Process understanding on high shear granulated lactose agglomerates during and after drying

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Proceskennis over lactose agglomeraten gegranuleerd in een hoge snelheidsmenger tijdens en na het droogproces

(met een samenvatting in het Nederlands)

Proefschrift

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door

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Preface

Pharmaceutical manufacturing takes place in a highly regulated and controlled industrial environment. The drug product is supposed to meet narrow specifications in a consistent and robust way. From this perspective however, it is remarkable that the design of a product is at least partially empirical and based upon the principle of first time right. In a worst case scenario, unexpected deviations in manufacturing cannot be solved instantaneously due to the lack of process understanding. In 2001, in response to public and pharmaceutical industrial awareness of this phenomenon, the FDA launched the Process Analytical Technology (PAT) initiative.

Process analytical technology is defined as *a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. It is important to note that the term analytical in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner.* A desired goal of the PAT framework is to design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process. Such procedures would be consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency (Food and Drug Administration, 2004). Critical process and product attributes can only be acknowledged upon a thorough process understanding.

Within the field of solid dosage form development significant research has been done on high shear granulation. The key process parameters that are involved in the wet granulation process, including granule breakage, binder liquid penetration and dispersion were determined (e.g., Ennis et al., 1990, Iveson and Litster, 1998, Iveson et al., 2001, Reynolds et al., 2005, Rumpf, 1958). Although the relevance of these critical process parameters towards the formation of inhomogeneous granules have been reported (Van den Dries, 2004) the consequences of the described inhomogeneity phenomena in granules in further processing have not been elaborated yet. After the wet granulation process, a drying step is always necessary to obtain a basis for the final drug product. This drying step will be the key process studied in this thesis.

This thesis aims to investigate the behavior of the granules throughout the drying process and the consequences of granule heterogeneity during and after the drying process.

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2

Introduction

The drying of granules, which is the key topic of the current thesis, cannot be studied without a thorough knowledge of the critical parameters of granulation. In this introduction both process and product aspects regarding granulation and heterogeneity phenomena in granules will be elaborated. Thereafter, a description will be given of the following drying methods; tray drying, fluid bed drying and micro-wave drying.

2.1 Granulation

Two types of granulation systems are commonly used: fluid bed granulation and high shear mixing. The two systems differ fundamentally in the mode of granule growth (Faure et al., 2001). In fluid bed granulation, the powder mix is fluidized in an air stream originating from the bottom. A binder liquid is sprayed upon the powder bed, either by top spray or bottom spray. Initially the granules result from the collision of solid particles with the liquid droplets that encounter the bed. Granule growth is determined by the spraying mode (Faure et al., 2001). Simultaneously, partial drying by the air stream will occur. Once the binder liquid addition is stopped granules dry in the continuous air stream. The drying end point is traditionally recognized by an increase in product temperature, followed by equilibration of the temperature and humidity of the incoming and outgoing air stream. The difficulty of fluid bed granulation lies in the establishment of a stable regime which involves carefully balancing input variables such as temperature and humidity of the incoming air stream, air flow and binder liquid spraying rate (Faure et al., 2001). In the current thesis granules are solely prepared by high shear granulation. The remainder of this section and the next section are therefore solely dedicated to the theoretical background on high shear granulation.

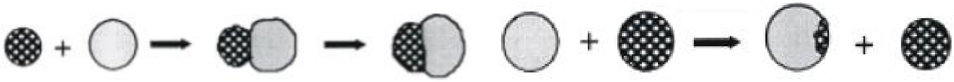
High shear wet granulation has been considered an art rather than a science for a long time. In high shear granulation the powder is first brought into a mixer bowl. Binder liquid is poured or sprayed over the moving powder bed. The powder mass is mixed with the use of both an impellor and chopper.

The first extensive scientifically based review focused on the acting forces in granules (Rumpf, 1958). Upon addition of binder liquid to the powder mass, the binder liquid was distributed. Newitt and Conway Jones (1958) identified three macroscopic liquid-solid stages in the formation of the granules upon binder addition: the pendular, funicular and capillary state. In the pendular state, granule strength is ascribed to capillary pressure and surface tension of the liquid. By either increasing the liquid volume or by reducing the pore volume of the granules (e.g. by densification) liquid rings in the agglomerate tend to coalesce to form a continuous network. This is described as the funicular state. When the void volume of the granules is completely filled by the liquid a capillary state is reached (Sastry and Furstenau, 1973).

Formation of granules has traditionally been explained by nucleation, layering (snow-balling), coalescence, abrasion transfer and breakage and layering. Layering, also described as coating, snow-balling or onion-skinning, may occur after addition of new material to existing granules or after breakage of granules, whereby the resulting fines are redistributed over the other remaining granules (Figure 2.1) (Sastry and Furstenau, 1973).

1. Nucleation **2. Layering (snow-balling)**

3. Coalescence **4. Abrasion transfer**

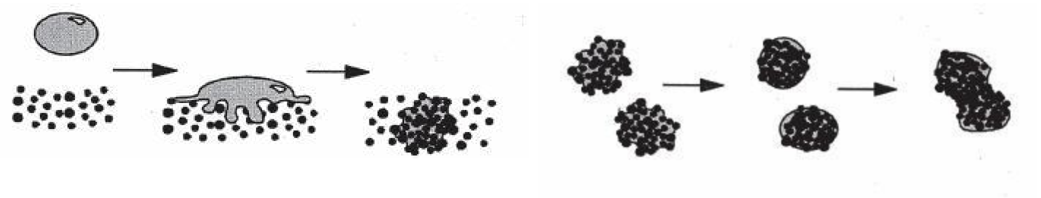


5. Breakage and layering

Figure 2.1 Traditional schematic of granulation process (based upon Sastry and Furstenau, 1973).

More recently, granulation behavior has been described in three stages as pictured in figure 2.2 (Ennis and Litster, 1997). Wetting and nucleation refers to the formation of initial granules as liquid drops are added to the powder mass. Consolidation and growth are then thought to occur as these wetted agglomerates are agitated and collide with each other. Breaking and attrition are thought to occur when granules grow either too large or dry out and become weak and brittle (Iveson and Litster, 1997, Iveson et al., 2001).

1. Wetting and nucleation **2. Consolidation and coalescence**



3. Attrition and breakage

Figure 2.2 Modern schematic of granulation processes as proposed by Ennis and Litster, 1997.

Iveson and Litster (1998) proposed that there are two main types of growth behavior: steady growth behavior and induction growth behavior. Steady growth occurs when the average granule growth linearly increases upon ongoing granulation time. As the granules are weak, deformation is easy. In case of induction growth, the granule growth is characterized by a period of almost no growth followed by a rapid growth period. This type of growth occurs if granules are very strong and do not deform easily. As time progresses, granules slowly consolidate. Binder liquid will be forced to the outer surface enabling rapid coalescence (Iveson and Litster, 1998, Iveson et al., 2001). Other type of granule growth is known as crumb behavior. In this case the formulation is too weak to form stable granules. Loose crumb material is formed instead. When there is insufficient binder liquid to enhance further growth, the initial growth process is described as 'nucleation only' growth. In contrast to this situation, over wetting occurs when too much binder liquid is added (Iveson and Litster, 1998, Iveson et al., 2001) (Figure 2.3).

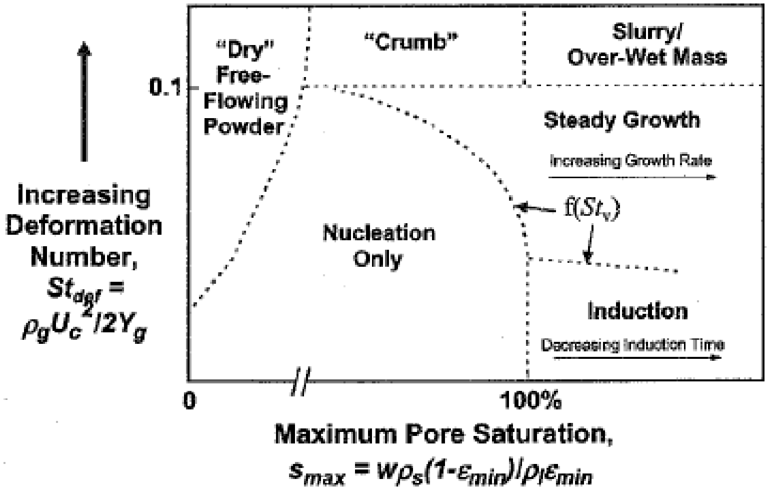


Figure 2.3 Growth regime map. The nucleation-to-steady growth boundary and the steady-growth-to-induction-growth boundaries are functions of St_v and the maximum pore saturation (Iveson et al., 2001).

The growth regime map initially developed by Iveson and Litster is based upon two hypotheses: granule growth is a function of the system's liquid content and impact deformation occurs during granulation.

Maximum granule pore saturation (s_{max}) is used as a measure of the liquid content.

$$s_{\max} = \frac{w\rho_s\left(1-\varepsilon_{\min}\right)}{\rho_l\varepsilon_{\min}}$$ **Equation 2.1**

Where w is the mass ratio liquid to solid, ρ_s is the density of the solid particles, ε_{min} is the minimum porosity the formulation can obtain during the particular set of operations and ρ_l is the liquid density.

The granule impact deformation is a function of both the granule rheology and process agitation intensity. The extent of deformation of granules during an impact in a granulator is described as function of the deformation number (*De*)

$$De = \frac{\rho_g U_c^2}{Y_g}$$ **Equation 2.2**

Where ρ_g is the density of the granule, U_c is representative collision velocity for the granulator and represents the process intensity. Y_g is the granule dynamic yield stress. Therefore *De* is a measure of the ratio of impact kinetic energy to plastic energy absorbed per unit strain. It takes into account both the process agitation intensity and the granule rheology, and indicates the amount of deformation during a typical impact (Iveson and Litster, 1998). Nucleation and wetting effects are not taken into account in the map. Furthermore the rate of the granule growth is not predicted by the system (Iveson and Litster, 1998).

Tardos et al. (1998) developed a model to predict maximum granule size that can be produced at a given set of operating procedures by balancing shear and viscous forces. Granule deformation is expressed by the Stokes deformation number (St_{def}). This is the ratio of externally applied kinetic energy to the energy required for deformation. Once they are beyond the critical value granules start to deform and break. Originally, the St_{def} was defined in terms of the flow stress of a non-Newtonian liquid. If the deformation number, *De,* is divided by two it becomes equivalent to the St_{def}. In contrast to the St_{def}, the deformation number is defined in terms of dynamic yield stress of a solid (Iveson et al., 2001). This difference reflects the debate on whether to define wet granular masses as solids or liquids.

Iveson et al. (2001) applied the Stokes deformation number in the granule growth regime map.

$$St_{def} = \frac{\rho_g U_c^2}{2Y_g}$$ **Equation 2.3**

The nucleation to steady growth and the steady to induction growth boundaries depend on several factors; most significantly on the binder viscosity (figure 2.3). This value is characterized by the viscous Stokes value (St_v) (Ennis et al., 1991).

$$St_v = \frac{2mU_0}{3\pi\mu a^2}$$ **Equation 2.4**

Where m and U_0 depict respectively the granular mass and initial velocity. μ represents the binder viscosity and a the granule particle radius. The influence of the viscosity on granule growth is complex. Ennis et al., (1991) assumed that growth occurs by coalescence of surface wet granules. When two granules collide, a viscous liquid layer surrounding the granules dissipates the impact energy. If the impact energy is too high, the viscous layer cannot dissipate all the energy and rebound of the granules will occur. If all the energy is absorbed the granules will coalescence (Ennis et al, 1991, van den Dries, 2004). If the impact energy equals the maximum dissipated energy this is called the critical viscous Stokes number. Therefore if the viscous Stokes number is higher than the critical viscous Stokes number rebound instead of coalesce of granules or particles will occur (Ennis et al., 1991).

It is assumed that granules with a saturation level of 100% grow rapidly, regardless of whether or not they deform greatly during collisions (Iveson et al., 2001). The regime map is not quantitatively applicable to each and every substance and binder liquid, but it does provide a possibility to visualize the granule growth phenomena and the most significant characteristics determining these phenomena (Bouwman et al., 2006).

2.2 Heterogeneity phenomena in wet granulation

Common high shear mixing can give rise to de-mixing phenomena. In table 2.1 an overview is given of the existing literature on inhomogeneity phenomena in high shear granulation. From table 2.1, several research topics on granule heterogeneity can be extracted. The first studies were started as a consequence of problems that had arisen in the content uniformity in drug products. These content uniformity problems had apparent consequences for final product quality. The research was primarily focused on the phenomena and the causes of these phenomena. In relation to product quality, final tablet characteristics were often used as quality parameters.

Table 2.1 Inhomogeneity phenomena in high shear granulation and the conclusions and consequences of the observed phenomena.

Subject	Conclusions and consequences of observed phenomena	References
Unit to unit variance in tablets, granules and dry blends.	A methodological sampling study has been performed. No conclusions upon causes or consequences of the observed inhomogeneity phenomena.	Lachman and Sylwestrowicz, 1964

Subject	**Conclusions and consequences of observed phenomena**	**References**
The distribution of small concentrations of lynestrenol in tablet granules.	Highest lynestrenol content was found in the largest granules, whereas the smallest granules did contain less than half of this concentration. It was hypothesized that large granules have a larger void fraction than small granules and thereby contain more active substance.	Cox et al., 1968
The effect of massing time on the drug concentration in different sized granules.	Initially the smallest granules contain the water soluble drug. Continuous massing time produced a shift in distribution. The largest granules had the highest borax content.	Selkirk, 1973
Distribution of component in granular size fractions.	Largest granules arise from the wettest part of the powder mass. Coarser lactose particles produced larger content variations in lactose granules than finer fractions and un-fractionated lactose. Coarse granules of un-fractionated lactose contained the same proportion of ingredients as the original mixtures.	Opankunle and Spring, 1977
Effect of binder solution composition on the distribution of the drug.	Active component distribution is dependent on binder distribution in the granules. The largest granules contain most binder and therefore active component. It was hypothesized that the variation in drug concentration in differently sized granules is related to the differences found in over wetted regions during massing.	Ojile et al., 1982
Fluidized bed granulation of an ordered powder mixture to minimize segregation effects.	The de-mixing potential, a coefficient of variation, is used to describe the distribution of the active component over the granular fractions. Ordered mixing before granulation prevents segregation in the granule and subsequently in tablets.	Thiel and Nguyen, 1982
The effect of particle size of the drug and diluent on drug distribution on granule size fractions.	If the drug particles were smaller than the diluent the coarse granules were super-potent and smaller granules sub-potent. If the drug particles were coarser than the diluent particles small granules were super-potent and coarse granules sub-potent. It is hypothesized that this is related to granule growth as small particles enhance granule formation.	Egermann and Reiss, 1988

Subject	**Conclusions and consequences of observed phenomena**	**References**
The influence of mixing techniques on the distribution and incorporation of a low dosed drug in granules by granulation in a fluidized bed granulator.	Best distribution of the low dosed drug was established by dissolution of the drug in the granulation fluid. Manual or double cone mixing did not improve drug distribution over the granular fractions. Both a minimal granulation liquid amount and minimal atomizing pressure are required to obtain better distribution.	Wan et al., 1992
An auto-layering model for the granulation of iron ore fines.	It is acknowledged that auto-layering granulation models have an inability to predict the layer thickness as function of feed size distribution and its moisture content, due to insufficient understanding of e.g., the capillary and viscous inter-particle bonding mechanisms operating under dynamic conditions in the high shear mixing device.	Kapur et al., 1993
Effect of process variables on the properties and binder distribution of granules in high shear mixing.	The largest granular size fraction contains the highest amount of binder. Hypothetical interpretation of the consequences; milling or screening may improve distribution.	Kokubo and Sunada, 1996
Effect of binder (PEG) particle size in melt pelletization in a high shear mixer.	Effect of binder particle size on the pellet formation interacts with the binder viscosity. At low binder viscosities, binder particle size has a minor influence. Dominant growth mechanism is the distribution of the molten binder on the surface of the solid particles. At high viscosity pellets are formed by immersion of the solid particles in the molten binder.	Schæfer and Mathiesen, 1996
Optimization of the high shear granulation process of high and poorly soluble drug substances to improve granule size dependent content uniformity.	Solubility of the drug in the binder solution determines the distribution in high shear granulation. The study does not deal with further optimization other than high shear granulation.	Miyamoto et al., 1998
Kinetics of liquid distribution and growth in high shear mixing.	A bimodal distribution of granule sizes was obtained after addition of liquid (pour-on, spray-on and melt-in). Fine granules contain significantly less binder liquid than coarse granules. This difference remains even at long mixing times.	Knight et al., 1998

Subject	Conclusions and consequences of observed phenomena	References
Effects of high shear granulation on granule homogeneity.	A correlation between particle size of the granule constituents and distribution in granular size fractions was established; Coarse granules were found to be super-potent up to 150% of the mean drug content. This was related to the primary particle size and mixing intensity.	Vromans et al., 1999
Relation of binder addition (pour-on or melt-in of PEG) and heterogeneity in granules.	Method of binder addition determines nucleation and growth phenomena and therefore heterogeneity. Large granules consist of fine particles and small granules are made up of large particles. In the extreme, some of the small granules are single large primary particles.	Scott et al., 2000
Influence of process parameters (amount of binder liquid, viscosity, granulation time and wettability of solid constituents) in high shear granulation on the composition of the resulting granules.	The amount of liquid in the binder solution and the viscosity are strongly interactive with respect to homogeneity. The homogeneity of the granules is more sensitive to changes in the amount of binder solution than to changes in viscosity. At a low viscosity deformability is too high resulting in breakage. A higher viscosity will decrease the deformability of granules resulting in a decrease of granule growth. There is therefore an optimum viscosity of the binder solution.	De Vegt et al., 2001
Relation of the distribution of the active component and granular growth phenomena.	Heterogeneity phenomena are determined by granule strength and preferential growth. The particle size differences determine the extent of heterogeneity.	Van den Dries and Vromans, 2002
Granule breakage phenomena; consequences process and formulation variables on heterogeneity.	When granule breakage is absent, preferential layering by the smallest particles of the intact granules induced heterogeneity.	Van den Dries et al., 2003
Effect of solid formulation on the manufacture of high shear mixer agglomerates consisting of zeolite or calcium carbonate and a high viscosity binder	Reduction of the mean particle diameter leads to a reduced process time to the endpoint state.	Rough et al., 2005
Effect of particle size and binder viscosity on heterogeneity.	Inter-granular heterogeneity can be reduced by increasing the binder viscosity. Granules contain small primary particles in the centre and larger primary particles on the outskirt of the granule. This leads to intra-granular heterogeneity.	Schæfer et al., 2004

Subject	Conclusions and consequences of observed phenomena	References
Relationship between Carr’s index and dissolution rate constant.	Granules prepared from small acetaminophen powders have a higher Carr’s index, higher porosity, are more homogeneous and higher in dissolution rate constant compared to granules prepared from larger particles. An empirical relationship between dissolution of the drug product and formulation design was established.	Lee and Hsu, 2007

De-mixing phenomena have been explained by the mechanism of destructive nucleation growth during granule formation (Vromans et al., 1999).

Nucleation is the first step in granule formation. The binder liquid is dispersed in the powder mixture. When water is added to the powder mass, local over-wetted regions will be formed instantaneously. Schæfer and Mathiesen (1996) proposed two nucleation mechanisms: the distribution and immersion mechanism (figure 2.4). If droplets of binder, smaller or of a comparable size to the solid particles coat the surface, this nucleation mechanism is referred to as the distribution mechanism. The wetted particles coalesce and will form granules. In the immersion theory, the nucleation mechanism is described as the embedding of solid particles in larger liquid binder particles.

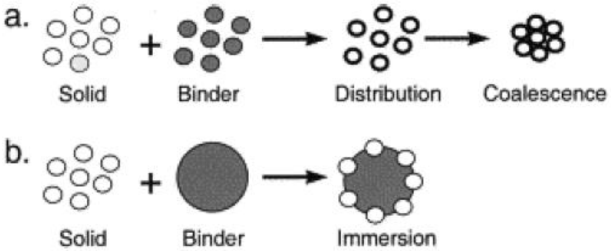


Figure 2.4 Nucleation mechanisms (a) Distribution mechanism (b) Immersion mechanism (Schæfer and Mathiesen, 1996).

Scott et al. (2000) stated that the small particles will preferentially nucleate by the immersion mechanism, in the case of poured on binder addition, and that the capillary force enabling this mechanism increases at decreasing particle size. Melt-in binder addition would lead to the nucleation distribution mechanism (Scott et al., 2000). The shape of granules formed by the immersion mechanism partly resembles the shape of the binder droplet (Schæfer et al., 2004).

Granules are preferentially formed by liquid penetration and partially by coalescence (Van den Dries, 2004). The liquid penetration mechanism is responsible for observed discrepancies in binder distribution (Opankunle and Spring, 1977; Ojile et al., 1982; Kokubo and Sunada, 1996; Schæfer and Mathiesen, 1996; Knight et al., 1998). Substances with a high wettability form granules at a higher rate (Miyamoto et al, 1998). If the newly formed granules withstand the shear forces during granulation they persist to exist. The initial inhomogeneity in distribution of the liquid continues to exist throughout the process (Van den Dries, 2004). If these initial agglomerates cannot withstand the impact forces of the impellor or chopper, a constant destruction occurs. This leads to a constant rearrangement of the primary particles (Vromans et al., 1999). The strength of agglomerates during high shear granulation is related to the saturation level. Upon impacts the density of granules increases, porosity decreases and finally saturation increases.

Granules containing small primary particles will reach the critical state where they can survive the destructive shear forces earlier than granules containing larger primary particles. The former will therefore be able to grow, whereas the latter will be broken and rearranged further. This leads to the formation of large strong granules containing the small primary particles and small granules containing the coarse primary particles (Vromans et al, 1999).

If a pore at the surface of the newly formed granule is sufficiently filled with liquid a primary particle can reach the liquid phase in the pore and a new liquid bridge may result. During growth, the binder liquid is drained from pores inside the original agglomerate to the pores formed by the adherence of new primary particles. The driving force for this liquid flow is the capillary pressure difference between the pores inside and pores at the boundary of the granule. The capillary pressure difference can be described as function of the saturation difference between the pores in the agglomerate and the pores with a lower saturation near the surface (Schaafsma et al., 1998). Until this saturation level reaches a minimum value, the so called wetting saturation, growth may continue. The wetting saturation is the minimum saturation in which liquid bridges can be formed between the agglomerate and new primary particles (Schaafsma et al., 1998).

Surface asperities on a granule may disable the layering of large primary particles. Small particles can penetrate the partially saturated pores and adhere to the wetted surface. Particles that are too large to enter a pore will encounter a dry surface and will not be able to bind. A porous granular surface can, therefore be considered dry for large particles and wet for smaller particles. This leads to preferential layering of smaller particles, inducing heterogeneity. In contrast, breakage or crumb behavior of the granules, consisting of the largest primary particles, retards densification and inhomogeneity phenomena (Van den Dries, 2004). The size of the primary particles in the granules therefore determines the breakage behavior and strength (Kristensen et al, 1985), whereas the particle size difference determines the degree of granule inhomogeneity by the preferential layering growth mechanism (Van den Dries, 2004). The tensile strength of the granule under dynamic conditions is directly proportional to the viscosity of the binder liquid, and inversely proportional to the particle size of the primary particles and to the inter-granular porosity (Van den Dries, 2004). The formation of granules as proposed by Van den Dries is described in figure 2.5.

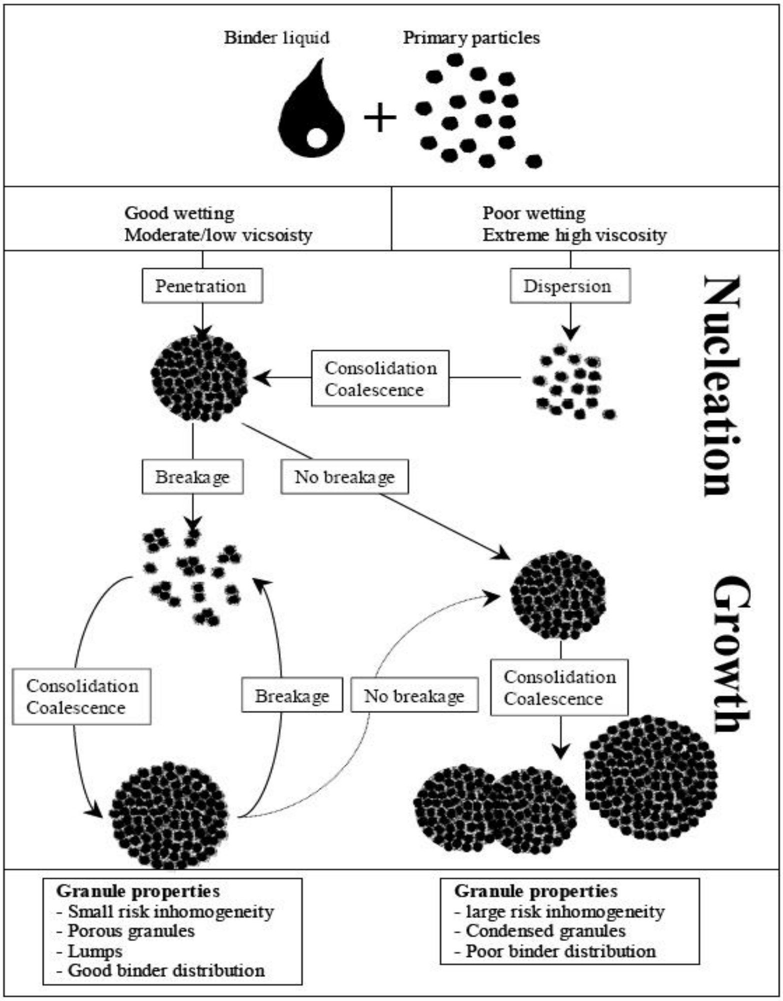


Figure 2.5 Schematic summary of high shear granulation (Van den Dries, 2004, pp 138) (see text for explanation).

High shear granulation is only one of the process steps in the manufacturing of a drug product. The total manufacturing process may consist of the following steps (chronological order): dry mixing – granulation – drying - milling – dry mixing - tableting/capsulation – packaging (primary and secondary packaging). The impact of granule heterogeneity on the subsequent process steps such as drying and milling or on the physical-chemical stability of the end product has not been the subject of previous research. In the current study, research is focused on the drying process and the physico-chemical stability of the dried granules. Granules are prepared by high shear granulation either on small (1 kg) scale or large (14 kg) scale. It is assumed that the formation of granules as depicted in figure 2.5 is applicable to both the small and large scale formation of granules.

2.3 Heterogeneity phenomena in drying

In all studies, as summarized in table 2.1, intermediate process steps such as drying were not taken into account in relation to the observed inhomogeneity phenomena. Although the number of publications is rather large the consequences of the granule heterogeneity for drying processes were not part of any of the research projects. The drying step was not considered to be of any influence in these research projects. In contrast, the characteristics of the dried granules were often used to determine influence of the granulation process parameters (Opankunle and Spring, 1977).

The influences of drug solubility and especially drug migration on heterogeneity phenomena have been subjected to research. During drying of wet granules drug migration may occur. Drug migration was correlated to solubility of both the drug and the excipient, particle size of the drug and excipient and binder viscosity. Drug migration was also related to intra-granular structure. In absence of an internal structure by insufficient packing, drug migration is shown to be significantly decreased (Kiekens et al., 1999). High binder viscosity decreases migration also (Warren and Price, 1977b; Kiekens et al., 2000). Drying temperature or drying method did not influence the drug distribution heterogeneity according to these authors. Dyer et al (1994) found that fluid bed drying limited solute particle migration in pellets in comparison to tray drying. Only the effects of the drying methods on drug migration and granule heterogeneity have been subject to research. The influence of the granule composition heterogeneity on the drying process has not been investigated.

Table 2.2 Heterogeneity in granules by migration of water soluble and insoluble drugs.

Subject	Conclusions and consequences of observed phenomena	References
Inhomogeneity in granules due to drug migration of water soluble drugs.	The water soluble drug (borax) and excipient (lactose) migrate towards the surface of the granule during the drying process. This leads to intra-granular inhomogeneity. An increase in granulation liquid increased the observed inhomogeneity. The formation of a lactose rich crust upon drying was explained by the higher water solubility of lactose, which had therefore a higher migration tendency. Upon dry screening, the crust was removed leading to smaller granules with higher drug content.	Selkirk, 1976
Inhomogeneity in high shear granules due to drug migration during drying of water soluble drugs.	Variations in particle size of the major diluent in high shear granulation result in inhomogeneity problems for water soluble drugs due to drug migration during drying. As the particle size of the diluent, lactose, decreased, drug migration increased.	Warren and Price, 1977a
Inhomogeneity in high shear granules due to drug migration during drying of water soluble drugs.	Drug migration decreased with increasing binder solution viscosity. No significant influence of the drying temperature was detected. Drug migration during drying resulted in tablet-to-tablet content variation even after mixing of the dried granules.	Warren and Price, 1977b
Effects of solubility and drying method on the drug content of various size fractions of granules.	Drug migration during drying and abrasion as explanations for drug distribution variances were found to be insufficient to explain the obtained results. It was hypothesized that highly water soluble drugs at low concentration remain preferentially in the crystal bridges between particles. These contribute mainly to the fines when the granules are dried. Solubility of the drug has no influence on the distribution of the drug in the granule fractions. The method of drying has a minor effect on variation of drug concentration in the different size fractions.	Whitaker and Spring, 1977

Subject	**Conclusions and consequences of observed phenomena**	**References**
Comparison of the inter- and intra-granular drug migration of a water soluble and water insoluble drug in tray and freeze dried granules and compacts.	By freeze drying water migration is abolished. The water is immobilized in the granules. No inhomogeneity is observed. The water soluble drug needed a very high binder viscosity (twice as high as the water insoluble drug) to diminish drug migration. The water insoluble compounds migrated to a smaller extent than the water soluble compounds. If granules are insufficiently packed, migration is limited due to an insufficient available migration network.	Kiekens et al., 1999
Influence of drying temperature and granulation liquid viscosity on the inter-granular and intra-granular drug migration in tray-dried granules.	A poorly-water-soluble drug was granulated with lactose. Drying temperature had no influence on the distribution of the active compound. During the drying process, poorly-soluble drug migrated towards the top and bottom layer of the granules. Binder liquid viscosity increase decreases inhomogeneity.	Kiekens et al., 2000

2.4 Drying

Wet granules may be dried on trays, in a fluid bed, by gas stripping (dry air or nitrogen), by microwave, by infrared, under vacuum or any combination thereof (Faure et al., 2001). Gas stripping consists of the injection of gas through the granule mass. Under vacuum conditions the injected gas expands inside the bowl and acts as a vapor carrier, thus speeding up the drying process (Giry et al., 2006).

In most publications concerning up-scaling of wet granulation processes, wet granules produced at different scales were dried at the same fixed conditions. Effect of variations in drying conditions on tablet quality has nearly always been considered negligible (Faure et al., 2001). The drying step is considered easy in up-scaling. Therefore the properties of dried granules are used as output parameters for wet granulation studies. In the current thesis, the properties of granules at the different stages of the drying process are used as output parameters, as drying is considered to influence the granule properties such as granule size and formation of fines.

Upon drying, a minimum residual amount of water is often preserved in the granules, e.g. to maintain the ingredients in a hydrated state or to reduce static electric charges (Giry et al., 2006). This residual amount may affect physical, chemical and microbiological stability. The remaining water activity after drying is therefore a critical factor for product quality.

Due to safety (explosion risk) and environmental requirements, high shear granulation is mostly performed with water based binder liquids. Previously used organic binding liquids (e.g. aceton) have a low evaporation energy. The removal of water after high shear granulation is more complicated as water has high evaporation energy and a low vapor pressure.

2.4.1 Tray drying

Traditionally drying of granules has been performed by tray drying. Granules are positioned on a tray in a thin layer and dried for several hours at moderate temperatures. The time-consuming process can be enhanced by the application of a vacuum system. A dynamic balance between the rate of moisture movement from the granules (including intra-granular movement) and the evaporation of the moisture from the solid surface exists. The drying rate is determined by the film thickness of the vapor above the bed (Zoglio et al., 1975) and the bed depth (Carstensen and Zoglio, 1982).

2.4.2 Fluid bed drying

In fluid bed drying, a gas stream is led through the wet granular bed to cause floating and intermixing of the granules with the fluidizing gas (Hlinak and Saleki-Gerhardt, 2000). Fluidization of the granule bed occurs when an upward flow through the interstices of the bed attains a frictional resistance equal to the weight of the bed. At this point, an increase in the fluid rate will lift or support the granules. By increasing the air flow bubbles or voids are created that mix the granular bed when they rise, which increases bed homogeneity (Handbook of powder science and technology, 1997). Bubbles are created at the distributor plate. Bubbles do not mix in a horizontal plane, but coalesce whenever a bubble is less than one bubble diameter behind in a vertical plane. Bubble size is therefore smaller above the distributor plate than higher up in the bed (Zoglio et al., 1975). If the material is difficult to fluidize, the bed will tend to form channels through which the air will escape, rather than being dispersed between the granules. If the particles are too large and heavy, an air flow regime with resemblance to a spouted bed will be formed. In this case, a high velocity spout of air punches through the granule bed, thereby transporting granules to the top of the bed. The other granules will move downward around the spout, thus resembling a spouted bed behavior. Segregation will occur for granules with a wide size distribution (Palzer, 2007).

The inlet air flow plays a crucial role in maintaining proper fluidization to enable uniform drying (Gao et al, 2000). Sufficient mixing of the drying granules occurs only above the minimum fluidization velocity. Coarser and wetter fractions tend to accumulate near the distributor plate (Zoglio et al., 1975).

Upon sufficient fluidization an efficient heat transfer between the granules and the air is possible, and water can vaporize into the air stream.

The rate of drying of solids can be divided into three distinct phases: the constant rate period, falling rate period and equilibrium period. The phases are distinguished by the rate of solvent removal and the intrinsic limitation mechanisms as elaborated hereafter.

The first phase of the drying process is characterized by a short heating up period. In this period, the equilibrium between heat and mass transfer is established and the solid takes on a temperature at which the heat transfer to the solid equals the heat needed to vaporize the water. At the beginning of the constant rate period the surface of the granule is wetted due to the constant migration of water to the surface. The temperature of the solid is constant.

Removal of the moisture is limited to the heat available for evaporation and the capacity of the air to absorb the moisture. Inlet air temperature and humidity determine the evaporation rate.

During the falling rate period, the abundant amount of free water is no longer available at the surface. The mass transfer of water to the surface is slower than the mass transfer from the surface. Water diffuses through the maze of pores towards the surface. Due to the capillary pressure, water moves from the larger to the smaller pores. The rate of drying depends on the intra-granular structure. The drying rate is unique and limited by the solid characteristics of the material to be dried, thus composition pore structure, particle size and saturation level will limit the drying rate.

In the equilibrium phase, a thermodynamic equilibrium is reached with the surrounding air. The final water content is determined by the granule temperature and the partial pressure of water in the air stream (Hlinak and Saleki-Gerhardt, 2000). In practice, the end-point is reached when the temperature and humidity of the incoming air are equal to the temperature and the humidity of the outgoing air. In case of non-pretreated air, environmental (weather) conditions have a significant influence on the residual moisture content in the granules. In figure 2.6, the subsequent drying stages have been depicted.

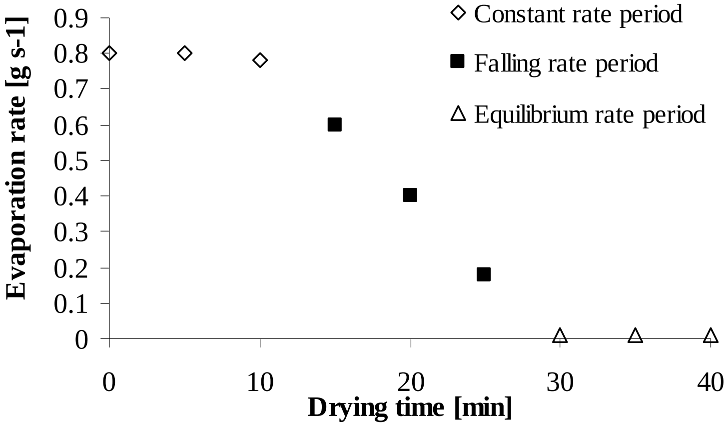


Figure 2.6 Theoretical graph of the drying phases in fluid bed drying.

Hlinak and Saleki-Gerhardt (2000) used heat and mass transfer equations to calculate the evaporation rate of water during the fluid bed drying cycle. Theoretically, an energy balance across a controlled volume surrounding the drying granular bed can be used to determine the evaporation rate of water:

$$m_{H_2O} = \frac{m_{air} C_{p,air} \left(T_{in} - T_{out}\right) - Q_{loss}}{h_{fg}}$$ **Equation 2.5**

Where m_{H2O} is the mass flow of water evaporated in the bed, $C_{p,air}$ is the specific heat capacity of air at constant pressure, m_{air} is the mass flow of air through the the dryer, T_{in} is the inlet temperature and T_{out} is the outlet temperature. Q_{loss} is heat loss to the environment through thermal convection. h_{fg} is latent heat of vaporization of water at the dryer outlet temperature (Hlinak and Saleki-Gerhardt, 2000). By means of equation 2.5, the evaporation rate in the constant rate period as function of inlet air temperature and mass air flow is calculated for a bed with a constant specific heat capacity and heat loss to the environment. This is depicted in figure 2.7.

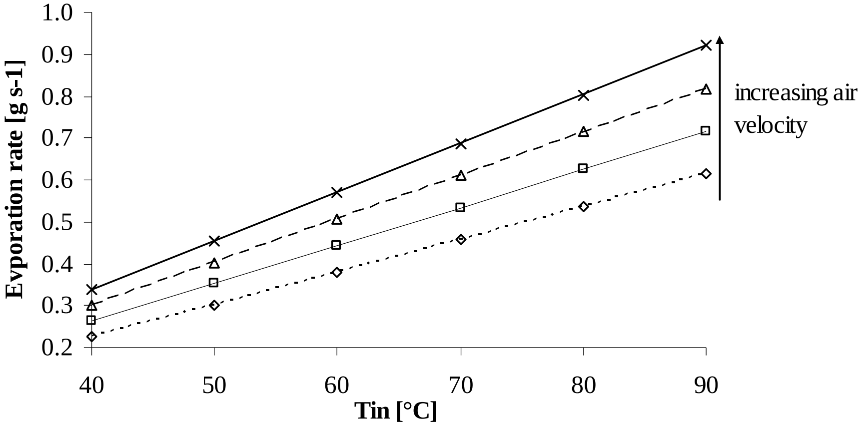


Figure 2.7 Theoretical evaporation rate of water in the constant rate period at increasing T_{in} and air flow rate as determined by equation 2.5.

2.4.3 Microwave drying

Microwaves, originally developed for use in wartime radar (Vromans, 1994), are a form of electromagnetic radiation within the GHz frequency range (300 MHz – 300 GHz). Heating frequencies permitted to use in household, medical or industrial applications are 915 and 2450 MHz. These frequencies have been chosen to avoid interference.

Microwave or high frequency drying is a less used drying technique within the pharmaceutical industry. Limited experience, inhomogeneous electric fields and unawareness of dielectric characteristics of both the active ingredients and excipients do not enhance the development of this technique. Water has an unfavorably high latent heat of vaporization; therefore it has been disputed if high frequency drying for water containing products is the method of choice.

Advantages lie in the availability of contained systems to avoid contact of product and operators. Furthermore, high frequency drying is a volumetric drying technique. In contrast to fluid bed drying or plate drying, where the drying rate is dependent on drying surface, in high frequency drying, drying rate depends on the dielectric properties of liquid and solids. Microwave drying is shown to have an efficiency advantage over traditional conductive drying (Vromans, 1994). It provides rapid drying at relatively low temperatures, which enables the drying of substances vulnerable to prolonged heating at higher temperatures (Travers, 2000).

Microwaves are not a form of heat but forms of energy that are manifested as heat through their interaction with materials. It is as if they cause materials to heat themselves (Schiffmann, 1995). There are many mechanisms for this energy conversion such as ionic conduction, dipole rotation, interface polarization and dipole stretching (Schiffmann, 1995). As wet granules in this thesis are considered to consist primarily of water and lactose, the following theoretical explanation focuses on dipole rotation as elaborated hereafter.

Many molecules, such as water, are dipolar in nature. The principle of dielectric heating is based upon the absorption of radiation energy by either induced or permanent dipoles. Dipoles are influenced by the changing polarity of the applied electric field. Normally dipoles are randomly oriented. The electric field attempts to pull them into alignment. As the field decays to zero, the dipoles return to the random orientation. As the electric field builds up the opposite polarity the dipole is pulled again into alignment. This relaxation and alignment is occurring at a frequency of many millions of times per second and causes an energy conversion from electrical field energy to stored potential energy in the material, and finally to thermal energy (Schiffman, 1995). This heat, in turn, evaporates the liquid.

In general, polar substances with a high dielectric constant absorb more energy than non polar substances. However, the resulting intensity of vibration, i.e. the degree of orientation, depends upon the structure of the molecule (size and shape), viscosity, temperature and intermolecular bonds. The sensitivity of materials to microwaves is highly variable. In complex mixtures as pharmaceutical granules the total permittivity of the radiance is difficult to predict. The permittivity consists of two parts: the relative dielectric constant and the loss factor. The loss factor of a material describes how much heat is generated inside a material per unit time when an electric field is applied (McLoughlin et al., 2003). The total loss factor of a wetted material is derived from that of the skeleton solid, and the bound and free water. Preferably the loss factor of the solid constituents in the granule is close to zero as this prevents the induction of thermal destabilization of the solid compounds. A low loss factor for the solid constituents implies that the solid does not absorb any energy and that the temperature in the solid will be low. A high loss factor means that the material absorbs the radiation really well.

The wet granules can be considered as a two component system of solid and wet material. The loss factor varies with moisture content. Crystal water molecules are less rotationally free than water absorbed to the first uni-molecular layer and all the subsequent present water. Completely “free” water will have a higher loss factor than bound water; therefore the temperature rise in free water is higher, inducing evaporation of the free water by the formation of steam as explained above.

It is known that if the loss factor is too high this will influence the penetration depth of the radiation. In this situation the incident energy is absorbed within the first few millimeters of the material leaving the inside unaffected, which causes non-uniform heating. By mixing the wet materials during radiation exposure, more material is exposed and in total will be dried more evenly (Vromans, 1994).

Microwave drying under vacuum has the advantage that the vulnerable pharmaceutical preparation doesn’t have to be heated to the evaporation temperature of water (100 °C). By the low pressure, the boiling point lowers.

An effective end-point control system is important for microwave drying. Once all water is evaporated, the next most excitable molecule will be triggered. By extensive heat generation, this may lead to irreversible degradation (Giry et al., 2006).

2.5 Attrition and breakage in drying processes

Attrition and breakage are common terms in the description of granulation and drying processes (Bika et al., 2001).

The type of breakage mechanism that will occur during drying processes varies according to the extent and direction of the force that is applied (Verkoeijen et al., 2002). In figure 2.8, several mechanisms are depicted. Attrition is caused by normal forces of low magnitude. Sharp edges and other surface asperities are removed to form fine dust and the original granule becomes more spherical. Abrasion is caused by tangential forces of low magnitude. Fine dust is formed and the original granule becomes smoother and rounder. Breakage processes can be described by fragmentation and chipping. Fragmentation occurs due to high to normal forces. The original granule is split into several fragments. Chipping occurs due to high tangential forces. Bits and pieces are chipped off the surface to leave a rougher and less spherical granule (Verkoeijen et al., 2002). In the current thesis, the occurring processes are divided in attrition, all processes resulting in the formation of fines and breakage, resulting in significant larger changes in granule size distribution.

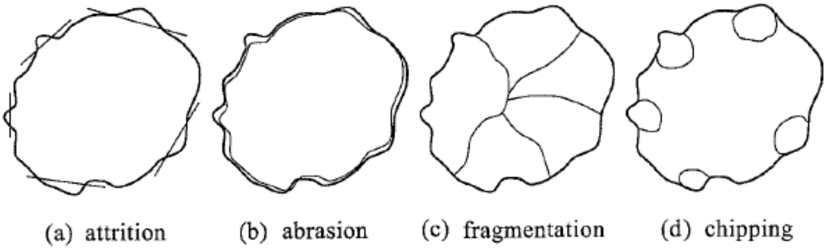


Figure 2.8 Schematic illustration of described breakage mechanisms (Verkoeijen et al., 2002).

In fluid bed drying, each granule is isolated from its neighbors and migration of solute between granules is not possible. Migration of the solute within the granule is possible however (Travers, 2000). Formation and entrainment of fines tends to occur as drying proceeds upon loss of surface moisture (Chaplin et al., 2005). Inter-granular collisions and collisions with the dryer wall can decrease granule size by attrition. Attrition of the solute-rich outer layer and elution of fines can therefore result in an overall loss of drug substance (Travers, 2000) or fines influencing further processing as tableting and milling (Juslin and Yliruusi, 1996b). The occurrence of breakage and attrition has been associated with the inlet air temperature and the drying time. It has been shown that breakage and attrition depend mainly on mechanical resistance and secondarily on the drying time. (Schæfer and WØrts, 1978, Niskanen and Yliruusi, 1994). As it is known that attrition and breakage occurrences are higher near the distributor plate than higher in the bed, air flow is of primary importance (Patel et al., 1986). Within a gas fluidized system, the main variables affecting breakage and attrition can be grouped in two categories;

1. Properties of the granules, e.g. size, shape, surface roughness and strength and binder viscosity (Patel et al., 1986, Juslin and Yliruusi, 1996b)

2. Environmental properties, e.g. air flow, height of the bed, pressure temperature and humidity (Patel et al., 1986).

The occurrence of breakage and attrition is based upon the equilibrium of strength of the granules and the applied forces upon these granules.

In the current thesis focus will lie on the properties of the granules affecting breakage and attrition.

2.6 Lactose

One of the most often used excipients in the formulation of solid drug products is lactose. Especially in high shear granulation, the relatively cheap and readily obtainable lactose, is used very often.

Lactose is a natural sugar, which is found almost exclusively in milk (Visser, 1983). Lactose is a disaccharide consisting of two monosaccharide moieties: galactose and glucose. The moieties are connected with a O-bridge (1,4). Two isomers are known: α-lactose and β-lactose. Galactose is identical in both isomers; the glucose α or β moiety determines the form of the molecule. Lactose is available in several morphologies; α-lactose monohydrate, anhydrous α-lactose, anhydrous β-lactose and amorphous lactose.

Lactose has a relative high water solubility (18.9 g per 100g water at 25 °C) Nowadays in high shear granulation, aqueous binder solutions are used in contrast to formerly used organic solvents. The dissolution of the excipient in the binder liquid has been subject of debate (Remon and Schwartz, 1987, Jørgensen et al., 2004).

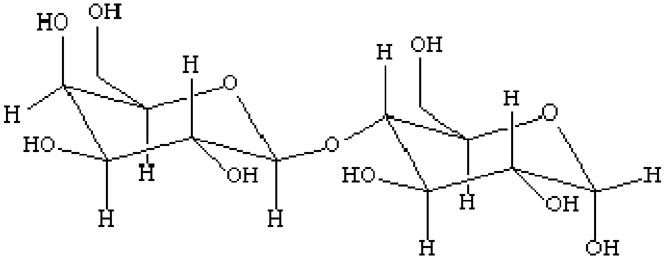


Figure 2.9 α- lactose (left moiety galactose, right moiety α- glucose, $C_{12}H_{22}O_{11}$, M_w 342.31).

Differences in granular friability have been explained by differences in solution rate of the excipient. Granules made from direct compression lactose and purified water have a lower friability after drying than granules produced from regular lactose and purified water. Direct compression lactose may dissolve faster than regular lactose and could therefore act as a more efficient binder. Furthermore, granulation of lactose with a 10% lactose solution yielded larger granules, less fines, more coarse particles and a lower friability (Remon and Schwartz, 1987). It was even hypothesized that by the high dissolution of lactose, a water soluble drug like borax would be encapsulated by the lactose. Upon mechanical friction leading to attrition, borax would then remain in the granule, whereas lactose would be abraded (Selkirk, 1973).

If lactose dissolves to form its own binder, re-crystallization of the dissolved material is observed (Juslin and Yliruusi, 1996a). Based upon the known heterogeneity of binder liquid distribution in high shear granulation granules in relation to granule size the extent of re-crystallization of the lactose solution in the different size fractions can differ. This in turn can affect product quality. Furthermore it is not known which crystalline or non-crystalline state will be formed upon drying. In the current thesis, solely lactose is used as solid constituent and water is used as binder liquid, no binder material as hydroxypropylcellulose or polyvinyl pyrrolidone are added.

Abbreviations

a	Granule radius (μm)
$C_{p,air}$	Specific heat capacity of air at constant pressure ($1 \cdot 10^3$ J kg^{-1} K^{-1})
De	Deformation number (-)
ε_{min}	Minimum granule porosity (-)
h_{fg}	Latent heat of vaporization of water at the dryer outlet temperature ($2.26\ 10^6$ J kg^{-1})
m	Granule mass (g)
m_{air}	Mass flow of air through the the dryer (kg s^{-1})
m_{H2O}	Mass flow of water evaporated in the bed (kg s^{-1})
μ	Binder viscosity (Pa $\cdot$ s)
PEG	Polyethylene glycol
ρ_g	Granule density (g $\cdot$ cm^{-3})
ρ_l	Liquid density (g $\cdot$ cm^{-3})
ρ_s	Solid density (g $\cdot$ cm^{-3})
Q_{loss}	Heat loss to the environment through thermal convection (J s^{-1} K^{-1})
St_{def}	Stokes deformation number (-)
St_v	Viscous Stokes value (-)
s_w	Maximum pore saturation reached by formulation in the granulator (-)
T_{in}	Inlet air temperature (K)
T_{out}	Outlet air temperature (K)
U_0	Initial relative granule collision velocity (cm $\cdot$ s^{-1})
U_c	Collision velocity in the granulator (g $\cdot$ cm^{-3})
w	Mass ration liquid to solid (-)
Y_g	Dynamic yield stress (kPa)

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3

Granule breakage during drying processes

Abstract

The drying of wet granules often involves an unwanted and uncontrolled size reduction. Current FDA PAT guidance stresses importance of process control and understanding. The aim of this study is to determine and understand the breakage phenomena during drying processes in order to control these processes. High shear granulated lactose granules with water as binding liquid were dried during variable periods. Subsequently the (partially) dried granules were exposed to agitation by the impellor and chopper in the granulator. Granule characterization revealed that the change in granule size of (partially) dried granules is dependent on water content and follows a three phase system characterized by a growth, plateau and breakage phase. The derived yield stress of the granules is a function of velocity. From this it is concluded that in the plateau phase above minimum water content, stress behavior of granules can be described with Rumpfs' dynamic granule strength, whereas below minimum water content (breakage phase) granule strength is determined by the solid bridges. The extent and velocity of stress and water content of the granules during the process determine the size reduction phenomena.

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Introduction

Wet granulation is a particle size enlarging process widely applied within a diverse range of industries. Paradoxically, the subsequent drying step often involves a size reduction, which is considered to be both unwanted and uncontrolled. The deteriorating effects of attrition on flowability of powders masses (Aulton, 2000) or inhomogeneity (Van den Dries et al., 2003) of active substances in the granules in pharmaceutical processes have been described. In oil industry unwanted breakage of catalyst particles (Kelkar and Ng, 2002) has been investigated while in the detergent industry the breakdown of detergent enzyme granules has been studied (JØrgensen et al., 2005). Although unwanted size reduction of pharmaceutical granules during fluidized bed granulation, drying (Niskanen et al., 1994) or high shear granulation (Van den Dries et al., 2003) has been reported, attrition has received relatively little attention. Currently, growing attention is given to process understanding because of FDA guidance, which stresses the importance of process control as a means of quality assurance (FDA, 2004). The wish to understand the size reduction processes and the requirement to control these phenomena urged us to start this study.

In the current literature attrition and breakage are defined in several ways. Bemrose and Bridgewater (1987) considered attrition as an unwanted size reduction irrespective of cause. Verkoeijen et al. (2002) described breakage mechanisms as function of the magnitude and direction of the force. Attrition reflects removal of sharp edges whereby fine dust is formed. Granule shape becomes more spherical upon attrition. Abrasion points to removal of crumbly material from the surface of the granule. Granule shape also becomes rounder and smoother and fine dust is formed (Verkoeijen et al., 2002). Formation of fines by attrition or abrasion is in practice an important parameter because it can affect flowability of the granule mass.

In this chapter, the term breakage is defined as unwanted size reduction. Attrition is used to describe the formation of fine dust or fines.

Most research has been performed on breakage phenomena in homogeneous model granules or in individual particles (Ning et al., 1997, Boerefijn et al., 1998, Subero et al., 1999, Subero and Ghadiri, 2001, Reynolds et al., 2005). In practice “true” granules represent however a bulk. The difference in numbers, mass and heterogeneity versus homogeneity indicate the need for research in bulk.

During handling granules are often exposed to normal forces and shear. To prevent unwanted breakage knowledge of breakage propensity is desirable. Most models and studies so far deal with either dry or wet granules, whereas also the effects of storage under different humidity conditions on breakage of dry lactose agglomerates have been studied (Boerefijn et al., 1998). In this particular study it was shown that by influence of humidity, crystal bonds are formed by local dissolution and subsequent crystallization on contact points. The formed bonds yielded a more rigid and brittle structure, resulting in a lower breakage propensity (Boerefijn et al., 1998). For dry lactose agglomerates and glass pearl granules brittle or semi-brittle breakage as function of impact (velocity) has been studied (Boerefijn et al., 1998, Verheezen et al., 2004). It has been argued that terminology as brittle and semi-brittle are solely applicable for model homogeneous continuum solid particles. In contrary, granular solids are clusters of small particles held together by inter-particle bonds (Reynolds et al., 2005). The nature and nett sum of these bonds will determine the strength or resistance to breakage of the granules. In wet granules of crystalline organic material the influence of water on the resistance to breakage has been investigated (Verkoeijen et al., 2002). Granules exhibited the maximum strength at high moisture content. Until now, the intermediate situation between wet and dry state as existing during drying has not been studied extensively.

The objective of this study was to determine the factors influencing the extent of breakage during drying processes and to understand the drying related breakage phenomena in order to control these phenomena.

3.1 Materials and methods

3.1.1 Granulator experiments

Lactose 200M (1.4 kg, obtained from DMV-Fonterra, Veghel, The Netherlands) was granulated in a high shear mixer (Gral 10, Colette, Wommelgem, Belgium) for 15 minutes (impellor rotation rate 250 rpm, chopper rotation rate 1500 rpm). 225 ml de-mineralized water was used as binding liquid. The binder was poured onto the moving powder mass. The viscosity of the water and was 0.001 $Pa \cdot s$ (Brookfield Rheometer). The surface tension of the water was 0.073 $N \cdot m^{-1}$ (Tensiometer Krüss GMBH K10). After granulation the granules were dried on trays during variable periods up to 240 minutes in an airflow cabinet (Marius, Tiel, The Netherlands) at 40°C. After (partial) drying the granules were transferred back into the granulator and exposed to agitation of the impellor and the chopper (250 rpm and 3000 rpm or 50 rpm and 1500 rpm respectively for impellor and chopper). To determine the influence of the chopper on breakage behavior additional experiments were performed in which the partially dried granules were exposed to the impellor alone.

3.1.2 Compression experiments

For compression experiments two independent lactose granule batches were prepared as described above. After (partially) drying the granules were collected and stored at 5°C until further use. The granules were weighed in portions of 500 mg and compressed in an automated compaction simulator (ESH, Brierley Hill, UK) at 20°C and 51% RH. The compaction rates applied were 3 and 300 $mm \cdot s^{-1}$. A sine wave compaction profile was used. Different compaction forces (10, 20 and 40 kN) were used. Before each compression cycle the die was lubricated with magnesium stearate. During compression force and displacement of the upper punch were recorded. From the true density, the weight of the compressed tablets, the volume under pressure and upper punch force the yield pressure was determined by means of a Heckel plot (Heckel, 1961).

3.1.3 Characterization

The water content of the granules was determined with an automated Karl Fischer titration (Metrohm KF coulometer 756K with oven sample processor 774 at 150°C). Particle size distribution of the granules was determined by sieving 100 g of granule samples on a Retsch AS 200 control siever. The mean particle size of the samples was estimated as a median weight diameter. The effect of the sieving equipment on the attrition and breakage of granules was assessed. It was found that sieving of the granules did not significantly influence the obtained results from the granulator experiments.

3.2 Results and Discussion

The formation of fines is often used as a parameter for attrition and abrasion. In this chapter, fines are defined as particles < 212 μm. Figure 3.1 depicts fines formation as a function of the granule water content. It can be observed that fines are mainly formed at low water content.

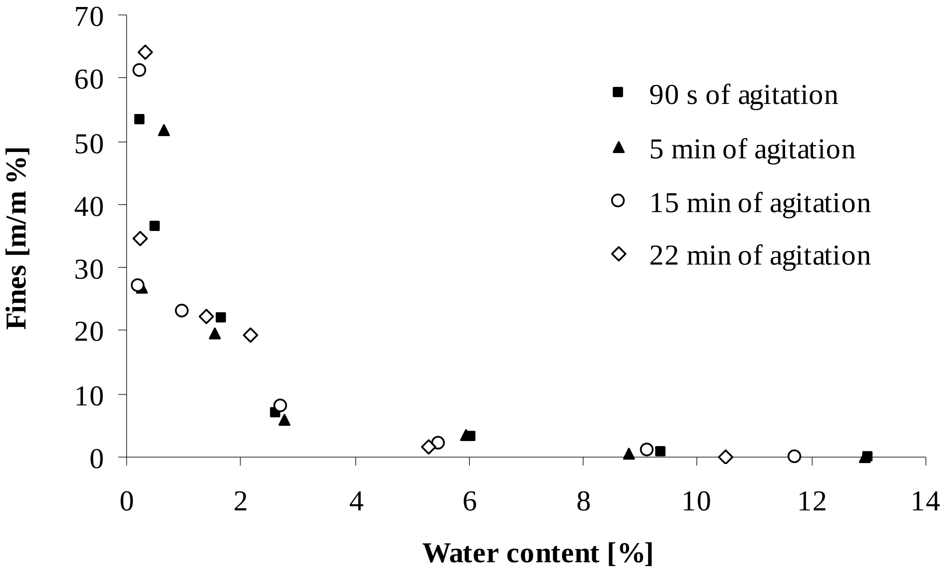


Figure 3.1 Formation of fines in the total granular mass as function of water content and in relation to the duration of agitation time in the high shear mixer.

Figure 3.2 shows the change in granule size upon increasing exposure to stress for granules granulated with water. A positive change indicates an increase in mean granule size which reflects a growth effect, while a negative change represents granule size reduction. Basically this figure shows that the wetter granules experience a nett size increase whereas dry granules reveal primarily nett size decrease breaking phenomena. In line with what has been found previously (Iveson and Litster, 1998, Iveson et al., 2001) there is also breakage of granules ongoing at high water content, but breakage phenomena seem to be counteracted by growth phenomena as seen from figure 3.2 and 3.3 where at higher water content a nett size increase is perceived.

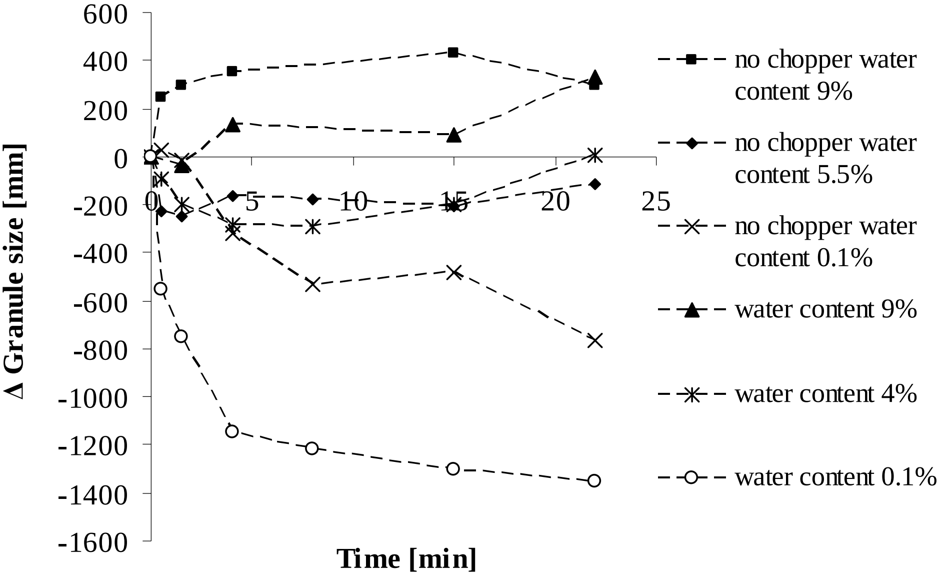
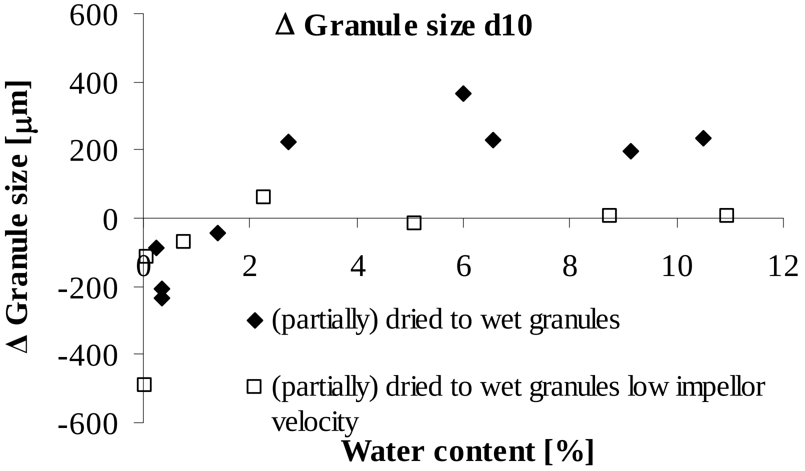
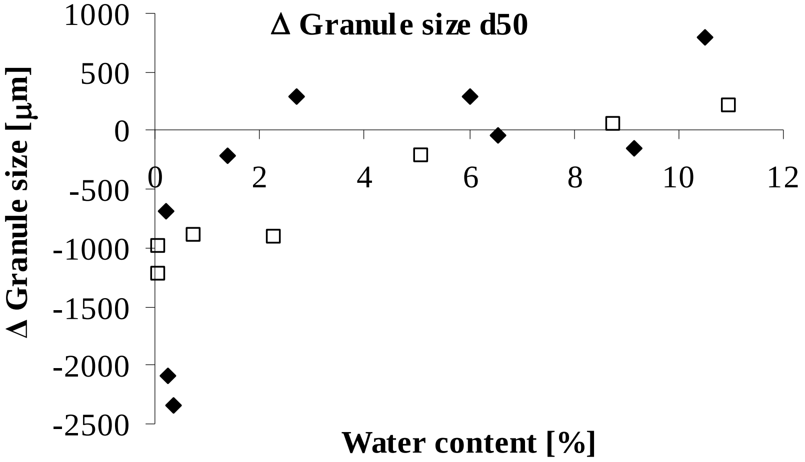


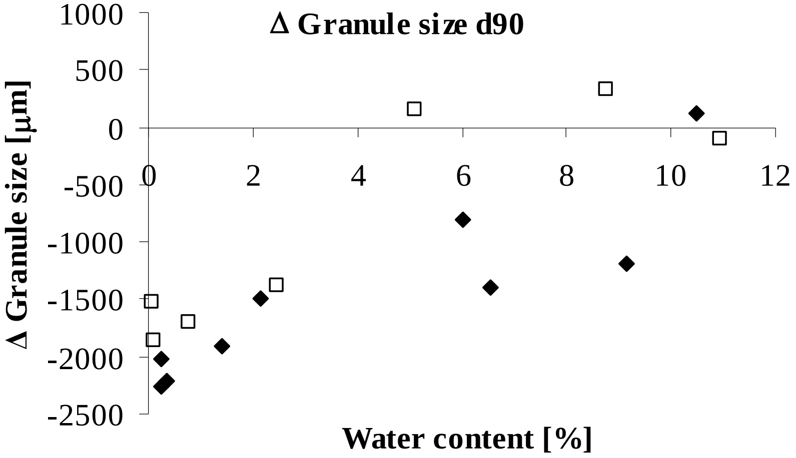
Figure 3.2 Influence of chopper on nett granule size decreasing breakage and nett granule size increasing growth phenomena of binderless granules (impellor velocity 250 rpm (~ 3 m/s), chopper velocity 3000 rpm (~ 11 m/s) or absent).

To determine the impact of the chopper the (partially) dried granules were exposed to the impellor in absence of the chopper. From figure 3.2 it is clear that the chopper has a significant effect on the outcome. Figure 3.3 plots the changes in granule size (d_{10}, d_{50}, d_{90}) as function of the water content for granules exposed to 22 minutes of agitation. An increase in d_{10} and decrease in d_{90} upon agitation reveals a granule-size-redistribution upon agitation for the partially dried granules. When the granules are completely dried the formation of fines, as seen in figure 3.1, is extensively influencing the span of the distribution. The increase in d_{10} and the formation of fines in relation to the water content points to the existence of growth phenomena. The d_{90} is related to the formation of large agglomerations. These large agglomerations can apparently not resist the high impellor velocity whereas they can resist the lower impellor velocity. The foregoing figures illustrate that the change in granule size is primarily attributed to the amount of water. In fact

. three different domains can be identified.







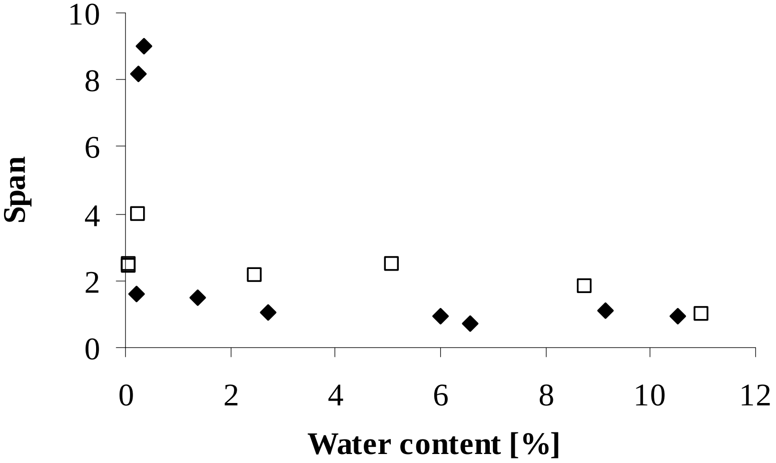


Figure 3.3 a,b,c,d. Influence of water content on granule size and span of the distribution after 22 min. of agitation by impellor and chopper. Granules exposed to agitation with low impellor (50 rpm, ~ 0.6 m . s-1) and chopper velocity (1500 pm, ~ 5.5 m . s-1) and high impellor (250 rpm, ~ 3 m . s-1) and chopper velocity (3000 rpm, ~ 11 m . s-1) are shown. a) d10, b) d50, c) d90, d) Span.

At low moisture levels there is a considerable amount of attrition apparent. Above a water content of approximately 1-2% (see figure 3.3) there exists a plateau where a change in water content does not really alter the resistance to breakage. Finally, at a water level above 9% the nett result of applied stress becomes positive, i.e. some granule growth is observed.

When a dependency of granule strength of water is apparent this suggests a granule strength dependency as described by Rumpf (1958) and Schubert (1975). Schubert investigated tensile strength of wet granules in relation to saturation level. Tensile strength is expected to increase with increasing saturation in the funicular state. The tensile strength is expected to decrease as the granular mass is oversaturated and becomes a paste.

Earlier Rumpf (1958) described granule strength in terms of saturation level (S), porosity and starting material characteristics as $d_{3,2}$ and γ. This is expressed as

$$\sigma_c = 6S\frac{(1-\varepsilon)}{\varepsilon}\frac{\gamma}{d_{3,2}}$$ **Equation 3.1**

where σ_c is static granule strength , ε is the inter-granular porosity, γ is surface tension of the binder solution and $d_{3,2}$ is the surface mean diameter of the primary particles. The static granule strength describes the forces acting between two particles related to a capillary liquid bridge.

For the derivative granule strength viscous effects are considered negligible because the granules are considered stationary (Rumpf, 1958). Here the surface tension of the binder solution and the surface mean diameter of the primary particles are considered to be constant. The saturation level, directly related to the water content and porosity, is hence the most important parameter in this equation.

The saturation level of a granule is defined as the ratio of pore volume occupied by liquid to the total volume of pores available in the granule. This can be expressed as:

$$S = \frac{H(1-\varepsilon)}{\varepsilon}\rho_s$$ **Equation 3.2**

where H is the mass ratio of liquid to solid, ε is the intra-granular porosity and ρ_s is the density of the particle relative to the density of the liquid (Faure et al., 2001). Knowing the mass ratio of liquid to solid and the values for the intra-granular porosity and the density, it is possible to calculate the saturation level.

For breakage to occur the granule strength, σ_c, must be smaller than the impact stress, σ_{impact}. The impact stress of the chopper and impellor is expressed as (Vromans et al., 1999; Van den Dries and Vromans 2002):

$$\sigma_{impact} = \frac{2}{3}\rho_g v_i^2$$ **Equation 3.3**

where ρ_g is the granular density and v_i is the tip velocity of either the impellor or the chopper. The impact stress of the chopper and the impellor were calculated and are shown in figure 3.4a as horizontal lines and in figure 3.4b as vertical lines. Obviously, the impact stress from the chopper is higher than the impact stress from the impellor, based on the higher tip velocity. Most important in the figure is that above a saturation of 40 % granule strength is theoretically high enough to resist impact stress and hence to avoid breakage.

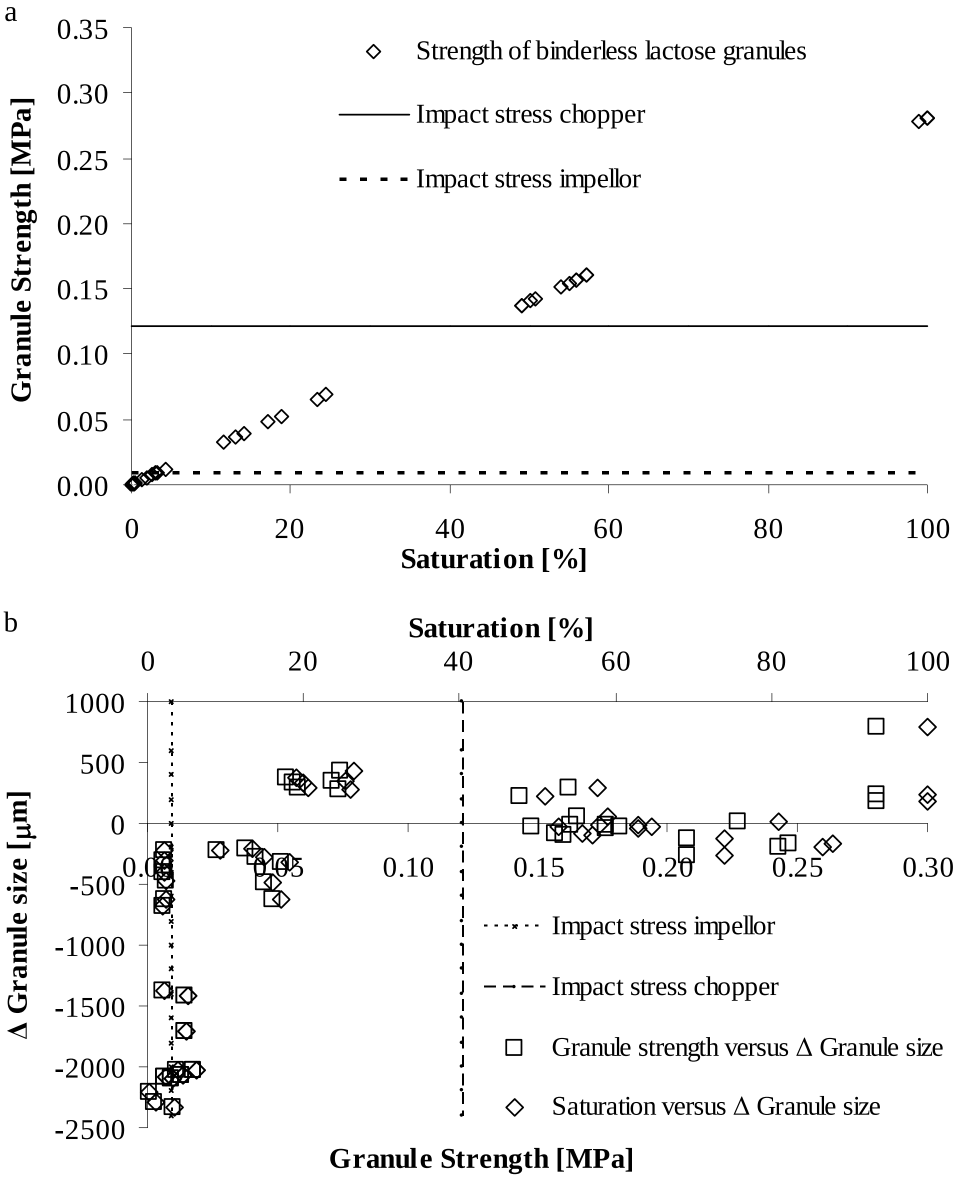


Figure 3.4 (a) Static granule strength as function of saturation of granules without binder. The impact stress of the chopper and the impellor was calculated. Impellor velocity 250 rpm (v_i) ~3 m· s^{-1}; chopper velocity 3000 rpm (v_i), ~11 m· s^{-1}. Values used for calculations $d_{3,2}$, 10 μm ; ρ_g, 1500 kg · m^{-3}; γ, 0.073 N · m^{-1}; ε, 0.135. (b) Calculated static granule strength and saturation level versus the change in mean granule size of (partially) dried binderless granules (Δ d_{50}); impellor velocity 250 rpm (v_i), ~3 m· s^{-1}; chopper velocity 3000 rpm (v_i), ~11 m· s^{-1} ; ρ_s, 1500 kg · m^{-3}.

In figure 3.2 the influence of the chopper on the mean granule size can be seen. Notice that the influence of the chopper is more abundant for relatively dry granules. Figure 3.4b plots the change in mean granule size as seen in figure 3.2 and 3.3 versus both theoretical static granule strength and saturation level. By the dependency of the static granule strength on saturation, the data sets are as observed highly correlated.

The figure shows that below a saturation-level of approximately 20% breakage of the granules is abundant. However, above this level, breakage is limited. When the granule strength is compared with the impact stress, it is obvious that these results are not really consistent with the expected outcomes. Granules with strength considerably weaker than the chopper impact stress are able to survive this stress (figure 3.4b). This may be due to the simple fact that the powder bed shows a certain bulk movement as has been reported by Ramaker et al. (1998), who demonstrated that wet granules in a working high shear mixer exert a toric flow profile. This flow profile is stable under various impellor velocities and presence or absence of the chopper. The toric velocity is smaller than the impellor or chopper velocity. It proved to be impossible to determine the mean velocity of the whole toric flow profile (Ramaker et al., 1998). This would mean that the impact stress the granules really undergo is lower than calculated. Yet it is remarkable that the chopper exhibits a marked effect on the breakage (figure 3.2).

The Rumpf equation (3.1) can not sufficiently clarify the observed dependency of the granule strength on water content and chopper/impellor velocities although it is observed that saturation level of the granules does influence the behavior of the drying granules under stress. Basically, the Rumpf equation (3.1) describes static granule strength. When applying this equation it is assumed that the rate of granule deformation upon impact is low. This situation may be valid for low intensity mixers, but is not likely to be valid for high shear granulators, although it is not precisely known what relative velocities are, as has been argued above. Ennis et al. (1990) showed that at relatively high velocities of the particles a viscous force determines the strength of a liquid bridge. Therefore, the so-called dynamic granule strength (σ_v) may describe the findings more accurately. The tensile strength of a granule under dynamic conditions is derived by the following equation:

$$\sigma_v = \frac{9}{8}\frac{(1-\varepsilon)^2}{\varepsilon^2}\frac{9\pi\mu v_p}{16 d_{3,2}}$$ **Equation 3.4**

in which ε is the intra-granular porosity, μ is the viscosity, v_p is the relative velocity of the moving particles and $d_{3,2}$ is the surface mean diameter of the primary particles. This equation is based on the general equation for tensile strength of a granule as developed by Rumpf, the Reynolds lubrication equation describing the viscous force of liquid bridge and the Kozeny model as elaborated by Van den Dries and Vromans (2002).

The dynamic or viscous character of the liquid bridge is considered to describe the observed phenomena under drying conditions. In contrast to equation 3.1 where the static strength of the granules is highly dependent of the saturation level of the granules the dynamic strength of the granules is dependent on the number of contact points between the moving particles (Van den Dries and Vromans, 2002) and independent of the liquid saturation within certain limits. At the contact points between particles a liquid bridge can be formed. As can be seen from equation 3.2, the most important variables in the experimental set up as discussed is the relative velocity of the particles as porosity, primary particle size and viscosity can be assumed to be constant. In the plateau phase influence of saturation level is minimal as the granule size does not change upon continuous agitation as seen in figure 3.3 and 3.4.

It is therefore of interest to evaluate the deformation of the granules as a function of water content at various deformation rates. In tableting research deformation behavior of excipients under pressure is a well investigated topic. The pressure exerted on excipients in tableting can be compared to the stress exerted to the granules in the previous described experimental set-up. When the (partially) dried granules are compacted several overlapping stages occur. Firstly the granules rearrange. Secondly at a certain relative density, densification is no longer possible without deformation of the brittle granules. Brittle materials as dried lactose break at relatively small compaction stress.

Heckel (1961) developed a method to transform the applied pressure and relative density of metal powders to a partial linear plot.

$$-\ln(\varepsilon) = K \cdot p + A$$

Equation 3.5

where ε is porosity, p is compaction pressure and K and A are constants.

This equation can also be used to describe the densification of pharmaceutical powders or granules during compaction (van der Voort Maarschalk et al., 1996; Nicklasson and Alderborn, 2000). The first part of the Heckel plot can be related to densification by particle movement and rearrangement processes (Heckel, 1961).The second part of the linear Heckel plot corresponds to densification by particle deformation and failure or plastic deformation where inter particle bonding already has become dominant (Heckel, 1961). In the first part the influence of present water in the current lactose granules is thought to be appreciably higher than at higher pressures at the linear region of the plot.

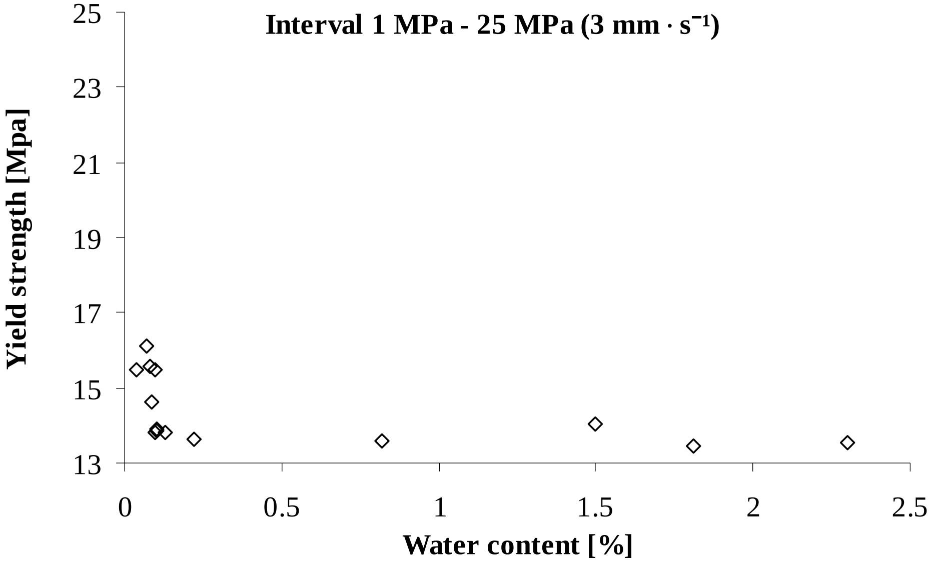
The effect of water on the compaction behavior of pharmaceutically used crystalline solids has been previously studied (Ollet et al., 1993). From this study it was concluded that the effects of water content in compaction of pharmaceutical powders are complex. In crystalline powders, water was considered to act as a lubricant (Ollet et al., 1993).

From the Heckel plot the yield strength can be extracted by the relation:

$$\sigma_y \cong \frac{1}{3 \cdot K}$$

Equation 3.6

To determine the influence of water on the granule deformation properties the first compaction pressure interval at 1 – 25 MPa has been chosen representing the first stage of compaction (Horisawa et al., 2000). For the drying lactose granules water is considered most important in this stage of compaction. The derived strength value is considered to represent the yield strength. The derived calculated yield strength is plotted versus the water content of the granules in figure 3.5. A plateau phase is observed where the yield strength of the granules is independent of the water content but dependent on the compaction rate. At higher water content (> 10% data not shown) the yield strength rises fast. At this point granules are almost fully saturated and densification of the wet granular mass will be opposed by the present water. In the presence of a small quantity of water the strength of the granules changes significantly. There is a remarkable difference in this change, dependent upon the rate of compression. The lower velocity results in the lower stress whereas the reverse is true for the high rate. For both compaction velocities the yield strength for the dried lactose granules approaches 17 MPa.



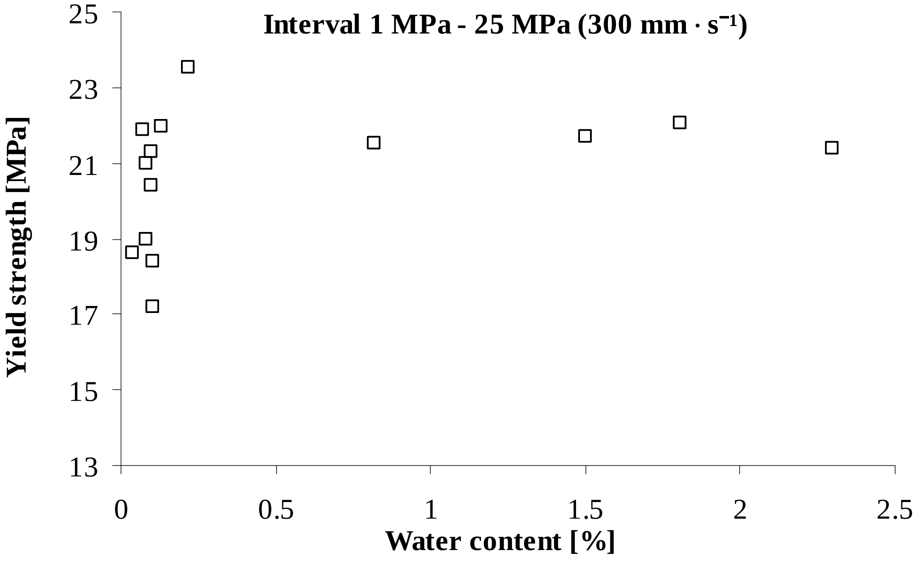


Figure 3.5 (a and b) Yield strength as function of water content in particle movement and rearrangement interval: (a) compaction velocity 3 mm $\cdot$ s^{-1}; (b) compaction velocity 300 mm $\cdot$ s^{-1}.

The strength of dry lactose granules is determined by adhesive forces and crystal bridges. The solid bridges in the granules can be formed upon drying by re-crystallization or precipitation of the dissolved lactose (Boerefijn et al., 1998; Bika, et al., 2005). It is known that solid bridges formed from saturated lactose solutions develop in several stages from a mostly non-crystalline (liquid) and amorphous state to a crystalline structure (Farber et al., 2003). Finally the obtained bridges are polycrystalline and brittle (Farber et al., 2003, Farber et al., 2005). The time required for the completion of the stages is in the order of hours to days so that the final bridge microstructure is not obtained immediately (Farber et al., 2003). In other words even when the granules are considered dry, the final bridge strength is not necessarily obtained yet. This may be one reason why the yield strength value varies considerably at zero water content. Brittle breakage is difficult to measure quantitatively and reproducible and therefore also fluctuating values for the yield strength may be obtained.

The effect of increasing compaction rate on the observed strength as seen in figure 3.5 suggests a dynamic relationship (equation 3.4) when densification by particle movement and rearrangement occurs. In figure 3.5 the yield strength in the plateau phase is not influenced by water content, but is by compaction rate. As argued, dynamic strength is independent of liquid saturation above a certain liquid bridge volume (Ennis et al., 1990). Furthermore dynamic strength does depend on velocity of the particles. Granule behavior in the observed plateau phase can therefore be described in terms of dynamic strength. It is then assumed that the minimal liquid bridge volume has been reached once the plateau phase starts.

According to this line of thought the same dynamic strength plateau phase can be recognized in figure 3.3 for the (partially) dried granules exposed to agitation by the impellor and the chopper. Here the impellor and chopper velocities determine the changes in granule size and therefore the strength of the granules. At low impellor velocity more breakage effects are observed confirming the statement that granule behavior in the plateau phase can be described with a dynamic strength model. When wet granules are exposed to agitation in a high shear mixer constant growth and breakage processes are observed and described. Growth can occur by coalescence and layering growth (Iveson and Litster, 1998, Iveson et al., 2001, Van den Dries et al., 2003). In the current study during the exposition to agitation the wettability characteristics of both lactose and the binding liquid are considered constant, therefore minimum saturation level, porosity related to consolidation and binding liquid penetration determine growth phenomena (Iveson et al., 2001, Van den Dries and Vromans, 2002, Van den Dries et al., 2003).

The breakage phase before the plateau phase in figure 3.3 can be correlated to the developing solid bridges, as explained above that are not strong enough to withstand the exerted agitation of the impellor and the chopper (Bika, et al., 2005, Farber et al., 2005). A higher agitation level induces an abundant breakage pattern. Less breakage is observed for the dry granules at low impellor and chopper velocities (figure 3.2 and 3.3). The formation of fines has the same dependency on water content as the change in d_{10} (figure 3.1 and 3.3a). From figure 3.1 it cannot be concluded that fines are not formed at higher water contents. Figure 3.3a suggests namely that during agitation exposition size redistribution occurs above minimal water content. Here the fines can be part of a layering growth or coalescence growth process (Van den Dries et al., 2003).

3.3 Conclusion

The formation of fines and change in mean granule size as function of water content describe the attrition and breakage behavior of granules under drying conditions. The current data reveal a three phase system whereby water content and extent of stress determine the size reduction behavior and strength of the granules. Below a minimum liquid bridge volume the presence of very small amounts of water or developing solid bridges cannot prevent abundant size reduction. This can be observed as a sudden increase in breakage and high levels of attrition as seen by the large changes in granule size and the formation of fines. Above a minimum liquid bridge volume the granule strength is independent of water content and dependent on impact or compaction velocity revealing a dynamic strength system. This phase is characterized by a plateau phase where changes in granule size are stable and comparable. After the plateau phase a growth phase can be observed characterized by size enlargement of the granules. This growth phase is based upon available surface water enabling layering growth and coalescence upon consolidation. Rumpfs' static strength model, highly dependent on saturation level of the granules, cannot explain the behavior of the (partially) dried granules when exposed to agitation. The derived Rumpf dynamic strength model describes the granule behavior in the plateau phase where changes in granule size or yield strength are independent of water content and dependent on compaction rate or impact velocity.

Abbreviations

A	Constant in Heckel equation
γ	Surface tension (N m^{-1})
$d_{3,2}$	Surface mean diameter of the primary particles (µm)
d_{10}	Cumulative 10 % frequency undersize (µm)
d_{50}	Cumulative 50% frequency undersize (median granule size) (µm)
d_{90}	Cumulative 90% frequency undersize (µm)
ε	Intra-granular porosity (-)
H	Mass ratio of liquid to solid (-)
k	Slope of the Heckel plot (see Heckel equations (5, 6))
μ	Viscosity (Pa·s)
p	Compaction pressure (MPa)
ρ_s	Density of the particle relative to the density of the (binder) liquid (-)
σ_c	Static granule strength (Pa)
σ_{impact}	Impact stress (Pa)
σ_y	Yield strength (Pa)
σ_v	Dynamic granule strength (Pa)
v_i	Tip velocity of either the impellor or the chopper (m s^{-1})
v_p	Relative velocity of the moving particles (m s^{-1})

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4

Granule characterization during fluid bed drying by development of a near infrared method to determine water content and median granule size

Abstract

Water content and granule size are recognized as critical process and product quality parameters during drying. The purpose of this study was to enlighten the granule behavior during fluid bed drying by monitoring the major events i.e. changes in water content and granule size. NIR spectra collected during drying and water content of sampled granules were correlated by principal component analysis (PCA) and partial least squares regression (PLSR). NIR spectra of dried granules were correlated to median granule size in a second PCA and PLSR. The NIR water model discriminates between various stages in fluid-bed drying. The water content can be continuously predicted with errors comparable to the reference method. The 4 PLS factors of the granule size model are related to primary particle size of lactose, median granule size exceeding primary particle size and amorphous content of granules. The small prediction errors enable size discrimination between fines and granules. For product quality reasons, discrimination between drying stages and end-point monitoring is highly important. Together with the possibilities to determine median granule size and to distinguish fines this approach provides a tool to design an optimal drying process.

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4.1 Introduction

As elaborated in chapter 2 granulation is a common unit operation in manufacturing of oral dosage forms. Granules are often prepared by wet processes which have been extensively studied. Remarkably, the subsequent drying step has received relatively little attention. In batch production, drying is often the bottleneck either for time or product quality reasons. Plate drying is a slow process. In the fast fluid-bed drying process attrition, a size reduction phenomenon which leads to the formation of fines is considered a product quality diminishing side effect (Travers, 1988). As seen in the previous chapter pharmaceutical granules exhibit an intrinsic breakage propensity during drying which is dependent on water content and extent of stress exposed to the granules. By use of an in-line technique to monitor water content this critical process step can both be acknowledged and followed. Moreover granule characterization during fluid bed drying enables better process understanding which leads to better process control.

Process understanding receives more and more attention. This is because product quality assurance can only be achieved by thorough knowledge of the critical process steps. Therefore, process understanding and control using in-line analytical techniques such as near infrared spectroscopy (NIR) have received much attention (Beyer and Steffens, 2003, Findlay et al., 2004, Frake et al., 1998, Green et. al., 2005, Higgins et al, 2003, Rantanen et al., 2000, Zhou et al., 2004). NIR spectra can contain information about both physical and chemical parameters which are both quantitatively and qualitatively interpretable (Beyer and Steffens, 2003, Findlay et al., 2004, Frake et al., 1998, Green et al., 2005, Higgins et al., 2003, Zhou et al., 2004). Furthermore NIR is fast, robust and non-invasive, requires no sample preparation and will not produce any waste products. Therefore NIR can be considered almost an ideal tool for process monitoring and control.

Although NIR spectra might be fully spectroscopically explained, the subsequent chemometric modeling, interpretation and calibration of the data set in relation to the product or process parameters proves often a more difficult and time-consuming task, and does not provide a basic understanding of the process itself. It is however of significant importance to fully elucidate the interpretation of the chemometric fitting. If a reliable and quantitative model based upon input of NIR spectral data is desired several aspects have to be acknowledged; at first it is necessary that the information needed to correlate NIR data versus product properties is present within the spectrum. Secondly, it should be acknowledged that the spectrum might not contain enough or optimal information needed to predict the property of interest within the level of certainty required (DiFoggio, 2000). Thirdly if the NIR spectrum does not contain the desired information mathematical statistical handling cannot extract it. I.e. information cannot be created by multivariate data analysis.

As process understanding is a key goal of the Process Analytical Technology (PAT) initiative (FDA, 2004) the control tools, such as NIR, should be fully understood as well. In other words; black box processes should not be monitored and controlled by black box methods.

NIR has often been applied for the determination of water content. In fluid-bed drying different phases are defined in relation to the evaporation rate of water: the constant rate period, the falling rate period and the equilibrium period (Travers, 1988). For process monitoring in fluid-bed drying the different phases in drying should be distinguished by the NIR model. For end point determination the known dry point should be acknowledged preferably with an error similar or smaller to the current used off-line water determination methods as Karl Fischer coulometry or heat balance methods. It is known that sodium tartrate with an absolute water content of 15.5% can be determined with a standard deviation of 0.3%. Therefore a standard deviation of 0.3% is used as a comparison to the error obtained with the NIR method.

Apart from following water content, NIR spectroscopy is theoretically able to follow other changes like granule size distribution Findlay et al., 2004, Frake et al., 1998, Gupta et al., 2004, Pasikatan et al., 2001, Rantanen et al., 2005). NIR waves encountering a granule will penetrate the outermost layers first. When a boundary, e.g. a primary particle surface, is encountered the direction of the light beam will be changed. This can occur by scattering i.e.: reflectance, refraction and random diffraction at surfaces of various particles. Part of the beam will be absorbed by the material. Upon scattering and absorption of the light, the intensity decreases. Light that re-emerges from the surface layer is called diffuse reflectance light (Pasikatan et al., 2001). Diffuse reflectance depends on the composition of granule (type of material, internal and external structure), depth of penetration and wavelength. As the particle size decreases, light encounters more surfaces or boundaries. This increases the scattering level and decreases the penetration depth of the light. As the path length that the light travels is decreasing, the absorbed fraction of the light increases and the diffuse reflectance is increases as well (Pasikatan et al., 2001). Several physical factors such as mean particle size, composition, particle size distribution, particle shape and packing density influence the penetration of light in the sample and therefore influence the diffuse reflectance (Gupta et al., 2004, Pasikatan et al., 2001).

To distinguish granules from primary particles or fines in the NIR-granule size model the prediction error should be similar or smaller than the particle size of the original primary particles. Otherwise no distinction is possible between granules, primary particles or attrited material.

Water content and granule size are recognized as critical process and product quality parameters during drying processes. By NIR spectroscopy theoretically both water content and granule size can be monitored in-line. Granule characterization during the drying process will increase process understanding. The aim of this study was to develop a fully understood NIR model to monitor both water content and granule size during fluid-bed drying processes and thereby increase process understanding.

4.2 Materials and Methods

4.2.1 Drying process

4.2.1.1 Fluid bed drying

1.4 kg Lactose 200M (DMV-Fonterra, Veghel, The Netherlands) was granulated in a high shear mixer (Gral 10, Colette, Wommelgem, Belgium) for 10 minutes (mixer rotation rate 450 rpm, chopper rotation rate 1500 rpm). 225 ml de-mineralized water was used as binding liquid. The water was poured onto the moving powder bed. The wet granules were transferred to a fluid-bed dryer (Granulator Niro Aeromatic MP-1, Bubendorf, Switzerland). To obtain a stable temperature during the drying process, the equipment was heated up for 30 min before use with the following parameters: inlet temperature 60 °C, air flow 60 $m^3 \cdot h$. In the fluid-bed drying experiments inlet air temperature (40, 50 or 60 °C) and inlet air flow (60, 70, 80 or 90 $m^3 \cdot h$) were varied. All the different combinations of parameters were explored in order to evaluate the influence on drying rate and subsequent water content. The drying process was extended for 20 minutes. Inlet and outlet temperature and relative humidity were monitored throughout every experiment. The experiments were monitored in-line with a NIR probe as described below.

4.2.1.2 Microwave drying

11 kg Lactose 200M (DMV-Fonterra, Veghel, The Netherlands) was granulated in a high shear mixer (Gral 75 / Vactron, Colette, Wommelgem, Belgium) for 5 minutes (mixer rotation rate 130 rpm, chopper rotation rate 1500 rpm) with 1700 ml of water as binding liquid. Vacuum (50 kPa, absolute value) was

applied and the granules were exposed to microwave radiation (3 kW, electric field 100%) until the granules were dry. This point is characterized by a steep increase in back reflection and decrease in applied power to a steady state situation. Microwave drying can currently not be monitored in-line by NIR spectroscopy. Spectra of dried samples are collected off-line after 12 weeks storage at room conditions. The microwave dried samples were used as reference.

4.2.2 Data acquisition and pre-treatment water measurement

The NIR probe (FOSS NIRSystem Analyzer, software package Vision®, Birchwood, U.K.) was placed into the wall of the fluid-bed dryer at the same height of the system integrated sampling probe. Probe position was optimized by spectral analysis to ensure continuous, reliable and accurate monitoring. The NIR probe was secured tightly in the wall of the vessel to obtain stable recordings and to prevent influence of the probe on the process or the product.

In-line diffuse reflectance NIR spectra were recorded for each fluid-bed drying experiment. The drying process was continuously monitored by means of NIR recordings every 30 seconds, starting at the same time point as the drying process. Each spectrum is the average of 32 individual scans in the wavelength region between 1100 and 1900 nm, with a resolution of 1.6 cm^{-1}. NIR data analysis was done using The Unscrambler©, version 9.2 (Camo AS, Oslo, Norway). Starting at $t = 0$, every minute a sample for reference water content determination was collected. The water content of the granules was determined with an automated Karl Fischer titration (Metrohm KF coulometer 756K with oven sample processor 774 working at 150°C, Herisau, Switzerland). The coulometer has been calibrated before every analysis (maximum of 28 samples) with sodium ditartrate (mean water content 15.5 %, sd 0.3%).

To determine the optimum wavelength interval or precise wavelength to correlate spectra data to water content the influence of water on NIR spectra was considered. Water or hydrogen has a large absorption band around 1420 nm (Beyer and Steffens, 2003, Zhou et al., 2003). The water band basically consists of multiple overlapping bands. The exact position of these bands is dependent on the nature of the samples. The shift of the overtone bands is related to the changes of the individual bands forming the combined band (Schenk et al., 2001). Static NIR spectra of each collected sample were recorded and compared to the recorded in-line spectra. In this way the correlation between each NIR spectrum and the corresponding water content value was confirmed.

By comparison of principal component analysis (PCA) and partial least square regression (PLSR) based upon in-line or off-line spectra it was confirmed that by the probe position and load of the bed similar spectra were recorded for in-line and off-line spectra. In total, 163 reference samples and spectra were used. For the water content correlation the 163 spectra were normalized (SNV) and transformed to 1st derivative spectra by means of Savitzky-Golay algorithm prior to PLS regression analysis.

4.2.3 Data acquisition and pre-treatment NIR-median granule size model

For the granule size model fully dried granules were used. The granules were sieved in size fractions (Retsch control 200 '*g*' sieve). Granule sizes (d_{10}, d_{50}, d_{90}) were determined by laser diffraction in threefold (Malvern Mastersizer S. (U.K.)), using a 1000mm lens with 2-propanol as dispensing medium (Fraunhofer analysis). To determine the primary particle composition of the granules, agglomerates were dispersed in 2-propanol and placed on an ultrasonic bath for a total of 2 hours. After 2 hours the distribution of the de-agglomerated granules did not change anymore. It was shown that the ultrasonic treatment did not influence the primary particle size of lactose 200M by measuring the particle size distribution before and after the full de-agglomeration time.

Off-line spectra of the sieve fractions of fluid-bed dried and microwave dried granules were collected. To obtain optimal spectral information a Nicolet Antaris FT-NIR RTS was used (Thermo Electron), wavelength area 1000-2500 nm, resolution 1.6 cm^{-1}, number of scans per spectrum, 32). To enable a comparison with the NIR probe the used wavelength area for analysis and modeling was 1100 -1900 nm. Four independent batches of fluid-bed dried granules were used. One batch of microwave dried granules was used as reference batch. This reference was used to detect possible influence of the drying process on the model not detected with the four batches containing fluid-bed dried granules, i.e. to assess the robustness of the model. For the granule size model the 64 derived spectra were not preprocessed prior to PCA and PLS regression analysis. 64 full zero order data spectra (42 fluid-bed dried and 22 microwave dried samples) obtained from fully dried and sieved granules were used for calibration and validation of the PLS model.

The influence of fines and attrition was tested by adding extra fines to the granule samples.

The influence of amorphous content of the granules was tested by NIR measurement of fully crystalline and fully amorphous fractions. 100% amorphous freeze dried lactose was generously provided by DMV-Fonterra, Veghel, The Netherlands.

4.2.4 Strategy Multivariate data analysis and modeling

PCA analysis was used to interpret the obtained spectra in relation to the reference value qualitatively. The relevance of the data points and the presence of possible outliers were analyzed by comparison of leverage and residual variance (influence plot). If outliers solely based upon the spectral data were detected, they were more thoroughly investigated and if necessary removed. Calibration of the PLS model was quantified by standard error of calibration (SEC), indicating the fit between NIR spectra and off-line values. Validation was done by full cross-validation. The NIR-median granule size model was validated and tested with 7 independently granulated and fluid-bed dried granule samples. During validation, the standard error of cross validation (SECV) was calculated. It is expected that the SECV represents the SEP (standard error of prediction). The SEP is used to evaluate the uncertainty of the future predictions. To avoid influence from outliers on the PLSR based upon the reference method (Karl Fischer or laser diffraction), all reference values and methods were checked, and if necessary removed from the data set.

4.3 Results and Discussion

4.3.1 NIR –water content model

In figure 4.1 the spectra of the drying granules during one fluid-bed drying experiment are shown. The spectra were collected every 30 s and therefore represent the fluid bed drying process in time starting with wet granules (thick dashed line in figure 4.1) to fully dry granules (overlying spectra). During drying granules were sampled every minute. The water content of sampled granules was determined. The results were correlated to the obtained NIR spectra. The peaks observed in this wavelength interval are known to correlate to water, either free or bound (Beyer and Steffens, 2003, Kloeden, 1999, Zhou et al., 2003).

In figure 4.1 the distance between the curves around 1400 nm (first overtone O-H in H_2O) from top to bottom first is constant, then declining and finally zero. As the water content of the sampled granules and the time interval between collection of the spectra are known, (figure 4.1), the distances between the spectra seem to be correlated to a change in water content. A constant, declining and zero distance variation is then related to respectively the constant rate, falling rate and equilibrium period during the fluid-bed drying process.

PCA revealed that all spectral data were primarily correlated to one principal component (data not shown). The analysis revealed no more distinctive features of the data. Thereupon the data set was used in the PLS regression.

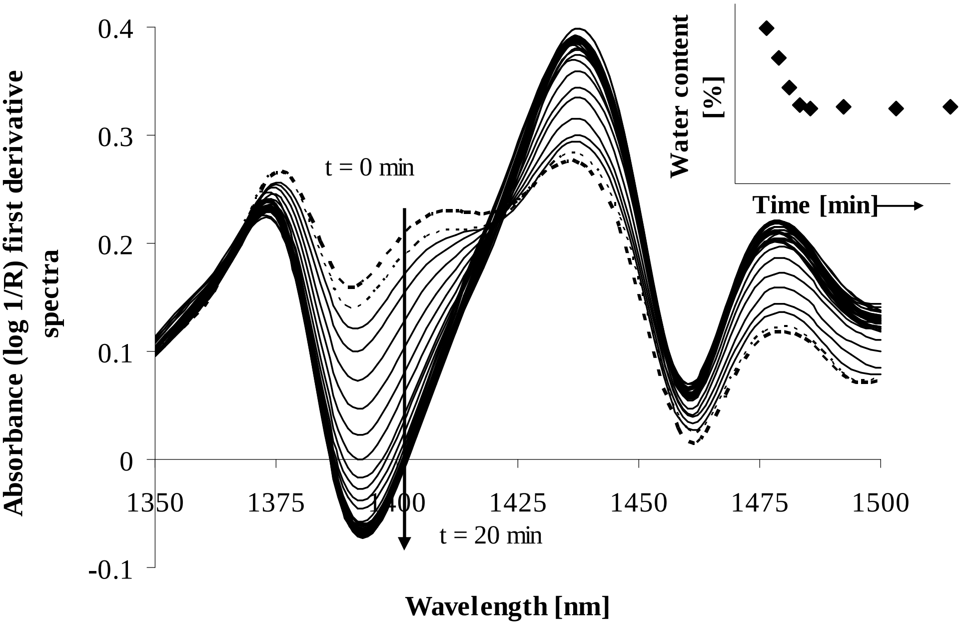
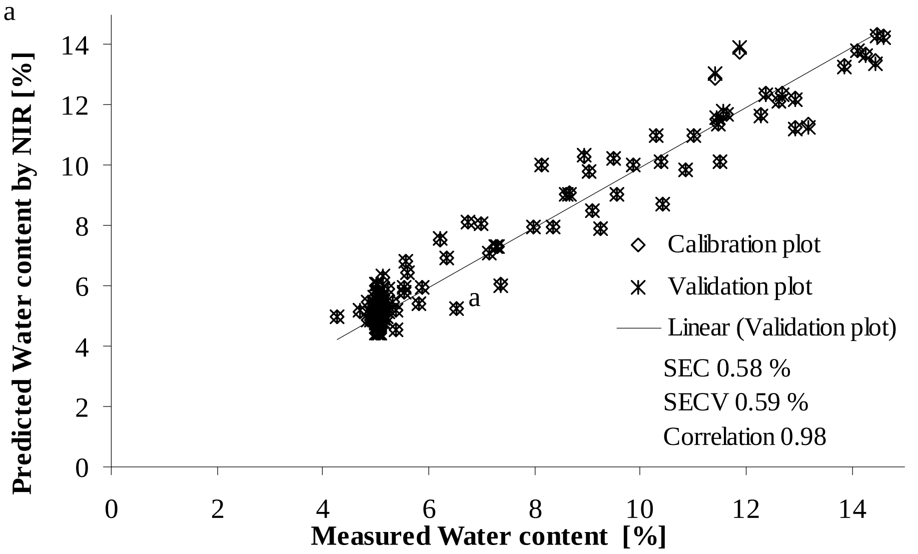


Figure 4.1 In-line NIR first derivative spectra of lactose granules during one fluid-bed drying experiment inlet air temperature 60 °C, air flow 60 m3/h. One NIR spectrum is an average of 32 scans per 30 seconds. t = 0 s thick dashed line spectrum, highest water con content, t = 30 s thin dashed line spectrum, t = 1 min very thin dashed line spectrum etc. In the small inserted graph the change in absolute water content of the sampled granules as determined by Karl Fischer analysis in time is shown.

The 1-factor PLS fit from data of the wavelength interval 1350 – 1500 nm appeared to be superior to that using the single 1400 nm data only. It gives the lowest standard error of calibration (SEC) and standard error of cross validation (SECV) with the highest correlation.

Figure 4.2a shows the fit between the determined (Karl Fischer) and predicted (NIR) water content. The large number of dry granule samples obtained during drying under various process conditions (21 experiments, inlet air temperature 40 – 60 °C, air flow 60 – 90 $m^{3} \cdot h$) accounts for the large data point cloud at low water content (left in figure 4.2a). In all experiments granules were all completely dried after 10 minutes. All the drying processes were extended to 20 minutes. NIR spectra were recorded every 30 s and therefore many data points for dry granules were obtained. The SECV for the dried granules (water content up to 5.2%) is 0.28%. This small error is beneficial for an accurate in-line end-point determination of the drying processes. The regression coefficients plot (figure 4.2b) represents the maximum spectral response to change in granule water content. Logically, the maximum spectral variation is the difference between the spectra of the wettest (the thick discontinuous line) and the driest granules (the overlying spectra) in figure 4.1.

As can be seen only one PLS factor is needed to yield an acceptable fit between spectral data and water content. If more factors would be needed to describe a single change this would suggest the existence of a more complex correlation where solely decreasing water content is not the only determinant of the observed changes in the spectra (NØrgaard et al., 2005). The inclusion of more than one PLS factor did not improve the correlation, but did increase the inclusion of noise. In the obtained model, 85% of the spectral variance is correlated with 96% of the water variance.



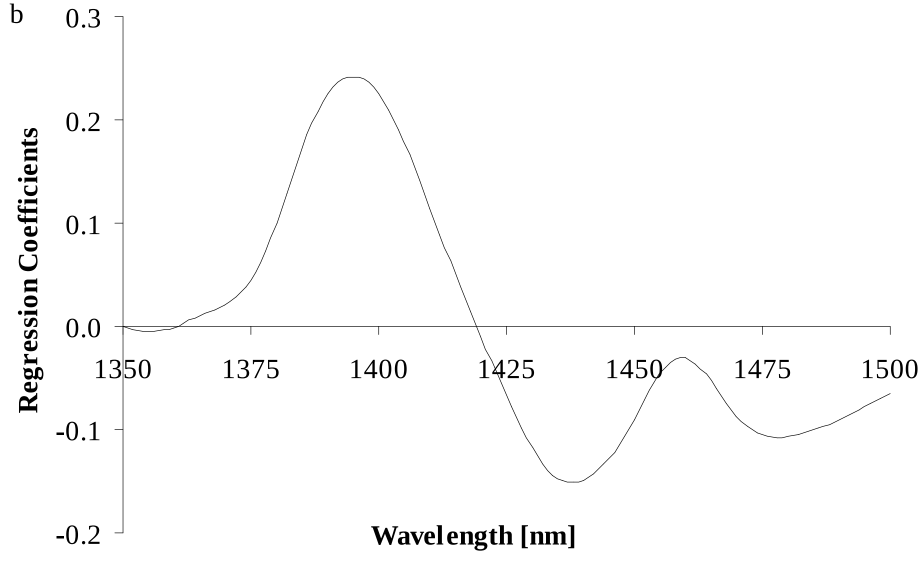


Figure 4.2 (a) PLS regression of measured water content reference values (Karl Fischer) and NIR predicted water content of lactose granules in the fluid-bed drying process from the total data set (21 fluid-bed drying experiments, inlet air temperature 40 - 60 °C, a air flow 60- 90 $m^{3} \cdot h$, no influence of process conditions are observed). (b) NIR – PLS regression coefficients plot of the model.

From the score plot (not shown) and the regression coefficients plot it is concluded that the various process conditions as air flow and inlet air temperature do not affect the prediction of water content by NIR in any way. The data points per experiment are all evenly distributed throughout the plots. The SEC and SECV of the NIR water content model are comparable to the reported relative standard deviation of the reference method (Karl Fischer) (Kloeden, 1999). For dryer granules the SECV is even smaller than the reported value. Therefore the model is considered a valid in-line alternative to the off-line Karl Fischer water content determination.

4.3.2 NIR – granule size model

4.3.2.1 Principal Component Analysis

For end point determination of fluid-bed drying processes not only the water content of the granules but also median granule size and the formation of fines are important. With NIR it is possible to measure both water content and granule size simultaneously by use of different models. The direct effect of increasing granule size (dry granules) upon spectral absorption can be observed in figure 4.3.

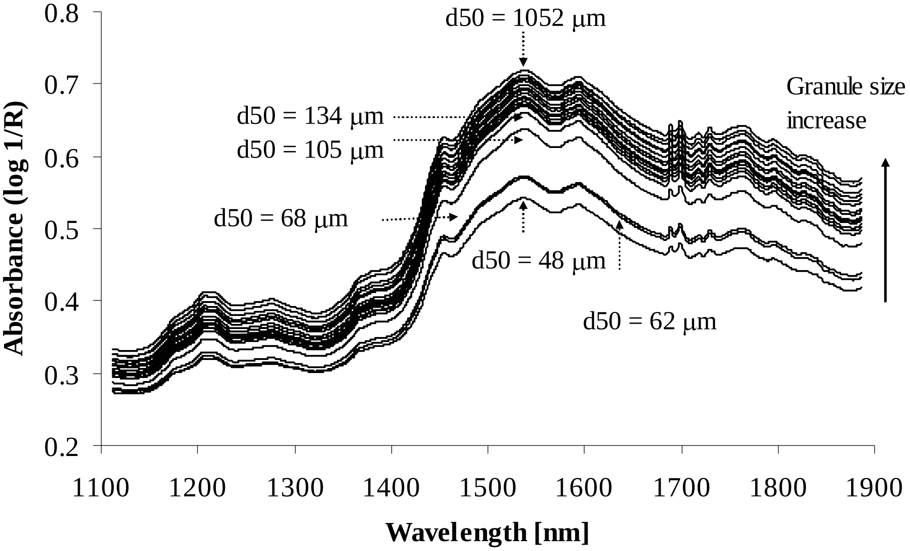


Figure 4.3 Full data 0-order spectra of lactose fluid bed dried granules with size range 48-1052 µm (d_{50}). For clarity reasons not all available spectra of the data set are shown, but only the spectra collected of granules of one batch. The smallest granule size c corresponds to the lowest spectrum in the figure. Absorbance increases upon granule size increase.

Upon increasing granule size diffuse reflectance decreases and consequently increased absorbance is observed. Each spectrum corresponds to a different size class wherein the median granule size varies between 48 and 1052 µm. The difference between the spectra of the smallest and the largest granules is remarkable; large differences in absorbance level are observed between the granules of the smallest size classes, whereas this difference decreases upon size enlargement.

To specify the influence of the increasing granule size on the NIR spectra further PCA is performed. The principal component analysis of the 64 spectra reveals that two principal components (PC) sufficiently describe variation of the spectra (figure 4.4a and b). In the score plot (figure 4.4a) the first principal component (horizontal axis) covers the whole spectral data set correlated to granule size from the smallest to the largest particles (left to right). Data points located close to the horizontal axis are better described by the first PC than particles located further away from the axis. 96% of the spectral variation is described by the first PC, whereas the second PC describes only 4% variation. The first PC describes the most important variation in the total data set, but the remaining 4% is enough to investigate the nature of the second PC more thoroughly. The second PC (vertical axis, from top to bottom) concerns data points correlated to granules with somewhat larger median granule size (i.e. 134 μm to 1167 μm). As for the first PC; data points located further from the vertical axis are less well described by the second PC. This implies that the data points correlated to the smallest granule size are less well described by the second PC.

The x-loadings plot (figure 4.4b) shows that the first PC has a positive value throughout the whole plot at every wavelength, which indicates a constant offset variation. This gives a strong correlation with the continuously increasing granule size. The second PC has very distinctive peaks around 1540, 1600, 1700, 1720 and 1730 nm. The chemical content of the granules does not change throughout the fluid bed drying experiments. Therefore the sharp peaks can only be related to physical changes in the granules. This will be elaborated hereafter.

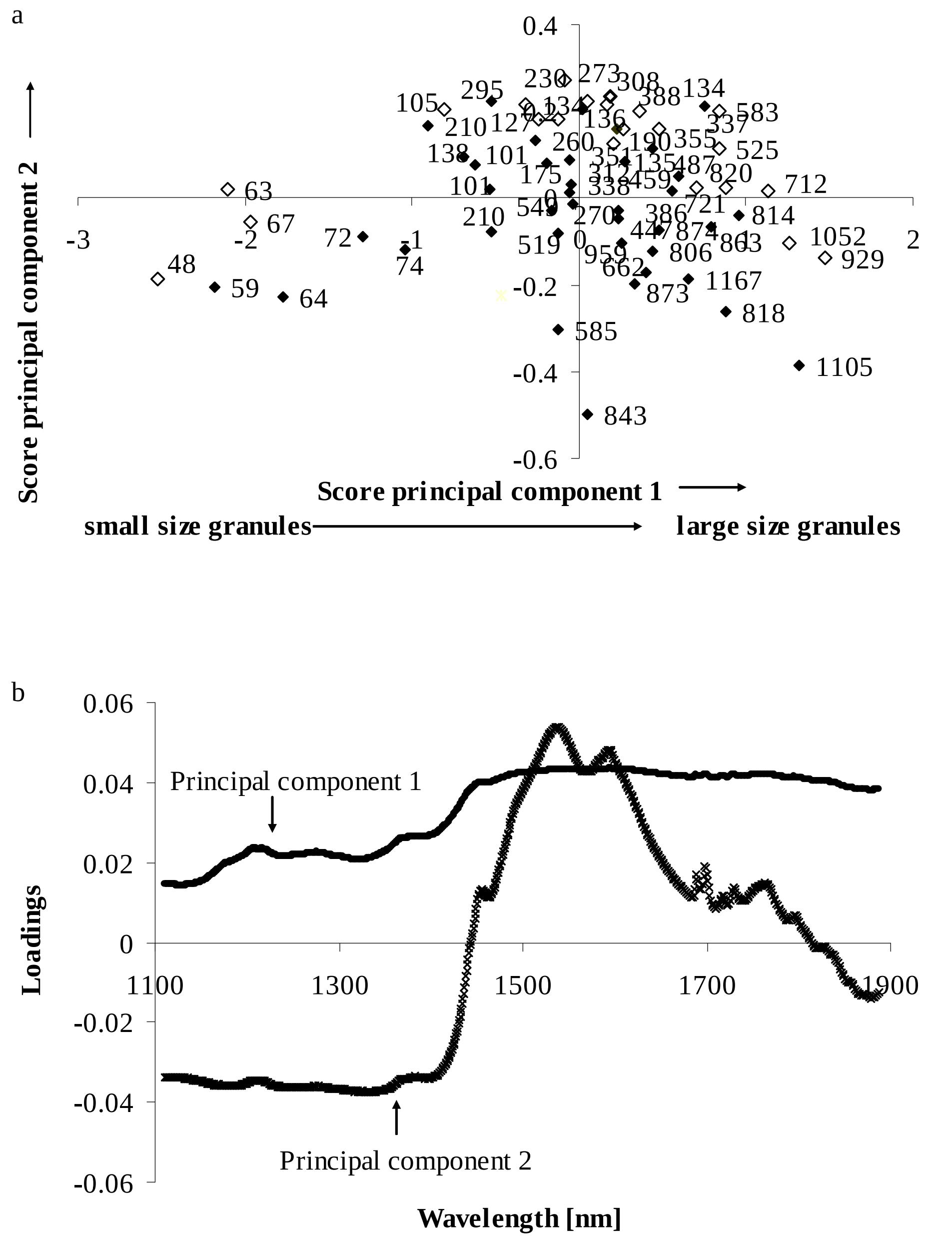


Figure 4.4 (a) Plot of PCA NIR spectra lactose granules with size range 48-1052 μm. The closed squares correspond with spectra from fluid-bed dried granules, open squares represent microwave vacuum dried granules. (b) x-Loadings plot of the two principal components.

4.3.2.2 Partial least squares regression

To find a potential fit between the spectral information and the median granule size PLSR was performed. When the individual NIR spectra of fluid bed dried sieved granules are correlated to the median granule size of the granules by PLSR, an appropriate fit can be derived (R^2 = 0.98, SECV = 43.0 µm, SEC = 34.0 µm). The NIR spectra of the microwave dried sieved granule fractions with a narrow size margin yield a similar model (R^2 = 0.99, SECV = 46.2 µm, SEC = 36.3 µm). The score plots and regression coefficients plot were comparable. The microwave dried granules are used to detect possible influences of the drying technique upon the spectral information. Differences in granule characteristics, based upon drying method, can potentially have a large influence on the NIR scattering and absorbance. These influences are not detected by the current method. Therefore the two different size sample sets were combined in one NIR granule size fit (64 spectra with corresponding median granule size determined by laser diffraction).

The calibration- and prediction error for this model are each small (R^2 = 0.98, SECV = 70.4, SEC = 59.6). In the regression coefficient plot (figure 4.5) the different factors are shown, required to correlate the NIR spectra with the granule size. From figure 4.5 it can be concluded that PLS factor 1 and 2 show a high resemblance with PC 1 and 2 as seen in figure 4.4b. The optimum fit between median granule size and the spectral data is gained taking four PLS factors. For clarity reasons only three PLS factors are shown in figure 4.5. As with the water model one variable (granule size) is considered versus the spectral data. Therefore it is interesting that so many factors are needed to achieve an optimum correlation. The first PLS factor describes 95% of the total variance in x values (NIR) but only 55% of granule size effects variance. The second component designates 4% of x-variance and 24% of granule size variance. The third and fourth components represent only a very small part of the spectral variance but each cover 7% size variance.

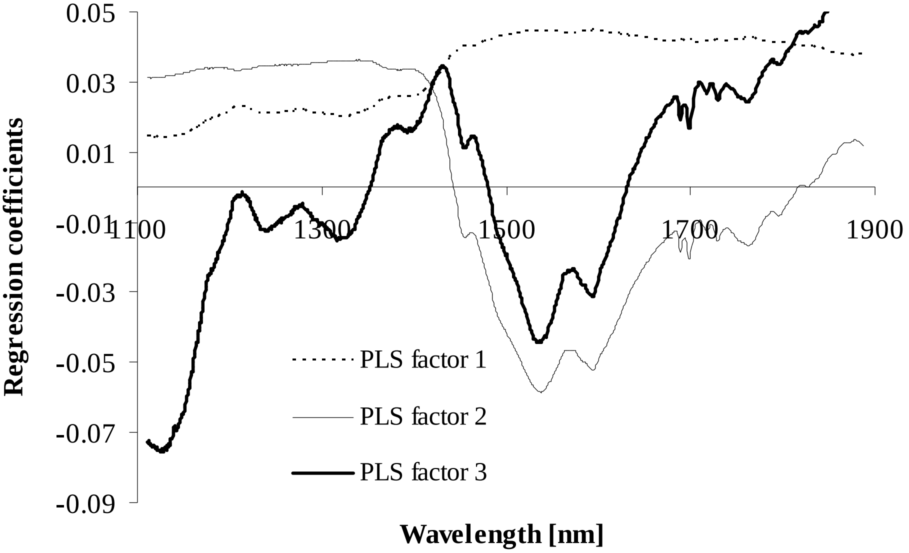


Figure 4.5 Regression coefficients plot of three of the four PLS factors used to correlate NIR data to granule size (For clarity only three PLS factors are shown).

When so many factors are needed for an adequate correlation further revelation of the characteristics of the PLS factors is necessary. A fit based on the first principal component only has some very distinctive features as seen in figure 4.6; granules with a granule size larger than 136 μm (encircled), all have a fairly constant predicted granule size around 400 μm according to the fit.

Lactose 200M (d_{10} 9.6 μm, d_{50} 40.1 μm, d_{90} 104.4 μm) has a wide size distribution with the largest particles (d_{90}) just above 104 μm. It is therefore evident to relate the first PLS factor to the size of the primary particles and the smaller granules. Furthermore the first PLS factor has a constant positive value and is therefore related to the constantly increasing granule size as seen in figure 4.5. Figure 4.3 exhibits large differences between the raw spectra for small granules, whereas for larger granules small differences are observed. This suggests that large granules and small granules are described by different factors. This is the reason that more than one PLS factor is needed to obtain an appropriate correlation.

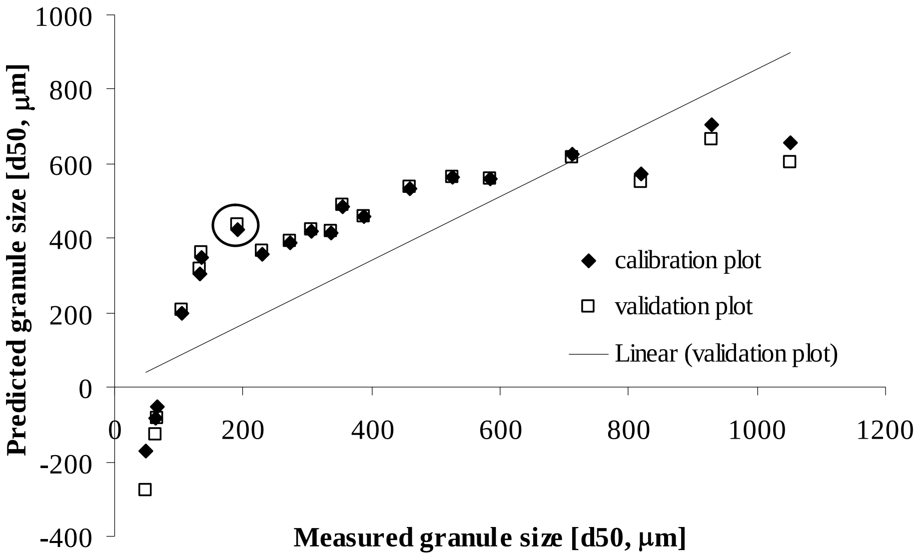


Figure 4.6 Correlation between NIR and granule size based upon the first PLS factor seen in figure 4.5.

In figure 4.4a the PC data are positioned to elucidate the distinction between the individual spectra. From figure 4.4a it is seen that the data points relate to the d_{50}, although the first PC exhibits a more obvious correlation than the second PC. In order to obtain an idea of the nature of the second PC a closer look at the spectra may yield some indications: The second and third PLS factor have very distinctive peaks around 1540, 1575, 1597, 1686, 1696, 1715, 1725, 1745, 1794 and 1827 nm (Figure 4.5). From 1540 to 1900 nm these two PLS factors are the mirrored image of PC 2. The sharp peaks in the spectra can be correlated to the orientation of an intact crystal lattice. Upon increasing crystal lattice disorientation often less sharp or flattened peaks are observed (NØrgaard et al., 2005). It is hypothesized that granules can have variations in crystal orientation related to granule size. It is known that upon solidification of lactose solutions (as in spray drying) amorphous lactose can be formed (Chidavaenzi et al., 2001, Farber et al., 2003). To investigate the possibility of the existence of amorphous lactose in the granules, the zero order NIR spectra of 100% amorphous lactose (freeze dried lactose) and 100% crystalline lactose were collected (figure 4.7). NIR has often been used for quantitative determination of the crystallinity of lactose (Buckton et al., 1998, Chidavaenzi et al., 2001, Hogan and Buckton, 2001, Lane and Buckton, 2000).

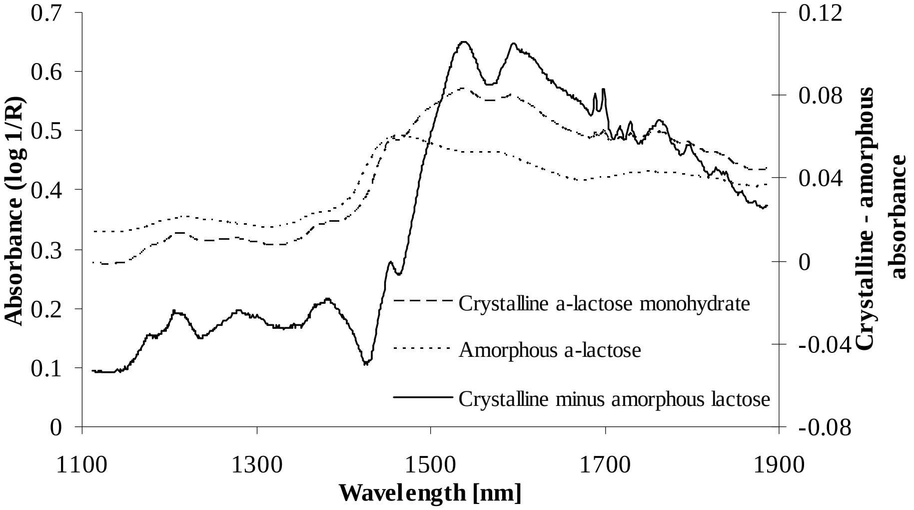


Figure 4.7 Spectra of 100 % crystalline (lactose 200M) and 100% amorphous (freeze dried) lactose. The spectrum of the amorphous lactose is characterized by the presence of broad peaks and absence of sharp peaks. On the right hand axis the difference in absorbance between the NIR spectrum of the crystalline and amorphous lactose is shown.

If PLS factor 2 and 3 are susceptible to physical features of the granules and if it is assumed that increasing amorphous content is included, the PLS factors should be related to the difference between the spectra of 100% crystalline and 100% amorphous lactose. When the spectrum of the amorphous lactose is subtracted from the spectrum of the crystalline lactose a “spectrum” remains with great similarities to PLS factor 2 and 3.

This similarity is seen in the 1690 – 1770 nm region characterized by sharp bands. Especially PLS factor 3 has more similarities with the resulting "spectrum" over the whole wavelength range with corresponding peaks around 1146, 1175, 1206, 1240, 1277, 1332 and 1380 nm.

The similarities of the PLS factors 2 and 3 with the subtraction spectrum seems to argue that a direct relation to the amorphous content of the granules exists. From the above this would mean that the amorphous lactose content could increase upon increasing granule size. This hypothesis is further tested by further granule characterization. As shown by Van den Dries et al. (2004) and Scott et al. (2000) large granules can be preferentially built up from fine primary particles and small granules from large primary particles. The primary particle composition of the lactose granules was determined by ultra sound dispersion of the granules and subsequent laser diffraction size measurements. The difference in composition is shown in table 4.1.

Table 4.1 Change in Primary particle composition of different sized microwave dried lactose granules

Size							
Original granule size (d_{50}) (μm)	48.1	57.4	66.8	230.0	337.0	458.7	1052.0
Primary particle size (d_{50}) (μm)	44.2	33.4	51.7	20.4	23.0	5.8	7.6

Large granules with a median size of 1052 μm consist of primary particles with a median granule size of 7.6 μm. Very small granules with a median size of 48.1 μm consist of primary particles with a median size of 44.2 μm. These measurements show that the largest granules are indeed composed of small primary particles whereas small granules consist of large primary particles. If granules are composed of relatively small particles a larger internal surface will be expected as a consequence of which the granule contains relatively more water. Therefore wet small granules do contain relatively less water than larger wet granules. This was confirmed by determination of the water content of wet granules of four separate high shear granulated batches. Wet granules were sieved in a closed system to prevent evaporation. The water content of the sized granules was determined by Karl Fischer. Every decreasing granule size class of sieved wet granules appeared to have a decreasing water content (student's paired t-test, $n = 4$, $p \leq 0.05$, granule sieve classes 2500 – 3350 μm, 1250 – 2500 μm, 850 – 1250 μm, 600 – 850 μm and 450 – 600 μm).

Upon drying of saturated lactose solutions the formation of amorphous lactose has been shown by Farber et al. (2003). Therefore higher relative amorphous lactose content, formed upon drying of the lactose solution is possible. From the above it is concluded that upon increasing granule size more amorphous lactose can be present. Small granules consisting of large crystalline primary particles exhibit a minor internal surface and are therefore almost fully crystalline. As stated earlier, PC 2 describes larger granules exceeding primary particle size. Therefore primary particles are less well described by PC 2 and corresponding PLS factor 2 and 3.

Although with the current method the degree of crystallinity is based upon the chemometric interpolation between fully crystalline and fully amorphous lactose, the exact character of the amorphous content is not revealed. In a two phase model a mixture of amorphous and crystalline regions is assumed whereas in a one phase model a continuous transition with increasing lattice disorder from a fully crystalline to a 0% crystalline state is expected (Hüttenrauch, 1978, Suryanarayanan and Mitchell, 1985). If it is believed that the primary particles do not physically change, the only location of the amorphous content will be between these primary particles. As the transition to crystalline is a time-consuming process up to several days or even weeks

(Farber et al., 2003) the chance that a physical mixture of fully crystalline and fully amorphous regions is present is small. Regions with disordered lattice structures are more likely to occur.

Next to an understanding of the nature of the relation between PLS factors and characteristics of the analyzed substance a good PLS model should also meet requirements towards the calibration error, prediction error and correlation. To distinguish fines from granular material the SEC and SECV should be small. If the calibration and prediction error are large this distinction worsens. In figure 4.8 the finally derived model is shown. Small particles are predicted less well than the larger granules. This is confirmed by the use of independently obtained validation samples consisting of granules spanning the full calibration range of particle sizes. Granule samples with a median granule size between 300 and 800 μm are predicted best. Samples containing only granules and primary particles smaller than 53 μm are predicted negatively according to the model, but with a SECV of 128 and a correlation of still 0.96. The attractive consequence of this is that attrition phenomena, characterized by excessive formation of fines, will be recognized easily. For in-line monitoring of the fluid-bed drying process this is a desired feature as attrition is unwanted for product quality reasons.

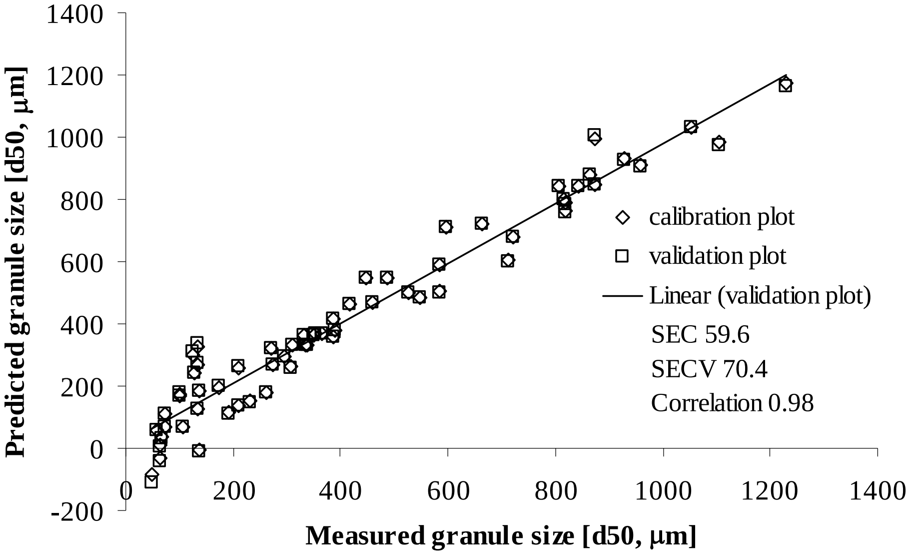


Figure 4.8 PLS regression fit correlating measured median granule size (laser diffraction method) to predicted median granule size (NIR).

4.3.3 Combined applicability of models

Currently the correlation between NIR and water content can be used to do process monitoring and end-point determination. For granule size determination humidity of the granules has been proven substantially influential to the NIR spectrum (Rantanen et al., 2005). Furthermore it is shown above that larger granules contain more water than smaller granules. A more extensive data set has to be developed to be able to make the correlation between NIR and the granule size of wet granules. Under most process circumstances granules are dried after 10 minutes to such an extent that interference of water on the full spectrum is minimal. This point can easily be detected by NIR monitoring of the granule water content during the process. The NIR method to monitor the granule size and attrition effects can then be used when the influence of water is less pronounced.

4.4 Conclusion

For product quality reasons, discrimination between drying stages and end-point monitoring is highly important. The currently developed NIR granule water content model provides an effective real time method for monitoring of the fluid bed drying process. The low SEC and SECV and high correlation coefficient confirm the reliability of the fit. The correlation is independent of process conditions. Although it is demonstrated that differences in water content exist as a function of granule size, the estimated water content represents a median value of the water content of the granules. NIR monitoring can replace currently used off-line techniques. The relative error of the NIR determination is comparable to Karl Fischer analysis. The end-point of the drying process can be adequately acknowledged. The end-point can be determined faster than with current time-consuming off-line techniques. The NIR granule size model is based upon four PLS factors. The first factor is related to the primary particle size and small granules. The second factor is related to the larger granules and the amorphous content of the granules. With these two parameters 100% of the spectral information and 79% of the granule size variation is included by the model. Information related to the granule size is revealed by factor 3 and 4 which both correlate another 7% of the granule size information to the model. The character of these two factors is also related to the amorphous content in the granules. The fit provides an effective method to monitor granule size and attrition effects. This approach provides a tool to design an optimal drying process.

Abbreviations

d_{10}	Cumulative 10 % frequency undersize (µm)
d_{50}	Cumulative 50% frequency undersize (median granule size) (µm)
d_{90}	Cumulative 90% frequency undersize (µm)
KF	Karl Fischer
NIR(S)	Near infrared (Spectroscopy)
PAT	Process Analytical technology
PC	Principal Component
PCA	Principal Component Analysis
PLS	Partial Least Squares
PLS(R)	Partial Least Squares (Regression)
SEC	Standard error of calibration
SECV	Standard error of cross validation
SEP	Standard error of prediction

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5

The consequences of granulate heterogeneity towards breakage and attrition upon fluid bed drying

Abstract

High shear granulated lactose granulates were dried in a fluid bed dryer at various conditions. Granules were characterized by water content and size analysis. It is shown that the drying process is very dynamic in terms of growth and breakage phenomena. Granular size heterogeneity, composition and water content determine the granule behavior upon drying. Large granules consist of small primary particles and contain more water than small granules that consist of large primary particles. This differentiates the drying rate and extent of size reduction of the different granule size classes. The results enable a critical evaluation of process control and process monitoring. Understanding of granule behavior and continuous monitoring of the fluid bed drying process enables process and product optimization.

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5.1 Introduction

Granulation is a common unit operation in the manufacturing of oral dosage forms. Granules are often prepared by wet processes which have been studied extensively (e.g., Darelius et al., 2006, van den Dries and Vromans, 2002, Iveson and Litster, 1998, Iveson et al., 2001, Rumpf, 1958, Vromans et al., 1999). Remarkably, the subsequent drying step has received relatively little attention. In batch production, drying is often the bottleneck either for time or product quality reasons. In the fluid-bed drying process attrition, an unwanted size reduction phenomenon which leads to the formation of fines is considered a product quality diminishing side effect (Bemrose and Bridgewater, 1987, Travers, 1988). The deteriorating effects of attrition on flowability of powder masses (Bemrose and Bridgewater, 1987) or on homogeneity of granulate (van den Dries et al., 2003) have been described. To prevent unwanted attrition or breakage during the fluid bed drying process, better process understanding is needed.

In the second chapter it has been shown that the extent of attrition and breakage during drying is primarily dependent on the amount of water present in the granules. In fact three different domains can be distinguished. Initially at a water level above 9% the net result of applied stress becomes positive, i.e. granule growth is observed. At intermediate water content (2 - 9%) a plateau exists where a change in water content does not really alter the resistance to breakage. Finally, at low moisture levels considerable attrition and breakage is apparent. These outcomes have been explained on the basis of strength or resistance to breakage of the granules. Granule strength has been related to water content by Rumpf (1958) and Schubert (1975). Rumpf (1958) described granule strength in terms of saturation level (S), porosity (ε) and starting material characteristics as $d_{3,2}$ and γ. This is expressed as:

$$\sigma_c = 6S\frac{(1-\varepsilon)}{\varepsilon}\frac{\gamma}{d_{3,2}}$$ **Equation 5.1**

where σ_c is static granule strength, ε is the intra-granular porosity, γ is surface tension of the binder solution and $d_{3,2}$ is the surface mean diameter of the primary particles. The static granule strength describes the forces acting between two particles related to a capillary liquid bridge. When applying this equation it is assumed that the rate of granule deformation upon impact is low. When the primary particle size, porosity, surface tension of the binding agent and granule porosity are considered to be constant, the saturation level is hence the most important variable in this equation. The saturation level (S) of a granule is defined as the ratio of pore volume occupied by liquid to the total volume of pores available in the granule. This can be expressed as:

$$S = \frac{H(1-\varepsilon)}{\varepsilon}\rho_s$$ **Equation 5.2**

where H is the mass ratio of liquid to solid and ρ_s is the density of the particles relative to the density of the liquid (Faure et al., 2001).

In contrast to the theory of the static strength Ennis et al. (1990) showed that at relatively low particle velocities the viscous force determines the strength of a liquid bridge. Therefore, during the dynamic fluid bed drying process, the so-called dynamic granule strength describes the granular strength more accurately. The tensile strength of a granule under dynamic conditions (σ_v) is derived by the following equation:

$$\sigma_v = \frac{9}{8}\frac{(1-\varepsilon)^2}{\varepsilon^2}\frac{9\pi\mu v_p}{16 d_{3,2}}$$ **Equation 5.3**

in which μ is the viscosity and v_p is the relative velocity of the moving particles. This equation is based on the general equation for tensile strength of a granule as developed by Rumpf (1958), the Reynolds equation describing the viscous force of liquid bridge and the Kozeny model (van den Dries and Vromans, 2002). In contrast to equation 5.1 where the static strength of the granules is highly dependent on the saturation level of the granules, it is assumed that the dynamic strength of the granules is dependent on the number of contact points between the moving particles in combination with the viscous force at the contact point and insensitive to the liquid saturation within certain limits (van den Dries and Vromans, 2002).

It has been demonstrated that, due to preferential growth (Schæfer et al., 2004) of particles granulated with low viscosity binder in high shear granulation, larger granules consist of small primary particles whereas smaller granules contain larger primary particles (van den Dries and Vromans, 2002, Scott et al., 2000). As explained in the previous chapter by the difference in internal composition the small granules contain relatively less water than bigger ones. As a consequence, equations (5.1 - 5.3) show that large granules are stronger than small granules. In high shear granulation this heterogeneity leads to a granule size dependent difference in behavior throughout the process (van den Dries and Vromans, 2002, Faraq Badawy and Hussain, 2004). Therefore it is important not only to study the bulk behavior during the drying process but also the effects in the different size classes.

Current FDA Process Analytical Technology (PAT) guidance stresses importance of process understanding and control. The guidance is intended to support innovation and efficiency in pharmaceutical development, manufacturing and quality assurance. Process Analytical Technology is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality (FDA, 2004). Product quality assurance can only be achieved by knowledge of the critical process steps. Starting point of the quality by design approach is a thorough understanding of the potential risks, which is based on an in depth knowledge of the processes involved. A robust process results when all critical parameters are “in control”. Therefore, the critical parameters should be monitored constantly. Currently the fluid bed drying process is most often controlled by monitoring the temperature and humidity of the incoming and outgoing air. Usually the process is considered to be finished when the humidity of the outgoing and incoming air is equal. The monitoring of these values does not enable absolute water content measurements in the granular bed.

In the fluid bed drying process three drying phases can be distinguished based upon the evaporation velocity of water; the constant rate period when granular surface water is abundantly present, the falling rate period when evaporation velocity decreases due to the limited presence of water at the granular surface finally ending in the equilibrium period. The possibilities of near infrared (NIR) in-line measurement of water content or other granular characteristics in fluid bed granulation or fluid bed drying has been acknowledged (e.g., Findlay et al., 2005, Green et al., 2005, Rantanen et al., 1998, Räsänen et al., 2003, Wildfong et al., 2002). As shown in chapter 4 it is possible to measure the water content of the granules directly by the NIR method which enables both determination of the process stage as well as the end-point determination.

The objective of this study was to determine critical factors influencing the granule behavior during the fluid bed drying process and to understand the process related growth and breakage phenomena.

5.2 Materials and methods

5.2.1 Fluid-bed drying

12 kg Lactose 200M (DMV-Fonterra, Veghel, The Netherlands) was granulated in a high shear mixer (Gral 75, Colette, Wommelgem, Belgium) for 5 minutes (mixer rotation rate 150 rpm, chopper rate 1500 rpm). 1585 ml de-mineralized water was used as binding liquid. The water was poured onto the moving powder bed. The wet granules were divided in 1 kg portions and transferred to a fluid-bed dryer (Granulator Niro Aeromatic MP-1, Bubendorf, Switzerland). The equipment was heated for 30 min before use with the following parameters: inlet temperature (T_{in}) 60 °C, air flow 60 $m^3 \cdot h^{-1}$ (1.8 $m \cdot s^{-1}$), product temperature 20 °C. Product temperature was set at 20 °C throughout the drying process. By an automated system, intrinsic to the equipment, the system is regulated by the temperature of the incoming air.

In the fluid-bed drying experiments inlet air temperature (40 and 60 °C) and inlet air flow 60, 70, 80 or 100 $m^3 \cdot h^{-1}$ were varied. 60, 80 or 100 $m^3 \cdot h^{-1}$ correspond with linear velocities of 1.8, 2.4, 3.0 $m \cdot s^{-1}$ based on the type of air distribution grid. All various combinations of parameters were tested in order to evaluate the influence of process settings on particle breakage. For each combination of parameters except 70 $m^3 \cdot h^{-1}$ (inlet air temperature and air flow) the drying time was varied between 2, 3, 4, 5, 6, 8, 10, 12 and 15 minutes.

5.2.2 Granule Characterization

Starting at t= 0, every minute a sample for reference water content determination was collected. The water content of the granules was determined with an automated Karl Fischer titration (KF coulometer 756K with oven sample processor 774 at 150°C, Metrohm, Herisau, Switzerland). For each sampled granular fraction the water content was determined in twofold. Furthermore determination of the water content in granules at t = 0 and t = 15 is assumed to be most difficult. To verify these data the water content of these granules is determined for 32 experiments. Since it is assumed that if the SD for all these experiments does not exceed 0.3% the method can be assumed valid for the whole experimental set. The coulometer has been calibrated before every analysis (maximum of 28 samples) with sodium ditartrate (mean water content 15.5 %, SD 0.3%).

Particle size distribution of the wet and dried granules was determined by sieving 100 g of granule samples on a Retsch AS 200 control 'g'sieve (Haan, Germany). The mean particle size of the samples was estimated as a median weight-based diameter. The effect of the sieving equipment on the attrition and breakage of granules was assessed. It was found that sieving of the granules did not significantly influence the obtained results from the granulator experiments. All sieving test were performed at least in threefold.

5.2.3 Near infrared (NIR) water content analysis during fluid bed drying

For the continuous monitoring of the water content an in-line NIR system was used as described in the previous chapter. Before measurement the NIR was automatically calibrated by a 100% reflection standardization measurement. The NIR probe (FOSS NIRSystem Analyzer, software package Vision®, Birchwood, U.K.) was placed into the wall of the fluid-bed dryer at the same height of the system integrated sampling probe. Probe position was optimized by spectral analysis to ensure continuous, reliable and accurate monitoring. The NIR probe was secured tightly in the wall of the vessel to obtain stable recordings and to prevent influence of the probe on the process or the product. In-line diffuse reflectance NIR spectra were recorded every 30 seconds, starting at the same time point as the drying process. Each spectrum is the average of 32 individual scans in the wavelength region between 1100 and 1900 nm, with a resolution of 2 nm. NIR data analysis was done using the software package Vision® (Birchwood, U.K).

A quantitative water content model for lactose was created based on the first O-H overtone (1350-1500 nm). First derivative spectra (Savitsky-Golay) were normalized (SNV) prior to PLS regression analysis.

Calibration of the PLS model was quantified by standard error of calibration (SEC), indicating the fit between NIR spectra with off-line derived water content values. Validation and optimization of the number of PLS factors was done by full cross-validation. During validation, the standard error of cross validation (SECV) was calculated. It is expected that the SECV represents the SEP (standard error of prediction). The SEP is used to evaluate the uncertainty of the future predictions.

Sample selection and identification was based upon mahalanobic distance determinations (Massart et al., 1997). From this function the probability that the given sample belongs to the distribution represented by the model based spectral set can be calculated. Qualification of the spectra for quantitative use was based upon maximum distance in wavelength space.

5.3 Results and Discussion

During the fluid bed drying process the granules collide with each other as well as with the wall of the drying vessel. As a result granule attrition and fines formation takes place.

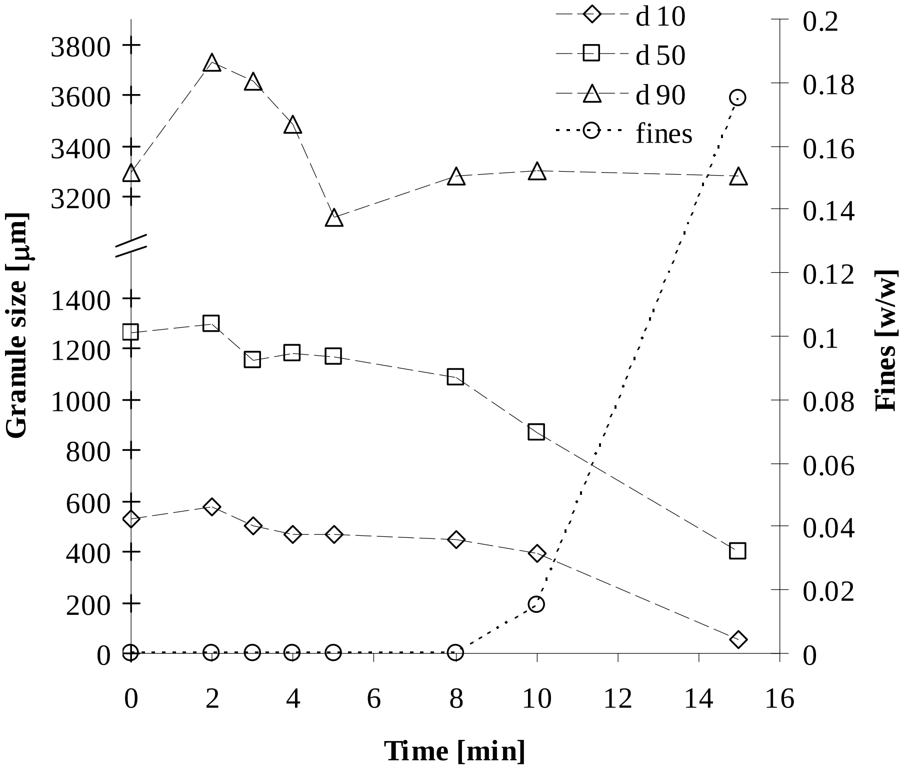

Figure 5.1 Granule size (d10, d50, d90) versus drying time throughout the fluid bed drying process. Temperature incoming air (Tin) 40 °C, air velocity 1.8 m . s^{-1}. On the right hand axis the formation of fines is shown. At the start of the drying process the average d_{10} is 512 µm (standard deviation 40 µm), the d_{50} is 1285 µm (standard deviation 63 µm) and the value for the d_{90} is 3289 µm (standard deviation 212 µm). After 15 minutes of drying, based upon NIR read-outs, the granules were considered to be completely dried (water content < 0.1%).

In figure 5.1 the granule size for the largest (d_{90}), median (d_{50}) and smallest granules (d_{10}) is shown throughout the fluid bed drying process. In addition the formation of fines is shown. In this paper the definition of fines is arbitrarily set at particles < 100 μm. Whereas the largest granules show a size increase in the first minutes of drying the smaller granules show a size decrease throughout the entire drying process. The initial growth of the larger granules is annihilated upon further drying. As can be seen, the granules undergo significant size changes during the process, suggesting a highly dynamic situation. Apparently not only during the granulation process itself (van den Dries and Vromans, 2002, van den Dries et al., 2003, Iveson and Litster, 1998, Iveson et al., 2001) but also during the subsequent drying step constant growth and breakage phenomena occur. It has been demonstrated that within a batch of granules, prepared by high shear granulation, differences in granule composition exist (van den Dries et al., 2002, chapter 4). More specifically, the large granules contain smaller primary particles than smaller granules. This also makes that the large granules contain relatively more water than small granules. Figure 5.2 shows the water content profiles of the large, median and small granules versus time. The water content of the fines (if sufficiently formed) is also depicted. First the characteristic sizes (d_{10}, d_{50} and d_{90}) have been determined as a function of drying time. Subsequently the moisture content of the different size fractions has been determined. The figure shows that the initial water content of the large granules is higher than that of the smaller granules. This water content difference remains throughout the drying process. Large granules consistently contain more water than the small ones.

Figure 5.1 shows that the majority of fine particles are formed in the latest stage of drying. Moreover, the small granules show more size reduction earlier in time (figure 5.1) and meanwhile, these granules are dryer than the large ones (figure 5.2). This is an indication that moisture content and fines formation are interrelated.

The fines formation rate has been defined. For simplicity reasons it is assumed that the number of impacts is proportional to both the air velocity and the process time.

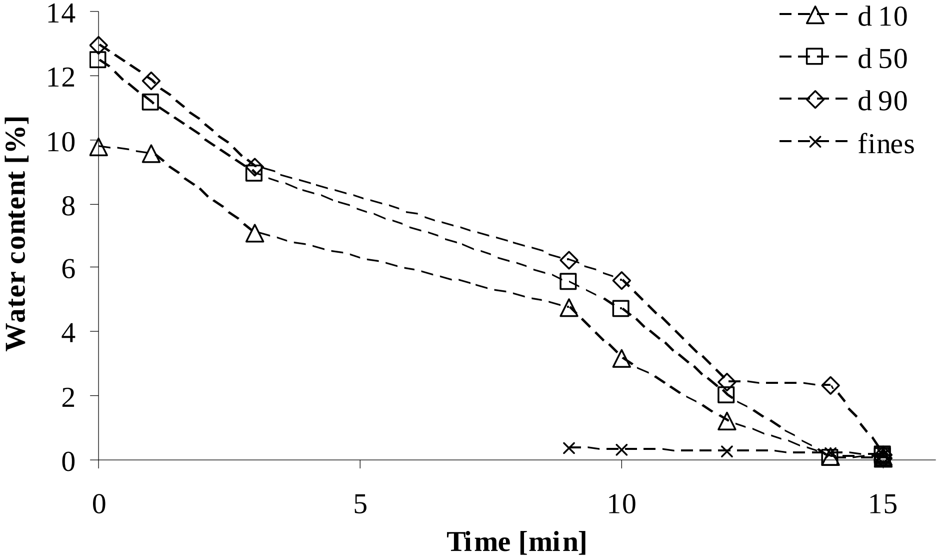

Figure 5.2 Water content of the granules versus the drying time. The characteristic sizes (d10, d50 and d90) have been determined as a function of time and the moisture contents of the corresponding sieve fractions have been depicted. Temperature incoming air (T_{in}) 40 °C, air velocity 1.8 m · s^{-1}. For each time point the water content values of the granules and fines are correlated; the data points per time point all come from one batch.

So a granule dried for 4 minutes at a certain air flow will endure twice the number of impacts compared to a granule dried for 2 minutes at the same air flow. This occurs of course only above the minimum fluidization velocity of the granule bed. Below this velocity, breakage or formation of fines by impact is assumed to be minimal (Ray and Jiang, 1987). In the used equipment the minimal fluidization velocity for wet granules was determined to be 0.6 m · s^{-1} (20 $m^3 \cdot h^{-1}$). Upon drying this velocity decreases to 0.3 m · s^{-1} (10 $m^3 \cdot h^{-1}$). The air flow has always been significantly higher than the minimum fluidization velocity.

So the fines formation has been defined as:

Formation of fines ((w/w) (m^{-3})) =

Fraction of fines in total mass (w/w) / (impact exposure time (h) x (air flow minus minimal fluidization flow ($m^3 \cdot h^{-1}$)))

This normalization of the data for the number of impacts enables comparison of the different drying regimes (differences in drying time and air flow). In figure 5.3 the formation of fines is plotted versus the bulk water content of the granules. The “bulk” water content is the average water content; no distinction in granule size classes has been made. Below a bulk water content of 6% fines are formed.

Fines formation increases dramatically upon further drying while it is nearly absent at higher water levels. When the effects of process conditions (temperature and air flow) are compared, it can be observed from the figure that the formation of fines is mainly dependent on water content. The shape of all curves obtained at different process settings are basically the same. Some effects of process settings, like temperature, may be visible. It is clear, however, that the impact of moisture content on fines formation dominates over all other variables. For each experimental condition, i.e. at varying inlet air temperature and air flow, the same trend is observed

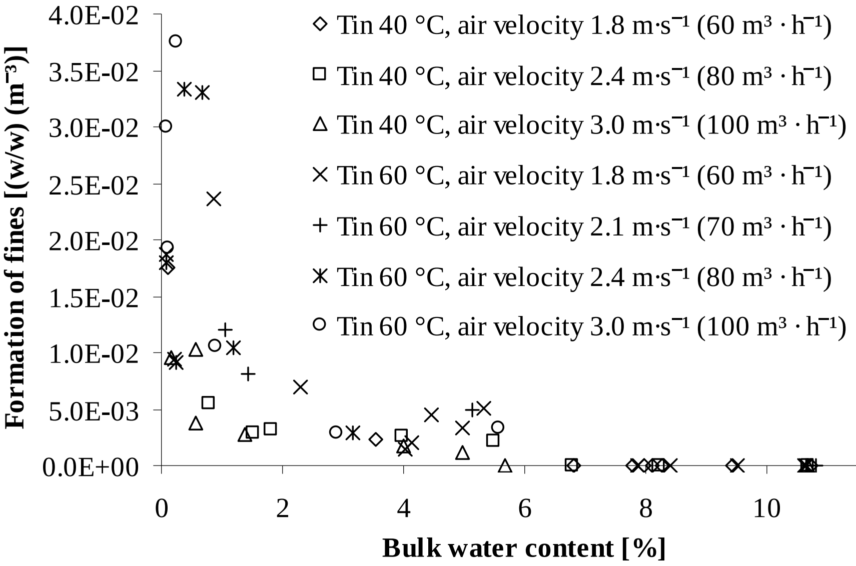

Figure 5.3 Formation of fines defined as percentage of total mass divided by the exposure time and divided by the air flow (air flow minus minimal fluidization velocity) versus the bulk water content of the granules. The T_{in} is set at 40 °C or 60 °C.

As shown in chapter 3 the change in granule size follows a three phase system characterized by a net growth phase, a plateau phase and a breakage phase. These phases are dependent on the net water content. To distinguish the growth and breakage behavior of the size classes as function of water content more clearly the change in granules size has been plotted versus water content in figure 5.4. The changes in granule size are expressed as:

$$\Delta d_x = d_t - d_{t=0} \qquad \textbf{Equation 5.4}$$

in which d_x can be d_{10}, d_{50} or d_{90}. Hence, Δd_{50} expresses the change in size of the median size granules since the start of the granulation process ($d_{t=0}$). A Δd_{50} above zero reflects a net growth of the granular bulk.

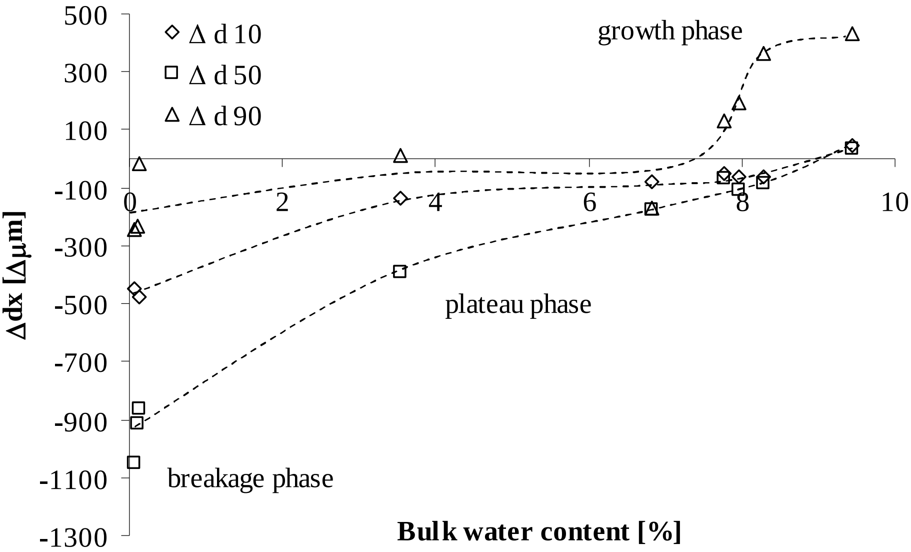

Figure 5.4 Growth, plateau and breakage phase as function of bulk water content. T_{in} 40 °C, air velocity 1.8 $m \cdot s^{-1}$.

In figure 5.4 Δd_x is plotted versus bulk water content. It can be seen that these subsequent phases (i.e. growth, plateau, breakage are present for all particles, but do not appear at the same bulk water content. As also seen in figure 5.1 at the beginning of the drying process (on the right hand side of the x-axis) the Δd_{90} values are highly positive, illustrating that the large granules grow initially, which effect is annihilated upon further drying. The d_{50} and d_{10} show hardly any growth. A clear plateau phase, in which granule size does hardly change, is present for d_{50} and d_{90} but not for d_{10}. Clearly, the size classes do show a different behavior during drying. This different behavior is observed under all tested conditions (inlet air temperature 40 and 60 °C, inlet air flow 60, 80 or 100 $m^3 . h^{-1}$). It can be concluded that within a granulate, breakage, growth and the formation of fines are a function of size, composition and water content.

Realizing that the strength of granules is determined by water content, which becomes apparent by the different stages (growth, plateau, breakage) in the drying process, it becomes clear why the size fractions do not show these changes simultaneously. Small granules, exhibiting lower water levels early on in the drying process have then already lost their strength and are vulnerable to attrition or breakage. This may account for the fact that also at relatively high bulk water content (6%) fines are already formed (figure 5.3). Even at the end of the drying process (bulk water content 0.35%) the largest granules still contain a relatively large amount of water. Thus most of the available water is then located in the largest granules. The large granules (d_{90}) consist of small primary particles (chapter 4, van den Dries and Vromans, 2002) whereas smaller granules consist of larger primary particles. According to equation 3.4 the dynamic strength of the granules increases at decreasing primary particle size. This implies that large granules, composed of small primary particles are stronger (chapter 3, 4 van den Dries and Vromans, 2002). The total of results should be clarified from this perspective. Theoretically the strength increase is related to the increased total number of contact points between the particles within the granule (van den Dries and Vromans, 2002). As elucidated in the introduction the theory of the dynamic strength only applies for granules that are wetted, i.e. saturation is not a part of the equation (van den Dries and Vromans, 2002, Ennis et al., 1990).

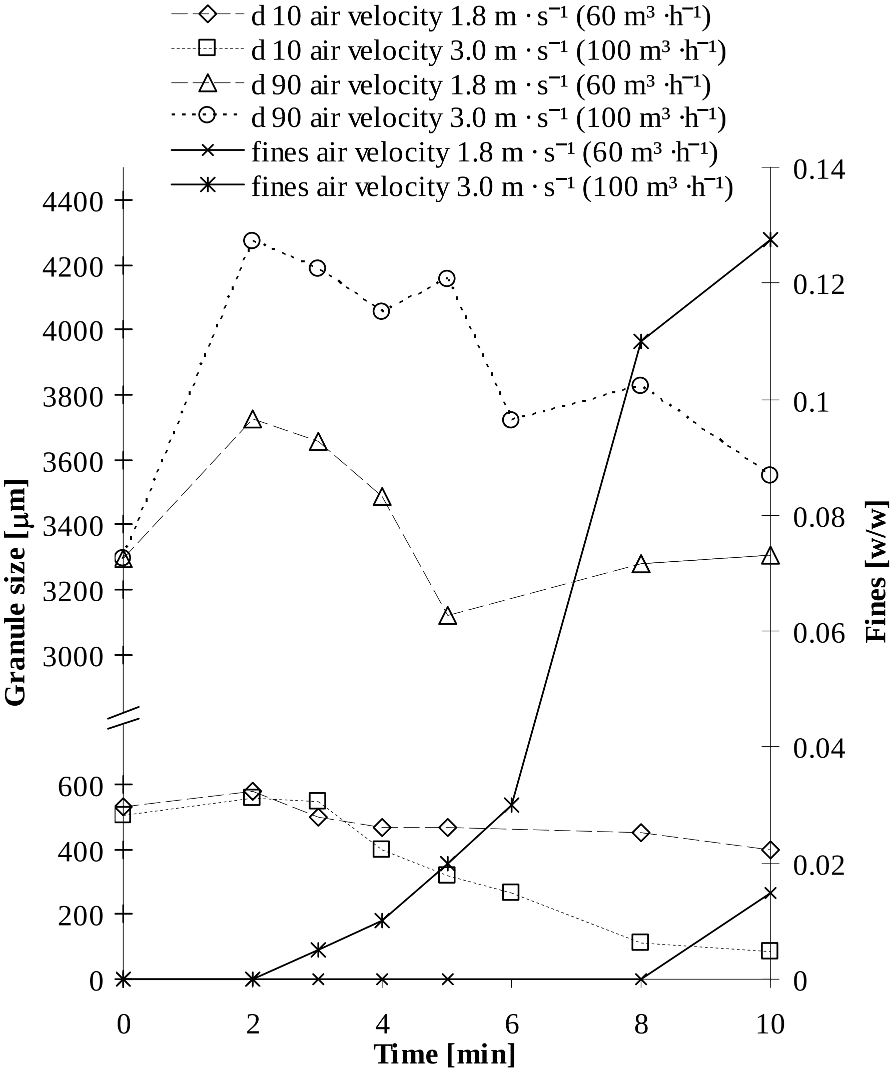

Figure 5.5 Granule size versus drying time of granules dried under high or low air velocity. T_{in} 40 °C, air velocity 1.8 $m \cdot s^{-1}$ or 3.0 $m \cdot s^{-1}$. On the right hand axis the formation of fines is shown.

Also according to equation 5.3, the dynamic strength increases at increasing air velocity as it is assumed that the relative velocity of the moving particles equals the air velocity. Drying at higher air velocity has a number of consequences.

The drying process will be faster, but the number of impacts will be higher too. In figure 5.5 the effect of increased air velocity on the granule size is illustrated.

Temperature was in this case maintained at 40 °C. As can be seen there a relatively limited growth or breakage effects for the granules exposed to an air velocity of 1.8 $m \cdot s^{-1}$ (60 $m^3 \cdot h^{-1}$), whereas granules exposed to the highest air velocity of 3.0 $m \cdot s^{-1}$ (100 $m^3 \cdot h^{-1}$) show large effects. Significantly larger size increasing effects or the largest granules and size decreasing effects for the finer granules are seen. Towards the end of the drying process the size increasing effects are annihilated again. At higher air velocity formation of fines starts earlier. The effect of increased air velocity on the water content of granules is illustrated in figure 5.6 for the larger and smaller granules and fines. To further illustrate the effect of granule composition water content is here replaced by the saturation level. According to equation 3.2 composition (reflected in porosity) and water content of a granule determine the saturation level. Smaller granules have intrinsically a lower saturation level than larger granules. Throughout the drying process they will lose water, the binding force, earlier than larger granules.

If the primary particle size of the wet granules, the relative velocity of the moving particles, the porosity and viscosity are used to calculate dynamic strength of the granules a strong dependency of primary particle size and composition is seen. A higher air flow and a composition of smaller primary particles lead to a higher dynamic strength of the wet granules.

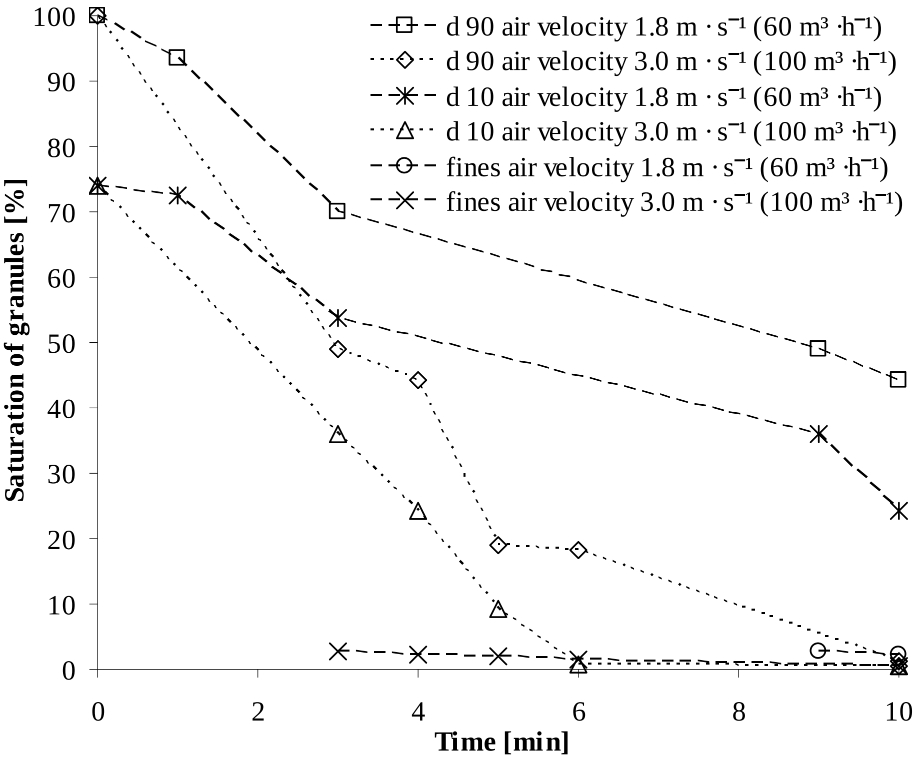

Figure 5.6 Saturation level of granules in time. The saturation level of the largest (d_{90}) and smallest granules (d_{10}) are shown in combination with the saturation level of the formed fines. Two air velocities have been used (1.8 and 3.0 m $\cdot$ s^{-1}). Values used for calculation ρ_s 1.5, ε 0.15 (d_{10} and fines), 0.165 (d_{90}).

This effect is plotted in figure 5.7. The largest granules (d_{90}) indeed show a velocity dependency which is in line with theory. The same dependency holds for the small granules (d_{10}), although this is not visible in the resolution of the figure. Smaller granules have under wetted conditions intrinsically a lower dynamic strength. Based upon the saturation level and the dynamic strength small granules will always differentially from large granules throughout the whole drying process.

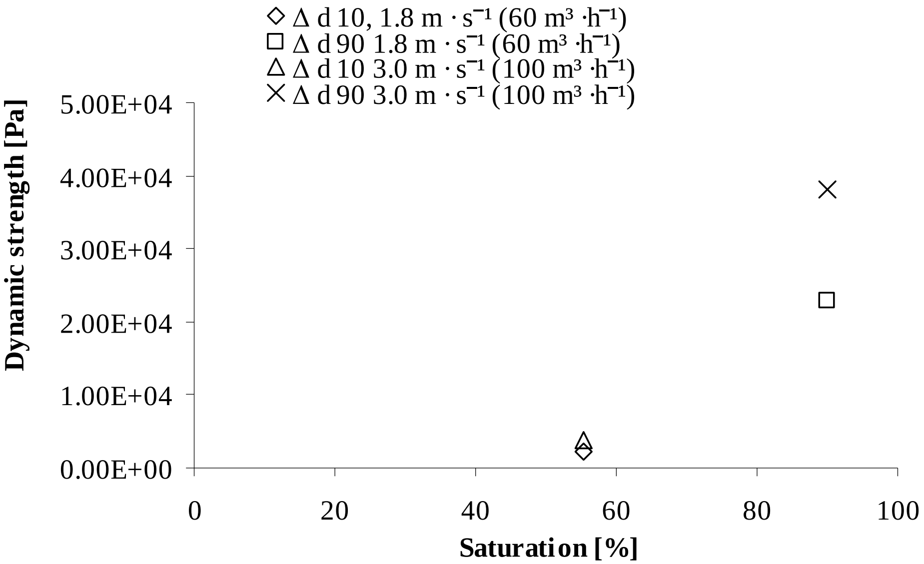

Figure 5.7 Dynamic strength versus saturation level of granules after 2 minutes of drying (T_{in} 40 °C, air velocity 1.8 m · s^{-1}). By the water content and composition difference between the granules the saturation level of the small and large granules differs. Values used for calculation ρ_s 1.5, μ 0.001 Pa · s, v_p 1.8 or 3.0 m · s^{-1}, ε 0.15 (d_{10}) and 0.165 (d_{90}), $d_{3,2}$ 4 μm (d_{10}) and 50 μm (d_{90}).

Process understanding of the fluid bed drying process implies continuous assessment of process circumstances. Determination of the changes in the humidity of the incoming and outgoing air, the standard process characteristics, do not give direct information on water content of the granules. Direct monitoring of the water content of the lactose granules with NIRS as described in the previous chapter is used to increase our process understanding of the fluid bed drying process. It is assumed that the NIR water content determination gives the average water content of the granular bed during the fluid bed drying process under the tested process conditions. At the start of the drying process it was observed that a change in air velocity above minimal fluidization velocity from 0.6 to 1.8 m · s^{-1} resulted in an increase in the NIR water content readings. The increase of the air velocity to the set value is not instantaneous once the process is started. This implies that it takes a significant time (1 min) to develop a completely fluidized bed. As it is shown that smaller granules contain less water than larger granules, it can be argued that the larger granules are positioned under the smaller granules during the first phase and mix again upon air flow increase. By the NIR method the differences in air flow regime as related to air velocity can be detected; the granular bed size distribution is highly heterogeneous and changes upon air flow increase above minimal fluidization velocity. Besides water content determination the NIR measurements can also be used for granule size analysis. The combination of average water content and average granule size analysis enhances understanding of the fluid bed drying process.

5.4 Conclusion

For high shear granulated granules containing active material it is known (van den Dries and Vromans, 2002) that the behavior of the drug substance is correlated to the particle size. The active drug substance consists in general of very small particles. Preferential growth of the small particles in favor of the larger particles induces inhomogeneity. The current study illustrates that the granular bed, the granule size, the inter-granular composition and water content are completely heterogeneous throughout the drying process. This heterogeneity leads to a granule size dependent difference in behavior throughout the fluid bed drying process.

Attrition, growth, breakage and segregation are unwanted effects of the drying process. The dynamic size-changing effects during the drying process potentially lead to inhomogeneity of drug substance and therefore to lack of content uniformity, which is detrimental for the end product. It has been stated (Palzer, 2007) that increasing air flow leads to decreased lumping risk by the reduced contact time of the granules, increased shear stress in the bed and accelerated drying process. In the situation of wet lactose granules we have shown that increase of the air flow rate leads to the formation of larger granules, which seems to be conflicting. However, what is clear from the present study is that water content as well as granule composition should always be a part of the discussion. The increasing shear stress may lead here to increased consolidation and agglomeration tendency upon contact of the granules. Ideally the granular characteristics, with exception of the water content of the granules, do not change at all throughout the process. From the results it can be concluded that the behavior of the large granules differs very much from the behavior of the small granules. When working on quality by design, one should check which consequences this has on the ultimate quality of intermediate and end product.

Abbreviations

γ	Surface tension ($N \cdot m^{-1}$);
$d_{3,2}$	Surface mean diameter (μm)
$\Delta d_{10,\ norm}$	Change in cumulative 10 % frequency undersize (μm)
$\Delta d_{50,\ norm}$	Change in cumulative 50% frequency undersize (median granule size) (μm)
$\Delta d_{90,\ norm}$	Change in cumulative 90% frequency undersize (μm)
ε	Porosity (-)
H	mass ratio of liquid to solid (-)
KF	Karl Fischer
μ	viscosity ($Pa \cdot s$)
NIR(S)	Near infrared (Spectroscopy)
PAT	Process Analytical technology
PC	Principal Component
PCA	Principal Component Analysis
PLS(R)	Partial Least Squares (Regression)
ρ_s	Density of the particle relative to the density of the (binder) liquid (-);
σ_c	Static granule strength (Pa)
σ_v	Dynamic granule strength (Pa)
S	Saturation level (-)
SD	Standard deviation
SEC	Standard error of calibration
SECV	Standard error of cross validation
SEP	Standard error of prediction
SNV	Standard normal variance
T_{in}	inlet air temperature (°C)
v_p	Relative velocity of the moving particles ($m \cdot s^{-1}$).

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6

Structure variations in granulated lactose by influences of drying method and storage

Abstract

The wet granulation step involves the addition and drying of water. When lactose is granulated, the disaccharide partly dissolves in the aqueous binding liquid. Upon drying solidification of the dissolved lactose occurs. The objective of this study is to determine the physical state of lactose in both granulated and spray dried lactose in relation to the drying method and storage conditions. Subsequently the effect of the physical state on tablet strength is determined. A NIR regression model was developed to determine the presence of crystalline and disordered structures in powders and granules quantitatively. The different drying methods led to significantly different compositions of granules. Upon drying at high temperatures more disordered structures were formed. More disordered structures were found in the larger than in the smaller granules. Storage of both the spray dried powder and granules at conditions above 75% RH affected strength of compacts negatively. Upon continuous storage at these conditions re-crystallisation to α-lactose monohydrate occurred.

Therefore in product development there should be awareness to the consequences of drying method and storage conditions of the intermediate powders and granules on the physical quality of the drug product.

6.1 Introduction

As explained in chapter 4 the desire to monitor critical parameters has resulted in the development of in-line analytical methods, such as near infrared spectroscopy (NIRS). In chapter 4 NIRS was used to monitor water content and granule size of lactose granules in the fluid bed drying process. The large high shear granulated granules consist of smaller primary particles than the small granules, which consist of large primary particles. This makes that the large granules contain relatively more water than small granules. As seen in chapter 5 this difference in water content leads to differences in granule behavior during the drying process. By use of a different wavelength area or other data pre-treatment procedures multiple features of processes and products can be analyzed. NIR analysis may also be used in the detection of the amorphous and crystalline structures (Buckton et al, 1998; Gombas et al., 2003; Fix and Steffens, 2004; Lehto et al., 2006).

As more elaborately explained in the introduction, lactose is one of the most often used excipients in the formulation of solid drug products. It is available in several morphologies; α-lactose monohydrate (αL-1aq), anhydrous α-lactose (αL), anhydrous β-lactose (βL) and amorphous lactose (AL). In aqueous solution lactose molecules exhibit mutarotation. Below 93.5 °C the equilibrium in aqueous solution between the solid and dissolved lactose is expressed as:

$$\alpha L - 1aq - (s) \quad \rightleftharpoons \quad \alpha L - (aq) \quad \rightleftharpoons \quad \beta L - (aq)$$

Where (s) and (aq) refer to the solid and aqueous state respectively.Above this temperature equilibrium with βL (s) is established. In a saturated solution below 93.5 °C at fixed temperature, total solubility is limited by αL-1aq. The solution is saturated with αL and under saturated with βL (Visser, 1983). During wet granulation lactose dissolves in the aqueous binder liquid. This results in saturated lactose solution. Farber et al. (2003) have shown that upon drying of wet lactose granules newly re-crystallized material differs from the starting material in both crystalline and anomeric form (Farber et al., 2003). Formation of inter-particle bridges from lactose solutions in drying granules has been shown to be a multi-step process, characterized by several subsequent transitions from non-crystalline to crystalline bonds (Farber et al., 2003). Transformation of AL to the crystalline state is possible if the molecular mobility is high enough to permit crystallisation (Sebhatu et al., 1994b). Upon drying of lactose solutions or granules the formation of amorphous structures and αL-1aq is initially predominant. It has been shown that after several hours βL was formed whereas the amorphous content was decreased (Farber et al., 2003). At sufficiently high humidity levels βL is known to undergo mutarotation to αL as described by the above equilibrium (Angberg et al., 1991). After mutarotation and incorporation of water the thermodynamically stable αL-1aq is formed (Joupilla et al., 1998).

Amorphous lactose as present in spray dried lactose powder enables direct compression into tablets (Sebhatu et al., 1994a; Busignies et al., 2004). The crystallisation of amorphous regions in spray dried lactose during pre-compaction or post-compaction storage has a direct influence on tablet tensile strength (Sebhatu et al., 1994b). The presence of non ordered structures in lactose has been studied extensively (Sebhatu et al., 1994a, Buckton et al., 1995, Buckton et al., 1998, Joupilla et al., 1998, Hogan and Buckton, 2000, Kawakami et al., 2002, Gombas et al., 2003, Dilworth et al., 2004, Fix and Steffens, 2004, Mahlin et al., 2004, Newell and Buckton, 2004, Price and Young, 2004, Ramos et al., 2005, Burnett et al., 2006, Lehto et al., 2006, Savolainen et al., 2006, Timmerman et al., 2006, Zhang et al., 2006) as it is known that residual amorphous regions affect physical-chemical stability of excipients and drugs (Ahlneck and Zografi, 1990, Buckton and Darcy, 1995, Hogan and Buckton, 2000; Qiu et al., 2005).

The objective of this study is to determine the physical state of lactose in both spray dried and granulated lactose in relation to the drying method and storage conditions. Subsequently the effect of the physical state on tablet strength is determined.

6.2 Materials and methods

6.2.1 Materials

Lactose 200M (α-lactose monohydrate), spray dried lactose DCL 11, micronized α-lactose monohydrate, micronized β-lactose and amorphous lactose were provided by DMV – Fonterra, Goch, Germany). Anhydrous α-lactose was obtained by thermal heating under vacuum of lactose 200M (140 °C, < 5 mBar, 2 hours). Amorphous lactose was stored in an open container at the laboratory for four months (25 °C 50% RH) to obtain re-crystallized lactose.

6.2.2 Granules and DCL 11

1.2 kg of lactose 200M was high shear granulated (Gral 10, Colette, Wommelgem, Belgium) (mixer speed 313 rpm, chopper speed 1500 rpm) with 140 ml saturated lactose solution (Lactose 200M in de-mineralized water). After granulation the batch was divided in three parts.

- One part was dried in a plate drying air flow cabinet at 90 °C (Marius Instrumenten, Utrecht, The Netherlands).
- The second part was dried at room temperature (25 °C 50% RH).
- The third part was plate dried in an oven at 40 °C, a vacuum was applied < 5 mBar (Elbanton, Kerkdriel, The Netherlands)

After the drying process the granules were sieved on a Retsch AS 200 control ‘g’ sieve (Haan, Germany) to obtain size fractions. The granules of the smallest

(212 – 300 μm) and largest (1700 – 2360 μm) sieve fraction were stored at 40 °C 18% RH, 40 °C 40% RH, 40 °C 75% RH and 40 °C 95% RH for 2 days.

Compacts were made of the freshly dried material and of the stored material (sieve fraction 1700 – 2360 μm, 11 mm die, compression force 10 kN, 2 seconds, Weber, Maschinen und Apparatebau, Remshalden - Grunbach, Germany). Tensile strength of all compacts (tablets) was determined 60 minutes after compaction (Erweka Multicheck, Medican Pharmatechniek, Leusden, The Netherlands). Tablets and granules were analyzed by NIR, DSC and water sorption analysis as described below.

Spray dried lactose DCL 11 was stored at 40 °C 18% RH, 40 °C 40% RH, 40 °C 75% RH and 40 °C 95% RH. At day zero and day 14 the samples were analysed by NIR and DSC. Furthermore, DCL 11 powder was stored at 30 °C 40% RH for a total of 21 days. Tablets were made at day 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14 and 21. To study the effects of preservation 110 tablets were compressed as described above at day 0 and subsequently stored at 30 °C 40% RH and analyzed at the denoted days. Both tablets and DCL 11 powder were analyzed by NIR and DSC as described below.

Tensile strength of tablets was determined 60 minutes after compaction (Erweka Multicheck, Medican Pharmatechniek, Leusden, The Netherlands).

6.2.3 Strategy multivariate data analysis and NIR modeling

Analytical weighed binary mixtures of micronized βL and αL-1aq, AL with αL-1aq and AL with βL were made. Also mixtures of αL with αL-1aq and αL with βL were made. NIR spectra of all the mixtures and αL-1aq, αL, DCL 11, micronized αL-1aq, micronized βL, AL and re-crystallized lactose were recorded at the Nicolet Antaris FT-NIR RTS (Thermo Electron, Waltham, USA). Wavelength area was set at 1000 – 2500 nm with a resolution of 1.6 cm^{-1}. Per spectrum 32 scans were made. NIR data analysis was done using The

Unscrambler, version 9.6© (Camo AS, Oslo, Norway). The spectra were normalized (standard normal variance, SNV) and transformed to 2nd derivative spectra by means of the Savitzky-Golay method to avoid influence of off-set or baseline influences. For determination of crystalline and amorphous regions the use of second derivative spectra is advisable to avoid interference by scattering (Shah et al., 2006).

Several regions were explored to detect the region with utmost distinction between the different samples. The interval of 1975 – 2208 nm enabled the most distinction between the different types of lactose. The region around 1900 nm was deliberately not used to avoid conclusions solely based upon the influence of adsorbed water (Savolainen et al., 2006).

PCA was used to interpret qualitatively the obtained spectra in relation to the reference values. The relevance of the data points and the presence of possible outliers were analyzed by comparison of leverage and residual variance (influence plot). If the NIR data point of a new analyzed sample did not fall within the model range or had a high residual variance the validity of the NIR measurement or the sample was verified; a new sample was analyzed and both samples were verified by DSC analysis as elaborated in paragraph 6.2.4. The influence of non-hydrate water on the model has been verified; up to a water activity of 0.93 in the lactose samples no influence on the model is observed.

In the PCA model the crystallization process of amorphous lactose could be distinguished. Based upon these observations it was assumed that also possible physical changes in powders or granules would be distinguishable by NIR analysis and that different conditions could be detected simultaneously.

Calibration of the partial least squares 2 (PLS-2) model was quantified by standard error of calibration (SEC), indicating the fit between NIR spectra and reference values. Validation was done by cross-validation. During validation, the standard error of cross validation (SECV) was calculated. It is expected that the SECV is a good estimation of the SEP (standard error of prediction). The SEP is used to evaluate the uncertainty of the future predictions. Physical mixtures with known amounts of αL-1aq, βL and AL were measured to determine the accuracy and validity of the system.

The effect of particle size on the model was addressed chemometrically. A small spectral difference was observed in presence or absence of SNV and second derivative Savitzky Golay (SG) modification. After SNV and second derivative SG modification both the score and loading plot of the PCA/PLS-2 model did not change when larger lactose 200M particles were included in the model. The largest granules (> 1700 μm) did however interfere with the model. This was seen as a deviation in the values for residual variance.

The crystalline state could be verified by DSC and water sorption analysis. Based upon these reference measurements the deviation in the NIR model could be ascribed to scattering differences intrinsic to the surface of the large granules. To avoid further interference the largest granules were milled gently before NIR measurement.

6.2.4 Differential Scanning Calorimetry and water sorption analysis

DSC analysis was performed on a Mettler Toledo DSC 822^e, Tiel, The Netherlands, (40-250 °C, 10 °C min^{-1}, N_2 flush 40 ml min^{-1}). All samples were measured in open pans in twofold. The water isotherms were measured as function of the RH over a range of 0 – 90% in steps of 10% at a temperature of 25.0 °C ± 0.1°C (DVS-1, Surface Measurements Systems Ltd, London, UK, dry N_2 200 ml · min^{-1}).

6.3 Results and discussion

6.3.1 Structure analysis by NIR modelling

Each type of lactose exhibited its own characteristic NIR pattern. Crystalline lactose produced narrow bands with high signal intensity whereas samples consisting of amorphous lactose did give more featureless, broad and overlapping NIR spectra throughout the whole spectral interval. As molecules are tightly bound in a crystal lattice only a limited amount of movements is possible. Spectral peaks of crystalline substances are therefore well defined and identifiable. The non-crystalline structures have more possibilities for movements as they are located in random conformations, leading to less distinct spectra. If water is incorporated within the crystal lattice this does influence the vibrations of the lactose bonds. This enables distinction between crystalline molecules with and without hydrates. Especially in the regions 2040 – 2100 nm (OH stretch + OH deformation) and 2220 – 2280 (OH stretch and OH deformation) the differences in the spectra were clearly visible (NØrgaard et al., 2005). Samples consisting of αL-1aq or βL showed a NIR absorption pattern with opposing peaks.

Freeze dried amorphous lactose was re-crystallized under lab conditions (25 °C 50% RH). Throughout the experiment, spectra were recorded at regular intervals (15 minutes). The progressive formation of more crystalline bonds in re-crystallizing AL was reflected in spectra as a significant change from the broad bands of the AL to the increasingly sharp distinguishable bands of the crystalline structures.

The visual differences in spectral response of the lactose type were the basis for the principal component analysis (PCA). Within this analysis the differences in crystalline state could be distinguished based upon three principal components which correspond to the largest differences between the amorphous and crystalline spectra and between the different crystalline types. In figure 6.1 the scores of the various principal components are shown. The first principal component (PC) describes 58% of the differences and the second PC describes 31% of the differences. The last PC describes 10% of the spectral differences.

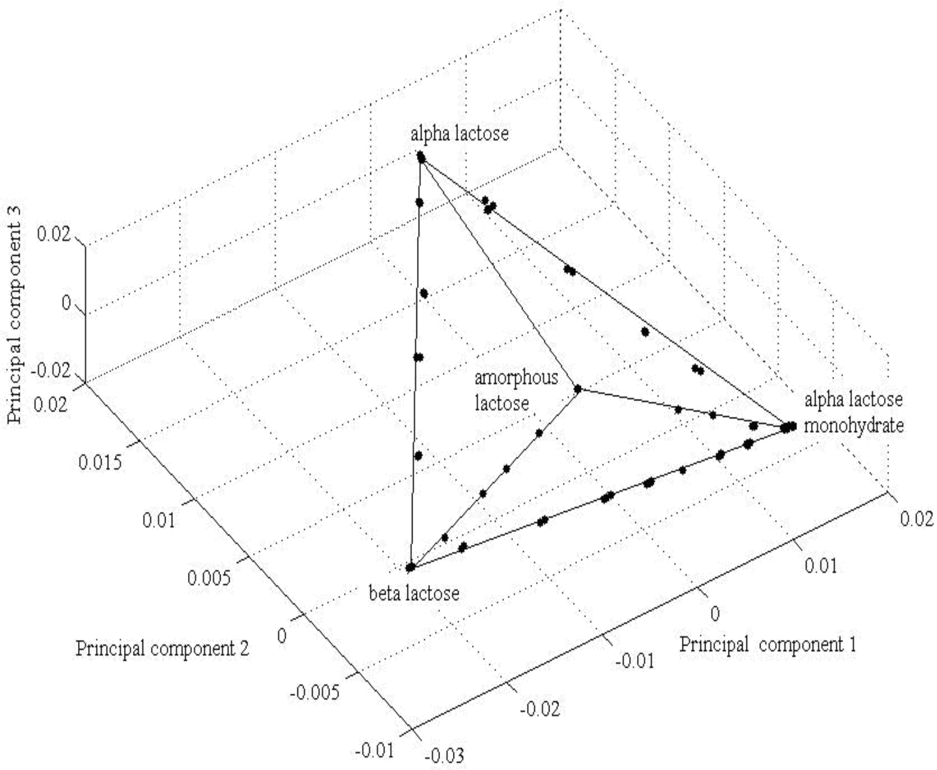

Figure 6.1 Score plot of various lactose types including physical mixtures of αL-1aq and βL, αL-1aq and AL (100% freeze dried amorphous lactose) and mixtures of βL and AL (100% freeze dried amorphous lactose). Individual data points are connected by lines to distinguish the model 'pyramid' visually. The lines do not represent a mathematical function. Spectra of binary mixtures were recorded. Mixtures of βL and αL-1aq, Al and αL-1aq, AL and βL, αL and αL-1aq, αL and βL were used for development of the model.

The first PC corresponds to the spectral differences between αL-1aq and βL. This is verified by calculation of the absorbance differences per wavelength between the spectra of these two components. This resulting 'spectrum' corresponds to the first PC. Furthermore the cross correlation coefficient between the loading of the PC and resulting ‘spectrum’ is very high (0.98). This confirms the association of the first PC and the difference between αL-1aq and βL. The second PC describes the difference between the crystalline hydrate water containing αL-1aq and the crystalline non-hydrate-water-containing αL (cross correlation coefficient 0.99). The third PC describes the spectral differences between the amorphous and all crystalline structures (cross correlation coefficient 0.91).

To enable quantitative analysis of the crystalline and amorphous content of both lactose powders and granules a PLS-2 model was developed. In one analysis the total amount of αL-1aq, αL, βL and amorphous lactose (w/w %) is determined. In table 6.1 the model characteristics are shown.

Table 6.1 Summary of PLS-2 model characteristics.

Predicted content by NIR PLS-2 model	**SEC (%)**	**SECV (%)**	**Correlation coefficient**
α-lactose monohydrate	2.25	2.24	0.998
α-lactose	2.46	2.45	0.997
β-lactose	2.25	2.24	0.998
Amorphous lactose	2.08	2.07	0.998

The correlation coefficient of the model for all the different structures was very high, > 0.997. The reliability of the model is reflected in the very small deviation between the SEC and SECV for all components. The low SEC and SECV enable quantification of the components of the powders and granules. The error in the predicted values is lower than best reported values for the quantification of crystalline and amorphous structures by conventional DSC or XRPD analysis (Lehto et al., 2006). It has been shown that isothermal micro-calorimetry has lower limits of quantification, but the analysis time (> 6 hours) limits the possibility to perform multiple measurements in a fast and simple manner (Buckton et al., 1995) as desired in the current study.

It is acknowledged that in a PLS-2 model based upon three crystalline components with strong spectral features the prediction of amorphous lactose (fourth component) is strongly dependent on these crystalline components due to the lack of spectral features of amorphous lactose. In the remainder of this study amorphous lactose is defined as disordered structures with a substantial lack of crystallinity in the lattice. The terminology amorphous lactose and disordered structures will be alternated throughout the text.

6.3.2 Crystallization of spray dried lactose (DCL 11)

DCL 11 is known to be composed of αL-1aq and AL. Crystallization of the amorphous parts of the powder is undesirable before compaction. Spray dried lactose yields stronger tablets than the crystalline α-lactose monohydrate (Sebhatu et al., 1994a). Upon the start of the experiments the composition of the compound was determined by NIR analysis. DCL 11 as used in this study contained 82% αL-1aq, 1% βL and 17% AL. Upon storage for a period of 14 days at high temperature and high relative humidity a change in crystalline composition of material was anticipated based upon literature (Visser, 1983; Angberg et al., 1991; Sebhatu et al., 1994a). The composition of the spray dried powder as determined by NIR is shown in table 6.2.

Indeed the samples stored at the highest relative humidity (75 and 95% RH) showed that mainly αL-1aq was formed. In all powders the amorphous parts were significantly diminished. Whereas at 95% RH no βL remained in the powder, at lower RH values more βL has either been formed or remained. This cannot be explained by the known mutarotation equilibrium as storage temperature is below 93.5 °C.

The critical relative humidity for induced crystallisation of amorphous lactose has been subject of debate. The reported values vary between 37 and 50% (Vromans et al., 1986; Listiohady et al., 2006). It was shown in the current study that under all conditions crystallisation of the AL occurred. The amount of remaining AL decreased at increasing relative humidity. The presence of residual AL upon continuous storage has been reported earlier and ascribed to the impossibility of water to access the disordered regions due to structural features of the powder (Listiohady et al., 2006).

Table 6.2 Composition of spray dried powder after storage for 14 days as determined by NIR regression model. As the model is based upon physical mixtures of lactose with known mass balance, inherently the sum of the predicted content will add up to 100% w/w.

	α-lactose monohydrate	**β-lactose**	**Amorphous lactose**
Starting material	82.3	0.3	17.4
40 °C 18% RH	84.8	11.3	3.9
40 °C 40% RH	85.8	11.4	2.8
40 °C 75% RH	92.5	4.8	2.7
40 °C 95% RH	98.8	0.0	1.2

6.3.3 Tableting of DCL 11

To test the impact of the composition of the powder on tablet strength this powder was kept at fixed conditions (30 °C 40% RH) for a total of 21 days.

Based upon literature at this storage condition instantaneous crystallisation is not expected (Burnett et al., 2004; Burnett et al., 2006). At the days as depicted in the material and methods section, tablets were made of this powder. In figure 6.2 and remaining of paragraph 6.3 this material will be referred to as stored powder.

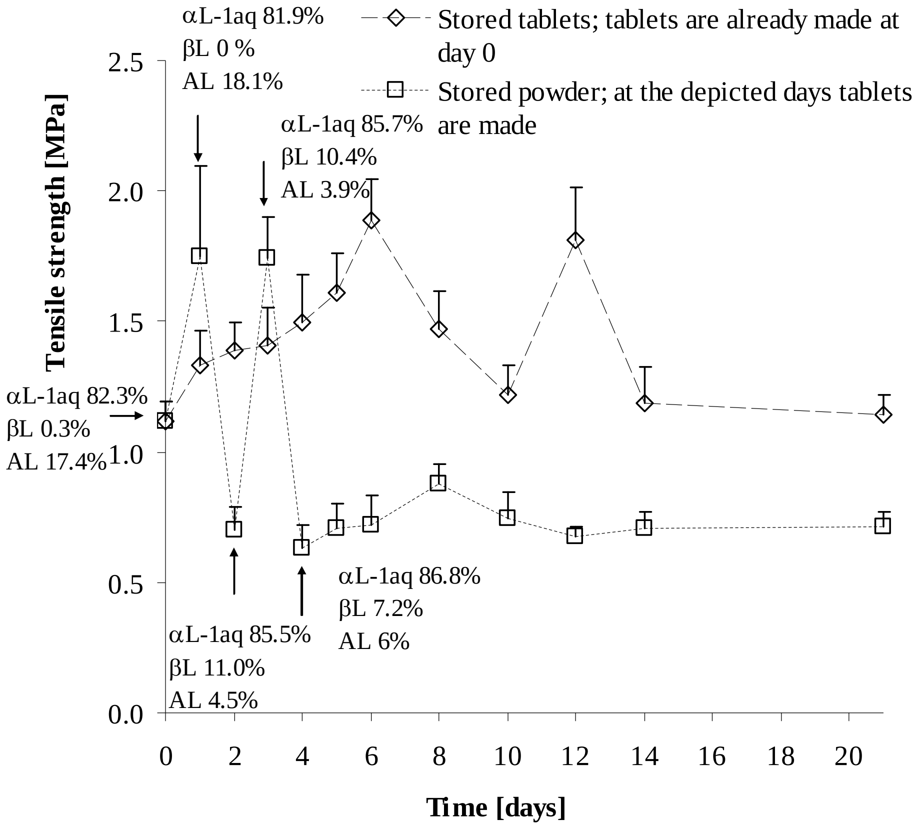

Figure 6.2 Tensile strength (MPa) of tablets manufactured of stored powder and tensile strength of stored tablets at 30 °C 40% RH. In the graph the composition of the stored powder as determined by NIR as function of the storage time at 30 °C 40% RH is shown. For clarity reasons this is only done for the data of the stored powder. The data for the stored tablets are highly comparable to the data for the stored powders. For clarity reasons data are not shown in this figure. Data points on tensile strength are shown including SD. Differences between tensile strength were confirmed statistical analysis. (two - tailed, paired student t-test ($p < 0.05$)).

To test the impact of expected composition variances in tablets, tablets were directly made out of the starting material. These tablets were also kept for a total of 21 days. In figure 6.2 and remaining of paragraph 6.3 this material will be referred to as stored tablets. The tensile strengths and composition of stored tablets and tablets made out of stored powder with related NIR spectra of the tablets were determined. The change in tensile strength is depicted in figure 6.2. Upon storage a change in the resulting tensile strength is seen.

In the current study two ‘peaks’ in tensile strength were observed for both curves. For the stored powder this occurs upon short-time storage at day 1 and day 3. The tensile strength of the stored tablets shows the same pattern, but the peaks are seen at day 6 and 12 respectively.

The differences in the crystal composition of the powder and the tablets were determined by the NIR PLS model. This led to the confirmation that indeed several processes are occurring within the powder. The determined values are shown in figure 6.2. At day 4 the amount of crystalline αL-1aq is slightly increased whereas the amount of βL is decreased. Clearly significant transitions in the crystalline state occur. It seems as if the amount of AL is increased as well. As explained in paragraph 6.3.1 as the model is based upon 100% crystalline lactose characterized by strong spectral features and 100% freeze dried amorphous lactose, characterized by the lack of spectral features, the model is strongly dependent on these crystalline components. The NIR predictions for all compositions were verified by DSC or water sorption analysis. At and after day 4 no amorphous material was detected by DSC or water sorption analysis. As the NIR values could not be confirmed by the other analysis techniques they are not shown in figure 6.2 In this case, transitions to a crystalline state occur which cannot be described exactly by the model.

Changes in tensile strength upon storage of compacts of spray dried lactose powder (DCL 11) have been reported earlier by Sebhatu et al. (1994b) and

Stubberud et al. (1996). Stubberud reported both positive and negative changes in tensile strength of compacts of DCL 11 and αL-1aq (Stubberud et al., 1996). Sebhatu et al. (1994b) reported subsequent tensile strength changes as function of pre- and post-compaction storage. These changes in tensile strength were related to subsequent transitions from the amorphous to the crystalline state and transitions within the crystalline state. Initially a strong increase in tensile was noted. Secondly a decrease in tensile strength to a value lower than the initial tensile strength was observed also at continuous storage up to two weeks. As the measurements were done at various time points at day 1 and day 14 intermediate events were not described (Sebhatu et al., 1994b). These observations are highly comparable to the first significant tensile strength increase and decrease as shown in figure 6.2. Furthermore Sebhatu et al., (1994b) described the effects of pre-compaction moisture sorption of post compaction tablet strength. The tablet strength of non stored DCL 11 fluctuated; after an initial decrease, a strong increase in tablet strength was noted. Afterwards a second smaller decrease, increase and decrease in tablet strength were seen. No further explanation on the nature of the composition was given.

Farber et al. (2005) reported on the bridge strength of drying lactose solutions between two slides during the first hours of drying. Lactose bridges dilated during drying. It was shown that at room temperature the drying bridge first experienced a decrease followed by an increase in stress. The bridges consisted of very fine crystals (Farber et al., 2005). In earlier studies Farber et al. (2003) have shown that formation of inter-particle bridges from lactose solutions in drying granules has been shown to be a multi-step process, characterized by several subsequent transitions from non-crystalline to crystalline bonds, potentially influencing the mechanical properties (Farber et al., 2003).

When amorphous solids are exposed to water, water-solid interactions are significantly different than for crystalline solids. Considerably more water is taken up in the amorphous form relative to the crystalline form (Ahlneck and

Zografi, 1990). In contrast to crystalline solids water will be absorbed in the disordered amorphous forms. Here it can act as a plasticizer. As a consequence in this state, higher molecular mobility is obtained. The molecules can be described as activated (Ahlneck and Zografi, 1990). Upon compaction the increased plasticity of the solid results in denser contact between particles and increased deformability (increase in tensile strength). However, amorphous lactose, especially in the presence of water can crystallize, resulting in brittle material. When this material is compressed, fragmentation rather than plastic deformation occurs, resulting in tablets with decreased tablet strength (Sebhatu et al., 1994b). In total this process can explain the observed initial increase and decrease in tensile strength (Sebhatu et al., 1994b).

The question arises what phenomena cause the second increase and decrease in the tensile strength. It is known that the crystallization of DCL 11 does not end after the initial crystallization of the amorphous parts (Angberg et al., 1991, Sebhatu et al., 1994b). By the experimental set-up the powders and tablets are continuously exposed to 30 °C 40% RH. In the presence of small amounts of water, mutarotation and further re-crystallization to the most stable state are known to occur (Angberg et al., 1991, Bronlund and Patterson, 2004). The composition achieved after the crystallization of amorphous lactose can therefore be described as meta-stable under the depicted conditions.

As stated above water uptake on crystalline surfaces is smaller than in amorphous regions. In accordance with Leeson – Mattocks kinetics water is known to be able to form a layer at crystalline surfaces (Leeson and Mattocks, 1958). In the presence of defects in the crystal lattice water uptake will even be higher. Uptake of water will again lead to enhanced molecular mobility (Ahlneck and Zografi, 1990). Upon compaction this increases plasticity. It is assumed that crystallization will continue until the most thermostable lactose form remains with minimal crystal defects. This is the crystalline end product αL-1aq.

In figure 6.2 it can be seen that both the amount of crystalline compounds and disordered forms reaches equilibrium. Tensile strength does not show any significant variation from the start of this equilibrium situation (day 4 for stored powder and day 14 for stored tablets). In conclusion successively different composition states can be distinguished concomitant with differences in tensile strength of compacts.

6.3.4 Crystallisation in granules upon drying

When produced by wet high shear granulation, large granules contain more water than small granules as shown by van den Dries (2004) and in chapter 4 and 5. Upon drying of the granules, the lactose dissolved in the water will solidify. It was shown that removal of water either by vacuum from a frozen solution (freeze drying) or rapid evaporation (spray drying) from a liquid solution does not allow sufficient time for the lactose to crystallize. These drying methods produce a relatively stable form of amorphous lactose (Lubach et al., 2007). The question arises if the drying method affects the composition of granules.

Therefore granules were dried with an air cabinet and a vacuum drying method. As a reference granules were dried by plate drying at room temperature (25 °C 50% RH). After drying compacts were made and tensile strength determined. In figure 6.3 the effect of drying technique on tablet tensile strength is shown.

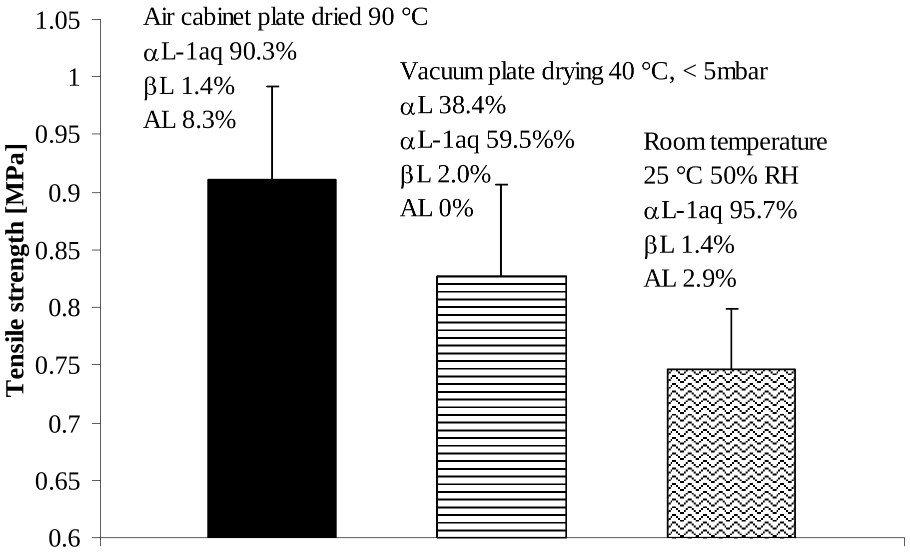

Figure 6.3 Tablet tensile strength of granules dried by different techniques; air flow cabinet, vacuum plate drying, plate drying room temperature (drying conditions as elaborated in the material and method section). Tablets are made directly after drying and cooling down to room temperature. Granule size class 1700-2360 μm. Tensile strength difference air cabinet plate dried granules and room temperature granules is significant (two-tailed, paired student t-test $p < 0.05$).

Air cabinet plate dried granules (90 °C, 1.5 hr, left bar in figure 6.3) showed a significant difference in tensile strength from granules dried at room temperature (right bar in figure 6.3). Compacts of vacuum plate dried granules (40 °C, vacuum < 5 mBar, middle bar in figure 6.3) showed an intermediate tensile strength.

According to the NIR analysis the content of disordered structures is higher in air cabinet plate dried granules than in granules dried at room temperature or under vacuum. The second significant composition difference between the granules is the presence of crystalline αL in the granules dried under vacuum. There is a total absence of amorphous lactose in these granules. Granules dried at room temperature did show the highest αL-1aq content. It is known that αL has worse compaction properties than amorphous lactose, but better compaction properties than αL-1aq (Busignies et al., 2004). Granules dried at higher temperature in the air flow cabinet had a significantly larger water uptake than granules dried at room temperature (1.2 versus 0.1% w/w respectively, granules size class 1700 – 2360 μm). This difference in water uptake has been ascribed to differences in disordered structure. In the presence of more disordered lactose structures higher water uptake is seen (Burnett et al., 2006). As explained for the DCL 11 compacts this is related to the differences in compaction behaviour of crystalline and non-crystalline lactose; in non-crystalline lactose the plasticity upon compaction is larger than in crystalline lactose where molecular mobility is very limited (Sebhatu et al., 1994b). Granules dried at room temperature have a very long drying time up to 7 days. In this time period crystallisation to the thermodynamically most stable state (αL-1aq) could occur.

6.3.5 Effects of granule size on granule composition

In table 6.3 the different composition of the air cabinet dried granules (90 °C) for the smallest and largest granules is depicted. After drying the smallest granules contain more αL-1aq than the larger classes. No αL was observed. The amorphous content was larger in the largest granules whereas the βL content was very small in the larger granules. In the water sorption analysis also differences are observed between the largest and the smallest granules. Whereas large granules 1700 – 2360 μm show a maximal water uptake of 1.2% w/w, the smallest granules exhibit a maximal water uptake of 0.2% w/w. The influence of surface availability or size itself on the water uptake is verified and excluded. The effects of size related granular heterogeneity are therefore not limited to the drying process itself, as elaborated in the previous chapter, but also to the compositional features of the granules.

Table 6.3 Size related crystalline composition of lactose granules after plate drying in air cabinet drying (90 °C, 1.5 h) as determined by the NIR PLS model.

Size (µm)	**212 – 300**			**1700 – 2300**		
	α-lactose mono hydrate	**β-lactose**	**Amorphous lactose**	**α-lactose mono hydrate**	**β-lactose**	**Amorphous lactose**
Composition after drying	93.4	2.2	5.0	90.3	1.4	8.3

6.3.6 Effects of storage on tablet strength

Whenever granules are dried, immediate transfer to the next process step (tableting) may be delayed. Granules can be kept until further processing is required. The influence of this temporary storage is mimicked by two days of exposure to controlled temperature and humidity. The granules were stocked up at conditions where limited (40 °C 18% RH), intermediate (40 °C 40% RH) and extensive crystallization is expected (40 °C 75%, 40 °C 95% RH). Afterwards the crystallization changes in the granules were determined by NIR. Compacts were made of the largest granules with the size class 1700 – 2360 µm and tensile strength was determined. Before storage tablets had an average tensile strength of 0.91 MPa. The composition as determined by NIR and the tensile strength of the tablets are shown in figure 6.4.

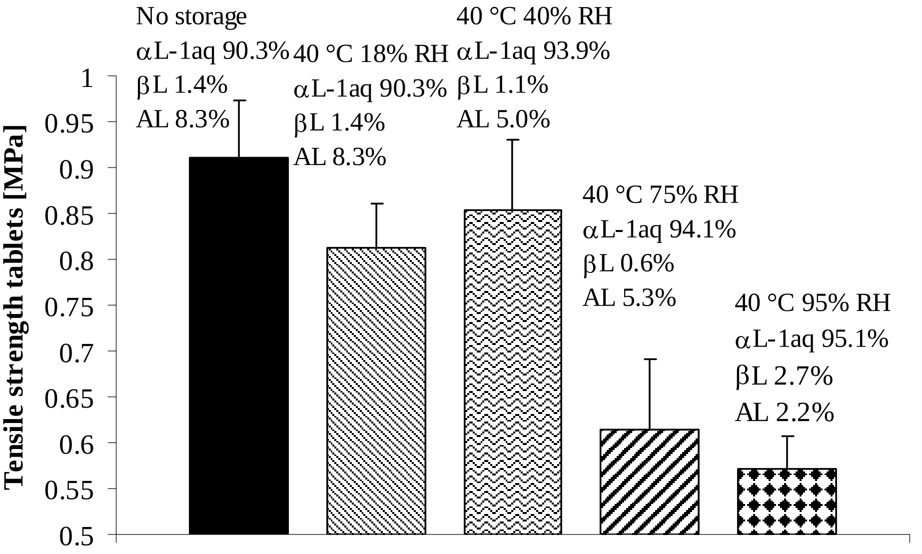

Figure 6.4 Tensile strength of tablets (air flow cabinet dried granules 1700 – 2300 µm) upon storage for 2 days. Tensile strength data are shown including SD. Granules stored at RH > 75% have a significant different tensile strength in comparison to tablets from the non-stored material. This is confirmed by student t-test (two-tailed, paired student t-test $p < 0.05$).

The tensile strength of tablets dried at high temperature and humidity (>75% RH) is significantly decreased compared to the original strength after drying ($p < 0.05$). At higher RH more amorphous lactose is re-crystallized. As crystalline material has a more brittle than plastic compaction behaviour a lower tensile strength was expected. Upon storage at lower RH (18% RH) relatively more amorphous content is still present. Tensile strength did not differ significantly ($p > 0.05$) between granules stored at 18 or 40% RH and the non-stored granules. Obviously not only the drying method influences the composition of the granules but also the storage after drying has a major influence as reflected in the tensile strength of tablets.

6.4 Conclusion

In this study it is shown by NIR analysis that physical changes do occur upon storage of powders and granules. By NIR analysis all the crystalline and amorphous lactose components can be detected simultaneously by one fast and simple measurement. The crystalline and amorphous content can be detected quantitatively with prediction errors comparable to reported analysis methods. The model is applicable to all dried granules and powders.

During earlier development of the NIR size model as elaborated in chapter 4 the effect of granule composition on amorphous content was shown. Large granules contained more amorphous lactose than small granules. One of the consequences of the granules composition heterogeneity in high shear granulation is the distribution of water in the granule. Large granules contain more water than smaller granules. Lactose will dissolve in the available water. It was shown that upon drying this enables the formation of different non-crystalline and crystalline structures in the granules. Large granules do contain more disordered structures than smaller granules as shown by water sorption and NIR analysis. The study confirms the presence of amorphous and anomeric lactose in granules after drying by several techniques. Amorphous lactose is here defined as disordered structures with lack of crystallinity. In the air cabinet, drying temperature 90 °C, most of this amorphous lactose is formed upon drying of the granules. The impact of the presence of these disordered structures, including re-crystallization of these structures upon storage at high relative humidity conditions on tablet tensile strength was shown. To ensure optimal product quality the impact of the drying method of choice on crystallization state should be evaluated. Upon storage of the spray dried lactose powders in time several successive transitions in tensile strength and corresponding composition were observed. Therefore in product development there should be awareness to the consequences of drying method and storage conditions of the intermediate powders and granules on the physical quality of the final drug product.

Abbreviations

AL	amorphous lactose
(aq)	aqueous state in relation to described equilibrium
αL-1aq	α-lactose monohydrate
βL	anhydrous β-lactose
αL	anhydrous α-lactose
DSC	Differential Scanning Calorimetry
DVS	Dynamic Vapour Sorption
NIR(S)	Near Infrared (Spectroscopy)
PAT	Process Analytical Technology
PC	Principal Component
SEC	Standard error of calibration
SECV	Standard error of cross validation
SEP	Standard error of prediction
(s)	solid state
SG	Savitzky – Golay
SNV	Standard normal variance
RH	Relative humidity
XRPD	x-Ray powder diffraction

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7

Dynamic effects during microwave drying of granules

Abstract

Microwave drying is a known fast drying technique The application within pharmaceutical technology is limited because of the limited experience and limited knowledge on dielectric characteristics of the exposed pharmaceutical materials.

The purpose of this work is to study the integrity of granules during drying in different scale microwaves. Furthermore the effect of applied vacuum during microwave drying is studied.

Microwave drying induces a dynamic granule bed, especially at a reduced pressure. This is reflected in de-mixing of the granule bed during the drying process where large granules tend to rise to the top of the bed and small granules tend to move downwards. Motion in the granule bed is induced by the appearance of vapor bubbles due to the vaporization of the water. In small scale microwave drying limited fines formation is observed. In contrast, in industrial scale microwave formation of fines is abundant. This can be related to the movement of the granules in the dynamic bed, but primarily to movements of the mixer arm in the last stages of the drying process. Granules lose their strength upon advanced drying. If mechanical agitations can be prevented, microwave drying is a good alternative to fluid bed drying or plate drying.

7.1 Introduction

Microwave or high frequency drying is a less often used drying technique within the pharmaceutical industry. Limited experience, inhomogeneous electric fields, unawareness of dielectric characteristics of both the active ingredients and excipients counteracts the development of this technique (Kelen et al., 2006). Water, mostly used as binder liquid, has an unfavorable high heat of vaporization. Therefore, it has been disputed if high frequency drying for water containing products is the method of choice. High frequency drying is known as a fast drying technique. Other advantages lie in the availability of contained systems to avoid contact with either the product or operators. In contrast to fluid bed drying or plate drying where the drying rate is dependent on drying surface, in high frequency drying the drying rate depends on the field strength as well as on the dielectric properties of water and the solids, present throughout the granule. Heating of the material is based upon the interaction of the microwaves with the exposed materials (McLoughlin et al., 2003).

The principle of dielectric heating is based upon the absorption of dielectric energy by either induced or permanent dipoles. Water is dipolar in nature and therefore susceptible to this drying technique. Dipoles are oriented by the changing polarity of the applied electric field. Normally dipoles are randomly oriented. The electric field attempts to pull them into alignment. As the field decays to zero power, the dipoles return to the random orientation. As the electric field builds up the opposite polarity the dipole is pulled again into alignment. This relaxation and alignment causes an energy conversion from electrical field energy to kinetic energy in the material, and finally to thermal energy (Schiffman, 1995). The resulting intensity of vibration, i.e. the degree of orientation, depends upon the structure of the molecule (size and shape), viscosity, temperature and intermolecular bonds. The sensitivity of materials to microwaves is highly variable (Vromans, 1994). The behavior of materials in the electric field is described by its dielectric properties or permittivity. In complex mixtures as pharmaceutical granules permittivity is difficult to determine and cannot be predicted based upon the individual constituents. The permittivity consists of two parts; the relative dielectric constant, ε', and the loss factor ε''. The loss factor of a material describes how much energy is absorbed and consequently how much heat is generated inside a material per unit time when an electric field is applied (McLoughlin et al., 2003). The rate of temperature rise of the material as the material absorbs microwave energy is depicted by equation 1:

$$\Delta T / \Delta t = P_v / \rho C_p \qquad \textbf{Equation 7.1}$$

Where ΔT is the temperature rise, Δt is the time interval, P_v is the power per unit volume, ρ depicts density and C_p represents the heat capacity. The power per unit volume is dependent of the frequency (f), permittivity of vacuum (ε_0), the loss factor (ε'') and the electric field strength in the microwave. Therefore it is expressed as:

$$P_v = 2\pi f \varepsilon_0 \varepsilon'' E^2 \qquad \textbf{Equation 7.2}$$

The total loss factor (ε'') of a wetted material is a determined by both the solid material and the bound and free water present on or within the material. Preferably the loss factor of the solid constituents in the granule is close to zero. This certainly applies for lactose (Vromans, 1994). This implies that the solid does not absorb any energy and that the energy dissipation in the solid skeleton will remain relatively low throughout the drying process. The wet granules can be considered as a two component system of a solid, lactose, and water. The temperature will be dominated by the boiling temperature of water at the pressure in the equipment. At reduced pressure the temperatures remains fairly low. In this case the solid will not be affected by significant temperature changes. This can be considered an advantage as the degradation of some solids is enhanced by local rise of temperature (Chee et al., 2005).

The purpose of the current work is to study the integrity of lactose granules during dielectric drying. A comparison is made between granule behavior in small scale development equipment and industrial scale drying equipment. Furthermore the effect of applied vacuum during microwave drying is studied.

7.2 Materials and Methods

7.2.1 High shear granulation

1 kg Lactose 200M (DMV-Fonterra, Goch, Germany) was granulated in a high shear mixer (Gral 10, Colette, Wommelgem, Belgium) for 5 minutes (mixer rotation rate 313 rpm, chopper rotation rate 1500 rpm). 160 ml de-mineralized water was used as binding liquid. The water was poured onto the moving powder bed.

7.2.2 Development scale microwave drying

The granular drying characteristics were examined using a microwave system as represented in figure 7.1. A glass tube perforated the microwave wall of the adapted domestic microwave (Sharp R-239, Sharp Electonics, Hamburg, Germany) as earlier described by Vromans (1994). The glass tube contained a fine maze metal filter in line with the wall of the microwave to prevent electromagnetic radiance leakage. The absence of leakage was verified by a microwave survey meter (Holaday industries, Eden Prairie, USA). Inside the microwave a round bottom flask was placed, whereas on the outer side the connections to the condenser and vacuum pump were made. The glass condenser was cooled with water. For all experiments a power of 240W was used. 50 g of the lactose granules was transferred to the round bottom flask. Pressure in the system was set at either 80 kPa or 101 kPa (atmospheric pressure). The progress in drying was evaluated at various time points up to 28 min. All experiments were performed at least in twofold.

To test granule bed behavior in relation to granule size a layer (0.5 cm) of large granules (1700 – 2360 µm) was placed in the flask. On top of this layer small granules (425 – 600 µm) were placed (0.3 cm). The granules were dried under reduced pressure. The experiment was performed in six fold.

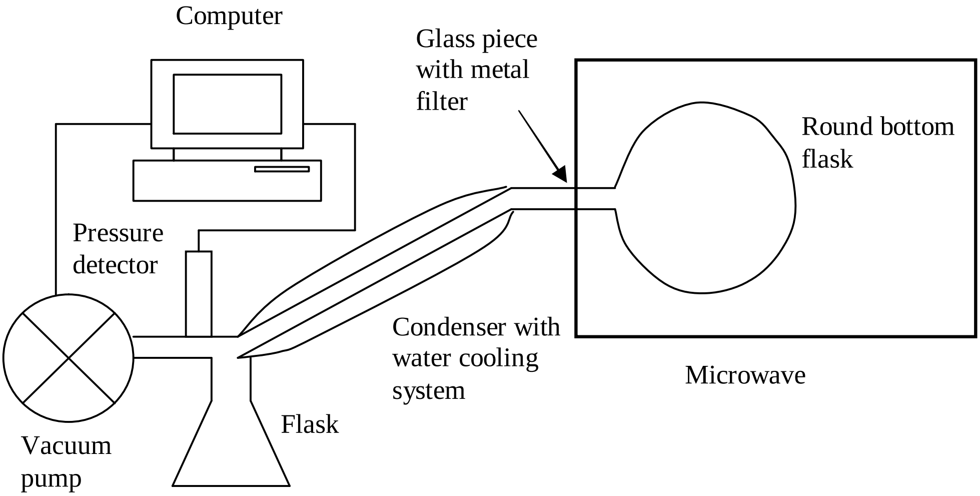

Figure 7. 1 Microwave drying system with connections to condenser, vacuum pump and PC.

7.2.3 Industrial scale microwave drying

11 kg Lactose 200M (DMV Fonterra,Goch, Germany) was granulated in a high shear mixer (Gral 75 / Vactron,, Colette, Wommelgem, Belgium) for 5 minutes (mixer rotation rate 130 rpm, chopper rotation rate 1500 rpm) with 1700 ml of water as binding liquid. Vacuum was applied and the granules were exposed to microwave radiation (3 kW) When the granules were completely dried the drying point is characterized by a steep increase in field strength as microwave

absorption is minimized. Each time the container closes the mixer arm makes two complete rounds. If the container opens the mixer arm does not rotate.

7.2.4 Particle size and water content analysis

Particle size distribution of the granules was determined by sieving 100 g of granule samples on a Retsch AS 200 control sieve (Haan, Germany). The mean particle size of the samples was estimated as a median weight-based diameter. The effect of the sieving equipment on the attrition and breakage of granules was assessed. It was found that sieving of the granules did not significantly influence the obtained results from the granulator experiments. All sieving tests were performed in twofold. The particle size distributions of granules dried by microwave were compared to data of granules dried under ambient conditions (20 °C, 50% RH) (chapter 6).

For each granule size fraction obtained after sieving a sample for reference water content determination was collected. The water content of the granules was determined with an automated Karl Fischer titration (KF coulometer 756K with oven sample processor 774 at 150°C, Metrohm, Herisau, Switzerland). For each sampled granular fraction the water content was determined in twofold per experiment.

7.3 Results and Discussion

7.3.1 Development scale microwave drying

In the small microwave it is observed that at the end of the drying process large granules tend to lie on top of the smaller granules. Intrinsically every experiment is started with a homogeneous bed. To test these de-mixing phenomena, the round bottom flask was filled with a layer of large granules. On top of this layer, small granules were placed. Already after three minutes of drying the two layers were not uniform any more. After six minutes the large and small granules layers were mixed. At the end of the drying process the smallest granules were located at the bottom of the flask, whereas the largest granules were located on these small granules. In fact, a complete reverse in location of the granules in the granular bed was observed. This implies that the granules move upon microwave drying. The microwave drying method is therefore not static but can be considered as dynamic drying system. In the small scale microwave the field strength and pressure can be varied. In absence of a microwave field the dynamic effect was not seen at all. In the presence of a dielectric field this effect is more pronounced at lower pressure. Motion in the granule bed may be induced by the appearance of vapor bubbles due to the vaporization of the water (Péré and Rodier, 2002). Under reduced pressure the volume of the developing vapor bubble is larger than at atmospheric pressure. This increases the effect of the vapor bubbles. The phenomenon that large particles or agglomerates tend to rise through the bed upon motion is known as the Brazilian nut effect (Shinbrot, 2004, Yan et al., 2003) and is e.g., observed in tableting (Spring, 1977). In this situation the motion in the bed is sufficient to cause de-mixing.

The question arises if motion in the bed can also induce growth and breakage effects as observed earlier during the drying of wet lactose granules in the dynamic fluid bed drying process as seen in chapter 5. In chapter 5 the extensive breakage of granules by influence of the air velocity and the intrinsic water content of the largest, median and smallest granules was described. In contrast to the fluid bed drying process where several drying rate phases are known to occur (chapter 5) during microwave drying the drying rate is very constant for all size classes. Throughout the drying process the median and largest granules have very similar water content. On the contrary, the smallest granules do have lower water content throughout the drying process. In earlier chapters it is shown that the water content of the smallest granules determines the extensive formation of small particles. The integrity of the granules upon drying in the small scale microwave was evaluated. In the small scale microwave the formation of fines is minimal. Therefore it cannot be concluded that in this situation the movement in the bed is sufficient to induce extensive breakage effects. With regard to the integrity of the largest granules it was noted that the largest granules consists of several adhered granules at the end of the drying process. This adherence effect was significantly larger upon drying at 80 kPa than at 101 kPa. This adherence may result from the increased movement of the largest wettest granules versus the smallest granules. As the larger granules contain more water than the small granules and the movement is related to the formation of vapor bubbles, large granules will move more than smaller granules potentially leading to increased adherence opportunities.

7.3.2 Industrial scale microwave drying.

Figure 7.2 depicts the formation of fines upon drying at different conditions. A large difference exists in terms of fines formation when comparing e.g., small scale plate drying with e.g. large scale dielectric drying. At an industrial scale, it appears that the opening of the bowl of the high shear mixer, which in fact comprises a certain degree of stirring of the bed, increases the formation of fines. This suggests that shear may yield particle breakage. It should be realized that the strength of granules is related to the presence of water.

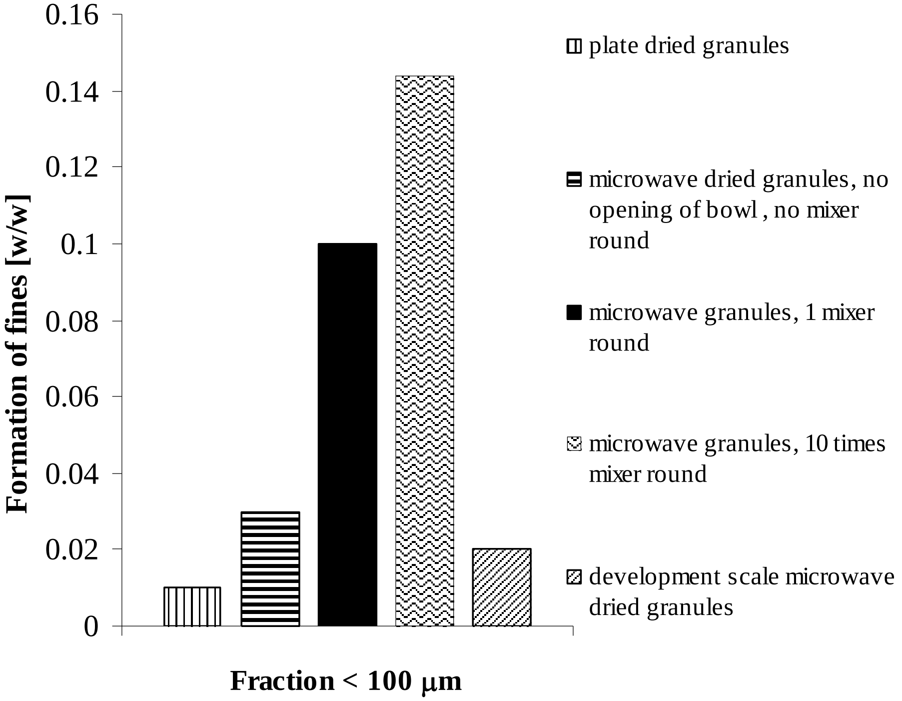

Figure 7.2 Formation of fines in dried granules upon plate drying and microwave drying. During microwave drying the number of mixer rotations is varied as depicted in the legend. As a reference the formation of fines in wet granules (non-dried) and granules dried in the development scale microwave with reduced pressure are shown. Wet granules did not contain fine particles.

It was shown in earlier chapters that the size reduction behavior and strength of the granules during fluid bed drying are determined by water content and extent of stress in a three phase system characterized by a growth, plateau and breakage phase.

Below a critical minimum liquid bridge volume the remaining amount of water is insufficient to prevent abundant size reduction. This can be observed as a sudden increase in breakage and high levels of attrition reflected by large changes in granule size and the formation of fines. This is also the case in the last stages of the microwave drying process, when the bulk water content is already limited. Here the amount of fines increases immensely upon one rotation of the mixer. In figure 7.3 the formation of fines in relation to the water content is shown. As also shown in chapter 5 smaller granules have intrinsically a lower saturation level than larger granules. Throughout the drying process they will earlier loose water, the binding force, than larger granules. Therefore it is concluded that once the critical water content point has been reached one mixer turn is sufficient to break granules and cause fine formation.

It is shown in chapter 3 and 5 that above a minimum liquid bridge volume the granule strength is independent of water content and dependent on impact or compaction velocity revealing a dynamic strength system. This phase is characterized by a plateau phase where changes in granule size are stable and comparable. Ennis et al. (1990) showed that at relatively high velocities of the particles a viscous force determines the strength of a liquid bridge. The tensile strength of a granule under dynamic conditions (σ_v) is derived by the following equation:

$$\sigma_v = \frac{9}{8}\frac{(1-\varepsilon)^2}{\varepsilon^2}\frac{9\pi\mu v_p}{16 d_{3,2}}$$ **Equation 7.3**

in which ε is the intra-granular porosity, μ is the viscosity, $d_{3,2}$ is the surface mean diameter of the primary particles and v_p is the relative velocity of the moving particles. This equation is based on the general equation for tensile strength of a granule as developed by Rumpf, the Reynolds lubrication equation describing the viscous force of liquid bridge and the Kozeny model as elaborated by Van den Dries and Vromans (2002). The microwave system is also considered to be dynamic as the granules move during drying as shown in the previous section.

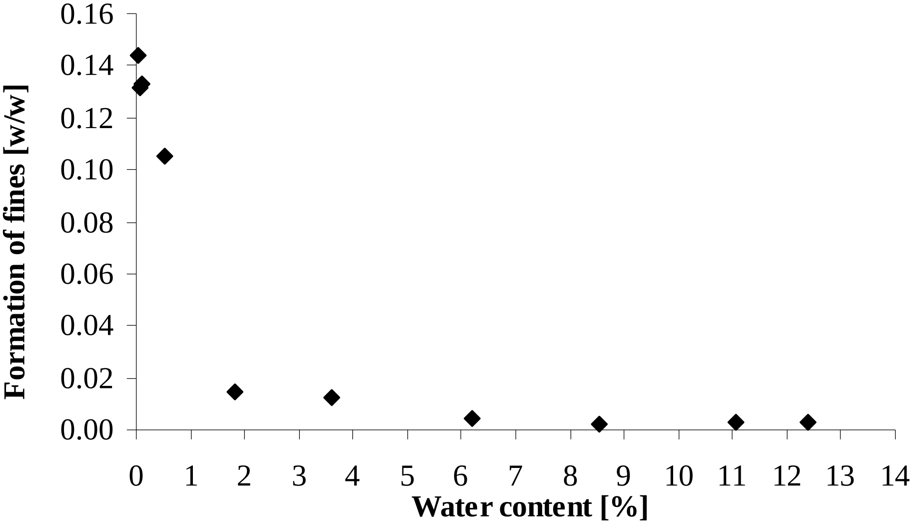

Figure 7.3 The formation of fines in lactose granules by industrial scale microwave drying versus average water content of the granules. Each time the bowl opens the mixer arm makes one complete round. The amount of fines is determined after opening of the bowl. In this experiment the bowl is opened 10 times.

In table 7.1 the size differences of the granules are shown. Results of industrial scale microwave drying are based upon the experiment as described for figure 7.3. The granules dried at industrial scale are exposed to the mixer arm 10 times. From analysis of the granule size of the smallest, median and largest granules throughout the drying process it is seen that the largest granules show growth effects (data not shown) in the first stages of drying when still a significant amount of water is present. These growth effects cannot be completely annihilated upon further drying and opening of the bowl. This observed growth phase is in line with the granule size increases for the largest granules as observed in chapter 3 and 5 for plate drying with subsequent friction and fluid bed drying.

As seen in table 7.1 clearly the influence of the rotating mixer arm is not limited to the formation of fines. The sizes of the smallest granules (d 10) and median granules (d 50) are also decreasing. As for the development scale microwave drying process a growth effect is observed for the largest granules.

Table 7.1 Granule size of smallest (d 10), median (d 50) and largest (d 90) granules after plate drying, microwave drying in small scale microwave and industrial scale microwave.

	Plate drying (no friction applied)	Development scale (80 kPa)	Industrial scale microwave drying
d10	451 µm SD 55.5 µm	369 µm SD 20.6 µm	70.4 µm SD 7.4 µm
d50	1858 µm SD 34.0 µm	1739 µm SD 39.5µm	1057 µm SD 35.5 µm
d90	3177 µm SD 75.8 µm	3910 µm SD 39.6 µm	4146 µm SD 85.6 µm

It has been stated that stirring may be necessary for powders containing starch to prevent hot spots and ensure a homogeneously dried bed (Vromans, 1994). Stirring of lactose granules to obtain a homogeneously dried bed is not necessary as the lactose itself does not absorb the electromagnetic radiance. On the contrary, stirring only induces breakage and formation of fines in these lactose granules at the end of the drying process when limited water is present to retain granule strength. Furthermore as shown by the data in the development scale microwave, the granular bed is dynamic during microwave drying under reduced pressure. The drying process takes approximately an hour; the granules are therefore exposed to this friction for a long time, making growth and breakage effects and formation of fines very likely.

7.4 Conclusion

Upon microwave exposure the granule bed is remarkably dynamic. This is reflected in the de-mixing of the bed where large granules tend to rise and small granules tend to move downwards. Motion in the granule bed may be induced by the appearance of vapor bubbles due to the vaporization of the water. Under reduced pressure the volume of the moisture vapor is larger than at atmospheric pressure. This increases the effect of the vapor bubbles.

Drying rate is constant throughout the drying process. Throughout the drying process the median and largest granules have very similar water content. The derived Rumpf dynamic strength model describes the granule behavior above minimal water content. Towards the end of drying process, below a minimum liquid bridge volume the presence of very small amounts of water or developing solid bridges cannot prevent abundant size reduction. Especially small granules have already lost most water and therefore their strength. One rotation of the mixer arm will therefore cause abundant formation of fines.

If stirring can be prevented, microwave drying is a good alternative to fluid bed drying or plate drying.

Abbreviations

C_p	Heat capacity (J kg^{-1} K^{-1})
d_{10}	Cumulative 10 % frequency undersize (μm)
d_{50}	Cumulative 50% frequency undersize (median granule size) (μm)
d_{90}	Cumulative 90% frequency undersize (μm)
$d_{3,2}$	Surface mean diameter of the primary particles (μm)
E	Electric field strength (V m^{-1})
ε	Intra-granular porosity (-)
ε_0	Permittivity of vacuum (8.85419 10^{-12} F m^{-1}),
ε''	Loss factor (-)
f	Frequency (Hz)
μ	Viscosity (Pa·s)
ρ	Density (kg m^{-3})
P_v	Power per unit volume (W m^{-3})
σ_v	Dynamic granule strength (Pa)
SD	Standard Deviation
ΔT	Temperature rise (K)
Δt	Time (s)
v_p	Relative velocity of the moving particles (m s^{-1})

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8

Lactose contaminant as steroid degradation enhancer

Abstract

Physical and chemical stability of the active compound is a critical quality factor in drug product development. By pharmaceutical processes and in the presence of solid excipients physical-chemical changes are known to occur, leading to increased rate of chemical degradation. The purpose of this work was to determine the critical aspects in the stability of a steroid in the presence of a commonly used excipient, lactose. Small lactose particles lead to a higher degree of degradation. Degradation was enhanced under warm humid conditions although the presence of water alone could not account for this effect. Lactose-phosphate, a known intrinsic contaminant in lactose is demonstrated to enhance the degradation of the steroid. Stability was improved in high purity lactose and deteriorated upon extra addition of phosphates. Since the exposure to the contaminant is a function of the surface area of the lactose, particle size differences of the excipient have a clear consequence. High shear granulated lactose granules exhibit a heterogeneous composition; large granules consist of small primary particles and vice versa. It is shown that the large granules, composed of the small primary lactose particles reveal the highest degree of degradation. Granule composition dictates the stability profile of the granules.

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8.1 Introduction

The degradation rate of a compound is related to the structural susceptibility of the substance and reaction conditions such as temperature, humidity and oxygen concentration. Unfortunately reactivity may also be enhanced by the presence of other compounds (e.g., water in wet granulation, aldehyde groups in excipients (Zi et al., 2006) or by changed physical-chemical states (e.g., as an effect of drying and tableting). The active substance and the excipients used are constantly exposed to stresses potentially leading to chemical and physical changes. The physical changes in granules are especially apparent during drying as described in all the previous chapters. Both high temperatures (Waterman and Adami, 2005) and the presence of water (Ahlneck and Zografi, 1990, Carstensen, 1988, Waterman et al., 2005, Zografi, 1988) can induce instability. Moreover during dynamic drying processes fine particles are produced thereby increasing the potential interaction area of the drug and the excipients (chapter 4 and 5).

The mechanism of chemical degradation in the solid state is described by different authors. Degradation of the solid into the gas, liquid and solid state has been distinguished (Carstensen, 1990). The theory of Prout and Tompkins is primarily used to explain solid to gas transitions. Once a molecule in the solid state has decomposed, its geometry within the lattice changes. This geometric change in the surrounding is thought to activate neighboring molecules. These activated molecules are then subject to degradation (Carstensen, 1990, Prout and Tompkins, 1944). The Leeson - Mattocks kinetics assumes that upon exposure of a solid mass to moisture, the unbound moisture forms a sorbed moisture layer, which behaves like a bulk liquid phase in which the drug substance and excipient will form a saturated solution (Leeson and Mattocks, 1958). Furthermore it is assumed that the decomposition can be totally accounted for by the decomposition of the dissolved drug (Carstensen, 1990).

This theory is opposed by the theory of occurrence of activated sites on the crystal surfaces. Degradation is locally enhanced by defects in the crystal lattice preferentially at the surface (Ahlneck and Lundgren, 1985, Ahlneck and Alderborn, 1988, Prout and Tompkins, 1944). Ahlneck and Zografi (1990) proposed that small amounts of water can be absorbed in these activated sites thereby increasing molecular mobility hence increasing chemical reactivity by the plasticizing properties of the water. The role of water as solubility facilitator has then been expanded to that of a chemical reactivity enhancer. Carstensen and Pothisiri developed a model in case of decomposition of the active compound in the solid and in the dissolved state including theories of Prout and Tompkins and Leeson and Mattocks (Carstensen and Pothisiri, 1975). Carstensen and Attarchi studied the decomposition of acetylsalicylic acid in the presence of limited amounts of water. It was hypothesized that the decomposition occurs in chains through activated molecules like the Prout-Tompkins theory (Carstensen and Attarchi, 1988). Activated molecules are subject to degradation by changes in the environment. Dissolved molecules provide a repository for water adjacent to these activated molecules (Carstensen and Attarchi, 1988).

In the presence of solid excipients several physical chemical changes of the active substances are described leading to increased rate of chemical degradation, reduction in degree of crystallinity or the formation of molecular complexes. The excipient itself can act as a source of humidity which causes water vapor to associate with the drug and influence stability (Ahlneck and Zorgrafi, 1990). The effect of excipients can also be related to the area of contact between drug and excipient, in addition to the total amount of excipient present (Ahlneck and Alderborn, 1988).

Lactose is very often used as filler in solid state drug products; tablets, capsules and dry powder inhalers. Lactose has two isomers (α and β lactose) and has the ability to form a hydrate. It is known to occur in several crystalline states and in the amorphous state. Processing of crystalline lactose can induce failures in the crystal lattice, candidates for enhanced chemical reactivity (Buckton, 1997) as the locally disordered regions (Saleki-Gerhardt et al., 1994) can influence the stability of drug particles. Moreover micronization of both excipient and active substance increases the surface area available for interaction. It has been discussed in chapters 4 and 5 that within a granulate heterogeneity exists. Large granules are composed of small primary particles and small granules are composed of larger primary particles. Consequently large granules exhibit a larger internal surface than small granules, thereby theoretically enhancing degradation.

The objective of the current study was to investigate the influence of physical state and excipient characteristics on the stability of a steroid.

8.2 Theory

Many steroids are known to degrade under influence of oxygen. In figure 8.1 the assumed degradation reactions of the compound used in this study are shown. The degradation into the primary degradation products is started by enolization of the active substance. The enolized molecule is more vulnerable to oxidative degradation. The enolization of the steroid can theoretically be enhanced both in acid or basic environment. From the transition products alcoholic and ketonic degradation products are formed. However the complete mass balance of the degradation reaction is not known. The decrease in steroid content is therefore appointed as main degradation criterion and not the formation of degradation products.

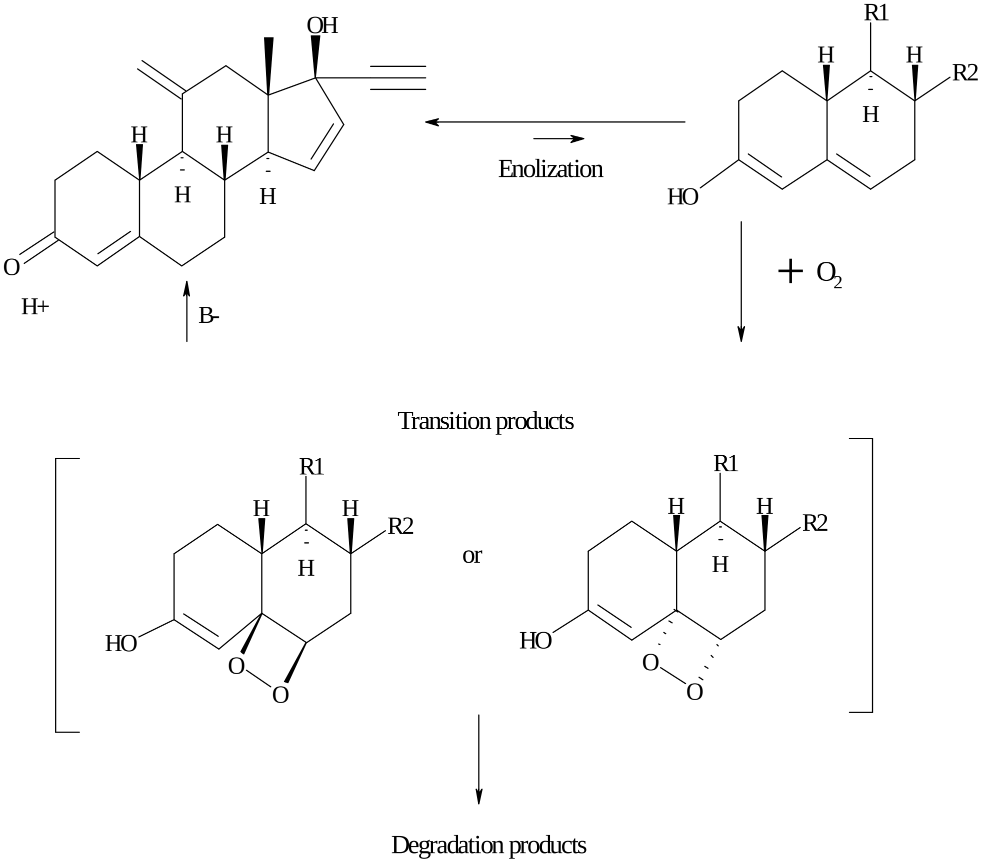

Figure 8.1 The enolization of the steroid Org 30659. Enolization is enhanced in the presence of acidic (H^+) or basic (B^-) components. Upon enolization the molecule is susceptible to oxidative degradation.

8.3 Materials and Methods

8.3.1 Excipient powder mixtures

A steroid hormone, Org 30659 (Diosynth, Oss, The Netherlands), was mixed (1 $mg \cdot g^{-1}$) with α-lactose monohydrate (Pharmatose 200M), micronized α-lactose monohydrate (both DMV-Fonterra, Veghel, The Netherlands), ultra-pure lactose (Fluka, Biochemika, Sigma-Aldrich, Buchs, Germany) and $CaHPO_4$ dihydrate (Chem. Fabrik Budenheim, Budenheim, Germany). Samples were prepared in threefold. The samples were either mixed in a Turbula Mixer or mixed with a mortar and pestle for 30 minutes.

The distribution of the steroid in the lactose mixtures was determined by NIR Imaging (Sapphire Go NIR Imager, Spectral Dimensions Inc, Olney, USA, operated with Isys Software 4.0, 1100 – 2500 nm, normalized second derivative spectra (Savitzky-Golay)). In case of an inhomogeneous distribution the steroid could be visualized and detected as clumps in the lactose.

The mixtures were stored in open containers at 40°C and 75% relative humidity or 5°C at ambient humidity (80% RH) for a total of 6 or 8 months.

At 0, 2, 4, 6 and 8 months the mixtures were analyzed with HPLC/UV detection to quantify remaining content and degradation products (reversed phase HPLC C-18 column, column temperature 30°C, eluent methanol / water (55 / 45, v / v %), flow 1.5 $ml \cdot min^{-1}$, UV detection 240 nm, injection volume 10 μl).

The mixtures were analyzed with differential scanning calorimetry to detect changes in excipient characteristics and to detect presence of disordered structures. (Mettler Toledo, Tiel, the Netherlands, DSC 822e, open pans, 25°C – 250°C, 10 $°C \cdot min^{-1}$, nitrogen flow 40 ml/min). No changes were observed upon storage. The micronized lactose did not contain amorphous structures at the start of the experiments.

Water vapor sorption isotherms of both the lactose 200M and micronized lactose were collected by DVS. (DVS -1 Surface Measurement Systems, Alperton, UK).

8.3.2 Granules

Org 30659 was mixed with lactose 200M (1 mg · g^{-1}) in a high shear granulator (Gral 10, Colette, Wommelgem, Belgium) for a total of 15 minutes (mixer velocity 313 rpm). The powder was granulated for 5 minutes (mixer rotation rate 313 rpm, chopper rotation rate 1500 rpm). Water (140 ml) was used as the binding liquid. The granules were dried for 4 hours under vacuum at 40 °C (Elbanton, Kerkdriel, The Netherlands). Granules were sieved with a Retsch control 200 '*g*' sieve, (Haan, Germany). Size fractions were collected and stored at 5 °C ambient relative humidity (80% RH), 40 °C ambient relative humidity (18 % RH) and 40 °C, 75% relative humidity. At 0, 1 and 2 months the steroid content was determined with the HPLC / UV method as described above.

8.3.3 Liquid Dispersions

Liquid dispersions of the steroid in water or saturated lactose solution were prepared in sixfold in two concentrations: 0.01 and 0.1 mg · ml^{-1}. The saturated lactose solution was prepared by dissolving lactose 200M. The lactose solution was mixed for 24 hours before the dispersion was filtered. The clear solution was used for preparing the steroid fluid dispersions. Solubility of the steroid is 50 µg · ml^{-1} at room temperature. At 40 °C in all cases Org 30659 was fully dissolved. 20 ml of the liquids was stored in closed 50 ml glass vials at 40 °C. At 0, 2 and 10 months the samples were analyzed with the above described HPLC method. The closed glass vials were only opened for sampling purposes for less than 2 minutes. $Na_2HPO_4 \cdot 2H_2O$ (Sigma-Aldrich, Buchs, Germany, analytical grade) was added after two months storage to a concentration of 0.1M.

8.3.4 Influence of pH on stability in water

NaOH 0.1 M and HCl 0.1 M were used to obtain aqueous solutions with pH 3, 4, 5, 7 and 8. Org 30659 was dissolved in the solutions and stored at 40 °C for 3 months. At 0 and 3 months steroid content was determined. pH was determined with the Inolab pH/Cond Level 1 (WTW, Weilheim, Germany).

8.3.5 BET Surface analysis

BET surface analysis was performed on a Tristrat 3000 (V6.00A, Micromeritics, Norcross, USA). The analysis adsorptive was N_2.

8.3.6 Lactose-phosphate and phosphorus content determination

Lactose-phosphate content was performed at Food Science Australia by direct capillary electrophoresis by the method as developed by Lifran et al. (2006) (Beckman Coulter P/ACE^{TM} MDQ series, Fullerton, USA). Detection was carried out by UV detection at 280 nm. Samples were run in duplicate.

Inorganic phosphorus content was determined by Flow Injection analysis using a Lachat Instrument (Hach Company, Loveland, USA) and the spectrophotometric method based on the reduction of molybdenum blue by an acidic reagent at Food Science Australia (FIL-International Dairy Federation, 1990). Phosphorus content of the saturated lactose solutions of both lactose 200M and ultra-pure lactose was determined by ICP-atomic emission spectrometry based on the reduction of molybdenum blue (Perkin Elmer, Optima 4300 DV, emission wavelength 213.62, 214.91 and 178.22 nm). Determination was done in duplicate.

8.4 Results and Discussion

8.4.1 Powders and liquids

NIR analysis of the steroid lactose blends made using the Turbula revealed that the steroid forms agglomerates within the excipient powder. This compromised the uniform distribution of the steroid in powder and granule masses, thus affecting sampling for analysis negatively. Moreover, it makes predication of drug excipient interaction very unreliable. Mixing of the powders by hand with a mortar and pestle provided a homogenous mixture. The powder samples were stored at 40 °C, 75% RH and 5 °C, ambient RH. For the last condition ambient RH corresponds to a relative humidity of 80%. As shown in figure 8.2 the steroid degraded most in the mixtures of micronized lactose when stored at warm humid conditions. For clarity reasons only the mixtures where degradation was observed are shown. At 5 °C and ambient relative humidity no degradation was observed except for the micronized lactose mixture. The results show that particle size and temperature both influenced the degradation.

Org 30659 is vulnerable to oxidative degradation. Oxidative degradation itself may be enhanced by temperature, humidity and oxygen concentration (Mahajan et al., 2005). The amount of oxygen available for oxidation is considered as a constant factor under these experimental conditions. Based upon the known role of water in degradation kinetics the amount of adsorbed water was determined for both lactose 200M and the micronized lactose. It is known that the packing density or very low amounts of amorphous structures affect the adsorption of moisture significantly (Bronlund and Paterson, 2004). Literature data on moisture isotherms are highly inconsistent. This is ascribed to the various methods of free moisture content determinations. Recently, the influence of particle size and analysis temperature on lactose moisture isotherms has been investigated (Bronlund and Paterson, 2004).

Drugs in solid dosage forms decompose in most cases much more slowly than the same drugs in suspension or solution form. The reason for this is that molecules in solids are fairly well fixed in space, whereas in solution they are subject to random movement, so that the interaction possibilities are greater (Ahlneck and Zografi, 1990).

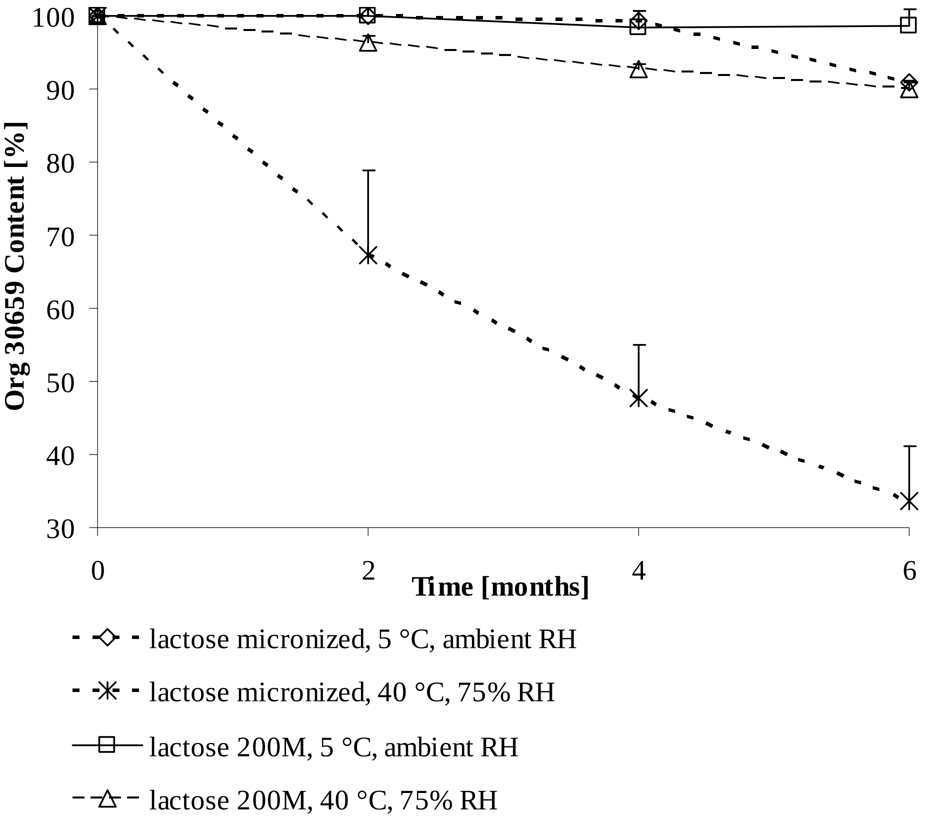

Figure 8.2 Degradation of the steroid mixed either with lactose 200M or micronized lactose mixtures (content 1 mg · g^{-1}). The powder mixtures are stored at 40 °C, 75% RH or 5 °C, ambient RH. Samples are presented including SD. At 5 °C, ambient humidity conditions, no degradation of Org 30659 was observed. In the absence of lactose at 40 °C, 75% RH Org 30659 did show a minimal degradation, smaller than the observed degradation in the presence of lactose (content 97.2% after 6 months storage at 40 °C, 75% RH).

As seen in the introduction, several degradation models have been proposed to explain observed degradation phenomena. Degradation is often ascribed to the presence of water on the surface of the solid particles. The exact role of water in the degradation reactions differs. As seen in fig. 8.3 the lactose particle size has minor influence on the water adsorption. The isotherms of lactose 200M are highly comparable to the data presented by Bronlund and Paterson (2004). The micronized lactose absorbs twice as much water as lactose 200M at the current constant storage conditions (75% RH).

It can be calculated that only a small fraction of the steroid (~ 0.01%) can be dissolved in this quantity of water. It is assumed that both in micronized lactose and lactose 200M the Org 30659 will be dissolved to the same concentration (up to saturation level) and that even when a limited amount of water is available for interaction this amount is higher for micronized lactose than for lactose 200M. Therefore it is not likely that the difference in these amount of dissolved Org 30659 (factor 2 between lactose 200M and micronized lactose) can account for the sevenfold higher degradation of the steroid in the presence of micronized lactose.

The degradation of the steroid in water and in saturated lactose solution was assessed. Although solubility of Org 30659 is only 0.050 $mg \cdot ml^{-1}$ at room temperature, the steroid was dissolved completely in water or lactose solution of 40°C. As seen in figure 8.4, degradation of the steroid in water is minimal. In contrast, in the presence of lactose the steroid degrades significantly.

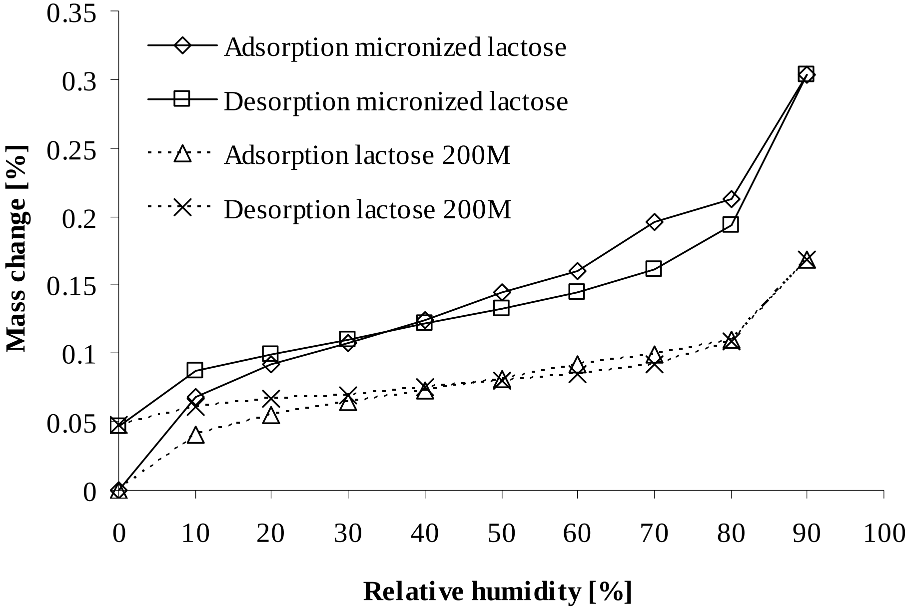

Figure 8.3 Moisture isotherms of lactose 200M and micronized lactose at 24.8 °C.

Obviously it is not the dissolved state, but the presence of lactose that enhances degradation. If the degradation in powders and in solution is compared several aspects have to be considered; the solubility of oxygen in water of 40 °C is only $2 \cdot 10^{-4}$ M, whereas air contains $4 \cdot 10^{-2}$ M O_2. In solution $3.2 \cdot 10^{-2}$ M Org 30659 (0.01 mg $\cdot$ ml^{-1} Org 30659) versus $2 \cdot 10^{-4}$ M molecular oxygen could be available for the oxidative degradation. In solution availability of oxygen may therefore limit degradation in both types of solutions.

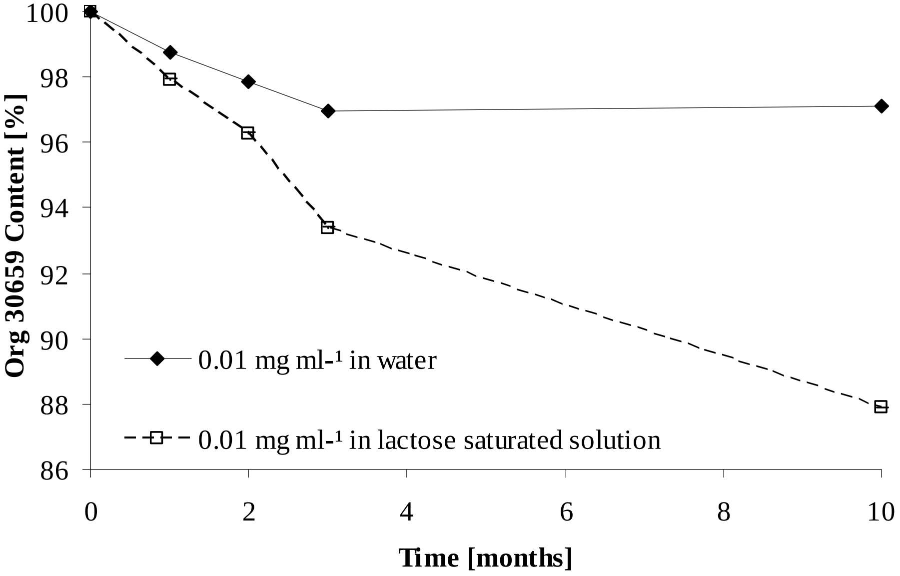

Figure 8.4 Degradation of Org 30659 in water or saturated lactose solution stored at 40 °C in closed vials. Saturated lactose solutions are prepared out of lactose 200M. Data points are shown including SD.

The Leeson-Mattock kinetic model assumes that degradation only occurs for the active compound in the dissolved state (Carstensen, 1990; Leeson and Mattocks, 1958). As seen in figure 8.2, degradation in powder is much higher than in solution. If it is assumed that the availability oxygen in solution and in the water layer adsorbed onto the powder surface is similar, the Leeson-Mattock kinetics cannot be applied to the current data set.

As it was observed that the degradation of the steroid is enhanced in solutions containing dissolved lactose, the cause of this catalyzing effect was studied. The pH of the solution could significantly enhance the degradation (figure 8.1) and therefore the pH of the lactose solution was considered. pH values of several types of lactose and $CaHPO_4$ in saturated solution were determined. $CaHPO_4$ was chosen as excipient with a known relatively high surface pH (Carstensen and Ertell, 1990). Saturated lactose solutions exhibited a pH value of 3.6 to 4 at room temperature, whereas the $CaHPO_4$ in solution had a pH value of 7.4. The low (surface) acidities for lactose have been reported earlier (Bernabe et al., 1995, Scheef et al., 1998). The low values can not be explained by the physico-chemical properties of lactose (pK value 13.6) but have been ascribed to the presence of lactose-phosphate (Visser, 1983).

The presence of the steroid did not influence the pH of the solution significantly. It should be noted that the buffer capacity of the solutions is very low. All lactoses used, with the exception of the micronized lactose, pass the test on the acidity as described in the Ph. Eur. (European Pharmacopeia 6.1). The direct influence H^+ and OH^- was determined by dissolving the steroid in water with pH 4, 5, 7 and 8 adjusted with either HCl or NaOH 0.1M. Remarkably no significant effect upon the degradation profile could be observed. Degradation varied between 0 and 4 percent without a correlation to increasing or decreasing pH values (data not shown). It is possible that this pH range is too limited. Upon storage pH of lactose solutions dropped to 3.1. This is lower than the lowest value in the range of solutions used.

Based upon the observation that pH did not clearly affect the degradation pattern the possibility that the phosphate group of lactose-phosphate could act as catalyzer was explored. Stability of the steroid was also tested in solution in the presence of lactose, phosphates and the combination of the two substances (figure 8.5). The steroid ($0.01\ mg \cdot ml^{-1}$) was dissolved in a saturated lactose solution (based upon lactose 200M). After two months $Na_2HPO_4 \cdot 2H_2O$ was added to one part of the lactose solutions. To verify the effect upon addition of phosphates the composition of the other part of the samples was not changed.

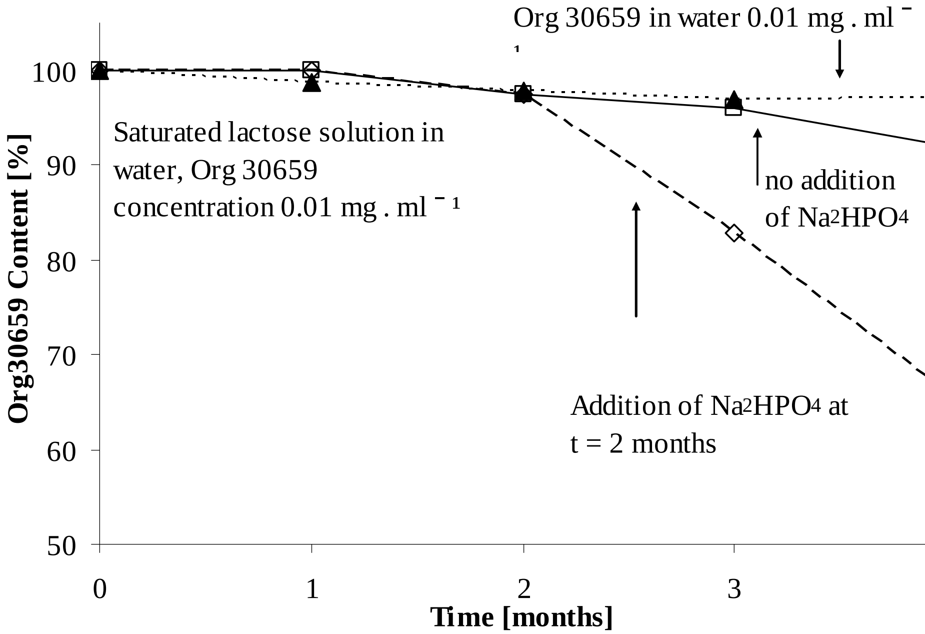

Figure 8.5 Degradation of Org 30659 in saturated lactose solution. After 2 months Na_2HPO_4 is added to half of the samples. All samples are continuously stored at 40 °C, 75% RH. As a reference the degradation of Org 30659 dissolved in water is shown.

In the presence of $CaHPO_4$ the degradation of the steroid is quantitatively highly comparable to the degradation in micronized lactose in the solid state. This result seems to indicate that the presence of phosphates may lead to this significant degradation. Phosphate groups coupled to monosaccharides are known to catalyze enolization in bio-molecules (Stein and Geiger, 1999, Thornalley et al., 1984). Based upon the results in the current study it was therefore assumed that phosphate could also act as a catalyzer for enolization under the observed conditions (see figure 8.1).

To test the influence of lactose-phosphate highly purified lactose was tested. In comparison to the saturated solution of lactose 200M (54 μg mL^{-1} PO_4^{3-}) or micronized lactose (44 μg mL^{-1} PO_4^{3-}), high purity lactose saturated solution contained only 17 μg mL^{-1} PO_4^{3-} . The pH of the saturated solution was 4.8. This indicates a diminished presence of lactose phosphate in the lactose. No degradation was observed during three months in the high purity lactose, whereas only limited degradation (1%) was observed from the fourth month at storage at 40°C and 75% RH. This degradation was smaller than the degradation seen in lactose 200M (8%) whereas the particle size is comparable after mixing with mortar and pestle; lactose 200M $d_{3,2}$ 10 μm ($d_{4,3}$ 49.7 μm), high purity lactose $d_{3,2}$ 13.1 μm ($d_{4,3}$ 51.6 μm). In lactose 200M up to 10% degradation occurred, after 6 months storage under the same conditions. The difference between the lactose samples was the lactose-phosphate content. In the high purity purer lactose less degradation is seen.

Known contaminants of lactose are riboflavin, potassium chloride and lactose-phosphate (Lifran et al., 2007). In literature riboflavin and potassium chloride are not known as reactive impurities or as enolization enhancers. Recently the presence of trace levels of hydroxyperoxides (Wasylaschuk et al., 2007) and aldehydes (Li et al., 2006) has been acknowledged. Hydroxyperoxides are detected at a level of < 10 nmol g^{-1} (≅ 3.6 ppm) in lactose. Hydroperoxides are known to enhance oxidative degradation (Wasylaschuk et al., 2007).

However the oxidative degradation of Org 30659 is initially dependent on the enolization of the molecule (figure 8.1). Hydroperoxides are not identified as enolization enhancers. Furthermore in lactose only formaldehyde and no other aliphatic aldehydes were detected at a low level of 0.1 μg g^{-1} (≅ 0.1 ppm) (Li et al., 2006). In dibasic calcium phosphate aldehydes were not detected, whereas it was shown in the current study that the degradation profile of Org 30659 was quantitatively highly comparable in calcium phosphate and micronized lactose. The influence of aldehydes on stability was therefore also excluded.

Pharmaceutical grade lactose is contaminated with 270 to 400 ppm lactose phosphate (Lifran et al., 2007). Lactose-phosphate is already present in milk

(Lifran et al., 2007, McGeown and Malpress, 1952, Visser, 1983) and is known as a natural crystallization growth retarder (Visser, 1983). Upon crystallization the lactose-phosphate is preferentially integrated in the crystals in layers. This monolayer can be covered again by lactose-phosphate-free lactose molecules (Lifran et al., 2007). Upon increasing crystallization time relatively more lactose-phosphate is included in the crystals (Lifran et al., 2007, Visser, 1983). It can be considered as a standard contaminant as even a large number of washes (Lifran et al., 2007) or re-crystallizations (Visser, 1983) cannot remove the lactose-phosphate.

Lactose-phosphate is labile under elevated temperature or acidic conditions. It is easily hydrolyzed to lactose and PO_4^{3-} (Lifran et al., 2006). Upon milling of the crystals the lactose–phosphate layers will be preferentially exposed at the surface. Subsequently less battered crystals with larger particle size will expose relatively less lactose-phosphate at the surface than the small micronized particles. The processing ‘history’ of particles therefore determines the amount of lactose-phosphate. In turn this determines the free organic phosphor content.

The lactose-phosphate content of lactose 200M and micronized lactose powders was determined. Lactose 200M appeared to contain a total of 476 ppm (SD 0.2) lactose-phosphate and 5.9 ppm (SD 0.2) free inorganic phosphorus content as determined in the completely dissolved lactose samples. Micronized lactose contains 423 ppm (SD 0.9) lactose-phosphate and 7.8 ppm (SD 0.2) free inorganic phosphorus content. These data reveal that the lactose samples as such do not differ significantly in lactose-phosphate content. This essentially means that exposure of a substance to the contaminant must be related to the way the compound is mixed with the lactose particles. In other words, it is important how the substance is in direct contact with the lactose particles and quantitatively speaking how large the specific surface area of the powder is. Therefore the surface area of the lactose samples was determined with gas adsorption measurements. The BET specific surface area of lactose 200M turned out to be 0.42 $m^2 \cdot g^{-1}$ while that of the micronized lactose was measured to be 1.45 $m^2 \cdot g^{-1}$. From the discussion so far it may be concluded that the lactose-phosphate contamination of the lactose is at least partially responsible for the increased degradation of the steroid. The degree in which this occurs may depend on the amount of water absorbed, but is certainly also determined by the way the steroid is exposed to the contaminant. Therefore the surface area of the lactose is an important parameter. Furthermore the presence of oxygen is a prerequisite for degradation (figure 8.1).

8.4.2 Granules

Inhomogeneity phenomena of high shear granulated powder mixtures have been reported extensively as explored in the introduction (chapter 2). As these have demonstrated to be dominated by particle size differences, it is interesting to check whether the current results are also visible within the granules. The granule heterogeneity is described as the result of the breakage and growth behavior within the high shear granulator (Van den Dries and Vromans, 2004, Vromans et al., 1999). The consequences of these mechanisms were that large granules are composed of small primary particles and small granules are composed of large primary particles (Van den Dries, 2004). Org 30659 is micronized. It is reasonable to assume that upon high shear granulation Org 30659 particles will behave similar to the smallest lactose particles and will be both preferentially located in the largest granule fractions.

Upon granulation Org 30659 was indeed not homogeneously distributed over the size fractions. On the contrary; the steroid was preferentially located in the largest granular fractions. The larger granules contained therefore a relatively high amount of the small steroid particles. This effect is shown in figure 8.6. The smaller granules contain less active material as they are formed of the larger primary lactose particles.

In the current study we have demonstrated that degradation appears to be determined by the surface area of the primary lactose particles. The direct consequence of this would be that the difference in primary particles composition for the largest and smallest granules would also affect the degradation patterns in these different granular size classes. Based upon the degradation pattern in the lactose 200M powder mixtures the expected degradation in the granules could be determined (see figure 8.2). It was assumed that in the original powder mixture the steroid is equally exposed to all size fractions of the particle size distribution.

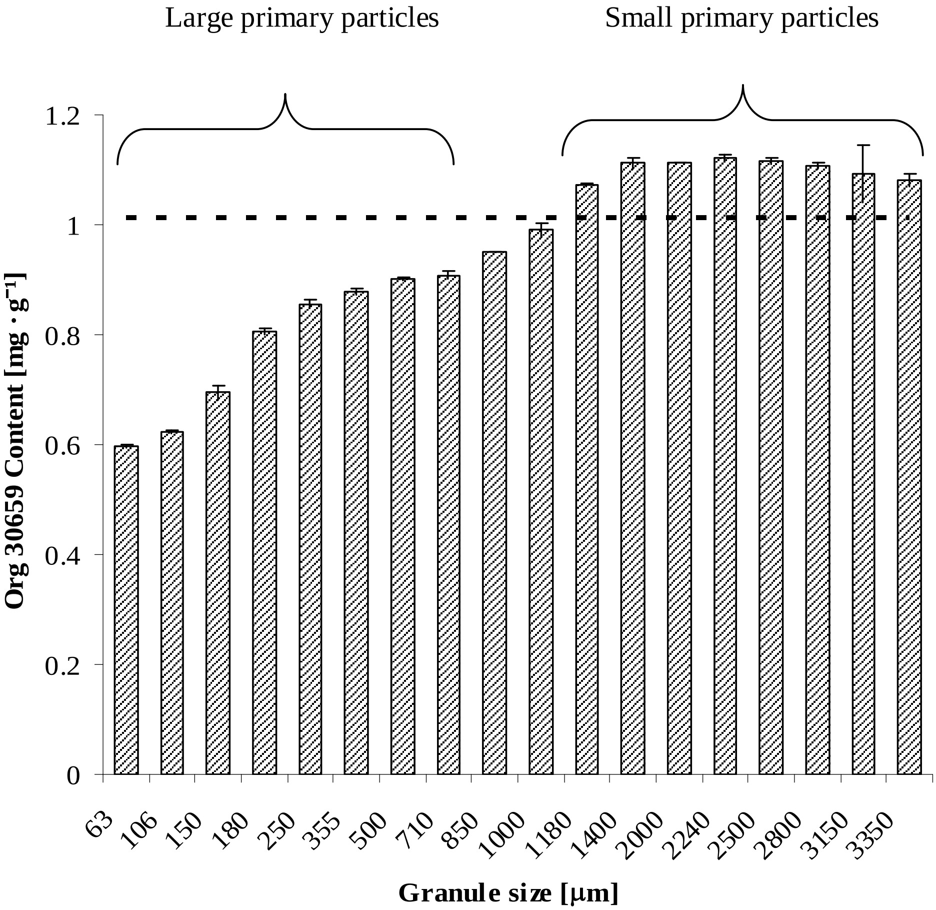

Figure 8.6 The distribution of Org 30659 over the different size fractions. The large granules on the right contain more active material than the small size fractions shown on the left. The average concentration (1 mg · g^{-1}) is shown as the dashed horizontal line. Data are presented including SD. Granules are made out of lactose 200M.

The observed degradation then represents the average degradation. Org 30659 mixed with lactose 200M powder showed an average degradation of 2% after 1 month of storage and 4% after 2 months of storage under the same conditions (40 °C, 75% RH). In figure 8.7 the degradation of the steroid in the different granule size classes is shown.

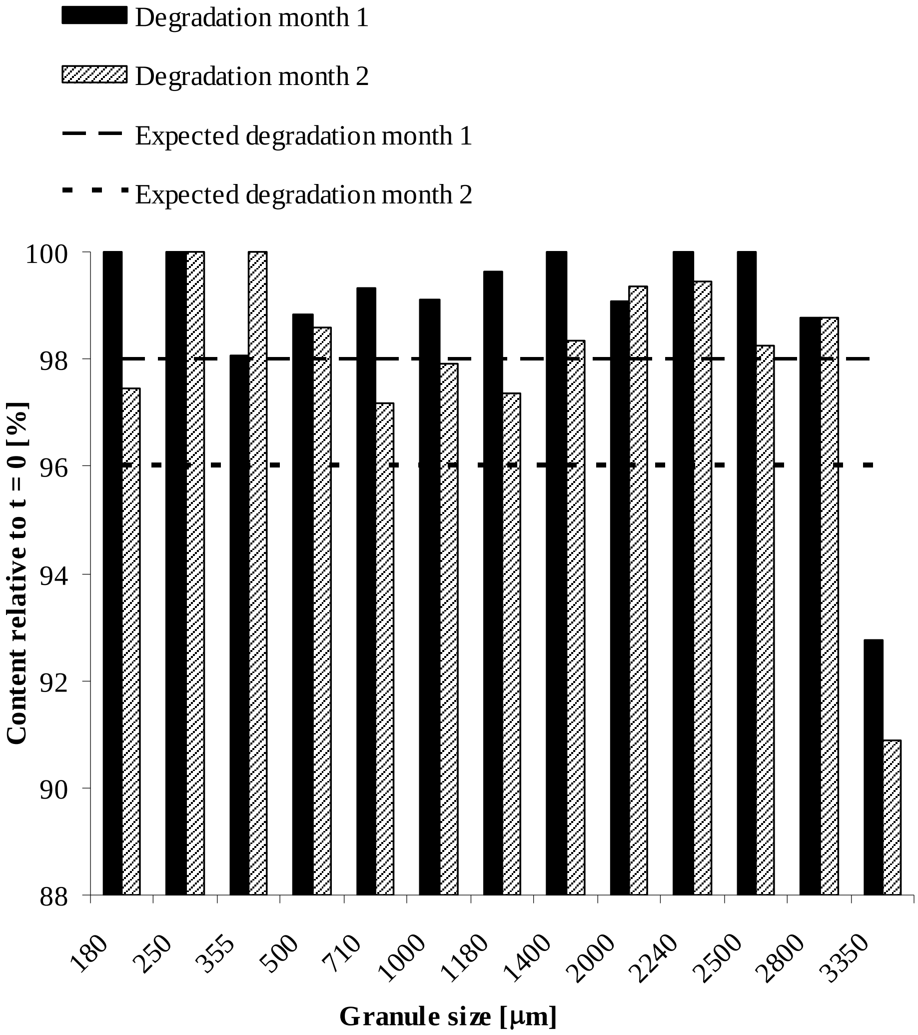

Figure 8.7 The degradation of Org 30659 in the different granular size classes. The horizontal lines represent the degradation observed in powder mixtures of Org 30659 and lactose 200M respectively after one month (98%) and two months (96%) of storage at 40 °C, 75% RH. Granules are made out of lactose 200M.

The data show that degradation in the larger granules (composed of the smallest primary lactose particles) was indeed significantly larger than the degradation in the small granules. Furthermore degradation in the larger granules was significantly higher than the degradation observed in the lactose 200M powder mixtures (figure 8.2). The difference in composition and presence of trace contaminants related to this composition is also reflected in the pH of the saturated solution of granules. A saturated solution of the largest granules has an average pH value of 4.1 (SD 0.06) whereas a saturated solution of the smallest granules exhibits a pH value of 4.5 (SD 0.28). Granule composition dictates the stability profile of the steroid granules.

The current knowledge on stability of Org 30659 related to available interaction surface can have implications for future technological development. Steroids are often used in the treatment of lung diseases. Fine lactose particles (5 – 8 μm) have been used as component of ternary formulations in dry powder inhalers (Jones and Price, 2006) used in the treatment of these lung diseases. The active substance is mixed with a coarse and very fine powder to optimize both flow properties of the powder and lung deposition. Although no definitive conclusion can be made by which mechanism fine excipient particles improve the performance of these formulations evidence of the positive influence of fine powder on the inhaled powder fraction is abundant (Jones and Price, 2006). It has been stated (Zeng et al., 2001) that the addition of fine particles may impair the stability of the formulation by the presence of amorphous structures in the fines. The data as presented here refute that hypothesis. At humidity levels above 75% amorphous structures re-crystallize fast. The continuous degradation during the test period stresses that even after re-crystallization significant degradation takes place. The presence of disordered structures alone can therefore not account for the observed stability problems. The detrimental effect of fine particle surfaces on the stability of the steroids as shown in this study emphasizes that further research is needed if steroids and fines are used in ternary mixtures for dry powder inhalers or granules.

8.5 Conclusion

The stability of Org 30659 is primarily dependent on the surface interactions with the contaminant lactose-phosphate. Larger particles with a smaller relative surface exhibit less interaction possibilities. Consequently degradation is smaller when compared to very fine particles. This particle size and surface dependent degradation profile has consequences for the stability in granules. As the composition of granules is highly heterogeneous and inter-granular composition is related to size; small granules consist of large primary particles whereas larger granules consist of small primary particles, consequently available interaction surface is also heterogeneous. The highest degree of degradation is observed in the largest granular size fraction. Granule composition determines the degradation profile of the steroid, directly related to available interaction surface.

8.6 Acknowledgements

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Abbreviations

RH	Relative humidity
SD	Standard Deviation

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9

Summary

General

In 2001 the FDA launched the Process Analytical Technology initiative as a response to the growing public and industrial awareness that there is a lack of process understanding required to have an optimal control of pharmaceutical manufacturing. The guidance stresses that control of critical process and product attributes is the basis of quality assurance. The current research project was initiated based upon the insight that critical process and product attributes can only be acknowledged upon a thorough process understanding.

This thesis can be seen as a follow up on the earlier research done on wet high shear granulation; key process parameters that are involved in the wet high shear granulation process, including granule breakage, preferential growth, binder liquid penetration and binder liquid dispersion were determined (van den Dries, 2004). Although the relevance of these critical process parameters towards the formation of inhomogeneous granules was reported extensively, the consequences of the described inhomogeneity phenomena in granules in further processing were not elaborated in that work (van den Dries, 2004). After the wet granulation process, a drying step is always necessary to obtain a basis for the final drug product. Therefore the drying step was the key process explored in this thesis.

The drying of granules could not be studied without a thorough knowledge on the critical parameters of granulation; granule breakage, nucleation mechanism upon binder addition, and granule growth by preferential layering. In ***chapter 2*** both process and product aspects regarding granulation and more specific heterogeneity phenomena in granules are elaborated. It is shown that although

the number of publications on granule heterogeneity is rather large the consequences of the granule heterogeneity for drying processes were not part of any of these previously published research projects.

On the other hand the drying step was not considered to be of any influence on the outcome of earlier performed studies. On the contrary, the characteristics of the dried granules were often used as output parameters for wet granulation studies, as the influence of drying on the results is considered to be negligible. Only the effects of the drying methods on drug migration and drug heterogeneity in the granule have been subject to research so far.

In this thesis, the properties of granules at the different stages of the drying process are used as result parameters, as drying is considered to influence the granule properties such as granule size and formation of fines.

A description is given on the often used tray drying technique, the fast and dynamic fluid bed drying process and the less often used micro-wave drying. Furthermore the terminology on attrition and breakage in the description of granulation and drying processes as used in this thesis is elaborated. Attrition is used in relation to the formation of fines, whereas breakage is defined as unwanted size reduction. The drying of wet granules often involves an unwanted and uncontrolled size reduction.

The aim of this thesis was to investigate the behavior of the granules throughout the drying process and the consequences of granule heterogeneity during and after the drying process.

This thesis provides the following scientific insights:

- Granular composition, size heterogeneity and water content are considered as the critical process and product quality parameters during drying. Granule characterization revealed that the change in granule size of (partially) dried granules follows a three phase system characterized by a growth, plateau and breakage phase. The growth phase is based upon available surface water enabling layering growth and coalescence upon consolidation. Below a minimum liquid bridge volume the presence of very small amounts of water or the formation of solid bridges cannot prevent abundant size reduction. In the plateau phase above minimum water content, behavior of granules can be described with Rumpfs' dynamic granule strength.

- In fluid bed drying the granular bed, the granule size, the inter-granular composition and water content are totally heterogeneous throughout the drying process. This heterogeneity differentiates the drying rate and extent of size increase and reduction of the different granule size classes in relation to the dynamic granule strength.

- Different drying procedures led to significantly different compositions of granules; varying amounts of non-crystalline and crystalline lactose components are found to be present. This composition difference has a direct influence on the functionality of the granules such as compactibility.

- In microwave drying the granular bed is remarkably dynamic. This is a consequence of the appearance of large vapor bubbles due to the vaporization of the water. As result large granules tend to rise to the top of the bed and small granules tend to move downwards. The fast dynamic microwave drying is a good alternative to the slow plate drying process. It is also a good alternative to the fast fluid bed drying process as less fines are formed in the absence of friction by external factors.

- The heterogeneous composition of high shear granulated lactose granules does not only determine the drying process and physical changes but also chemical changes. Granule composition therefore dictates both the critical physical and chemical stability and quality aspects of the granules.

- Near infrared spectroscopy (NIR) is shown to be a versatile method to further determine the critical process and product factors:

    1. In-line monitoring of water content of granules in fluid bed drying

    2. Monitoring of granule size and attrition effects

    3. Simultaneous detection of non-crystalline and crystalline lactose

- By NIR analysis, drying methods and granule behaviour during and after drying can be further explored.

Summary of chapters (experimental)

In ***chapter 3*** the changes in granule size and formation of fines for granules at several stages in the drying process are described. High shear granulated lactose granules with water as binding liquid were tray dried during variable periods. Subsequently the (partially) dried granules are exposed to agitation by the impellor and chopper in the granulator. The formation of fines and change in mean granule size as function of water content describe the attrition and breakage behavior of granules under drying conditions. Granule characterization reveal that the change in granule size of (partially) dried granules is dependent on water content and follows a three phase system characterized by a growth, plateau and breakage phase. The growth phase is based upon available surface water enabling layering growth and coalescence upon consolidation. Below a minimum liquid bridge volume the presence of very small amounts of water or the formation of solid bridges cannot prevent abundant size reduction. The derived yield stress of the granules is a function of velocity. From this it is concluded that in the plateau phase above minimum water content, stress behavior of granules can be described with Rumpfs' dynamic granule strength, whereas below minimum water content (breakage phase) granule strength is determined by the solid bridges. The extent and velocity of stress and water content of the granules during the process determine the size reduction phenomena. Water content and granule size are therefore considered as the critical process and product quality parameters during drying.

Based upon these observations an analysis method is developed to monitor these major factors. This analysis method to enlighten the granule behavior during fluid bed drying is described in ***chapter 4.*** NIR spectra collected during drying and water content of sampled granules are correlated by principal component analysis (PCA) and partial least squares regression (PLSR). The developed NIR granule water content model provides an effective real time method for monitoring of the fluid bed drying process as it discriminates between various stages in fluid-bed drying. The low SEC and SECV and high correlation coefficient confirm the reliability of the fit. The correlation is independent of process conditions. The water content can be continuously predicted with accuracy comparable to the reference method and the end-point of the drying process can be adequately acknowledged. The end-point can be determined faster than with current time-consuming off-line techniques.

NIR spectra of dried granules are correlated to median granule size in a second PCA and PLSR. The 4 PLS factors of the granule size model are related to primary particle size of lactose, median granule size exceeding primary particle size and amorphous content of granules. The small prediction errors enable size discrimination between fines and granules. The thoroughly explained NIR-granule size correlation provides an effective method to monitor both granule size and attrition effects. For product quality reasons, discrimination between drying stages and end-point monitoring is highly important. Together with the possibilities to determine median granule size and to distinguish fines this approach provides a tool to further explore the fluid bed drying process.

In ***chapter 5*** the fluid bed drying process is further analyzed with the available analysis methods including the newly developed NIR method as described in the previous chapter. It is shown that the granular bed, the granule size, the inter-granular composition and water content are completely heterogeneous throughout the dynamic drying process. This heterogeneity leads to a granule size dependent difference in behavior throughout the fluid bed drying process. Realizing that the strength of granules is determined by water content, which becomes apparent by the different stages (growth, plateau, breakage) in the drying process, it becomes clear why the size fractions do not show these changes simultaneously. Even at the end of the drying process most of the total available water is located in the largest granules. Small granules, exhibiting lower water levels early on in the drying process have then already lost their strength and are vulnerable to attrition or breakage. This may account for the fact that also at relatively high bulk water content fines are already formed. Smaller granules have intrinsically a lower saturation level and lower dynamic strength than larger granules.

The differences in water content and strength differentiate the drying rate and extent of size reduction of the different granule size classes. Therefore it is concluded that granular size heterogeneity, composition and water content determine the granule behavior upon fluid bed drying.

Based upon the known composition differences in granules and the subsequent consequences in drying as explored in ***chapter 5*** and the known differences in the formation of non-crystalline components as seen upon NIR size analysis in ***chapter 4***, in ***chapter 6*** the internal processes in the granule upon drying are further explored. The wet granulation step involves the addition of water. When lactose is granulated, the disaccharide partly dissolves in the aqueous binding liquid. Upon drying solidification of the dissolved lactose occurs. In ***chapter 6*** the physical state of lactose in granules and spray dried lactose powder in relation to the drying method and storage conditions is described. Subsequently the effect of the physical state on tablet strength is determined. A NIR regression model is developed to determine the presence of crystalline and disordered structures in powders and granules quantitatively. All the crystalline and amorphous lactose components can be detected simultaneously by one fast and simple measurement. It is observed that different drying methods led to significantly different compositions of granules. Upon drying at high temperatures more disordered structures are formed. Upon drying at room temperature minimal non-crystalline structures are formed and detected. Granules dried at room temperature have a very long drying time up to 7 days. In this time period crystallisation to the thermodynamically most stable state (α-lactose monohydrate) can occur. The presence of disordered and anomeric structures is related to the functionality of the granules such as tensile strength of compacts.

More disordered structures are found to be present in the larger than in the smaller granules. Storage of both the spray dried powder and granules at conditions above 75% RH affects strength of compacts negatively. Upon continuous storage at high humidity conditions re-crystallisation of the non-crystalline components and β-lactose to α-lactose monohydrate occurs. Therefore in product and process development there should be awareness of the consequences of drying method and storage conditions of the intermediate powders and granules on the physical quality of the product.

In addition to the plate drying process as studied in ***chapter 3*** and the fluid bed drying process as studied in ***chapter 4*** and ***5***, in ***chapter 7*** the drying behavior of granules in a development and industrial scale microwave drying is further explored. Furthermore the effect of applied vacuum during microwave drying is studied.

Plate drying is known as a static drying technique, whereas is it shown in ***chapter 4*** and **5** that fluid bed drying is a highly dynamic drying technique. In ***chapter 7*** it is shown that under vacuum and continuous microwave exposure the granule bed is unexpectedly dynamic. This is reflected in de-mixing of the granule bed during the drying process where large granules tend to rise to the top of the bed and small granules tend to move downwards. Motion in the granule bed may be induced by the appearance of vapor bubbles due to the vaporization of the water. Under reduced pressure the volume of the moisture vapor is larger than at atmospheric pressure. This increases the effect of the vapor bubbles. The phenomenon that large particles or agglomerates tend to rise through the bed upon motion is known as the Brazilian nut effect.

In development scale microwave drying very limited fines formation was observed, even at the end of the drying process. In contrast, in industrial scale microwave formation of fines towards the end of the drying procedure was abundant. As the strength of granules is dependent on the presence of water, limited formation of fines is observed in the early stages of the drying process. In the last stages of the drying process the limited amount of water is insufficient to retain the strength of the granule. Movement of the granules in the dynamic bed and movements of the mixer arm induce then significant formation of fines.

It is concluded that if this can be prevented, microwave drying is a good alternative to fluid bed drying or plate drying.

The last ***chapter 8*** differs from the previous chapters as it describes the chemical stability of a steroid in heterogeneous lactose granules. Based upon ***chapter 4*** and especially ***chapter 6*** physical changes are known to occur during drying processes. Furthermore, throughout the dynamic drying processes granules break and in addition fine particles are produced. The presence of fine particles increases the potential interaction surface of the drug and the excipients. In ***chapter 8*** it is shown that the presence of small lactose particles leads to a higher degree of chemical degradation. Lactose-phosphate, a known intrinsic contaminant in lactose, is demonstrated to enhance the degradation of the steroid. Stability improves in high purity lactose and deteriorates upon extra addition of phosphates. Since the exposure to the contaminant is a function of the surface area of the lactose, particle size differences of the excipient in powders and breakage of granules in drying processes have a clear consequence. In large granules, consisting of the finest lactose particles, most degradation is observed.

Most important is that the heterogeneous composition exhibited by high shear granulated lactose granules does not only determine the drying process (***chapter 3, 4, 5*** and ***7***) and physical state (***chapter 4*** and **6**) within the granule but also chemical stability.

Granule composition therefore dictates both the physical and chemical stability aspects of the granules.

References

Van den Dries K. 2004. Thesis: The paradox of high shear granulation; the formation of non-homogeneous granules. ISBN 90-393-3654-7.

10

Samenvatting

Algemeen

In 2001 werd door de Amerikaanse Food and Drug Administration (FDA) het Proces Analytische Technologie initiatief gestart. Dit initiatief was een reactie op de groeiende maatschappelijke en industriële bewustwording van het tekort aan wezenlijke proceskennis. Proceskennis is essentieel voor de optimale controle van farmaceutische productieprocessen. De bijbehorende richtlijn benadrukt dat proceskennis noodzakelijk is voor kwaliteitsborging. Het hier beschreven onderzoeksproject is geïnitieerd op basis van het inzicht dat kritische processtappen en productkenmerken alleen bepaald kunnen worden indien de productieprocessen volledig begrepen worden.

Dit proefschrift ligt in lijn met eerder onderzoek naar nat granuleren in hogesnelheidsmengers; van den Dries beschreef de kritische parameters in dit proces, zoals het breken van granules, preferentiële aangroei, penetratie van binder vloeistof in het poeder bed en verdeling van bindervloeistof over de poeder deeltjes (van den Dries, 2004).

Hoewel de relevantie van deze kritische parameters bij het vormen van inhomogene granules uitvoerig uiteen is gezet, is er geen aandacht geschonken aan de consequenties van inhomogeniteit voor de verdere processtappen (van den Dries, 2004). Na nat granuleren dient het verkregen granulaat altijd gedroogd te worden. Daarom staat in dit proefschrift het droogproces centraal.

Het drogen van granules kan niet bestudeerd worden zonder een gedegen kennis van de kritische parameters van granuleren; het breken van granules, de nucleatie-mechanismen na bindervloeistof toevoeging en het groeien van granules door preferentiële groei. In ***hoofdstuk 2*** worden zowel de proces- als productaspecten besproken die bepalend zijn voor het granuleerproces. Meer specifiek wordt ingegaan op de vorming van inhomogene granules. Hoewel het aantal publicaties over granule heterogeniteit tamelijk groot is, behandelt geen van deze publicaties de consequenties van de granule heterogeniteit voor droogprocessen. Veelal wordt er vanuit gegaan dat het droogproces zelf geen invloed heeft op de uitkomsten van het onderzoek. Het is zelfs zo dat de eigenschappen van gedroogde granules worden gebruikt in studies als resultaat van nat granuleren, waarbij de invloed van het drogen als verwaarloosbaar wordt beschouwd. Tot dusverre is alleen de invloed van drogen op de migratie van de actieve stof door de granule en de uiteindelijke verdeling van de actieve stof over de granule onderzocht.

In dit proefschrift worden granules gedurende het droogproces gevolgd om de effecten van drogen te beschrijven.

In ***hoofdstuk 2*** wordt een beschrijving gegeven van veelgebruikte droogtechnieken als plaatdrogen, het snelle en dynamische fluïde bed drogen en het veel minder vaak toegepaste microgolf drogen. De terminologie met betrekking tot attritie en breuk zoals gebruikt bij de beschrijving van granuleren en drogen wordt uiteengezet. Attritie wordt in dit proefschrift gebruikt om het ontstaan van fijne deeltjes te beschrijven. Breuk wordt gedefinieerd als ongewenste grootte-afname. Tijdens het drogen van granules wordt vaak een ongewenste en oncontroleerbare afname in granule grootte waargenomen.

Het doel van dit proefschrift is het gedrag van granules te onderzoeken gedurende het gehele droogproces en de consequenties van de granule inhomogeniteit vast te stellen tijdens en na het droogproces.

Dit proefschrift heeft de volgende inzichten verschaft:

- De samenstelling, grootte heterogeniteit en vochtgehalte van de granules worden beschouwd als kritische factoren voor proces- en productkwaliteit gedurende het drogen van granules. Door analyse van het granulaat is bepaald dat veranderingen in granule grootte van drogende granules verloopt volgens drie fasen. Onderscheiden wordt een groei-, plateau- en een breuk-fase. De groeifase wordt bepaald door de aanwezigheid van vocht aan het oppervlak van de granule. Bij consolidatie van twee granules kan door aanwezigheid van dit vocht, groei en hechting van de granules plaatsvinden. Wanneer de hoeveelheid vocht in de vloeistofbruggen onvoldoende is, kunnen noch de resterende hoeveelheden vocht noch de ontstane vaste stof bruggen voorkomen dat er breuk optreedt. In de tussenliggende plateaufase, wanneer de hoeveelheid water in de vloeistofbruggen boven het minimum is, kan het granule gedrag beschreven worden met behulp van de dynamische sterkte theorie van Rumpf. De dynamische of viskeuze granule sterkte volgens Rumpf beschrijft de sterkte van de granule onder dynamische omstandigheden. De dynamische kracht is, boven een minimaal saturatieniveau van de vloeistofbrug tussen de granule deeltjes, onafhankelijk van het absolute saturatieniveau. De dynamische sterkte is afhankelijk van de snelheid van de deeltjes ten opzichte van elkaar.

- In fluïde bed drogen zijn het granule bed, de granule grootte, de intergranulaire samenstelling en het vochtgehalte volledig heterogeen gedurende het gehele droogproces. De heterogeniteit differentieert de droogsnelheid en de verandering van granule grootte over de verschillende granule fracties.

- Verschillende typen droogprocessen leiden tot fysische verschillen in granule samenstelling; de aanwezigheid van wisselende hoeveelheden niet-kristallijn en kristallijnen lactose componenten kan worden aangetoond na drogen.

Verschillen in fysische samenstelling kunnen de functionaliteit van het granulaat beïnvloeden: Als voorbeeld wordt de compactibiliteit gegeven.

- Opmerkelijk is dat het granule bed tijdens microgolf drogen niet statisch, maar opmerkelijk dynamisch is. Dit is het gevolg van het ontstaan van grote dampbellen door verdamping van vocht. Door de beweging in het bed bewegen grote granules naar boven en kleine granules naar beneden. Het snelle microgolf drogen is een goed alternatief voor het langzame plaatdroogproces. Het kan ook een goed alternatief zijn voor het fluïde bed droog proces. Er worden minder fijne deeltjes gevormd, mits de mate van frictie met bijvoorbeeld de mengarm in de droger voorkomen wordt.

- De heterogene samenstelling van granules beïnvloedt niet alleen het droogproces en de fysische toestand, maar ook de chemische stabiliteit. De granule samenstelling dicteert zowel de fysische als de chemische stabiliteitsaspecten van de granules.

- Nabij infrarood spectroscopie (NIR) is een breed inzetbare analyse methode om kritische product- en procesaspecten te bepalen:

    1. Continue controle van het vochtgehalte van granules tijdens fluïde bed drogen

    2. Bepaling van granule grootte en attritie effecten

    3. Simultane detectie van niet-kristallijn en kristallijn lactose

Samenvatting van de hoofdstukken (experimenteel)

In ***hoofdstuk 3*** worden de veranderingen in granule grootte en de vorming van fijne deeltjes in het granulaat gedurende verschillende momenten in het droogproces beschreven. Granules, geproduceerd in een hogesnelheidsmenger met water als bindvloeistof, worden gedroogd op een plaat. Vervolgens worden de (gedeeltelijk) gedroogde granules teruggeplaatst in de hogesnelheidsmenger en blootgesteld aan de bewegende mengarm en de chopper. Het breukgedrag en attritiegedrag van de granules op verschillende momenten in het droogproces wordt vervolgens beschreven als functie van het vochtgehalte van het bulkgranulaat. Uit bestudering van het granulaat blijkt dat de grootteverandering van (gedeeltelijk) gedroogde granules afhankelijk is van het vochtgehalte van de granule. De grootteverandering is te onderscheiden in drie fasen, namelijk de groei-, plateau- en breuk-fase. De groeifase wordt bepaald door de aanwezigheid van vocht aan het oppervlak van de granule. Bij consolidatie van twee granules kan door aanwezigheid van dit vocht groei en hechting van de granules plaatsvinden. Wanneer de hoeveelheid vocht in de vloeistofbruggen onvoldoende is, kan noch de resterende hoeveelheid vocht noch de ontstane vaste stof bruggen, voorkomen dat er breuk optreedt. De sterkte van het granulaat, is een functie van snelheid. Daarom wordt geconcludeerd dat in de plateaufase, het granule gedrag beschreven kan worden met behulp van de dynamische sterkte theorie van Rumpf. Onder de minimale benodigde hoeveelheid water wordt de sterkte van het granulaat bepaald door vaste stof bruggen (breuk fase). De mate en snelheid van stress en het vochtgehalte van de granules gedurende het gehele droogproces bepalen de totale grootteveranderingen. Vochtgehalte en granule grootte worden derhalve beschouwd als de kritische proces en productkwaliteit bepalende factoren gedurende drogen.

Om het vochtgehalte en de granule grootte tijdens drogen te kunnen volgen werd een analyse methode ontwikkeld. De ontwikkeling van deze analyse methode om het granule gedrag tijdens fluïde bed drogen op te helderen wordt beschreven in ***hoofdstuk 4.*** Tijdens het droogproces worden NIR spectra opgenomen. Deze worden gecorreleerd aan het vochtgehalte van simultaan bemonsterde granules door middel van principale componenten analyse (PCA) en partial least square (PLS) regressie. Het ontwikkelde NIR model voor bepaling van vocht gehalte is effectief in het volgen van het fluïde bed droogproces omdat het onderscheid maakt tussen de verscheidene fases in het droogproces. De kleine SEC en SECV en de hoge correlatie coëfficiënt bevestigen de betrouwbaarheid van de correlatie. Deze correlatie is onafhankelijk van proces omstandigheden. Het vochtgehalte van de granules wordt continue bepaald met een nauwkeurigheid vergelijkbaar met de nauwkeurigheid van de referentiemethode. Het eindpunt van het droogproces kan eenduidig en sneller vastgesteld worden dan met de huidige tijdrovende off-line analyse technieken.

In een tweede PCA en PLS analyse zijn de NIR spectra van gedroogde granules gecorreleerd met de mediane granule grootte. De vier factoren van het resulterende model kunnen toegeschreven worden aan de mediane granule grootte, primaire deeltjesgrootte van lactose in relatie tot de mediane granule grootte en de aanwezigheid van amorfe componenten in de lactose granule. De nauwkeurigheid van het model maakt onderscheid tussen fijne deeltjes en granules mogelijk. Daarnaast maakt het model het mogelijk attritie en grootte effecten te volgen. Vanwege productkwaliteitseisen is het van groot belang dat onderscheid gemaakt kan worden tussen de verschillende fasen van het droogproces en het eindpunt. Door NIR analyse is het mogelijk vochtgehalte, mediane granule grootte en de vorming van fijne deeltjes te bepalen. Deze NIR benadering verschaft daarom de mogelijkheid het droogproces nog diepgaander te onderzoeken.

In ***hoofdstuk 5*** wordt de nieuw ontwikkelde NIR methode toegepast in de verdere analyse van het fluïde bed droogproces. Aangetoond wordt dat het granule bed, de granule grootte, de intergranulaire samenstelling en het vochtgehalte volledig heterogeen zijn gedurende het dynamische droogproces. Deze heterogeniteit leidt ertoe dat het droogproces verschillend verloopt voor de verschillende granule-fracties. Aangezien de granule sterkte bepaald wordt door het vochtgehalte, kan verklaard worden waarom de verschillende grootte fracties niet gelijktijdig hetzelfde gedrag vertonen. Zelfs tot aan het eind van het droogproces is het overgrote deel van het water gelokaliseerd in de grootste granules. De kleinste granules hebben gedurende het totale droogproces een lager vochtgehalte. Kleine granules verliezen gedurende het droogproces veel eerder bindingssterkte en zijn daardoor gevoelig voor attritie en breuk. Zelfs wanneer het bulk vocht gehalte dus relatief hoog is kunnen er al fijne deeltjes gevormd worden. Kleine granules hebben intrinsiek een lager verzadigingsniveau en kleinere dynamische sterkte dan grotere granules.

Het verschil in vochtgehalte en sterkte tussen de granule fracties differentieert de droogsnelheid en de mate van grootteveranderingen. Daarom bepalen granule grootte heterogeniteit, samenstelling en vochtgehalte het granule gedrag gedurende fluïde bed drogen.

Gebaseerd op de bekende verschillen in samenstelling tussen granules en de gevolgen voor het droogproces zoals gesteld in ***hoofdstuk 5*** en de verschillen in de vorming van niet-kristallijnen componenten zoals bepaald met NIR analyse in ***hoofdstuk 4***, worden in ***hoofdstuk 6*** de interne processen in de granule tijdens drogen verder onderzocht. Tijdens nat granuleren wordt water, de bindingsvloeistof, toegevoegd aan het poeder. Wanneer lactose wordt gegranuleerd, zal deze disaccharide deels oplossen in het water. Bij drogen zal het opgeloste lactose weer precipiteren. In ***hoofdstuk 6*** wordt de fysische staat van lactose in granules en gesproeidroogd poeder, in relatie tot de droogmethode en opslagcondities beschreven. Ook wordt het effect van de fysische toestand van de lactose op de tablet sterkte onderzocht. Een nieuw NIR regressie model wordt ontwikkeld om kwantitatief de aanwezigheid van kristallijne en niet-kristallijne structuren vast te stellen. Met behulp van de NIR methode kan gelijktijdig door een snelle en eenvoudige meting de aanwezigheid van kristallijne en amorfe lactose in het granulaat bepaald worden. Vastgesteld wordt dat verschillende droogmethoden tot vorming van verschillende fysische toestanden leidt. Wanneer bij hoge temperaturen gedroogd wordt, precipiteert de lactose als een minder geordende structuur. . Wanneer bij kamertemperatuur in de productieruimte gedroogd wordt vindt een hoge mate van kristallisatie plaats. De droogtijd is dan zeer lang. Deze kan tot 7 dagen voortduren. Gedurende deze periode kan kristallisatie plaatsvinden tot de meest stabiele lactose vorm (α lactose monohydraat). De aanwezigheid van amorfe en anomere structuren heeft consequenties voor de functionaliteit van de granules zoals sterkte na compactie. Grote granules bevatten meer ongestructureerd materiaal dan kleine granules. Opslag van granules bij een relatieve vochtigheid boven de 75% beïnvloedt de sterkte van de compacten negatief. Bij continue opslag bij hoge relatieve luchtvochtigheid kan rekristallisatie van amorfe componenten en β-lactose tot α lactose monohydraat optreden.

Tijdens ontwikkeling van producten en processen is het daarom van belang bewust te zijn van de consequenties van de droogmethode en de opslagcondities van poeders en granules op de fysische kwaliteit van het eindproduct.

Naast het plaatdrogen zoals beschreven in ***hoofdstuk 3*** en het fluïde bed drogen zoals beschreven in ***hoofdstuk 4*** en ***5***, wordt in ***hoofdstuk 7*** het drooggedrag van granules in microgolven beschreven. Ook wordt het effect van vacuüm tijdens microgolf drogen bepaald. Plaatdrogen wordt beschouwd als een statische droogtechniek, terwijl in ***hoofdstuk 4*** en ***5*** wordt aangetoond dat fluïde bed drogen een zeer dynamische techniek is. In ***hoofdstuk 7*** wordt aangetoond dat het granule bed tijdens microgolf drogen onder vacuüm opmerkelijk dynamisch is. Dit is vooral zichtbaar door de verplaatsing van grote granules naar de bovenkant van het granule bed en de verplaatsing van kleine granules naar de onderkant van het granule bed tijdens het droogproces. Dit is het gevolg van het ontstaan van grote dampbellen door verdamping van water. Onder vacuüm is het volume van deze bubbels groter dan bij atmosferische druk. Vacuüm tijdens microgolf drogen vergroot dus het effect van de dampbubbels. Het fenomeen dat grote delen of agglomeraten omhoog komen in een bewegend bed staat ook wel bekend als het Braziliaanse noten effect.

In een ontwikkelingsopstelling worden zeer weinig fijne deeltjes gevormd. Dit in tegenstelling tot de industriële apparatuur waarbij naarmate het droogproces vordert zeer veel fijne deeltjes gevormd worden. Aangezien de sterkte van de granules direct gerelateerd is aan het vochtgehalte worden bij aanvang van het droogproces zeer weinig fijne deeltjes gevormd. Naarmate het droogproces vordert is er echter steeds minder water aanwezig om sterkte van de deeltjes te behouden. Aan het eind van het droogproces is de beweging van het dynamisch granule bed of een beweging van de mengarm voldoende om vorming van fijne deeltjes te induceren. Wanneer deze frictie door de mengarm voorkomen zou kunnen worden is microgolf drogen een goed alternatief voor fluïde bed drogen en plaatdrogen.

Het laatste ***hoofdstuk 8*** verschilt van de voorgaande hoofdstukken omdat dit hoofdstuk de chemische stabiliteit van een steroïd in inhomogene lactose granules beschrijft. Zoals is gebleken uit ***hoofdstuk 4*** en ***6*** kunnen er fysische veranderingen optreden tijdens droogprocessen. Daarnaast is bekend dat gedurende het droogproces de granules breken en dat daarnaast fijne deeltjes gevormd worden. De aanwezigheid van fijne en kleinere deeltjes vergroot het potentiële interactieoppervlak van de steroïd en de lactose. In ***hoofdstuk 8*** wordt aangetoond dat de aanwezigheid van kleine lactose deeltjes leidt tot een vergrote chemische degradatie. Lactosefosfaat, een bekende intrinsieke vervuiling in lactose, versnelt de degradatie van het steroïd. De stabiliteit verbetert indien zuivere lactose gebruikt wordt en verslechtert wanneer fosfaten worden toegevoegd. De blootstelling van het steroïd aan het lactosefosfaat is een functie van het beschikbare interactieoppervlak. Daardoor heeft de granule samenstelling en hebben verschillen in deeltjesgrootten van het lactose granulaat duidelijke consequenties. In grote granules die kleine primaire lactose deeltjes bevatten vindt de hoogste degradatie plaats.

De heterogene samenstelling van lactose granules, geproduceerd in een hogesnelheidsmenger, is daarom niet alleen bepalend voor het droogproces (***hoofdstuk 3, 4, 5,*** en ***7***) en de fysische veranderingen in de granule (***hoofdstuk 4*** en ***6***), maar heeft ook gevolgen ten aanzien van de chemische stabiliteit.

Referenties

Van den Dries, K. 2004. Thesis: The paradox of high shear granulation; the formation of non-homogeneous granules. ISBN 90-393-3654-7.

Dankwoord

Het afronden van een proefschrift biedt een moment van reflectie. Als de titel, waarin de essentie van vier jaar onderzoek weergegeven moet worden, bepaald is, dan is echt de finish gehaald. Een mijlpaal die zonder de steun van vele personen echt niet zo soepel bereikt was. Een proefschrift schrijven is veelal een solitaire bezigheid. Maar voor de ondersteuning door velen voor het vormen en uitvoeren van mijn ideeën, redeneringen, motivaties en conclusies wil ik graag een dankwoord uitspreken.

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Curriculum Vitae

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