

Effect of Polymer Content and Molecular Weight on the Morphology and Heat- and Moisture-Induced Transformations of Spray-Dried Composite Particles of Amorphous Lactose and Poly(vinylpyrrolidone)

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Purpose. The aim was to investigate the influence of polymer content and molecular weight on the morphology and heat- and moisture-induced transformations, as indicators of stability, of spray-dried composite particles of amorphous lactose and poly(vinylpyrrolidone) (PVP).

Methods. Amorphous lactose and composite particles of amorphous lactose with different contents and molecular weights of PVP were prepared by spray drying. The nanostructure of the particles was analyzed by x-ray powder diffractometry, the morphology by light microscopy and SEM, the glass transition temperatures (T_g), crystallization temperatures (T_c), heats of crystallization and melting temperatures by differential scanning calorimetry, and moisture-induced crystallizations gravimetrically and by microcalorimetry.

Results. All the types of particles prepared were amorphous. The T_g was unchanged or only marginally increased as a result of the inclusion of PVP. However, crystallization temperature, time to moisture-induced crystallization, and particle morphology were affected by both content and molecular weight of PVP.

Conclusions. Increased content and molecular weight of PVP may have the potential to increase the physical stability of amorphous lactose. However, T_g seems not to be a relevant indicator for the stability of this type of amorphous composite materials.

KEY WORDS: amorphous lactose; poly(vinylpyrrolidone); spray-dried composite particles; polymer molecular weight; physical stability; morphology.

INTRODUCTION

Amorphous materials have properties that can be of advantage in formulation of drugs. An amorphous solid has a lower energetic barrier to overcome when entering a solution, so solubility (1), dissolution rate (2), and hence therapeutic effect (3) can be enhanced if a drug is made amorphous. It has also been shown that amorphous sugars lend stability to proteins in spray-dried or freeze-dried sugar-protein mixtures (4) and that the tableting properties of a substance can be improved if it is rendered amorphous (5,6).

Amorphous solids can be prepared (7) by rapid precipitation from a solution (e.g., lyophilization, spray drying), mechanical treatment of crystals (e.g., milling, compaction), or supercooling from a melt. The engineering of pharmaceutical particles with a view to optimizing their functional properties

has attracted increased interest in recent years. In this context, spray drying is a particle preparation technique in which properties such as particle shape and size, bulk density, flowability, moisture content, and solid-state properties of a material can be altered and controlled (8,9), making it suitable for preparation of pharmaceutical particles for inhalation and solid oral dosage forms, for example.

Spray-dried amorphous lactose has received much attention in the literature as an amorphous model substance, and it has also been shown to have different functional properties, such as significantly increased compactability, compared with crystalline lactose (6). Also, a spray-dried (partially amorphous) form of lactose for use as a direct compression aid is commercially available (10). However, the disadvantage with amorphous materials is their higher reactivity, which can result in spontaneous conversion to the crystalline state at a certain relative humidity and temperature, with subsequent effects on the properties of the dosage form. Attempts have therefore been made to modulate the solid-state reactivity of amorphous substances, and there are several reports in which a low-molecular-weight substance has been coprocessed (spray-dried, precipitated from organic solvents, or freeze-dried) with a small amount of a polymer with a high glass transition temperature in order to produce a composite material with increased physical stability (11–21). Different types of heat- and moisture-induced solid-state transformations (i.e., glass transition temperature, crystallization temperature, moisture-induced crystallization) have been used as indicators of stability in this context. Zografi and co-workers (13–18) have made a significant contribution to the literature on stabilization of amorphous materials, but their studies are limited to materials prepared by other techniques than spray drying. Despite the fact that preparation of an amorphous solid by spray drying may be pharmaceutically advantageous in terms of control of particulate properties of the material (size, shape, etc.) and suitability for production, only a few reports have discussed the properties of composites prepared by spray drying (11,12,19,20). It should, however, be pointed out that no clear definition of an amorphous composite material has been given in the pharmaceutical literature. Here, such a material is defined as one in which the compounds are dispersed at the molecular level and that consists mainly of a low-molecular-weight substance and a smaller fraction of a polymer.

Among polymers of interest as stabilization agents, PVP is an obvious candidate that has been used in this context. Besides being recognized as an excipient of acceptable safety for different routes of administration, it has a high glass transition temperature and a basic chemical group capable of donating electrons and thereby forming hydrogen bonds with other substances (16). It has been suggested that the ability of the polymer to form hydrogen bonds with the low-molecular-weight substance is of importance for the inhibition of crystallization (13,16,17).

The glass transition temperature of PVP is related to the molecular weight, a property that may affect the stability of the composite. However, somewhat conflicting results have been reported (17,21) regarding the importance of the molecular weight of PVP in this context. In this study, composites consisting of lactose and PVP of different molecular

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weights and in various concentrations have been prepared, and their morphology and stability investigated. The stability was assessed by a series of indicators based on the determination of stresses needed to cause solid-state transformations (glass transition and crystallization). These types of particles are also of particular interest from a functionality perspective, and in a subsequent study their tableting properties will be investigated.

MATERIALS AND METHODS

Materials

α -Lactose monohydrate with an apparent particle density of 1.54 g/cm³ (Pharmatose 200M, batch 675532/6, DMV, The Netherlands), poly(vinylpyrrolidone) with a viscosity-average molecular weight of 8,200 (PVPK17), a glass transition temperature of 140°C, and an apparent particle density of 1.18 g/cm³ (Kollidon 17 PF, batch 34-0462, BASF, Germany), and poly(vinylpyrrolidone) with a viscosity-average molecular weight of 1,100,000 (PVPK90), a glass transition temperature of 176°C, and an apparent particle density of 1.23 g/cm³ (Kollidon 90 F, batch 27-0592, BASF, Germany). Saturated salt solutions of NaCl (Merck Eurolab, Sweden), CuCl₂ (Kebo Lab AB, Sweden), and Mg(NO₃)₂ (Merck, Germany) were used to generate 75, 68, and 53% relative humidity (RH), respectively. P₂O₅ (Sicapent, Merck, Germany) was used as a desiccant.

Particle Preparation

Particles of only lactose or a mixture of lactose and 5, 10, or 25% w/w PVPK17 or PVPK90 were prepared by spray drying. The highest concentration of PVP corresponds to a PVP monomer/lactose molecule ratio of 1:1. The substances were dissolved in deionized water in a mass ratio of solid material/water of 1:28. The solutions were spray-dried in a countercurrent spray dryer (Niro Atomizer, Niro A/S, Denmark), equipped with a rotary atomizer. The pressure used for the atomizer was 5.6 kg/cm². The liquid feed rate was 17 ml/min (peristaltic pump, Watson Marlow 505S, Watson Marlow Ltd., England), and inlet and outlet temperatures were 170 ± 5°C and 95 ± 5°C, respectively. The yield from the spray-drying process was approximately 60–70%. The particles were stored in a desiccator over P₂O₅ (0% RH) for at least 7 days, after which a size fraction 5–15 μm was prepared by air classification (Alpine 100 MZR, Alpine AG, Germany). Finally, the particles were stored at room temperature and 0% RH for 7 days and then for 7 days at 40°C and 0% RH after air classification prior to characterization.

Physical Properties of the Particles

Crystallinity

The different particles were analyzed with a Diffractor D5000 (Siemens, Germany), equipped with a scintillation detector, using Cu-K α radiation, 45 kV and 40 mA. Bragg-Brentano focusing geometry was used, and the samples were scanned in steps of 0.02° from 5 to 35° (2 θ). The spray-dried composite particles of lactose and 25% PVPK90 stored at 75 and 53% RH for 2 and 14 days, respectively, were also analyzed by x-ray diffraction.

Morphology

Suspensions of the different particles (50 mg) in 10 ml liquid paraffin were prepared, and the particles were then inspected in an optical light microscope (Vanox, Olympus, Japan) at 40 times magnification. Particles stored over P₂O₅ and at 75% RH for 24 h were also inspected and photographed in a scanning electron microscope (Leo 1530 Gemini, Leo, UK).

Apparent Particle Density

The apparent particle density (sometimes also referred to as skeletal density) was determined using a helium pycnometer (AccuPyc 1330, Micromeritics, USA). The theoretical density of the composite particles was calculated from the density of the pure amorphous lactose and PVP particles according to the following equation:

$$\rho = (w_1 + w_2) / ((w_1/\rho_1) + (w_2/\rho_2))$$

where w_1 and w_2 are the weight fractions and ρ_1 and ρ_2 the densities of the components.

Stability Indicators

Heat-Induced Transformations

Heat-induced transformations, i.e., glass transition temperature (T_g), crystallization temperature (T_c), and heat of crystallization, were determined using a differential scanning calorimeter (DSC 220, SSC/5200H, Seiko, Japan). Approximately 2 to 4 mg of the materials was placed in aluminum DSC pans with a pinhole in the lid and analyzed under dry nitrogen purge. T_g is a dynamic property of a material that can depend, *inter alia*, on heating rate and moisture content. Consequently, the samples were heated to 20°C above their glass transition temperature, then cooled with liquid nitrogen to 20°C, and then reheated to 300°C. Heating and cooling rates of 10°C/min were used. The calorimeter was temperature- and heat-calibrated with indium, tin, gallium, and mercury.

From measures of the glass transition temperatures, determined as described above, of amorphous lactose and PVP, theoretical glass transition temperatures of the composite particles were calculated by the Gordon–Taylor equation (22). Based on the assumption of perfect volume additivity at T_g , this equation has been used to describe the glass transition behavior of many blends (23). If the glass transition temperature (T_g), true density (ρ), and weight fraction (w) of the components are known, the T_g of the mixture can be calculated as follows:

$$T_{g\text{mix}} = ((w_1 \times T_{g1}) + (K \times w_2 \times T_{g2})) / (w_1 + (K \times w_2))$$

The constant K can be estimated from the true densities and glass transition temperatures of the two components:

$$K = (\rho_1 \times T_{g1}) / (\rho_2 \times T_{g2})$$

Moisture-Induced Isothermal Transformations

To study moisture-induced isothermal (25°C) transformations (crystallizations) of the materials, a microcalorimeter (2277 Thermal Activity Monitor, Thermometric AB, Sweden) equipped with a humidity control device (perfusion cell) was

used. Dry nitrogen gas was pumped by means of a peristaltic pump into the humidity control device and mixed with different proportions of nitrogen gas saturated with 100% water in order to give different controlled relative humidities. The perfusion cell was calibrated with saturated salt solutions [NaCl, CuCl_2 , and $\text{Mg}(\text{NO}_3)_2$] according to a method described by Buckton (24). The material (30 ± 0.5 mg) was placed in the sample cell and then into the microcalorimeter and perfused with dry nitrogen gas in order to dry the material until no endothermic signal was observed. Thereafter, the humidity control device was set to the desired relative humidity, and this was considered as the starting point of the measurement. The time to the maximum value of the exothermic crystallization peak of the materials and the heat of crystallization were determined at 53, 68, and 75% RH. The advantage with the humidity control device was that the materials could be dried completely before the actual measurement because any residual moisture taken up during the weighing procedure could have affected the results.

The moisture-induced isothermal transformations of the materials were also investigated gravimetrically. Samples (500 ± 5 mg) of the different materials were weighed in 5-ml glass beakers and then stored in a desiccator over P_2O_5 until the weight change was less than 1 mg/24 h. Thereafter the materials were moved to desiccators (25°C) with relative humidities of 75% and 53%, and the samples were periodically taken out of the desiccators and weighed on an analytic balance.

RESULTS AND DISCUSSION

Physical Properties of the Original Particles

Crystallinity

Spray drying converts a solution or suspension into solid particles by rapid evaporation, and it is well known that this can produce high-energy amorphous materials and that the degree of disorder can be altered by the drying conditions and the properties of the material. In this study, the rationale for the choice of drying conditions was that completely amorphous particles of lactose and different contents and molecular weights of PVP could be obtained under the same conditions. X-ray powder diffraction analysis was used to analyze the nanostructure (25) and to confirm that the prepared particles were amorphous. In Fig. 1a, x-ray powder diffraction patterns for spray-dried pure lactose particles and composite particles with 25% PVP are shown. They exhibited broad and diffuse maxima with no sharp peaks, suggesting that the particles were completely amorphous. Similar patterns were obtained for the other types of particles (data not shown).

Morphology

Visual inspection by light microscopy and of SEM images of all the types of particles prepared indicated that they in general were spherical, and the particle diameter was estimated visually to roughly 5 to 15 μm (Fig. 2a–e). However, the morphology of the different particle types differed markedly. The surface of the pure amorphous lactose particles (Fig. 2a) was smooth, in contrast to that of the composite particles (Fig. 2b–e). The particles with PVPK17 (Fig. 2b,c) had a folded surface, whereas those containing PVPK90 (Fig.

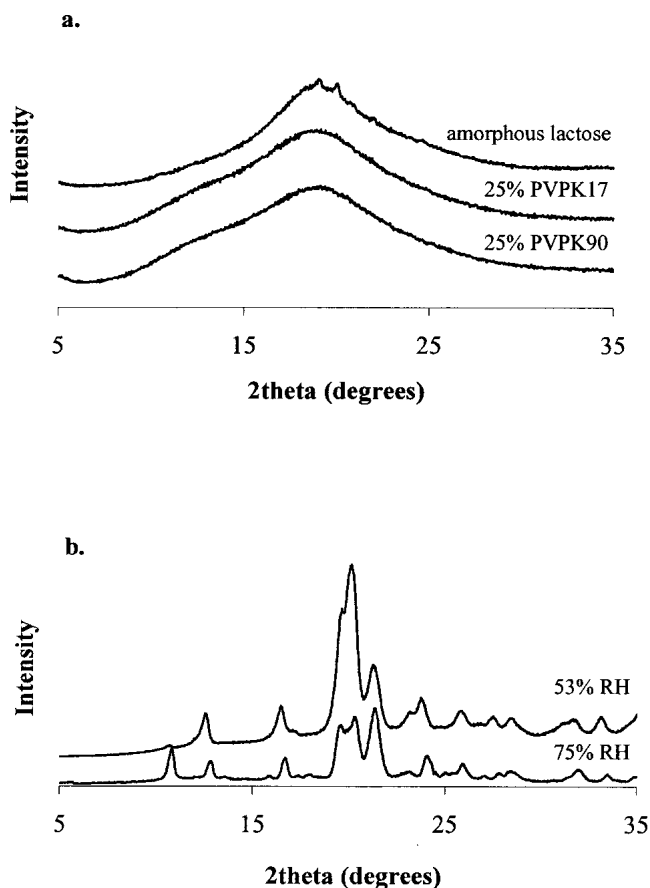


Fig. 1. X-ray powder diffraction patterns of (a) pure amorphous lactose particles, composite particles with 25% PVPK17, and composite particles with 25% PVPK90; and (b) composite particles with 25% PVPK90 stored at 53 and 75% RH.

2d,e) had larger cavities. The number and depth of the folds and cavities increased with increased concentration of PVP. The differences in the morphology of the dry particles can thus be explained in terms of an influence of concentration and molecular weight of PVP on surface viscosity during drying.

Apparent Particle Density

The visual inspection revealed no pores in the particles, and the measured particle densities of the composite particles were similar to the calculated densities (Table I). It thus seems that, in relation to the pure amorphous lactose and PVP particles, the composite particles had no significant volume of closed pores, i.e., structures impermeable to He gas. This finding does not, however, rule out the presence of open pores in the particles. The apparent particle density of the pure amorphous lactose was slightly lower than that of α -lactose monohydrate, and the density of the composite particles decreased with increased concentration of PVP.

Stability Indicators

Heat-Induced Transformations

The heat-induced transformations of the different particles were investigated by DSC, and the glass transition tem-

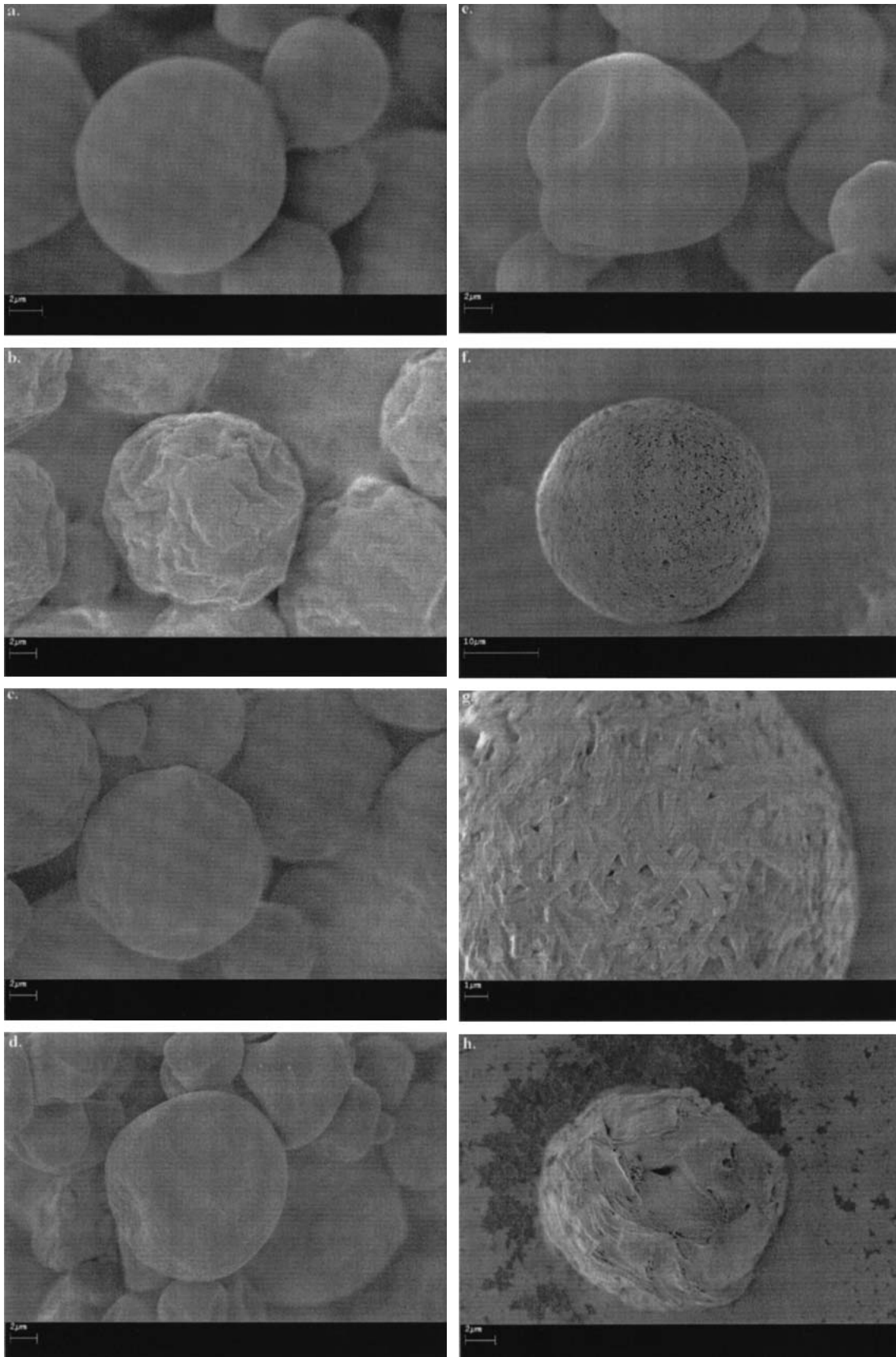


Fig. 2. SEM pictures of (a) pure amorphous lactose particles; composite particles with (b) 25% and (c) 5% PVPK17; composite particles with (d) 25% and (e) 5% PVPK90; (f) pure amorphous lactose particles exposed to 75% RH for 24 h; (g) composite particles with 25% PVPK17 exposed to 75% RH for 24 h; and (h) composite particles with 25% PVPK90 exposed to 75% RH for 24 h.

Table I. Apparent Particle Density and Results from DSC Runs of Amorphous Lactose and Composite Particles with PVPK90 and PVPK17

Material	Apparent particle density (g/cm ³)	Calculated density (g/cm ³)	T _g ^a (°C)	Theoretical T _g ^a (°C)	Specific heat of crystallization (J/g)	T _{m1} ^b (°C)	T _{m2} ^b (°C)
25% PVPK90	1.43 (0.057)	1.44	119.7 (0.174)	132.5	5.19 (5.4)	219.8 (0.115)	241.0 (0.133)
25% PVPK17	1.43 (0.038)	1.42	117.7 (0.298)	123.4	50.5 (7.9)	214.5 (0.0712)	226.0 (0.0511)
10% PVPK90	1.49 (0.051)	1.49	117.8 (0.255)	123.1	80.9 (1.1)	213.2 (0.0541)	226.0 (0.0511)
10% PVPK17	1.48 (0.013)	1.48	117.2 (0.215)	119.7	76.3 (3.0)	213.8 (0.0974)	230.1 (0.115)
5% PVPK90	1.50 (0.057)	1.51	117.5 (0.123)	120.0	85.0 (3.7)	213.4 (0.0469)	227.9 (0.116)
5% PVPK17	1.50 (0.048)	1.51	117.2 (0.0492)	118.2	84.2 (2.2)	212.2 (0.0471)	229.8 (0.126)
Amorphous lactose	1.53 (0.059)	—	116.8 (0.386)	—	88.0 (3.9)	212.4 (0.0942)	226.6 (0.117)

Note: Mean values ($n = 3$), relative standard deviation in percent in parentheses.

^a Glass transition temperature.

^b Melting temperature.

peratures (T_g) and crystallization temperatures (T_c) were used as indicators of the physical stability of the particles.

At T_g, a significant change in volume is expected that results in increased molecular mobility, reactivity, and propensity to crystallize. In the DSC thermograms for the different particles (Fig. 3), a change in heat capacity at approximately 120°C was observed, which was interpreted as the glass transition temperature. At higher temperatures an exothermic reaction, i.e., the crystallization temperature, was observed, followed by two melting endotherms. The T_g of the pure amorphous lactose particles was approximately 117°C, which is consistent with earlier results (16). The T_g of both qualities of PVP compared favorably with reported data (17). The shape of the glass transition became slightly broader with increased content and molecular weight of PVP. The observed glass transition temperatures were generally lower than predicted from the Gordon–Taylor equation. [It should be pointed out, however, that it has earlier been reported (15) that temperatures calculated using the Couchman–Karasz equation gives a better representation of experimentally determined temperatures.] Similar negative deviations from predicted values of T_g have been reported for lyophilized systems of sucrose and PVP and PVP/VA (15). In this study, there was a tendency for T_g to increase as the amount of PVP increased and for the higher molecular weight of the polymer to give a larger increase in T_g. The effects on T_g were, how-

ever, limited. Only in one case, the 25% PVPK90 system, was a significant (unpaired t test, $p < 0.05$) increase in T_g obtained compared with amorphous lactose (Table I). Although polymer content and molecular weight had only a minor effect on the T_g, the T_c showed a clear dependence on molecular weight (Fig. 4). The relationship between T_c and polymer content was linear in the range of polymer contents used, with a greater change in T_c for the higher molecular weight. The heat of crystallization (Table I) decreased with increased content of PVP, and the heat evolved for the particles with 25% PVP was lower than predicted from the value of pure amorphous lactose, compensated for the weight fraction of PVP.

The melting endotherms (T_{m1} and T_{m2} in Table I) observed at approximately 215°C and 230°C for all the different types of particles suggest that a mixture of α - and β -lactose was formed after crystallization (10). The melting temperatures were slightly higher for the composite particles.

Thus, the inclusion of PVP into amorphous lactose particles changed the thermal behavior of the materials, as assessed by DSC, in such a way that T_g was almost unchanged, and T_c increased significantly. The unchanged T_g is not expected from calculations and may reflect nonideal mixing between lactose and PVP. The increase in T_c was related to the concentration and molecular weight of PVP in the materials. The general view in the literature is that increased T_g reflects increased physical stability, and polymers with a high T_g have been chosen for composite materials in order to elevate T_g. It

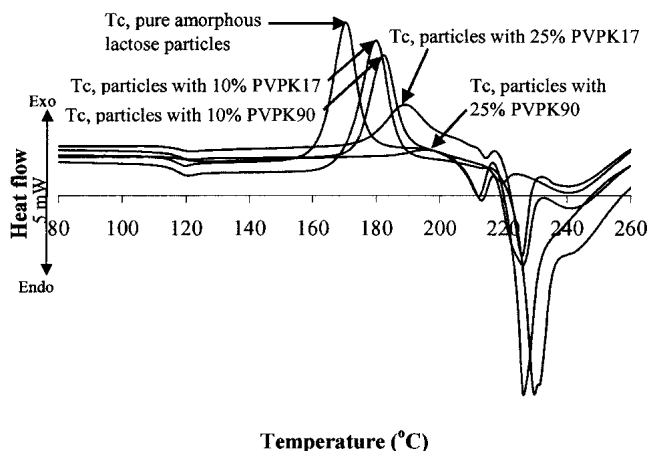


Fig. 3. DSC thermograms of pure amorphous lactose particles and composite particles with 10% and 25% PVPK17 and PVPK90.

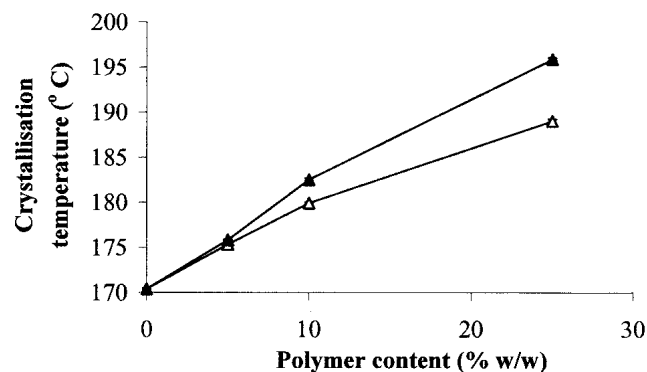


Fig. 4. Crystallization temperature as a function of PVP content for the composite particles with PVPK17 (Δ) and PVPK90 (\blacktriangle). Arithmetic mean values ($n = 3$); error bars show standard deviations.

has previously been found that T_g is increased by the addition of a polymer. It has been suggested that increased stability and influences on crystallization are related to increased T_g (13,14,19,20). However, for some systems at low levels of polymer content, it has been found that T_g is only slightly elevated, although stability has nevertheless been improved, which has led to the conclusion that other factors may also be of importance (13,14). It has been suggested that at low levels of PVP, in molecular dispersions with indomethacin, the inhibition of crystallization was related to hydrogen bonding between the two substances (17). It has also been suggested (16) that hydrogen bonds can be formed between PVP and lactose in lyophilized systems. The pattern reported here may indicate that stabilization can be achieved although the T_g is unaffected or, alternatively, that measurement of T_c is not an indicator of stabilization of an amorphous material. Thus, in order to further investigate the crystallization behavior of the materials, crystallization under isothermal conditions provoked by moisture uptake was studied.

Moisture-Induced Isothermal Transformations

Another means of obtaining an indication of the propensity of the different particles to crystallize was to study isothermal transformations induced by moisture. It is known that water from humid air can be absorbed, in significant amounts, into the amorphous structure, resulting in a lowering of the T_g , and if it is lowered to a sufficient degree, crystallization can occur spontaneously. Crystallization of amorphous lactose under isothermal conditions is associated with a release of energy (26) and also a weight loss (10). Consequently, the moisture-induced transformations of the materials at 25°C were investigated using calorimetric and gravimetric methods.

Figure 5a,b shows microcalorimetry heat flow curves at 75 and 53% RH for amorphous lactose and composite particles with 25% PVPK17 and PVPK90. Directly after introduction of humid gas, an exothermic reaction, which lasted for several hours, was observed. This first exotherm is related to the absorption of water and was followed by a second exotherm related to crystallization of the amorphous lactose (26). The crystallization event was generally associated with an exotherm followed by an endotherm. The latter may be related to the drying of the sample and the removal of water released during crystallization. The time to the crystallization peak was greater for the composite particles than for pure amorphous lactose. In addition, for the particles with the high molecular weight PVP, the time to crystallization was increased compared with the particles with the low molecular weight PVP. The time to crystallization and the differences between the materials generally increased with decreased relative humidity (Figs. 5a, b, Table II). It has been suggested (26) that the heat evolved during crystallization of amorphous lactose (calculated by integration of the microcalorimetry exothermal heat flow signal) can be used to estimate the degree of disorder in the sample. The values of the specific heat of crystallization of amorphous lactose were similar to reported values (26), suggesting that the amorphous lactose in this study was completely amorphous and that complete crystallization occurred at the different RHs. The specific heat of crystallization at 75% RH for the composite particles corresponded reasonably well with the value for pure amorphous

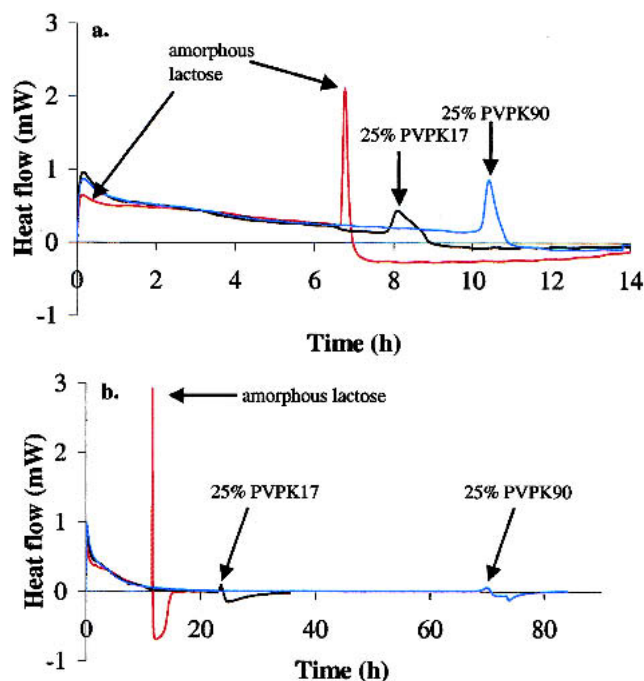


Fig. 5. Microcalorimetry heat flow curves at (a) 75% and (b) 53% RH for pure amorphous lactose particles and composite particles with 25% PVPK17 and PVPK90.

lactose (assuming that the particles contained 75% w/w amorphous lactose), suggesting that complete crystallization occurred at this RH. However, at lower RHs the specific heat of crystallization decreased, which may indicate that only partial crystallization of the amorphous lactose in the composite particles occurred under these conditions (Table II).

From the moisture sorption studies it was found that the materials absorbed a significant amount of water at the relative humidities investigated (Fig. 6) and that after a certain time the moisture content decreased as a result of crystallization. The amount of water absorbed and the time to the reduction in moisture content increased with increased content and molecular weight of PVP. The results of the moisture sorption study supported the microcalorimetry finding that moisture-induced transformation of the composite particles was affected by the molecular weight of the PVP.

In conclusion, it seems that the effect of PVP on moisture-induced crystallization was consistent with the results regarding the crystallization temperature. Despite the fact that T_g was little changed or unchanged by the addition of PVP in the composite particles, heat- and moisture-induced crystallization were affected by the content and molecular weight of the polymer. It is possible that the observed small changes in T_g with content and molecular weight of PVP can partly explain the increased stability of the composites. However, the change in propensity for crystallization with inclusion of PVP in the amorphous lactose may primarily be related to specific interactions formed between monomers and lactose molecules, such as hydrogen bonds. This explanation is supported by an earlier suggestion (18) that inhibition of moisture-induced crystallization of colyophilized sucrose-polymer systems was related to coupling of sucrose mobility to the motions of the polymer through hydrogen bonding.

Table II. Time to Crystallization Peak (t_{\max}) and Specific Heat of Crystallization of Amorphous Lactose and Composite Particles with 25% PVPK90 and PVPK17 Determined with Microcalorimetry

Material	t_{\max} 75% RH (h)	Specific heat of crystallization 75% RH (J/g)	t_{\max} 68% RH (h)	Specific heat of crystallization 68% RH (J/g)	t_{\max} 53% RH (h)	Specific heat of crystallization 53% RH (J/g)
25% PVPK90	11 (0.2)	28.7 (0.20)	11 (0.03)	27.0 (0.31)	70 (0.5)	4.95 (4.1)
25% PVPK17	8.5 (0.9)	25.1 (0.43)	8.7 (0.4)	18.3 (0.53)	26 (4.0)	3.94 (2.1)
Amorphous lactose	6.7 (0.2)	31.5 (0.25)	7.3 (0.1)	31.5 (0.049)	11 (1.3)	27.0 (0.26)

Note: Mean values ($n = 2$), range in parentheses.

Physical Properties of the Particles after Storage

Crystallinity

The material that was most stable (25% PVPK90) was also analyzed by x-ray powder diffraction after moisture-induced transformations at different RHs. The moisture-induced transformations of the material resulted in a significant change in the nanostructure, toward a more crystalline state. Markedly different x-ray powder diffraction patterns compared with the starting material were obtained, and in Fig. 1b patterns for the composite particles with 25% PVPK90 stored at 53 and 75% RH are shown. The results suggest that crystallinity was increased after exposure to moisture. The particles stored at 53% RH exhibited slightly broader peaks,

suggesting a lower crystallinity, compared with the particles stored at 75% RH. A distinct peak at about 10.5 degrees 2θ was observed for the particles stored at 75% RH, attributable to the formation of β -lactose (26).

Morphology

The morphology of the different particles was also significantly changed after moisture-induced crystallization. Inspection by SEM revealed individual particles similar in size to the original particles. However, on the surfaces of these particles, crystal-shaped structures were observed (Fig. 2f-h), which probably represent lactose. The particles with 25% PVPK90, though, exhibited fewer such structures than the other types of particles (Fig. 2h).

CONCLUSIONS

By using lactose and PVP, we have shown that spray drying can be used as a feasible procedure to prepare polymer-stabilized amorphous particles. For such spray-dried composite particles, the polymer content and molecular weight may be significant formulation factors for the stabilizing effect. The presence of a polymer in the spray-drying feed solution changed not only the reactivity of the particles but also their morphology. The obtained changed solid-state behavior referred to as a material stabilization was expressed as an increased resistance to provoked crystallization. The T_g was, however, unchanged or only slightly increased and seems therefore not to be a relevant indicator for the stability of this type of amorphous composite particles.

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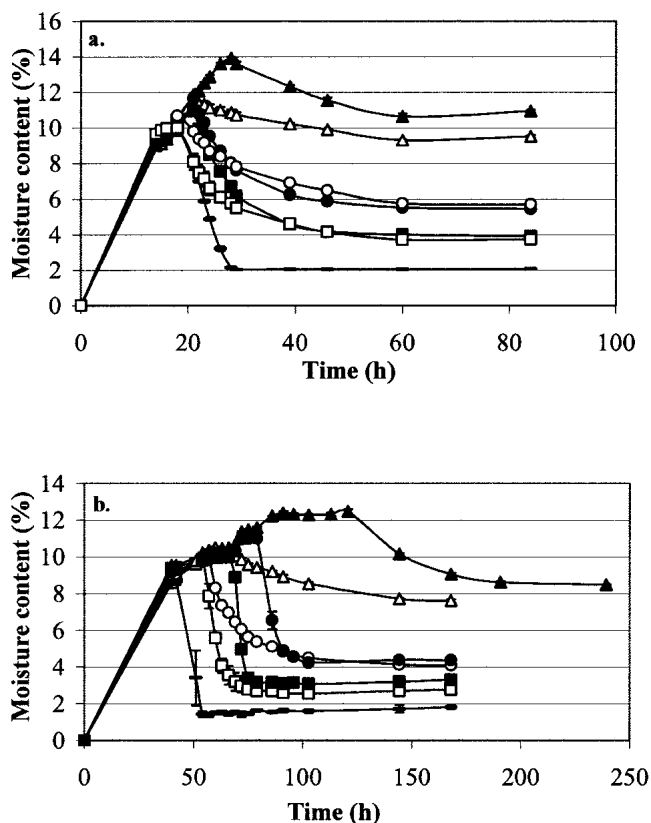


Fig. 6. Moisture sorption of amorphous lactose particles (—) and composite particles with 5% (□), 10% (○), and 25% (△) PVPK17 and PVPK90 at (a) 75% and (b) 53% RH. Filled symbols represent particles prepared with PVPK90. Arithmetic mean values ($n = 3$); error bars show standard deviations.

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