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The influence of PVP incorporation on moisture-induced surface crystallization of amorphous spray-dried lactose particles

Denny Mahlin[a,*,1], Jonas Berggren[a,2], Ulrik Gelius[b], Sven Engström[c], Göran Alderborn[a]

[a] Department of Pharmacy, Uppsala University, Box 580, SE-751 23 Uppsala, Sweden
[b] Department of Physics, Uppsala University, Box 530, SE-751 21 Uppsala, Sweden
[c] Department of Chemical and Biological Engineering, Chalmers University of Technology, SE-412 96 Göteborg, Sweden

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Abstract

We have recently shown that atomic force microscopy (AFM) may be an appropriate method for characterisation of the re-crystallization of amorphous particles. In this study, spray-dried composite particles consisting of lactose and polyvinyl pyrrolidon (PVP) were characterised by AFM and electron spectroscopy for chemical analysis (ESCA), and their response on increasing the relative humidity (RH) was investigated. The PVP content in the particles used was 0, 5 or 25 wt.% of either PVP K17 or PVP K90. All composite particles were found to be enriched with PVP at the surface. The incorporation of PVP in the particles influenced the way the particles responded to an increase in RH. The specific RH interval in which the surface of the particles smoothened and the RH where crystallization could be detected, increased with an increase in the amount and molecular weight of the PVP in the particles. The crystallization kinetics of single particles was analysed with AFM and by utilising the JMAK equation. The rate constant for this transformation increased in an exponential manner with increasing RH. Furthermore, above the RH needed for the crystallization to occur, the exponential increase in the crystallization rate was larger for particles with higher polymer content which indicates that the stabilising effect decreases as the water content in the particles becomes higher. In this study we report a method for determination of crystallization kinetics on single composite particles, which is valuable when evaluating the effect of stabilisers in amorphous powders.

Keywords: Lactose; Atomic force microscopy; Crystallization; Rate constant; Spray-dried particles; Electron spectroscopy for chemical analysis

1. Introduction

Making a component of a pharmaceutical preparation amorphous is a possible formulation approach for improving the bioavailability of drugs (Hüttenrauch, 1978). For example, an amorphous excipient, usually a sugar, can serve as a protective carrier for sensitive proteins and peptides (Pikal et al., 1991; Lai and Topp, 1999). Owing to the intrinsic physical instability of the amorphous state, environmental and formulation factors that control transformations in amorphous phases are discussed in the literature (Zhang et al., 2004). Many publications show that polymers which can be mixed with amorphous components so that a composite material is formed are potential inhibitors of re-crystallization (Shamblin et al., 1996; Stubberud and Forbes, 1998; Matsumoto and Zografi, 1999; Takeuchi et al., 2000; Berggren and Alderborn, 2003; Crowley and Zografi, 2003; Aso et al., 2004).

Exposing an amorphous powder to humid air may provoke a transformation of it into a crystalline solid. The rate of the crystallization is determined both by the absorption of humidity into the powder bed (Briggner et al., 1994; Stubberud and Forbes, 1998) as well as the nucleation and growth of crystalline regions within the material. In this context, it would be valuable to explore how the crystallization kinetics of a powder relates to the crystallization of single particles. Here, the atomic force microscopy (AFM) is useful for conducting analysis on both single solid particles or on powder compacts. We have earlier shown (Mahlin et al., 2004) that it is possible to use AFM to measure crystallization rate on the surface of single spray-dried lactose

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* Corresponding author. Tel.: +44 1603 591627; fax: +44 1603 592015.
E-mail address: d.mahlin@uea.ac.uk (D. Mahlin).
[1] Present address: School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich NR4 7TJ, UK.
[2] Present address: Recip AB, SE-120 54 Årsta, Sweden.

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particles in a carefully controlled environment with regard to temperature and relative humidity (RH).

Predictions of the physical stability of amorphous materials are preferably based on kinetic parameters, i.e. rate constants, for the crystallization process. An obvious way to conduct such a study is to keep samples under controlled storage conditions meanwhile the increase in crystallinity over time is monitored. Different kinetic models, e.g. the well-known JMAK equation, may be applied on measured data to determine rate constants for the crystallization of amorphous powders (Schmitt et al., 1999; Zhou et al., 2003; Miao and Roos, 2005). Commonly, the stability of an amorphous material is assessed by more simple kinetic parameters, such as the 'time to crystallization' after exposure of a sample to a specified relative humidity (Briggner et al., 1994; Sebhatu et al., 1994; Berggren and Alderborn, 2003) or the crystallization temperature during a temperature scan (Schmitt et al., 1999; Zhou et al., 2003), rather than by a rate constant.

The objective of this study was to derive rate constants for moisture provoked crystallization of a model composite using the AFM approach reported earlier, as a means to improve our understanding of the role of a stabiliser in a composite. The system studied was lactose and polyvinyl pyrrolidone (PVP) since it is commonly used in studies on the stability of composites. Surface active polymers, such as PVP, have a tendency to enrich at the surface of a particle when spray drying is used as particle preparation procedure (Huang and Wang, 1996; Elversson and Millqvist-Fureby, 2005). A surface composition analysis, i.e. electron spectroscopy for chemical analysis (ESCA) (Gelius et al., 1990), was thus used along with the AFM technique to evaluate the composites.

2. Experimental

2.1. Materials

α-Lactose monohydrate was obtained from DMV, The Netherlands, and poly(*N*-vinylpyrrolidone) with a viscosity-average molecular weight of 10,000 g/mol (PVP K17; Kollidon 17 PF) and 1,100,000 g/mol (PVP K90; Kollidon 90 PF) were obtained from BASF, Germany. The RCA2 cleaning liquid consisted of a mixture of one part hydrogen peroxide 30% (Fluka Chemie GmbH, Switzerland), one part ammonium hydroxide solution (Fluka Chemie GmbH, Switzerland) and five parts deionised water. P_2O_5 (Sicapent, Merck, Germany) was used as the desiccant.

2.2. Preparation of amorphous particles

The amorphous particles were prepared by dissolving PVP (5 and 25 wt.% of solid) and lactose in deionised water in a solid/water mass ratio of 1:28. The solution was then spray-dried (Niro Atomizer A/S, Denmark) using inlet and outlet temperatures of 170 ± 5 and $95 \pm 5\,^{\circ}\mathrm{C}$, respectively (Mahlin et al., 2004). By air classification (Alpine 100MZR, Alpine AG, Germany) a particle size fraction of approximately 5–15 μm was collected from all powders types and then stored in a desiccator at 0% RH. X-ray diffraction analysis indicated that the particles thus obtained were amorphous (Diffractor D5000 Siemens, Germany).

2.3. ESCA analysis

The ESCA analysis was made with a Scienta ESCA-300 instrument (Gelius et al., 1990) on tablets (Ø11.3 mm) prepared by the compaction (<10 MPa) of approximately 200 mg of spray-dried particles between freshly cleaved mica plates (lactose/PVP K90 samples) or between Teflon plates (lactose/PVP K17 samples) that had been cleaned by boiling in RCA2 liquid for 10 min and subsequently rinsed in deionised water and blown dry with N_2 gas. The sample preparation was done at an RH of less than 40% to avoid re-crystallization and all equipment used was thoroughly cleaned with ethanol and kept free of contamination through the use of protective gloves. The compacts were mounted on a standard sample holder and immediately inserted into the vacuum load-lock chamber of the ESCA-300 instrument. As the samples outgassed to a significant extent, they normally had to be kept in the load-lock chamber for a couple of hours before the samples could be transferred to the analysis chamber, which was constantly kept at an ultra high vacuum in the 10^{-9} mbar region. The samples were analysed at two different emission angles, 60° and 10° relative to the surface plane. At 60°, the main line intensity of these samples originates from the top layer of ca. 3–4 nm, while at a grazing angle of 10° the mean-thickness of the analysed surface layer is even smaller, estimated to be about 2 nm for these pressed microsphere surfaces, which still appear to be quite ruff on a microscopic scale. The analysis on each sample was conducted twice to ensure that the sample was not degraded by the X-ray exposure. During the ESCA analysis the samples were exposed to an excess of low energy electrons (1 eV) from a Scienta floodgun to control the electrostatic surface potential of these insulating samples, which, otherwise, would become unevenly positively charged. The weight percents of the different components on the surface was calculated from the relative amounts of the elements present determined by measuring the area under the oxygen 1s and nitrogen 1s lines in the ESCA spectra, and from the molecular formula of the components. In addition, for each sample, the carbon 1s spectrum and a survey spectrum (0–1000 eV binding energy) were recorded.

2.4. AFM analysis

AFM imaging was performed using a PicoSPM (Molecular Imaging, AZ, USA) in acoustic AC (tapping) mode. Si_3N_4 cantilevers (NCL Pointproes, Nanosensors AG, Germany) were used. During scanning the particles were dispersed on a glass slide, which made imaging of single particles possible. Topography and amplitude images were obtained from scans performed in N_2 gas at various RH and at 25 °C. The RH was adjusted by mixing dry N_2 gas with humidified N_2 gas (bubbled through deionised water) before introducing it into the hermetically sealed chamber in which the sample was scanned. The RH was monitored by a calibrated hygrometer while the scanning took place.

For kinetic measurements, single particles were scanned repeatedly at low RH whereupon the RH was increased rapidly to initiate the crystallization. The rise in RH was considered to be the start of the experiment. Images were then obtained, with each scan taking 10 min, until no more observable change could be detected.

The image analysis was performed according to the method described in a previous publication (Mahlin et al., 2004). The average deviation (AD, i.e. also known as the rugosity) was determined from the topography images obtained and the fraction crystallized surface (α) was calculated using:

$$\mathrm{AD} = \alpha \mathrm{AD}_{\mathrm{cr}} + (1 - \alpha)\mathrm{AD}_{\mathrm{am}} \quad (1)$$

where $\mathrm{AD}_{\mathrm{am}}$ is the rugosity of the un-crystallized smooth particle surface and $\mathrm{AD}_{\mathrm{cr}}$ is the rugosity of the surface after crystallization. These values were plotted over time for each particle studied and the Johnsson–Mehl–Avrami–Kolomogorov (JMAK) equation (Avrami, 1940):

$$\alpha(t) = 1 - \mathrm{e}^{-(kt)^m} \quad (2)$$

was fitted to the data, whereby the rate constant k and the exponent m was obtained.

3. Results and discussion

3.1. Particle surface structure and composition

AFM topography images of the dry particles are shown in Fig. 1. The spherical particles of pure lactose displayed relatively smooth surface topography, only minor indentations and humps, whereas the particles containing PVP had a more uneven surface with a folded structure. It was apparent that particles with the highest PVP content (25%) showed the highest degree of surface folding, although there was a certain amount of variation in the surface features among the same type of particles. The shape and size of amorphous particles are usually dependent on the properties of the solution and droplets from which the particles are formed during spray drying. Since a polymer increases the viscosity of water solutions, it affects the droplet contraction and subsequent drying of the solidified surface crust that takes place during the spray drying and, in that way, contributes to the folded surface topography. (Berggren and Alderborn, 2003; Elversson et al., 2003).

In order to confirm any enrichment of PVP in the surface of the particles they were studied by ESCA. When preparing the spray-dried particles into tablets for ESCA analysis it turned

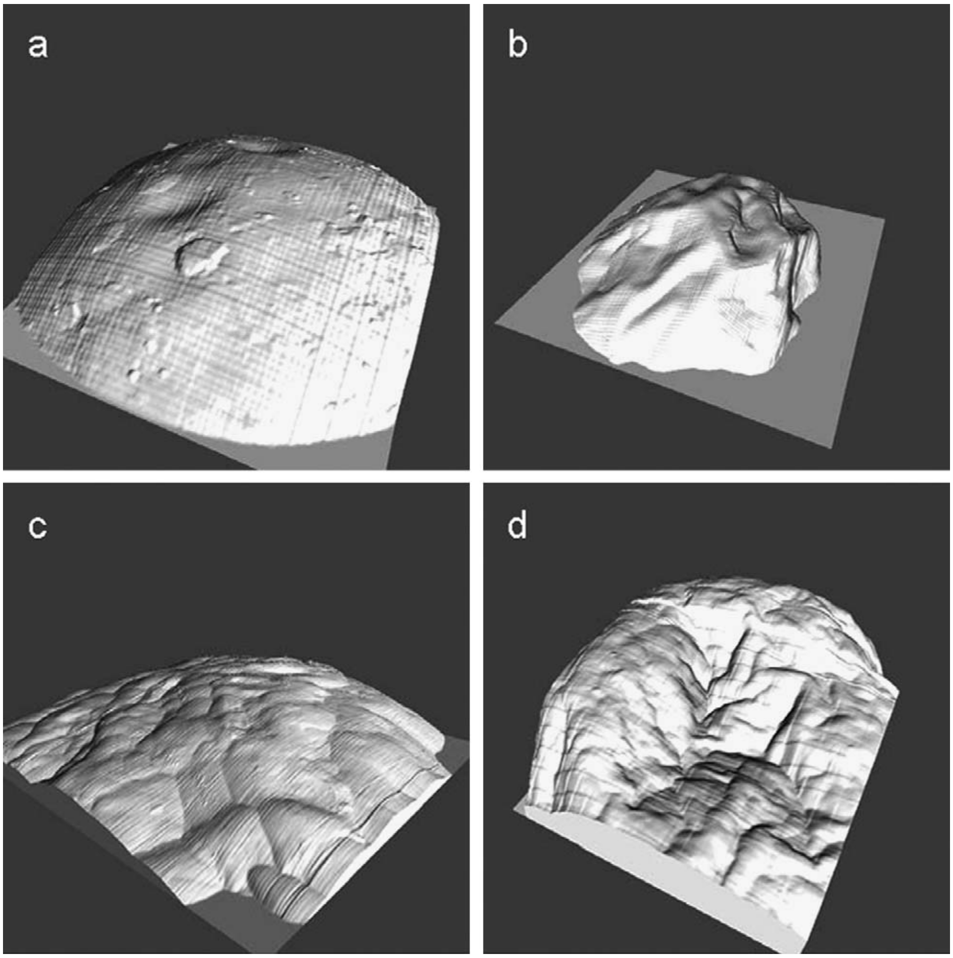

Fig. 1. 3D AFM topography images of dry spray-dried composite particles consisting of lactose and PVP. The compositions of the different particles are (a) pure lactose, (b) 25% PVP K17, (c) 5% PVP K90 and (d) 25% PVP K90. The length of the side of the 3D section is 10 μm.

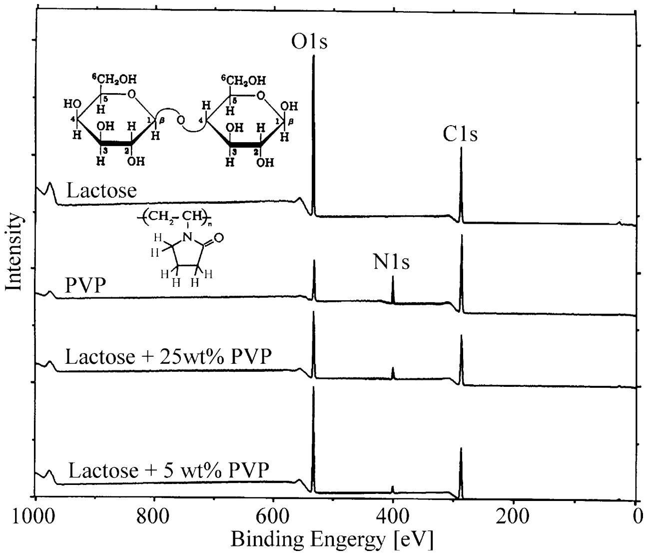

Fig. 2. ESCA spectra obtained from compacted particles of the pure components and lactose/PVP K90 in 5 and 25 wt.%. The peaks represents the energy from detected electrons originating in the 1s orbital of the element oxygen (O), nitrogen (N) and carbon (C). The electrons were detected at a 60° angle from the plane of the compacted samples.

out that pressing against freshly cleaved mica surfaces left no contamination on the lactose/PVP K90 samples, while the mica strongly adhered to the lactose/PVP K17. Silicon traces could be found in the ESCA spectra of the compacts with the latter composition. Because of this, RCA2 cleaned Teflon surfaces were used instead for preparing tablets of lactose/PVP K17, which made contamination undetectable on the tablet surface both visually and in the ESCA spectrum.

Fig. 2 shows typical ESCA spectra obtained from measurement at 60° angle from the plane of the compacted surface. The peaks visible represent the elements oxygen, carbon and nitrogen, respectively. As expected, only the samples containing PVP gave rise to a nitrogen peak that made this element suitable for quantitative analysis. The ratio between peak area for nitrogen and oxygen was used to calculate the surface composition. The composition of the particle surfaces is presented in Table 1. The surface of the spray-dried particles was richer in PVP than the samples as a whole; this was found to be the case for all particles containing PVP. The PVP surface enrichment was further confirmed by measurements at the 10° grazing angle, where all particles displayed an even higher degree of PVP surface enrichment (data not shown).

The degassing of the samples before the ESCA measurements made them essentially free from any water, which is not normally the case even when stored with a desiccant. We assume that this drying did not influence the surface composition, i.e. the relative amount of PVP and lactose in the surface layer. During the handling, the storage and the ESCA analysis, the samples were only exposed to temperatures well below their glass transition temperature (T_g), where their molecular mobility is very low and, hence, diffusion of the components considered negligible.

3.2. Particle response to increased relative humidity

When the particles in this study were exposed to increasing RH there were no significant changes in particle shape or surface morphology as observed with AFM and light microscopy at RHs below 40%. This was true for particles stored in 40% RH overnight, too. However, when the RH was increased further, a gradual swelling of the particles took place, with a smoothening of their surface being apparent within an RH interval, the average value of which was dependent on the particle composition (see Table 1). Typically, the surface roughness measured with AFM (here quantified by the AD-value) decreased from somewhere between 50 and 100 nm to approximately 5 nm in this RH interval. Particles containing PVP had to be exposed to a higher RH than those of pure lactose before the smoothening of the surface occurred.

The absorption of water upon exposure to various levels of RH has been studied in previous investigations on amorphous sugars (Stubberud and Forbes, 1998; Lehto and Laine, 2000; Zhang and Zografi, 2001). An increased RH results in a gradual uptake of water into the solid, whereby the T_g of the system decreases (Hancock and Zografi, 1994). For pure amorphous lactose the amount of water that has to be absorbed in order to lower the T_g to 25 °C, corresponds to an RH of approximately 40% (Jouppila et al., 1998). This is close to the RH at which the swelling of the pure lactose particles was observed (44–48%). Hence, it is likely that the swelling of the particle and the smoothening of the surface were enabled by the increased molecular mobility associated with the transition from the glassy state to a super-cooled liquid (the rubbery state). As the particles at a high RH, above the swelling interval, exists as a super-cooled liquid it is seems reasonable that the shape of the particles become more spherical and smooth, i.e. more like a liquid droplet.

The T_g of the samples has previously been measured (Berggren and Alderborn, 2003) in a dry condition by differ-

Table 1
Surface composition, RH interval of surface smoothening and bulk T_g of the lactose/PVP particles T_g, determined on powder samples (onset of change in heat capacity), obtained from Berggren and Alderborn, 2003.

Particle composition	Surface composition of particle (wt.% PVP)	Observed surface smoothing at RH (%)	T_g (°C) of dry powder
Lactose	–	44–48	116.8
5% PVP K17	31	52–56	117.2
5% PVP K90	26	51–56	117.5
25% PVP K17	56	57–60	117.7
25% PVP K90	51	60–66	117.8

ential scanning calorimetry (DSC). The T_g was not found to be greatly altered by the presence of PVP in concentrations up to 25% for both molecular weights used (see Table 1). These data implies that the molecular mobility of the particles with different composition is essentially equal. Hence, the response to an increase in RH, in terms of surface smoothening, should be similar. The observation of a decreased tendency for surface smoothening of the composite particles can therefore only be explained by the enrichment of PVP at the surface. Obviously, the high amount of PVP affects the particle surface viscosity in the way that the smoothing interval was shifting to higher RHs. This emphasizes the fact that AFM detects mainly surface features, but not necessarily the bulk properties, of the particle.

The smooth particles eventually crystallized and the general pattern of crystallization for the composite particles was similar to what we had observed in our previous study on pure lactose (Mahlin et al., 2004). Small crystallites appeared on the particle and grew continuously until the whole surface was covered. The crystallites of pure lactose could be described as rectangular shaped depressions which contour was somewhat distorted by the presence of 5% PVP. The surface of the particles containing 25% PVP displayed a clearly different pattern (see Fig. 3). Here the rectangles were essentially absent and humps, often arranged in lines or clusters, appeared at different locations. Over time these humps increased somewhat in size, but they did not grow to the same extent as the rectangular crystallites. Rather, they grew in number and, thereby, covering a larger area of the surface.

By comparing the crystallization pattern of particles with different compositions at specific RHs and at different crystallization rates it was clear that the shape and number of crystallites was only dependent on the amount of PVP added. It appeared as if the number of starting points for crystallites growth was reduced when PVP was present, but this observation could not be quantitatively confirmed. Owing to the irregular shape of growing crystalline regions, an accurate assessment of the number of crystallites was not possible.

As the crystallization proceeded, the particles contracted and, in some cases, pores appeared. This behaviour was most pronounced for particles containing PVP and is indicative of the whole particle being engaged in the crystallization, not merely the surface. The higher density of the crystalline phase compared to the amorphous one, and a reduction in the water content upon crystallization (Sebhatu et al., 1994; Lehto and Laine, 2000; Lechuga-Ballesteros et al., 2003) are the obvious explanations for this contraction.

Crystallization studied by AFM does not give direct information on the extent to which crystallization occurs inside the particles. The clearly observed crystallites on the pure lactose particles seemed to originate in the surface region, which is consistent with the proposed idea that a particle surface is rich in nucleation sites (Crowley and Zografi, 2003).

3.3. Crystallization kinetics by AFM

In a previous publication we have described a way of quantifying the crystallization rate and measuring the rate constant using AFM (Mahlin et al., 2004). In the present study we in the same way applied the surface roughness parameter AD on the

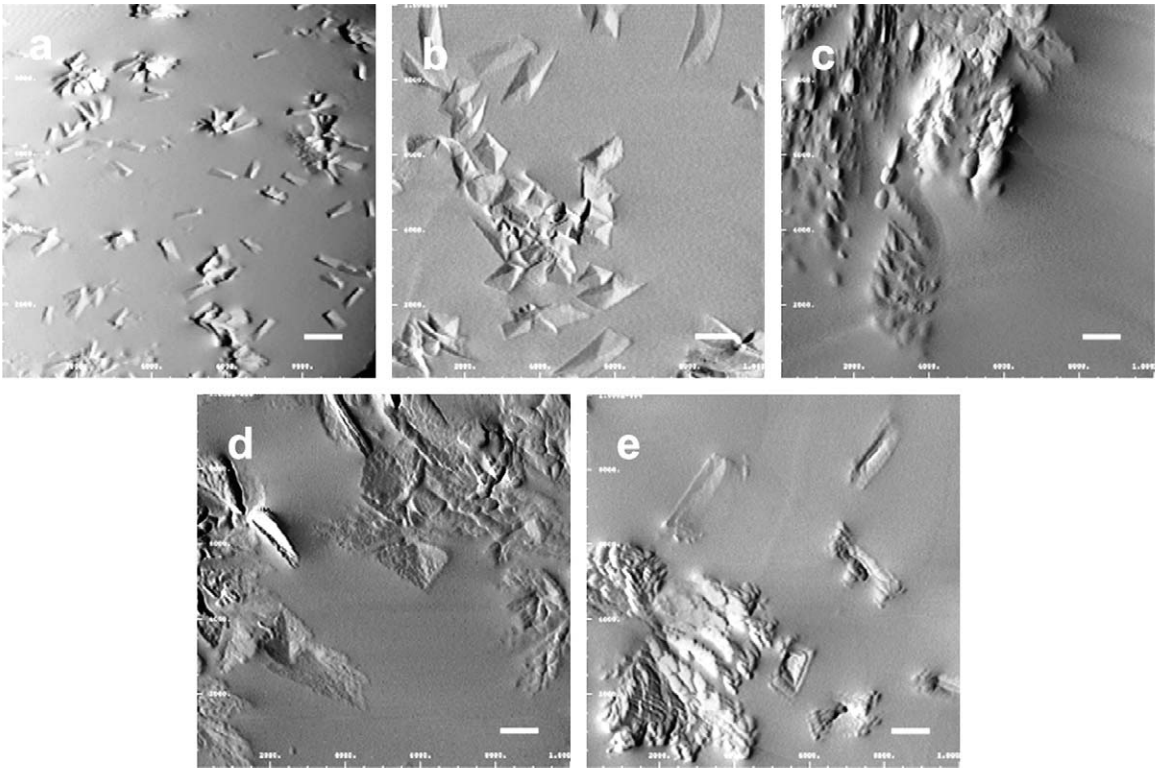

Fig. 3. AFM amplitude images of crystallizing lactose/PVP particles. (a) Pure lactose, (b) 5% PVP K17, (c) 25% PVP K17, (d) 5% PVP K90 and (e) 25% PVP K90. White bars in images indicate 1 μm.

AFM images to calculate fraction crystallized surface (α). The fitting of the JMAK equation to a plot of α over time yielded the rate constant k and the exponent m (see Eq. (2)). The variation in the m parameter was large (ranging from 1.0 to 3.3 with one outlier at 5.8) and no correlations between m and the amount or molecular weight of the polymer in the particles could be seen. According to the theory the m parameter reflects both the dimensionality of crystal growth and the rate of nucleation but owing to the wide spread in values no conclusions could be drawn from this parameter.

The possibility that the AFM probe partially induced crystallization of the surface was evaluated by comparing the images with images of particles that had been subjected to scanning stress to various degrees. The approximate number of crystallites that appeared was not altered, but a small increase in the overall crystallization rate was observed when the scanning rate was doubled, which indicates that constant scanning conditions, e.g. using the same mode and the same scanning rate, are important for obtaining reproducible results.

To be able to validate the reproducibility of the rate constant k it would be advantageous to repeat the measurements at a constant RH but unfortunately it was not possible with the equipment available. The RH attained was easily determined by a hygrometer in the environmental chamber where the AFM scanning took place but it was not easily adjusted to a predefined value by the custom built humidifier. However, importantly, it could be kept constant during each single run. Hence, instead of repeating the measurements at a specified RH each rate constant determined was plotted versus the RH obtained. As can be seen in the diagram in Fig. 4, the crystallization rate rose in an exponential manner as the RH increased. The obvious exception here was the samples containing 25% PVP K17, where the values are scattered and the dependence on RH was absent. Studying particles with this composition in a light microscope revealed that different particles in the same sample responded very differently to the increased RH, in contrast to all the other compositions, which responded more uniformly to changes in RH. The explanation for this could be that the number of sites for nucleation had decreased to such an extent that there was less than one nucleus per particle at a specific RH when PVP K17 was present in 25%. This explanation has been proposed when the same phenomenon was observed previously in a study on spray-dried pure lactose (Price and Young, 2004). Due to these observations, the samples containing 25% PVP K17 will be excluded from the discussions of the general trends below.

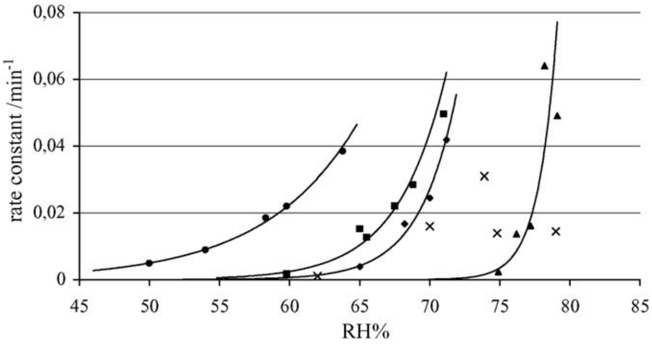

Fig. 4. The rate constant of surface associated crystallization plotted over RH for pure lactose (filled circles) and lactose with 5% PVP K17 (filled squares), 5% PVP K90 (filled diamonds), 25% PVP K17 (×) and 25% PVP K90 (filled triangles). The solid line curves indicate best fit of an exponential function.

Table 2

The parameters ($\ln k_0$ and b) obtained from the fit of the linear form of Eq. (3) to measured rate constants. The mean value and standard error is given for the parameters. R is the regression coefficient of the fit

Particle	$\ln k_0$	b (RH^{-1})	R
Lactose	−12.9 (± 0.24)	0.15 (± 0.0042)	0.9989
5% PVP K17	−23.4 (± 1.9)	0.29 (± 0.029)	0.9810
5% PVP K90	−29.9 (± 2.4)	0.37 (± 0.035)	0.9915
25% PVP K17	–	–	–
25% PVP K90	−62.2 (± 12.1)	0.75 (± 0.15)	0.9406

By assuming that the relationship was indeed exponential a fit of the linear form of the exponential function

$$k = k_0\,e^{b\mathrm{RH}}, \tag{3}$$

to the experimental data could be done and thereby $\ln k_0$ and b obtained (see Table 2). The fits achieved were fair as judged visually from the diagram and from the regression coefficients (R) which are presented in Table 2. This justifies the assumption of an exponential relationship, within this RH range, and that the obtained k values were consistent and did not spread to a large extent. Hence, even if there is a large variation in m, which describes the shape of the JMAK plot, the k values are reliable for quantifying the rate of crystallization.

The presence of PVP clearly inhibited crystallization in the sense that a higher RH was needed to obtain a crystallization rate measurable on a timescale of the AFM measurement, when amount of PVP was increasing in the particles. Above this ‘critical RH for crystallization’ the rate constant increased faster for the composite particles than for the pure lactose particles, as the RH was further raised. This phenomenon was also clearly reflected in the b-values of the different particle composition. Since the b-value reflects the magnitude of the exponential increase in rate constant as a function of RH, it increased with increasing PVP content in the particles (see Table 2). This observation can be interpreted as the particles with PVP being more sensitive to an increased humidity above the point where the onset of crystallization occurs.

It seems from Fig. 4 that the amount of PVP was more important for the inhibitive effect than the molecular weight. Increasing the molecular weight 100-fold (from 5% PVP K17 to 5% PVP K90) only resulted in a minor shift in RH required to initiate crystallization. On the other hand when increasing the amount from 5% (PVP K90) to 25% the RH had to be increased approximately 10% units to initiate crystallization. Normally, molecular weight is considered to be an important parameter in the sense that high molecular weight polymers are more viscous and hence decrease the crystallization rate more efficiently (Berggren and Alderborn, 2003). On the other hand, in the spray-dried particles studied here, the low molecular weight PVP was more concentrated at the surface than the PVP K90 probably leading to the more efficient inhibition of the observed crystallization.

Previously published data (Berggren and Alderborn, 2003) on the absorption of water at different RHs reveals that the rate of moisture absorption into the particles is not influenced by the presence of PVP. Hence, the difference in crystallization rate among the different kind of particles cannot be ascribed to a variation in moisture absorption. Instead, the inhibitive effect of PVP appeared to be associated with a reduction in nucleation and crystal growth. When PVP was present, a decreased molecular mobility of the particles was seen as the shift in the RH needed to induce surface smoothening and in the critical RH needed for crystallization. The higher sensitivity of composite particles to an increasing RH, above the critical RH for crystallization, is most likely due to that the interactions between the PVP and the lactose, which are important for the stabilisation, are influenced by the presence of water. This, in turn, impairs the stabilising effect imposed by the presence of PVP.

4. Summary and conclusions

It has been shown previously that the addition of PVP to spray-dried lactose stabilises the powder, in the sense that the lowest RH at which the material re-crystallizes during storage will increase (Berggren and Alderborn, 2003). To further study this behaviour, on an individual particle level, the crystallization kinetics was here studied by an AFM analysis procedure reported earlier (Mahlin et al., 2004).

As expected, the particle preparation by spray drying yielded nearly spherical particles, and the presence of PVP in the feed solution resulted in a more uneven and folded surface topography in comparison to the relatively smooth lactose particles. The tendency for the particle surface to smoothen as it passed through the glass transition, imposed by exposure to higher RHs, decreased with increasing molecular weight and amount of PVP in the particles. The interpretation of this was that the addition of PVP causes a reduction in the molecular mobility of the particle surface. This may be an important aspect of stability improvement since previous publications have shown that re-crystallization of particles has much of its origin in the surface region (Crowley and Zografi, 2003). ESCA was used to examine the incorporation of the PVP into the composite particles and it was evident that PVP was indeed enriched at the particle surface.

PVP inhibited the crystallization in the way that a higher RH was needed for crystallite formation to be detected on the composite particles compared to on the pure lactose. This ‘critical RH for crystallization’ increased with increasing amount of PVP in the particles but the effect of PVP molecular weight was limited. For all systems studied, the calculated crystallinity followed the JMAK equation when plotted over time. An analysis of the RH dependence of the rate constants showed that the crystallization rate for particles with a higher content of PVP was more sensitive to a change in RH above the critical RH for crystallization. These results show that the amount and the molecular weight of PVP have an impact on the stability of the particles but the stabilising effect is impaired by the presence of absorbed water.

We conclude that AFM and ESCA are appropriate methods for studying surface associated phenomena of spray-dried particles. AFM enabled us to study the crystallization kinetics of single particles and the effect of RH on the rate constant of crystallization. This is the first report on an analysis of how RH and the presence of PVP affect the crystallization rate on single composite particles at well-defined humidity and temperature conditions. The methods have potential to generate knowledge on the mechanism of stability of pharmaceutical and other particulate materials.

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