for a bench scale fluid bed granulator in order to determine the measurements expressing the changing conditions during the spraying phase of a fluid bed process. The in-line particle size measured by the spatial filtering technique (SFT) was an essential predictor variable. The study focused mainly on three in-line measurements (dependent variables): fluidisation parameter (calculated by inlet air flow rate and rotor speed), pressure difference over the upper filters and pressure difference over the granules (lower filter).

There was a correlation between fluidisation parameter and median particle size for all the batches. The median particle size was drawn as a function of fluidisation parameter values of all batches when an approximate steady state particle growth phase was achieved and 500-2000 g granulation liquid sprayed (Fig. 1, V). The correlation was linear, except for the deviating extremely moist batch 4. High levels of air humidity and granulation liquid feed resulted in uncontrollable granule growth (coalescence, ball growth) in this batch and the mass was partly collapsed at the end of the wet granulation phase. Remarkably, the yellow points of batch 4 in the line correspond to the beginning of the spraying phase when the mass was still fluidising properly, and a separated yellow group represents the measurements when the mass was partly collapsed.

The particle size was predicted at the end of the spraying phase by the last fluidisation parameter values. As illustrated in Fig. 5 (V), the fluidisation parameter values at the end of the spraying phase served as a quite good estimate of the median particle size except for batch 4 which had a deviating fluidisation. The bulk density of wet granules was about 0.6 g/ml compared to 0.4 g/ml in the dry state. The relatively high density of granules during the spraying phase likely contributed to the deviating fluidisation behaviour of batch 4.

Pressure difference over filters (dP1) and pressure difference over granules (dP2) were also thought as potential indicators of particle size and air flow through the granulating mass. The spraying stage 500-2000 g (stage III) of 16 batches was used for analyses as a uniform period. The same type of correlation with median particle size was tried to find for these parameters as for fluidisation parameter values previously. Correlation was found between dP1 and median particle size, The R^2 value was 0.75 when 500-2000 g of granulation liquid was sprayed (Fig. 6, V). The correlation for dP1 was, however, reversed compared with fluidisation parameter: smaller pressure differences were observed with larger particles. This is a normal occurrence, considering that small particles become lodged in the upper filters and thereby elevate the pressure difference. When further stages (700-, 800-, 1000-, 1500-2000 g) were compared, fluidisation parameter had still higher correlation with median particle size than dP1. For example, at the stage 1000-2000 g, R^2 was 0.80 for fluidisation parameter vs. median particle size compared with R^2 0.77 for dP1

vs. median particle size. Thereby the fluidisation parameter was considered to be a somewhat better indicator of particle size than dP1. Pressure difference over granules (dP2) was not correlated with median particle size. The partial least squares (PLS) analyses revealed the factors affecting both these pressure difference measurements more specifically (Table 3, V). The dP1 was mainly affected by air flow through the system and by particle size. The factors affecting dP2 were related to moisture in the system and pressure difference upstream.

Thus the pressure difference measurements over the granules and upper filters expressed diverse phenomena. A clear correlation between pressure difference over filters and particle size was observed. The dry conditions of wet granulation and the small particle size of the granules were seen as elevated dP1 values. Particle size did not affect pressure difference over granules. Instead, the moisture in the system (the amount of granulation liquid sprayed and cumulative water balance) clearly affected this parameter.

In production scale manufacturing, repeating fluidisation parameter values between different batches of the same material can indicate similar fluidisation conditions and thus uniform particle size, especially when moisture conditions are similar. On the other hand, deviating fluidisation parameter values can mean processing variations and a sliding out of the design space. Here, a deviation from the direct correlation curve could be considered as an indication of wide variation in fluidisation behaviour. This concept of determining correlations and identifying sources of variation is consistent with recent guidelines for highlighting continuous improvement in manufacturing processes (FDA, 2004, ICH Q8, 2005; ICH Q9, 2005). This type of instrumentation system is an invaluable aid to gaining more control for fluid bed processing to obtain repeatable granules for further manufacturing steps.

6. Conclusions

The automated fluid bed granulator equipped with a versatile instrumentation system enabled to study process related phenomena and to increase understanding of the process of fluid bed granulation and drying. Furthermore, various analyses of different measurements revealed critical relationships and variation sources, which could be used for the basis for constructing a design space for process performance. This type of instrumentation system is an invaluable aid to gaining more control for fluid bed processing to obtain consistent and uniform granules for further processing.

The heating effect of air related to humidity level was demonstrated within and between granulation batches in different parts of a granulator system. Temperature measurements at certain sites were found to describe the progression of drying better than humidity measurements. The effect of granulation liquid feed (pulsing) on temperature of fluidising mass was clearly shown. The effect of inlet air humidity and granulation liquid feed on granule size were evaluated. Both increasing inlet air humidity and granulation liquid feed increased the particle size.

Novel fluidisation parameter was developed. The more improperly the particles were fluidising the lower was the relationship of air flow rate and fan speed. Four different failure modes were identified and classified based on the fluidisation parameter: over fluidisation, risk of improper fluidisation, improper fluidisation and collapsed bed. It was possible to construct process trajectories for smooth fluidisation, which the optimal granulation process should follow.

Various drying end-point criteria based on temperature and humidity measurements were compared. With varying inlet air humidity, the commonly used ΔT temperature difference method was found to give a more precise estimation of the drying end-point than the constant temperature criterion. New insights were found into the correlation between moisture content and temperature of the fluidising mass. The fluidisation behaviour was found to affect greatly the end-point detection of drying. Therefore the use of the ΔT criterion requires proper fluidisation throughout the whole process.

The in-line particle size analyser (SFT) rapidly detected the actual granule size changes and these changes could be monitored both in real time and analysed more specifically afterwards. Various process phenomena and failure modes could be observed. These phenomena included a rapid increase in granule size related to the entrapment of fine particles in the filter bags and a decreasing particle size due to the adhesion of fluidising material on the distributor plate. Correlation and PLS analyses revealed significant relationships between various process parameters highlighting the particle size, moisture, and fluidisation effects. Correlation with in-line particle size was found between both the fluidisation parameter and the pressure difference over the upper filters. The pressure difference over the granules and the temperature of the fluidising mass expressed the moisture conditions of wet granulation.

References

Abberger T., Egermann H., 1994. Granule growth rates versus free humidity in fluid bed granulations. Eur. J. Pharm. Sci. 2, 110

Abbaerger T., Schlocker W., Egermann H., 1996a. Estimation of concentration of free moisture in fluid bed granulation. Eur. J. Pharm. Sci. 4, 185

Abberger T., Raneburger J.A., Egermann H., 1996b. Instrumentation of a laboratory-scale fluid-bed granulator for control of critical spray rate and of free moisture. Sci. Pharm. 64, 255-262

Abdel-Alim, H., Mahmoud, H.M., Zein El-Deen, E., 1986. Influence of physical properties of binders and powders on the characteristics of the granules. S.T.P. Pharma 2, 313-316

Ahlneck, C., Zografi, G., 1990. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. Int. J. Pharm. 62, 87-95

Airaksinen S., Karjalainen, M., Shevchenko, A., Westermarck, S., Leppänen, E., Rantanen, J., Yliruusi, J., 2005a. Role of water in the physical stability of solid dosage formulations. J. Pharm. Sci. 95, 2147-2165

Airaksinen S., Karjalainen, M., Kivikero, N., Westermarck, S., Shevchenko, A., Rantanen, J., Yliruusi, J., 2005b. Excipient selection can significantly affect solid-state phase transformation in formulation during wet granulation. AAPS PharmSciTech. 6, article 41

Alden, M., Torkington, P., Strutt, A.C.R., 1988. Control and instrumentation of a fluidized-bed drier using the temperature-difference technique. I. Development of a working model. Powder Tech. 54, 15-25

Alderborn, G., 1988. Granule properties of importance to tableting. Acta Pharm. Suec. 25, 229-238

Alkan, M.H., Yuksel, A., 1986. Granulation in a fluidized bed II. Effect of binder amount on the final granules. Drug Dev. Ind. Pharm. 12, 1529-1543

Amidon, G., Houghton, M.E., 1995. The effect of moisture on the mechanical and powder flow properties of microcrystalline cellulose. Pharm. Res. 12, 923-929

Ansari, M.A., Stepanek, F., 2008. The effect of granule miscrostructure on dissolution rate. Powder Tech. 181, 104-114

Aulton, M.E., Banks, M., 1981. Fluidised bed granulation – factors influencing the quality of the product. Int. J. Pharm. Tech. Prod. Manuf. 2, 24-29

Banks, M., Aulton, M.E., 1991. Fluidised-bed granulation: a chronology. Drug Dev. Ind. Pharm. 17, 1437-1463

Baughman, E., 2005. Process analytical chemistry: introduction and historical perspective. (in) Bakeev, K.A. (Ed.). Process Analytical Technology. First edition. Blackwell Publishing, Chap. 1

Berggren, J., Alderborn, G., 2001. Effect of drying rate on porosity and tabletting behaviour of cellulose pellets. Int. J. Pharm. 227, 81-96

Bhutani, B.R. and Bhatia, V.N., 1975. Drying rates of tablet granulations I: effect of certain granulating adjuvants on drying rates. J. Pharm. Sci., 1975, 135-139

Blanco, M., Coello, J., Iturriaga, H., Maspoch, S., de la Pezuela, C., 1998. Near-infrared spectroscopy in the pharmaceutical industry. Analyst 123, 135R-150R

Bouffard, J., Kaster, M., Dumont, H., 2005. Influence of process variable and physicochemical properties on the granulation mechanism of mannitol in a fluid bed top spray granulator. Drug Dev. Ind. Pharm. 31, 923-933

Carrier, W.H., 1921. The theory of atmospheric evaporation – with special reference to compartment dryers. J. Ind. Eng. Chem. 13, 432-438

Cooper, J., Swartz, C.J., Suydam Jr., W., 1961. Drying of tablet granulations. J. Pharm. Sci. 50, 67-75

Cooper, D.J., Clough D.E., 1985. Experimental tracking of particle-size distribution in a fluidized bed. Powder Tech. 44, 169-177

Cutt, T., Fell, J.T., Rue, P.J., Spring, M.S., 1986. Granulation and compaction of a model system. I. Granule properties. Int. J. Pharm. 33, 81-87

Davies, B., Ellis, S., 2005. Process analytical technology: the route to process understanding and control. Pharm. Tech. Eur. 17, pp. 17-20, 22-23

Davies, W.L., Gloor Jr., W.T., 1971. Batch production of pharmaceutical granulations in a fluidized bed I: Effects of process variables on physical properties of final granulation. J. Pharm. Sci. 60, 1869-1874

Davies, W.L., Gloor Jr., W.T., 1972. Batch production of pharmaceutical granulations in a fluidized bed II: Effects of various binders and their concentrations on granulations and compressed tablets. J. Pharm. Sci. 61, 618-622

Dawoodbhai, S., Rhodes, C.T., 1989. The effect of moisture on powder flow and on compaction and physical stability of tablets. Drug Dev. Ind. Pharm. 15 , 1577-1600

Debnath, S., Suryanarayanan, R., 2004. Influence of processing-induced phase transformations on the dissolution of theophylline tablets. AAPS PharmSciTech 5, 1-11

Drakulich, A., 2008. ICH Q10 moves to final stage: International Adoption. EPT - The Electronic Newsletter of Pharm. Tech. Jun 12 (www.pharmtech.com)

Ehrhardt, L., 1977. Drying granules in the fluid bed drier. Int. Tech. Pharm. 3, 181-190

Etzler, F.M., Sanderson, M.S., 1995. Particle size analysis: a comparative study of various methods. Part. Syst. Charact. 12, 217-224

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

Fitzpatrick, S., McCabe, J.F., Petts, C.R., Booth, S.W., 2002. Effect of moisture on polyvinylpyrrolidone in accelerated stability testing. Int. J. Pharm. 246, 143-151

Food and Drug Administration FDA, 2004. Guidance for Industry; PAT - a framework for innovative pharmaceutical development, manufacturing and quality assurance

Formisani, B., Girimonte, R., Longo, T., 2008. The fluidization pattern of density-segregating binary mixtures. Chem. Eng. Res. Design 86, 344-348

Frake, P., Greenhalgh, D., Grierson, S.M., Hempenstall, J.M., Rudd, D.R., 1997. Process control and end-point determination of a fluid bed granulation by application of near infra-red spectroscopy. Int. J. Pharm. 151, 75-80

Gao, J.Z.H., Jain, A., Motheram, R., Gray, D.B., Hussain M.A., 2002. Fluid bed granulation of a poorly water soluble, low density, micronized drug: comparison with high shear granulation. Int. J. Pharm. 237, 1-14

Garcia, T., Cook, G., Nosal, R., 2008. PQLI Key Topics – Criticality, Design Space, and Control Strategy (Product Quality Lifecycle Implementation Innovations). J. Pharm. Innov. 3, 60-68

Geldart, D., 1973. Types of gas fluidization. Powder Tech. 7, 285-292

Geldart, D., Baeyens, J., 1985. The design of distributors for gas-fluidized beds. Powder Tech. 42, 67-78

Georgakopoulos, P.P., Malamataris, S., Dolamidis, G., 1983. The effects of using different grades of PVP and gelatin as binders in the fluidized bed granulation and tabletting of lactose. Pharmazie 38, 240-243

Gore, A.Y., McFarland, D.W., Batuyios, N.H., 1985. Fluid-bed granulation: factors affecting the process in laboratory development and production scale-up. Pharm. Tech. 9, 114-122

Gorodnichev, V.I., El-Banna, H.M., Andreev, B.V., 1981. The construction and uses of factorial designs in the preparation of solid dosage forms. Pharmazie 36, 270-273

Gould, P.L., 1984. Optimisation methods for the development of dosage forms. Int. J. Pharm. Tech. Prod. Mfr. 5, 19-24

Green, R.L., Thurau, G., Pixley, N.C., Mateos, A., Reed, R.A., Higgings, J.P., 2005. In-line monitoring of moisture content in fluid bed dryers using near-IR spectroscopy with consideration of sampling effects on method accuracy. Anal. Chem. 77, A-H (www.pubs.acs.org)

Greenhalgh D., Westrup, J., 1997. Process control during fluid bed granulation - the importance of humidity control. J. Pharm. and Pharmacol. 49, 22

Guenard, R., Thurau, G., 2005. Implementation of process analytical technologies. (in) Bakeev, K.A. (Ed.). Process Analytical Technology. First edition. Blackwell Publishing, Chap. 2

Harbert, F.C., 1972. Technical paper. Automatic control of dryers. Metron Tech. 4, 1-5

Harbert, F.C., 1973. Moisture measurement and control in industrial processes: case studies carried out by Sira Institute, Report R505, 1-24

Harbert, F.C., 1974. Automatic control of industrial drying processes. Manufact. Chem. Aerosol News 45, 23-24

Hemati, M., Cherif, R., Saleh, K., Pont, V., 2003. Fluidized bed coating and granulation: influence of process-related variables and physicochemical properties on the growth kinetics. Powder Tech. 130, 18-34

Herman, J., Remon, J.P., Visavarungroj, N., Schwartz, J.B., Klinger, G.H., 1988. Formation of theophylline monohydrate during the pelletisation of microcrystalline cellulose-anhydrous theophylline blends. Int. J. Pharm. 42, 15-18

Hu, X., Cunningham, J.C., Winstead, D. Study growth kinetics in fluidized bed granulation with at-line FBRM. Int. J. Pharm. 347, 54-61

Hyland, M., Naunapper, D., 1986. Continuous control of product moisture content in drying processes. Pharm Ind. 48, 655-660

International Conference on Harmonisation, 2005. ICH harmonised tripartite guideline; Pharmaceutical Development Q8

International Conference on Harmonisation, 2007. ICH draft consensus guideline; Pharmaceutical Development Annex to Q8

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

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

Iveson, S.M., Litster, J.D., Hapgood, K., Ennis, B.J., 2001. Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review. Powder Tech. 117, 3-39

Jones, D.M., 1985. Factors to consider in fluid-bed processing. Pharm. Tech. 9, 50-62

Juslin, L., and Yliruusi J., 1996a. Granule growth kinetics and attrition of granules made of different materials in a fluidized bed granulator. S.T.P. Pharma Sci. 6, 321-327

Juslin, L., and Yliruusi J., 1996b. The effect of raw material and atomizing air pressure on the properties of granules prepared in a fluidized bed granulator. S.T.P. Pharma Sci. 6, 328-334

Kristensen, H.G., Schaefer, T., 1987. Granulation. A review on pharmaceutical wet granulation. Drug Dev. Ind. Pharm. 13, 803-872

Kristl, A., Mrhar, A., Kozjek, F., 1994. Physico-chemical evaluation and statistical assessment of wet granulation. Drugs made in Germany 37, 78-82

Kunii, D., Levenspiel, O., 1991. Fluidization Engineering. Second edition. Butterworth-Heinemann, Newton

Laitinen, N., Antikainen, O., Rantanen, J., Yliruusi, J., 2004. New perspectives for visual characterization of pharmaceutical solids. J. Pharm. Sci. 93, 165-176

Law, C.L., Mujumbar, A., 2007. Fluidized bed dryers. (in) Mujumbar, A. (Ed.). Handbook of industrial drying. Third edition. Taylor & Francis Group, Chap. 8

Lepore, J., Spavins, J., 2008. PQLI Design Space (Product Quality Lifecycle Implementation Innovations). J. Pharm. Innov. 3, 79-87

Leuenberger, H., Bier, H.-P., Sucker, H.B., 1979. Theory on the granulation-liquid requirement in the conventional granulation process. Pharm. Tech. Int. 2, 60-69

Leuenberger, H. 1982. Granulation, new techniques. Pharm. Acta Helv. 57, 72-82

Leuenberger, H., 1983. Scale-up of granulation processes with reference to process monitoring. Acta Pharm. Tech. 29, 274-280

Leuenberger, H., Imadidis, G., 1986. Monitoring mass transfer processes to control moist agglomeration. Pharm. Tech. 10, 56-73

Lewis, G.A., Mathieu, D., Phan-Tan-Luu, R., 1999. Pharmaceutical experimental design. First edition. Marcel Dekker, Inc., New York

Li, W., Cunningham J., Rasmussen, H., Winstead, D, 2007. A qualitative method for monitoring of nucleation and granule growth in fluid bed wet granulation by reflectance near-infrared spectroscopy. J. Pharm. Sci. 96, 3470-3477

Maroulis, Z.B., Kiranoudis, C.T., Marinos-Kouris, D., 1995. Heat and mass transfer modeling in air drying of foods. J. Food. Eng. 26, 113-130

Menon, A., Dhodi, N., Mandella, W., Chacrabarti, S., 1996. Identifying fluid-bed parameters affecting product variability. Int. J. Pharm. 140, 207-218

Merkku, P., Yliruusi, J., Hellén, L., 1992. Testing of an automated laboratory scale fluidised bed granulator using different bed loads. Acta Pharm. Fennica 101, 173-180

Merkku, P., Lindqvist, A.-S., Leiviskä, K., Yliruusi, J., 1994. Influence of granulation and compression process variables on flow rate of granules and on tablet properties, with special reference to weight variation. Int. J. Pharm. 102, 117-125

Miyamoto, Y., Ogawa, S., Miyajima, M., Sato, H., Takayama, K., Nagai, T., 1995. An evaluation of process variables in wet granulation. Drug Dev. Ind. Pharm. 21, 2213-2225

Morris, K.R., Stowell, J.G., Byrn, S.R., Placette, A.W., Davis, T.D., Peck, G.E., 2000. Accelerated fluid bed drying using NIR monitoring and phenomenological modeling. Drug Dev. Ind. Pharm. 26, 985-988

Morris, K.R., Griesser U.J., Eckhardt C.J., Stowell J.G., 2001. Theoretical approaches to physical transformations of active pharmaceutical ingredients during manufacturing processes. Adv. Drug Del. Rev. 48, 91-114

Moyers, C.G., Baldwin, G.W., 1999. Psychrometry, evaporative cooling, and solids drying (in) Perry R.H., Green D.W., Maloney J.O. (Eds.). Perry's Chemical Engineers Handbook. Seventh edition. McGraw Hill, Chap. 12

Mujumbar, A., 2007. Principles, classification, and selection of dryers. (in) Mujumbar, A. (Ed.). Handbook of industrial drying. Third edition. Taylor & francis Group, Chap. 1

Newitt, D.M., Conwey-Jones, J.M., 1958. A contribution to the theory and practice of granulation. Trans. Instn Chem. Engrs. 36, 422-442

Newman, A.B., 1931. The drying of porous solids: diffusion and surface emission equations. Trans. AICh.E 27, 203-219

Niskanen, T., Yliruusi, J., Niskanen, M., Kontro, O., 1990. Granulation of potassium chloride in instrumented fluidized bed granulator – Part I: effect of flow rate. Acta Pharm. Fennica 99, 13-22

Nokhodchi, A., 1995. An overview of the effect of moisture on compaction and compression. Pharm. Tech. 29, 46-66

Olsen, K.W., 1989. Batch fluid bed processing equipment, a design overview: Part 1. Pharmaceutical Technology 13, pp. 34, 36, 38, 40, 42, 44, 46

Ormós, Z., 1973. Studies on granulation in a fluidized bed I. Methods for testing the physical properties of granulates. Hung. J. Ind. Chem. 1, 207-228

Ormós, Z., Pataki, K., 1979a. Studies on granulation in a fluidized bed VII. The effect of raw material upon the granule formation. Hung. J. Ind. Chem. 7, 89-104

Ormós, Z., Pataki, K., 1979b. Studies on granulation in a fluidized bed VIII. Effect of the raw material initial particle size upon granule formation. Hung. J. Ind. Chem. 7, 105-116

O'Reilly, E., 1997. Pharmaceutical drying: how best to achieve this unit process and aspects of its validation. Irish Pharm. J. 75, 126-129

Parikh, D.M., 1991. Airflow in batch fluid-bed processing. Pharm. Tech. 15, 100-110

Parikh, D.M., 1996. Fluid bed processing in the 1990s. Pharm. Tech. 20, pp. 40, 42, 44-47

Pell, M., Dunson, J.B., 1999. Gas-solid operations and equipment. (in) Perry R.H, Green D.W. and Maloney J.O. (Eds.). Perry's Chemical Engineers Handbook. Seventh edition. McGraw Hill, Chap. 17

Rajniak, P., Mancinelli, C., Chern, R.T., Stepanek, F., Farber, L., Hill, B.T., 2007. Experimental study of wet granulation in fluidized bed: impact of the binder properties on the granule morphology. Int. J. Pharm. 334, 92-102

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

Rambali, B., Baert, L., Massart, D.L., 2001b. Using experimental design to optimize the process parameters in fluidized bed granulation on a semi-full scale. Int. J. Pharm. 220, 149-160

Rambali, B., Van Aelst, S., Baert, L., Massart, D.L., 2003. Using deepest regression method for optimization of fluidized bed granulation on semi-full scale. Int. J. Pharm. 258, 85-94

Rantanen, J., Lehtola, S., Rämet, P., Mannermaa, J.P., Yliruusi, J., 1998a. On-line monitoring of moisture content in an instrumented fluidized bed granulator with a multi-channel NIR moisture sensor. Powder Tech. 99, 163-170

Rantanen, J., Yliruusi, J., 1998b. Determination of particle size in a fluidized bed granulator with a near infrared setup. Pharm. Pharmacol. Comm. 4, 73-75

Rantanen, J., Antikainen, O., Mannermaa, J.P., Yliruusi, J., 2000a. Use of near-infrared reflectance method for measurement of moisture content during granulation. Pharm. Dev. Tech. 5, 209-217

Rantanen, J., Räsänen, E., Tenhunen, J., Känsäkoski, M., Mannermaa, J.-P., Yliruusi, J., 2000b. In-line moisture measurement during granulation with a four-wavelength near infrared sensor: an evaluation of particle size and binder effects. Eur. J. Pharm. Biopharm. 50, 271-276

Rantanen, J., Känsäkoski, M., Suhonen, J., Tenhunen, J., Lehtonen, S., Rajalahti, T., Mannermaa, J.P., Yliruusi, J., 2000c. Next generation fluidized bed granulator automation. AAPS PharmSciTech. 1, article 10 (www.aapspharmscitech.org)

Rantanen, J., Laine, S.J., Antikainen, O.K., Mannermaa, J.-P., Simula, O.E., Yliruusi, J., 2001. Visualization of fluid-bed granulation with self-organizing maps. J. Pharm. Biomed. Anal. 24, 343-352

Record, P.C., 1980. A review of pharmaceutical granulation technology. Int. J. Pharm. Tech. Prod. Mfr. 1, 32-39

Reich, G., 2005. Near-infrared spectroscopy and imaging: basic principles and pharmaceutical applications. Adv. Drug Dev. Rev. 57, 1109-1143

Räsänen, E., Antikainen, O., Yliruusi, J., 2003. A new method to predict flowability using a microscale fluid bed. AAPS PharmSciTech. 4, 418-424

Räsänen, E., Rantanen, J., Mannermaa, J.-P., Yliruusi, J., 2004. The characterization of fluidization behavior using a novel multichamber microscale fluid bed. J. Pharm. Sci. 93, 780-791

Schaafsma S.H., Kossen N.W.F., Mos M.T., Blauw L., Hoffmann, A.C., 1999. Effects and control of humidity and particle mixing in fluid-bad granulation. AIChE Journal 45, 1202-1210

Schæfer, T., Wørts, O., 1977. Control of fluidized bed granulation. I. Effects of spray angle, nozzle height and starting materials on granule size and size distribution. Arch. Pharm. Chemi Sci. Ed. 5, 51-60

Schæfer, T., Wørts, O., 1978a. Control of fluidized-bed granulation III: Effects of inlet air temperature and liquid flow rate on granule size and size distribution. Control of moisture content of granules in the drying phase. Arch. Pharm. Chemi Sci. Ed. 6, 1-13

Schæfer, T., Wørts, O., 1978b. Control of fluidized bed granulation. IV. Effects of binder solution and atomization on granule size and size distribution. Arch. Pharm. Chemi Sci. Ed. 6, 14-25

Schæfer, T., Wørts, O., 1978c. Control of fluidized bed granulation. V. Factors affecting granule growth. Arch. Pharm. Chemi Sci. Ed. 6, 69-82

Schæfer, T., 1988. Equipment for wet granulation. Acta Pharm. Suec. 25, 205-228

Schwartz, J.B., 1988. Granulation. Drug Dev. Ind. Pharm. 14, 2071-2090

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

Scott, M.W., Lieberman, H.A., Rankel, A.S., Chow, F.S., Johnston, G.W., 1963. Drying as a unit operation in the pharmaceutical industry I, Drying of tablet granulations in fluidized beds. J. Pharm. Sci. 52, 284-291

Sobrino, C., Almendros-Ibañez, J.A., Santana, D., de Vega, M., 2008. Fluidization of Group B particles with a rotating distributor. Powder Tech. 181, 273-280

Strictland, W.A., 1962. Study of water wapor sorption by pharmaceutical powders. J. Pharm. Sci. 51, 310-314

Sucker, H., 1982. Test methods for granulates. Pharm. Ind. 44, 312-316

Summers, M., Aulton, M., 2002. Granulation. In Aulton, M. (Ed.). Pharmaceutics, The science of dosage form design. Churchill Livingstone, Spain, pp. 364-378

Syahrul, S., Hamdullahpur, F., Dincer, I., 2002. Exergy analysis of fluidized bed drying of moist particles. Exergy, Int. J. 2, 87-98

Terrier de la Chaise, B., LePerdriel, F., 1972. The drying of granules. Pharm. Int. 6, 16-22

Türkoğlu, M., He, M., Sakr, A., 1995. Evaluation of rotary fluidized bed as a wet granulation equipment. Eur. J. Pharm. Biopharm. 41, 388-394

Vippagunta, S.R., Brittain, H.G., Grant, D.J.W., 2001. Crystalline Solids. Adv. Drug Deliv. Rev. 48, 3-26

Visser J. 1989. Van der Waals and other cohesive forces affecting powder fluidization. Powder Tech. 58, 1-10

Wan, L.S.C., Lim, K.S., 1991. Action of binders in the fluidized bed granulation of lactose. S.T.P. Pharma Sci. 1, 248-255

Wang, Z.H., Chen, G., 2000. Heat and mass transfer in batch fluidized-bed drying of porous particles. Chem. Eng. Sci. 55, 1857-1869

Watano S., Morikawa, T., Miyanami K., 1996a. Mathematical model in the kinetics of agitation fluidized bed granulation. Effects of moisture content, damping speed and operation time on granule growth rate. Chem. Pharm. Bull. 44, 409-415

Watano S., Fukushima, T., Miyanami K., 1996b. Heat transfer and granule growth rate in fluidized bed granulation. Chem. Pharm. Bull. 44, 572-576

Watano S., Takashima, H., Sato, Y., Yasutomo, T., Miyanami K., 1996c. Measurement of moisture content by IR sensor in fluidized bed granulation. Effects of operating variables on the relationship between granule moisture content and absorbance of IR spectra. Chem. Pharm. Bull. 44, 1267-1269

Westrup, J., 1996. Process control during fluid bed granulation. The importance of humidity control. Pharm. Res. 13, 220

Whitehead, A.B., 1981. Behaviour of fluidized bed systems. Int. J. Pharm. Tech. Prod. Mfr. 2, 13-18

Wildfong, P.L.D., Samy, A.-S., Corfa, J., Peck, G.E., Morris, K.R., 2002. Accelerated fluid bed drying using NIR monitoring and phenomenological modeling: method assessment and formulation suitability. J. Pharm. Sci. 91, 631-639

Wurster, D.E., 1959. Air-suspension technique of coating drug particles. J. Am. Pharm. Ass. 48, 451-454

Wurster, D.E., 1960. Preparation of compressed tablet granulations by the air-suspension technique II. J. Amer. Pharm. Assoc. Sci. Ed. 49, 82-84

Wørts, O., 1998. Wet granulation – fluidized bed and high shear techniques compared. Pharm. Technol. Eur. 10, 27-30

York, P., 1983. Solid-state properties of powders in the formulation and processing of solid dosage form. Int. J. Pharm. 14, 1-28

Zhang, G.G.Z., Law, D., Schmitt, E.A., Qiu, Y., 2004. Phase transformation considerations during process development and manufacture of solid oral dosage forms. Adv. Drug Del. Rev. 56, 371-390

Zhu, H., Yuen, C., Grant D.J.W., 1996. Influence of water activity in organic solvent + water mixtures on the nature of the crystallizing drug phase. 1. Theophylline. Int. J. Pharm. 135, 151-160

Zografi, G., 1988. States of water associated with solids. Drug Dev. Ind. Pharm. 14, 1905-1926