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Granule breakage during drying processes

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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 impeller 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.

Keywords: Drying; Granule; Breakage; Attrition; Water

1. 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, 1988) or in-homogeneity (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 and Yliruusu, 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 current paper, the term breakage is defined as unwanted size reduction. Attrition is used to describe the formation of fine dust or fines.

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Nomenclature

A	constant in Heckel equation
$d_{3,2}$	surface mean diameter of the primary particles (μm)
H	mass ratio of liquid to solid
K	slope of the Heckel plot (see Heckel Eqs. (5) and (6))
p	compaction pressure (MPa)
v_i	tip velocity of either the impeller or the chopper (m/s)
v_p	relative velocity of the moving particles (m/s)

Greek letters

γ	surface tension (N/m)
ε	intra-granular porosity
μ	viscosity (Pa s)
ρ_g	granular density (kg/m^3)
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)

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 interparticle 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.

2. Materials and methods

2.1. Granulator experiments

Lactose 200M (1.4 kg, obtained from DMV Veghel, The Netherlands) was granulated in a high shear mixer (Gral 10, Colette) for 15 min (impeller velocity 250 rpm, chopper velocity 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 s (Brookfield Rheometer). The surface tension of the water was 0.073 N m^{-1} (Tensiometer Krüss GMBH K10). After granulation the granules were dried on trays during variable periods up to 240 min in an airflow cabinet (Marius) at 40 °C. After (partial) drying the granules were transferred back into the granulator and exposed to agitation of the impeller and the chopper (250 and 3000 or 50 and 1500 rpm, respectively, for impeller 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 impeller alone.

2.2. 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/s. 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).

2.3. Granule characterization

The water content of the granules was determined with an automated Karl Fischer titration (Metrohm KF coulometer 756 K 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.

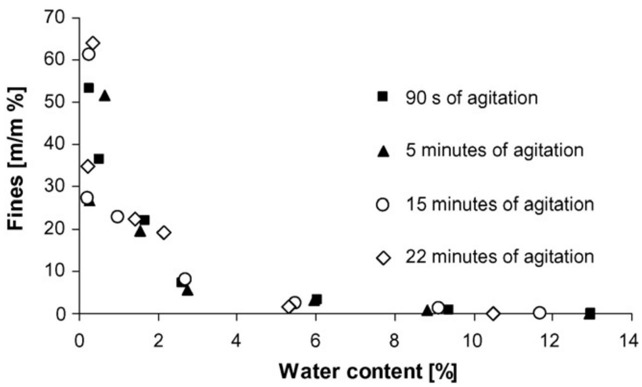

Fig. 1. Formation of fines in the total granular mass as function of water content and in relation to the duration of agitation time in the high shear mixer.

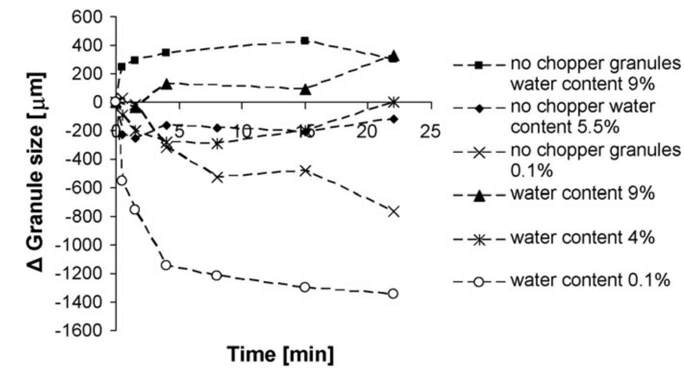

Fig. 2. Influence of chopper on nett granule size decreasing breakage and nett granule size increasing growth phenomena of binderless granules (impeller velocity 250 rpm (∼3 m/s), chopper velocity 3000 rpm (∼11 m/s) or absent).

3. Results and discussion

The formation of fines is often used as a parameter for attrition and abrasion. In this report, fines are defined as particles <212 μm. Fig. 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. Fig. 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 Figs. 2 and 3 where at higher water content a nett size increase is perceived. To determine the impact of the chopper the (partially) dried granules were exposed to the impeller in absence of the chopper. From Fig. 2 it is clear that the chopper has a significant effect on the outcome.

Fig. 3 plots the changes in granule size (*d*10, *d*50, *d*90) as function of the water content for granules exposed to 22 min 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 Fig. 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

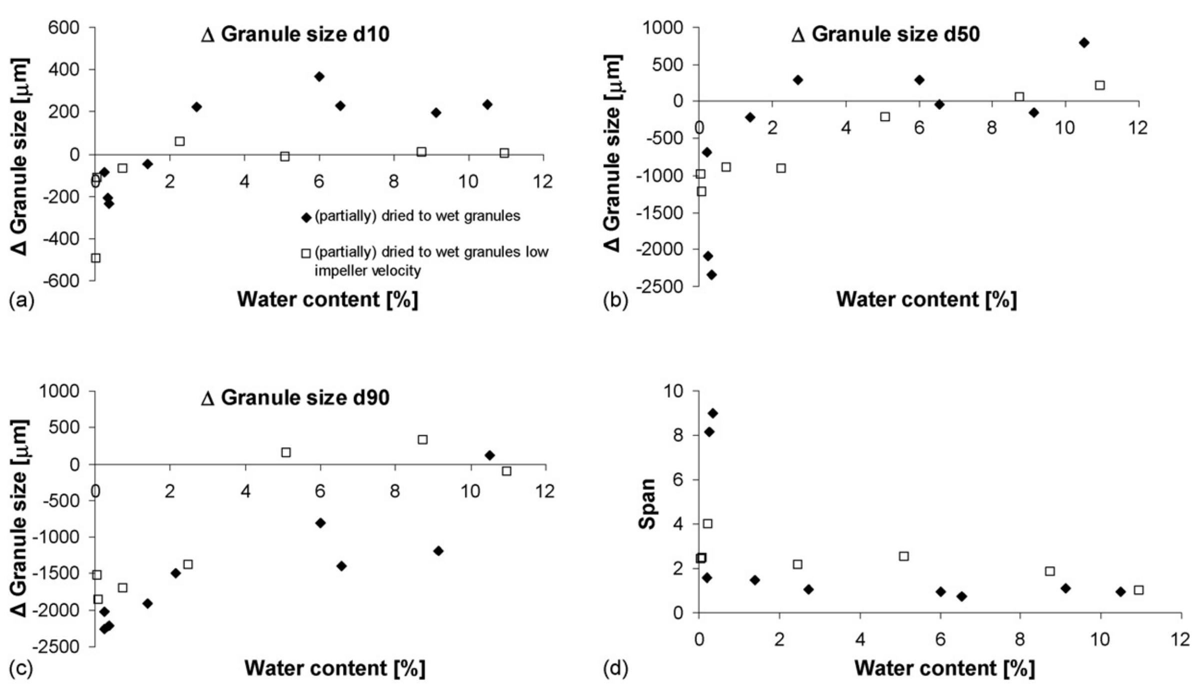

Fig. 3. (a–d) Influence of water content on granule size and span of the distribution after 22 min of agitation by impeller and chopper. Granules exposed to agitation with low impeller (50 rpm, ∼0.6 m/s) and chopper velocity (1500 pm, ∼5.5 m/s) and high impeller (250 rpm, ∼3 m/s) and chopper velocity (3000 rpm, ∼11 m/s) are shown. (a) *d*10; (b) *d*50; (c) *d*90; (d) Span.

large agglomerations. These large agglomerations can apparently not resist the high impeller velocity whereas they can resist the lower impeller 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. At low moisture levels there is a considerable amount of attrition apparent. Above a water content of approximately 1–2% (see Fig. 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, porosity and starting material characteristics as $d_{3,2}$ and γ. This is expressed as

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

where σ_c is static granule strength, γ 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:

$$S = \frac{H(1-\varepsilon)}{\varepsilon}\rho_s \quad (2)$$

where H is the mass ratio of liquid to solid, ε 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 impeller is expressed as (Vromans et al., 1999; Van den Dries and Vromans, 2002):

$$\sigma_{impact} = \frac{2}{3}\rho_g v_i^2 \quad (3)$$

where ρ_g is the granular density and v_i is the tip velocity of either the impeller or the chopper.

The impact stress of the chopper and the impeller were calculated and are shown in Fig. 4a as horizontal lines and in Fig. 4b as vertical lines. Obviously, the impact stress from the chopper is higher than the impact stress from the impeller, 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. In Fig. 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.

Fig. 4b plots the change in mean granule size as seen in Figs. 2 and 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

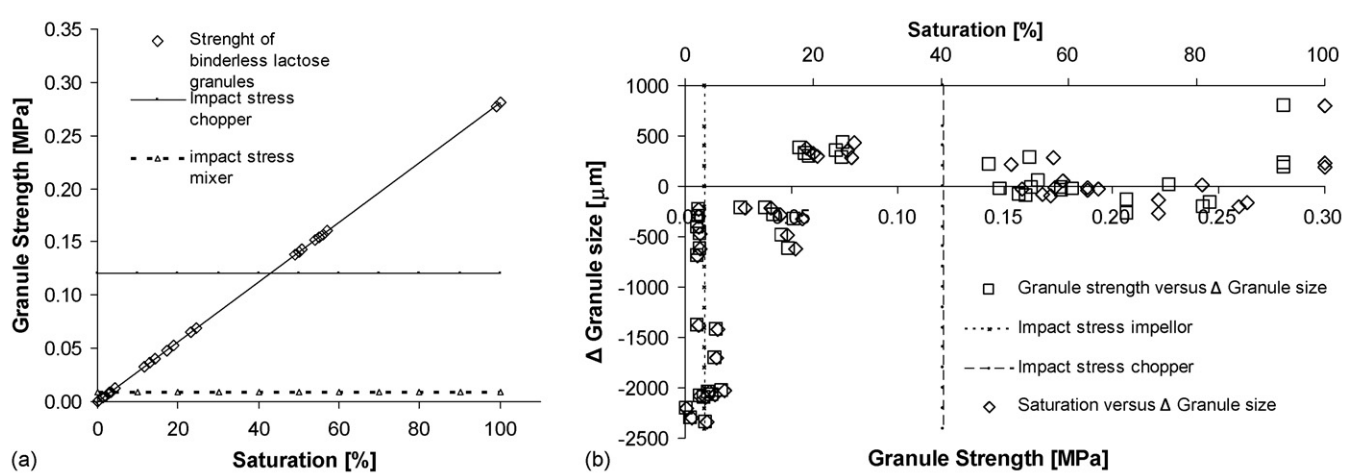

Fig. 4. (a) Static granule strength as function of saturation of granules without binder. The impact stress of the chopper and the impeller was calculated. Impeller velocity 250 rpm (v_i), ~3 m/s; chopper velocity 3000 rpm (v_i), ~11 m/s. Values used for calculations: $d_{3,2}$, 10 μm; ρ_g, 1500 kg/m^3; γ, 0.073 N/m; ε, 0.135. (b) Calculated static granule strength and saturation level vs. the change in mean granule size of (partially) dried binderless granules ($\Delta d50$); impeller velocity 250 rpm (v_i), ~3 m/s; chopper velocity 3000 rpm (v_i), ~11 m/s; ρ_s, 1500 kg/m^3.

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 (Fig. 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 impeller velocities and presence or absence of the chopper. The toric velocity is smaller than the impeller 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 (Fig. 2).

The Rumpf Eq. (1) cannot sufficiently clarify the observed dependency of the granule strength on water content and chopper/impeller velocities although it is observed that saturation level of the granules does influence the behavior of the drying granules under stress. Basically, the Rumpf Eq. (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 may describe the findings more accurately. The tensile strength of a granule under dynamic conditions is derived by the following equation:

$$\sigma_v = \frac{9}{8}\frac{(1-\varepsilon)^2}{\varepsilon^2}\frac{9\pi\mu v_p}{16 d_{3,2}} \quad (4)$$

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, 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 Eq. (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 Eq. (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 Figs. 3 and 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.

$$-\ln(\varepsilon) = Kp + A \quad (5)$$

where ε is porosity, p 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:

$$\sigma_y \cong \frac{1}{3K} \quad (6)$$

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 Fig. 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

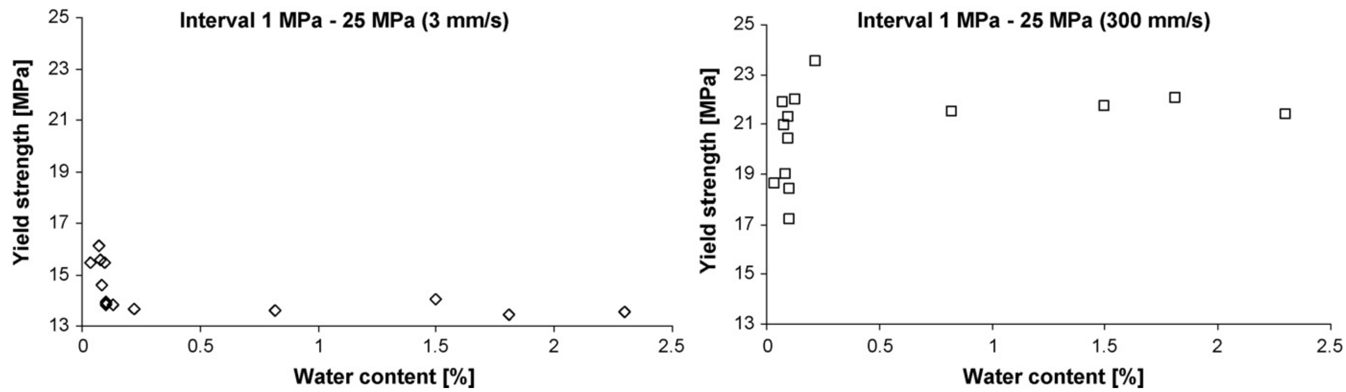

Fig. 5. (a and b) Yield strength as function of water content in particle movement and rearrangement interval: (a) compaction velocity 3 mm/s; (b) compaction velocity 300 mm/s.

velocities the yield strength for the dried lactose granules approaches 17 MPa. 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, 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 Fig. 5 suggests a dynamic relationship (Eq. (4)) when densification by particle movement and rearrangement occurs. In Fig. 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 Fig. 3 for the (partially) dried granules exposed to agitation by the impeller and the chopper. Here the impeller and chopper velocities determine the changes in granule size and therefore the strength of the granules. At low impeller 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 Fig. 3 can be correlated to the developing solid bridges, as explained above that are not strong enough to withstand the exerted agitation of the impeller 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 impeller and chopper velocities (Figs. 2 and 3). The formation of fines has the same dependency on water content as the change in $d10$ (Figs. 1 and 3a). From Fig. 1 it cannot be concluded that fines are not formed at higher water contents. Fig. 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).

4. 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. Rumpf's 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.

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