

Water solid interactions II. Effect of moisture sorption and glass transition temperature on compactibility of microcrystalline cellulose alone or in binary mixtures with polyvinyl pyrrolidone

Lars Stubberud^{a,b,*}, Hans G. Arwidsson^a, Annika Larsson^c, Christina Graffner^{a,b}

^aPharmaceutical R and D, Astra Läkemedel AB, S-151 85 Södertälje, Sweden

^bInstitute of Pharmacy, University of Oslo, N-0316 Oslo, Norway

^cPharmaceutical R and D, Astra Pain Control AB, S-151 85 Södertälje, Sweden

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Abstract

The relation between the moisture sorption and compaction properties of microcrystalline cellulose, MCC, and binary mixtures of MCC with polyvinyl pyrrolidone, PVP, has been examined. PVP is a completely amorphous polymer, whereas MCC contains various fractions of amorphous structure depending not only on the quality used but also on the pharmaceutical processing. The tensile strength of tablets of MCC is shown to depend upon the relative humidity, RH, prior to compaction. At an RH of about 70%, a decrease in strength is observed corresponding to the upward shift of the moisture sorption isotherm. For a dry blend of MCC and PVP as well as for a granulation, the tensile strength is determined by the properties of MCC at humidities below 70% RH. At humidities above 70%, a reduction of the glass transition temperature of PVP below the operating temperature (20°C) is the dominating factor, resulting in a decrease in tensile strength.

Keywords: Microcrystalline cellulose; Polyvinyl pyrrolidone; Processing; Moisture sorption; Glass transition temperature; Tensile strength

1. Introduction:

Sorption of water vapour onto solids is well documented over a wide range of relative humidities (Callahan et al., 1982). Substances with a high degree of amorphicity have a high capacity for water vapour sorption, i.e. the amount of water

vapour sorbed is greater than what could be accounted for only by surface adsorption. An increase in the amorphous fraction gives higher values for Equilibrium Moisture Content. Amorphous substances are, for example, polymeric excipients such as starch and polyvinyl pyrrolidone, PVP, and thermodynamically-activated low molecular weight substances. The latter may be created during pharmaceutical processing such as

* Corresponding author.

milling or spray-drying. Microcrystalline cellulose, MCC, can be considered as a partially amorphous polymer with microcrystalline regions.

Water vapour absorbed into the amorphous regions will act as a plasticiser and increase the molecular mobility due to the breakage of hydrogen bonds between molecules (Dawoodbhai and Rhodes, 1989). Consequently, the glass-transition temperature of the amorphous parts, T_g , which indicates the transition from a hard, rigid, glassy state to a soft, flexible, rubbery state, will be lowered (Oksanen and Zograf, 1990; Slade and Levine, 1991). The role of water acting as a plasticiser for amorphous material has been studied for a long time in food science (Slade and Levine, 1991), and has been found to be of significant importance in controlling the quality of food products.

Knowing T_g at different moisture contents and relative humidities, RH, and an understanding of its effects is therefore supposed to be of great value in the pharmaceutical formulation and processing work. In the present study, we have examined the relationship between moisture sorption and the compaction properties of MCC and binary mixtures of MCC with PVP. PVP is a completely amorphous polymer, whereas MCC contains various fractions of amorphous structure depending on the quality used (Rowe et al., 1994) and the pharmaceutical processing applied. The moisture sorption isotherms for MCC and the binary mixtures were characterized by using our previously described climate test chamber method (Stubberud et al., 1995) and were related to the compaction characteristics. Furthermore, the role of glass transitions of amorphous regions due to elevated moisture sorption has been examined.

2. Materials and methods:

2.1. Materials:

2.1.1. Microcrystalline cellulose, MCC

(Emcocel, Mendell, UK) 77% crystallinity, determined by an X-ray analytical method at Mendell, UK.

2.1.2. Milled MCC

Fifty grams MCC (above) was ball-milled (Planetary ball-mill, Retsch, Germany) in 500 ml cups for 30 h. Pot and balls were made of aluminium.

2.1.3. Polyvinyl pyrrolidone, PVP

100% amorphous (Plasdone K-25, GAF, USA)

2.1.4. Cast PVP

Cast PVP was prepared by evaporation of a 20% solution m/V of PVP (above) in ethanol.

2.1.5. Binary mixtures of MCC and PVP:

A dry blend of MCC/PVP in the relationship 19:1 was prepared in a high shear mixer (Niro-Fielder GPI, UK) for 10 min.

A granulation of MCC/PVP, 19:1, was prepared using the same mixer with a wet massing time of 10 min. PVP was dissolved in ethanol, 1:3, before granulating the MCC. The granulation was sieved through a 1.6 mm sieve before drying in a hot air oven.

2.2. Methods

2.2.1. Particle size

Particle size was measured by using laser diffraction (Master Sizer X, Malvern Instruments Ltd., USA). The samples were dispersed in Miglyol 812 prior to measurement. The presented values are the mean values of two analyses.

2.2.2. Surface area

The specific surface area (BET-surface area) was determined in a Gemini 2375 apparatus, Micromeritics, USA, with a reproducibility of $\pm 0.05 \text{ cm}^2/\text{g}$. The samples were degassed for 19 h at 50°C by using Micromeritics FlowPrep 060. Nitrogen was used as adsorbing gas at five relative pressures ranging from 0.05–0.15.

2.2.3. Powder X-ray diffraction analysis

Powder X-ray diffraction was measured at room temperature with a Philips X'Pert-MPD θ - θ diffractometer (Philips, Holland) using Cu-K α radiation 40 kV, 50 mA and a xenon detector. The samples were scanned in steps of 0.02° from 1 to 60° (2θ).

2.2.4. Moisture sorption kinetics

By using the earlier described climate test chamber method (Stubberud et al., 1995), the sorption kinetics of MCC, milled MCC and the binary mixtures of MCC and PVP were characterized. Samples (1 g) were dried for 24 h at 15% RH/ 30°C, and the moisture sorption was determined at 20°C after 2, 4 and 24 h at the different relative humidities. The equilibrium moisture content was obtained within 2 h for all samples, confirming that the method is fast.

2.2.5. Moisture sorption isotherms

The moisture sorption isotherms were characterized for MCC, milled MCC and the binary mixtures of MCC and PVP using our climate test chamber method at intervals of 5%, ranging from 10 to 85% RH.

2.2.6. Glass transition temperature

Differential Scanning Calorimetry, DSC, was performed on samples of PVP and cast PVP using a DSC-7, Perkin-Elmer, USA. Sample weights ranged from 10 to 20 mg and the heating rate was 20°C/min. The samples were equilibrated at different RH for two hours and thereafter hermetically sealed in coated aluminium pans within the climate test chamber to prevent from moisture loss during sample handling.

2.2.7. Water content

The total amount of water in the samples for the moisture sorption analyses, the DSC measurements and the compression studies was determined by Karl Fisher titration (Mettler DL 35, Mettler-Toledo, Switzerland). The solutions used were Karl Fisher solutions (one component system) and dry methanol (Merck, Germany). Although MCC is practically insoluble in alcohol, it showed sufficient solubility to allow the determinations.

2.2.8. Conditioning of samples

One gram samples of MCC and the binary mixtures were equilibrated by using our climate test chamber method for 2 h at 11, 31, 53, 69, 75 and 85% RH \pm 3% RH prior to compression.

sion.

2.2.9. Compression of tablets

Tablets were compressed in an instrumented single punch tablet press (Korsch EK0, Germany) at a compression force of 9.5 ± 1 kN and a compression speed of 35 rpm. Flat faced punches with a diameter of 11.3 mm were used. The powder for each compression was weighed separately under controlled relative humidity (climate test chamber) and transported in sealed containers to the tablet machine. The time before compression, i.e. outside controlled relative humidity, was 10 s or less.

2.2.10. Tensile strength of tablets

The radial tensile strength was measured immediately after compression, and the values will be referred to as initial tensile strength. The tensile strength were also characterized after storage at the same RH as prior to compaction for (a) 20 h in the climate test chamber or (b) 2 weeks in desiccators containing saturated salt solutions.

Tablets compressed of MCC and the dry blend after conditioning of the powder at 85% RH were also transferred to 11% RH for storage for 20 h (climate test chamber) or for 2 weeks (desiccators) prior to characterization. Accordingly, tablets compressed after conditioning of the powder at 11% were transferred to 85% RH for storage at 20 h or 2 weeks.

The radial crushing strength was determined (Tablet Hardness Tester C-40, Engineering Systems, England), and the tensile strength was calculated according to Fell and Newton (1970). The presented values are the mean values of 6 tablets.

2.2.11. Packing fraction

The packing fraction (P_f = bulk density/true density) of the tablets prior to the determination of tensile strength was calculated. The tablets were weighed to the nearest 0.1 mg and their thickness and diameter were measured to the nearest 0.01 mm. True particle density of the powders were measured using a helium pycnometer (Accupyc 1330, Micromeritics, USA).

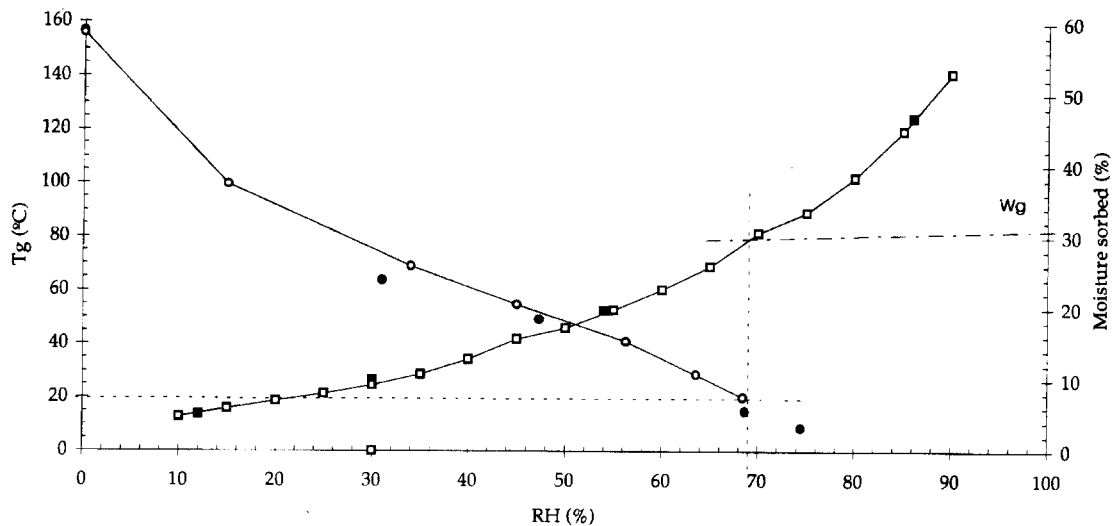


Fig. 1. Relationship between relative humidity, RH, and glass transition temperature, T_g , or amount of moisture sorbed. ● T_g , cast PVP; ○ T_g , PVP as powder; ■ Sorbed moisture, cast PVP; □ Sorbed moisture, PVP as powder.

3. Results and discussion:

3.1. Moisture sorption characteristics and glass transition temperature, T_g , for PVP

Fig. 1 shows the relationship between the relative humidity, RH, and the T_g or the moisture content for polyvinyl pyrrolidone, PVP, as a powder and in a cast form. T_g is reached at room temperature (20°C) at about 70% RH. At this specific humidity the physical structure will change from a glassy state to a rubbery state at a further increase. The amount of water sufficient for reducing T_g to 20°C, i.e. W_g , is 0.31 m/m PVP, corresponding to 31% moisture sorbed. This value can be determined from the sorption isotherm of PVP in the same figure. It agrees with data presented by Oksanen and Zografis (1990) who found W_g for PVP K-30 to be 0.34 m/m PVP at 20°C.

The degree of change in T_g is higher at comparatively low RH, i.e. when changing from 0 to 30% RH, T_g is reduced by about 90°C, whereas a change from 30 to 60% RH gives a corresponding lowering of T_g of about 40°C. The T_g values monitored are apparent, and strongly dependent on both the technique used and the parameter settings applied. For example, Elamin et al. (1995)

have shown that the scanning rate used in the DSC technique has a significant effect.

PVP is usually dissolved in an appropriate solvent prior to its use to produce granulations or spray dried mixtures, and this might influence its subsequent properties. Fig. 1, however, shows that T_g values as well as moisture sorption characteristics for cast PVP, that is, PVP dissolved in an ethanol followed by a drying procedure, are equivalent to those for untreated PVP.

3.2. Moisture sorption characteristics for MCC

Fig. 2 shows the moisture sorption isotherm for untreated MCC and for milled MCC. By milling

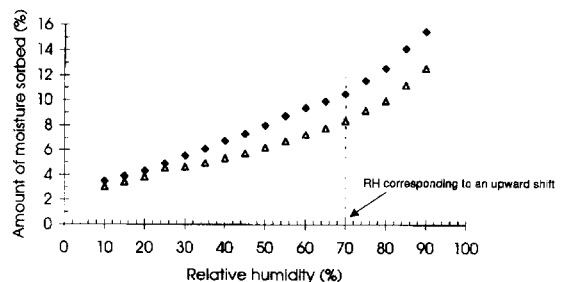


Fig. 2. Moisture sorption isotherm for microcrystalline cellulose, MCC. △ MCC; ◆ Milled MCC.

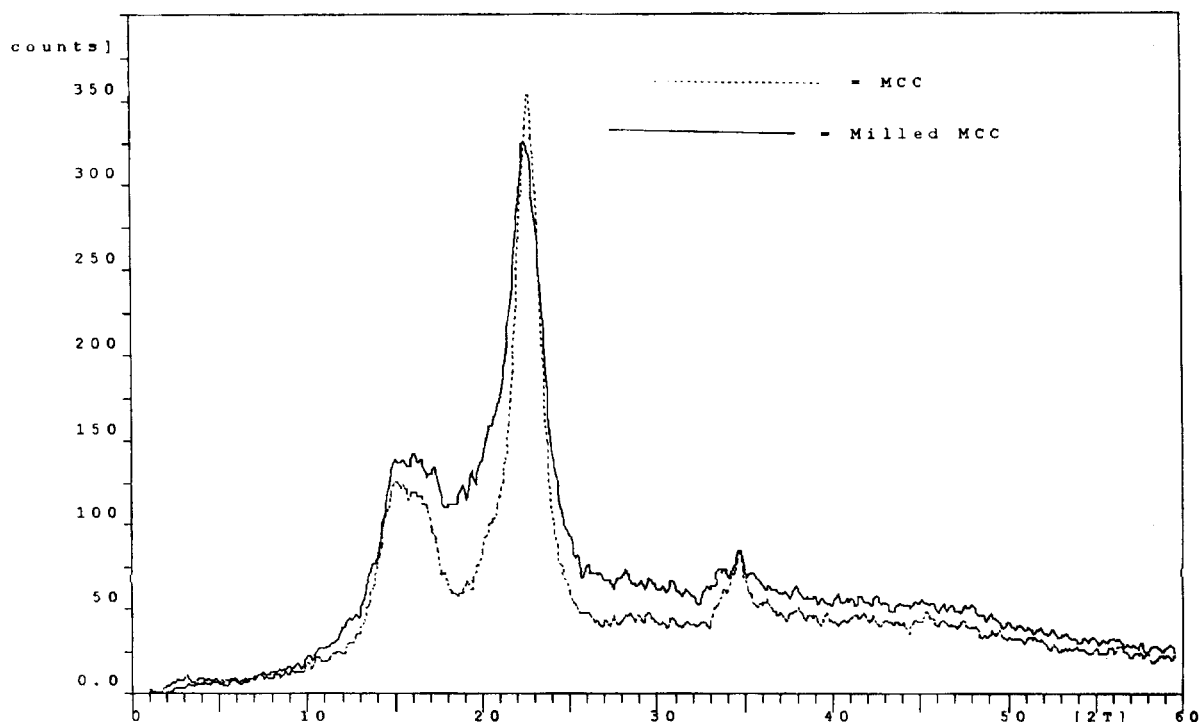


Fig. 3. X-ray diffraction pattern for MCC and milled MCC.

MCC, the amorphous fraction is increased as is shown by the X-ray diffraction pattern in Fig. 3. This supports the findings of Nakai et al. (1977). From Table 1, it is apparent that the BET surface area, determined by N₂ adsorption, is not altered although the mean particle size decreases from 83

to 25 μm . Thus, there are good reasons to conclude that the increase of the amount moisture sorbed at a given RH after milling is related to the increase in amorphous fraction as described by Zografis et al. (1984). For milled MCC as well as for untreated MCC, a deviation from linearity or an upward shift is observed in the region corresponding to an RH of about 70%.

Table 1
BET-surface area determined by nitrogen adsorption after drying, and particle size determined by laser diffraction

Substance	BET-surface area (cm ² /g)	Particle size (μm)
Powder mixture MCC/5% PVP	1.1	88
Granulation MCC/5% PVP	1.0	105
MCC	1.2	83
Milled MCC	1.2	25

3.3. Mechanical properties of tablets:

Fig. 4 shows the initial tensile strength as a function of RH for the MCC tablets as well as for tablets of MCC and PVP. Upon storage for 24 h or 2 weeks, no significant change of tensile strength was observed, except at 85% RH for MCC and the dry blend. Fig. 5 shows the moisture sorption isotherms for the binary mixtures compared to the isotherm for MCC. The isotherm for a mixture of MCC and PVP, calculated by adding the moisture sorption for pure MCC and PVP, is included as a reference. Above 50% RH,

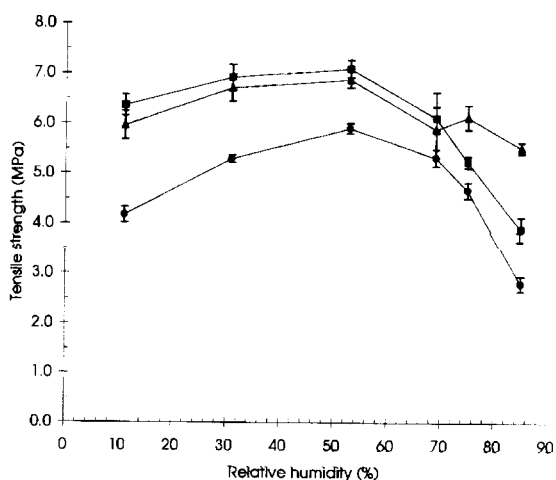


Fig. 4. Tensile strength for MCC and binary mixtures of MCC/PVP (95/5, w/w). —■— Dry blend MCC/PVP; - - -○- Granulation MCC/PVP; ····△···· MCC.

the mixtures show higher values for sorbed moisture relative to MCC, due to the hygroscopicity of PVP (Stubberud et al., 1995). Further, at these high humidities, the dry blend gives higher values than the granulation and the calculated values. Studies of the moisture sorption kinetics, by using the climate test chamber technique, show constant levels for moisture sorption, that is, when comparing moisture sorption values at 2 and 24 h. The time for attaining true equilibrium may, however, be longer. One explanation for the different results might, thus, be that the homogenous mix-

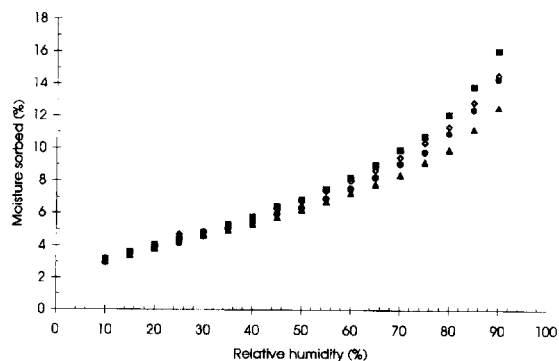


Fig. 5. Moisture sorption isotherms for MCC and binary mixtures of MCC/PVP (95/5, w/w). ■ Dry blend MCC/PVP; ◇ Calculated values MCC/PVP; ● Granulation MCC/PVP; ▲ MCC.

Table 2

Packing fraction, P_f , for tablets determined direct after compression (initial) and after storage for 20 hours and 2 weeks

RH (%)	Initial	20 h	2 weeks
<i>MCC</i>			
11	0.74	0.75	0.74
31	0.78	0.77	0.77
53	0.80	0.80	0.80
69	0.82	0.83	0.81
75	0.84	0.84	0.82
85	0.84	0.84	0.84
<i>Dry blend of MCC/5% PVP</i>			
11	0.76	0.76	0.75
31	0.78	0.78	0.79
53	0.82	0.82	0.82
69	0.84	0.84	0.83
75	0.85	0.85	0.84
85	0.85	0.85	0.84
<i>Granulation of MCC/5% PVP</i>			
11	0.75	0.76	0.76
31	0.79	0.79	0.79
53	0.84	0.84	0.83
69	0.86	0.86	0.86
75	0.86	0.85	0.84
85	0.85	0.86	0.85

ture of MCC and PVP particles favours fast sorption kinetics. For the granulation, however, PVP in cast form will partly cover the MCC particles, thereby prolonging the time for attaining true equilibrium.

Table 2 shows the packing fraction, P_f , for the tablets of MCC and the binary mixtures direct after compression and after storage. An increase in P_f is observed at higher relative humidities, whereas the storage time does not affect it.

3.4. MCC

Significantly stronger tablets ($P < 0.05$) are obtained when the RH of the unmilled MCC used is increased from 11 to 31% corresponding to a change in total water from 3.7% to 4.4% (m/W). No change in the tensile strength is seen at a further increase to 53% RH (6.7%), whereas a significant decrease is observed at 69% RH (7.7%). From 69 to 75% RH, there is no further effect.

Two significantly separated levels can be identified for tensile strength. The first is present between 31 and 53% RH, and the other between 69 and 75% RH, i.e. an increase of the RH above a certain level between 53 and 69% causes a drop in tensile strength. At 85% RH or a water content of 8.8%, the increased moisture sorption (Fig. 2) causes a further significant decrease ($P < 0.05$) in tensile strength.

The effect of moisture, described as water content (% m/W), has been studied by several authors. Malamataris et al. (1991) showed that the tensile strength for compacts of Avicel PH 101 is initially the same but decreases at humidities above about 5%. Wenzel and Kala (1984) showed a maximum in the crushing force at a moisture content of 3% and a pronounced decrease at about 8% for the same quality. For Heweten 40, (MCC, VEB Freiburger Zellstoff- und Papierfabrik, Weissenborn/Freiberg, Germany) they observed a maximum at 2.5% and a corresponding drop in the strength at about 6%. Both groups reported a plateau value with a following drop when the moisture content is increased. These discrepancies in moisture content at maximum tablet strength might be explained by differences in the applied compression force as described by Doelker (1993), or they can be related to the various qualities used and batchwise variations for MCC showing different crystallinity.

The water content at a given RH depends on the amorphous portion (Fig. 2) and also on the processing of the material. Provided that the degree of crystallinity is unknown, it is therefore strongly recommended that the effect of water on tensile strength is studied as a function of the equilibrium relative humidity, ERH, of the solid or the water activity, A_w , and not as an effect of the water content.

3.5. Binary mixtures of MCC and PVP

At humidities up to 69% RH, no significant difference can be seen between the actual values for initial tensile strength of MCC tablets and tablets of the dry blend of MCC and PVP even though the moisture sorption isotherms differ (Fig. 5). The compaction properties of the dry

blend are, thus, dominated by the properties of MCC. When the RH exceeds 69%, a significant deviation between the curves is observed, and the properties of PVP becomes dominating for the tablets of the dry blend. When the RH exceeds 70% at room temperature PVP is in the rubbery state, and the binding properties are thereby impaired. A significant lowering of the tensile strength is observed compared to the case at lower humidities. As the RH is increased to 85%, a collapse of the solid structure and a liquification of PVP is supposed to occur in the mixture, resulting in the pronounced decrease in the tensile strength of compacts that is observed both for the dry blend and the granulation.

A maximum tensile strength is obtained at 53% for tablets based on the granulation of MCC and PVP. Above this RH, a similar decrease in the tensile strength is observed as for tablets of the dry blend. The results are consequently consistent with what can be expected based on the similar T_g for PVP as dry powder and in cast form as shown in Fig. 1.

The tensile strength of tablets compressed at our experimental conditions of 9 kN is significantly lower when based on the granulation compared to the dry blend. During the granulation process, the MCC particles will be partly covered by the PVP which means that the latter is interrupting formation of intermolecular forces between the MCC particles during the compression. Thus, our findings indicate that the intermolecular forces are stronger between adjacent MCC particles than between particles of MCC and PVP. The values for particle size differs (Table 1) and this may also have an impact on the tensile strength. This is described by Karehill et al. (1990) who concluded that a decrease in the particle size and an increase in the particle roughness resulted in stronger compacts.

Table 2 shows that the P_f increases with higher relative humidities, probably due to an increase in the plasticity. As seen in Fig. 4, an increase followed by a decrease is observed for tensile strength of tablets of both MCC and the binary mixtures, corresponding to this increase in the packing fraction. Thus, other factors than the plasticity alone seem to be critical for tensile strength of tablets, as described above.

3.6. Storage of tablets at compression humidity

Tablets compressed of MCC showed no significant change of tensile strength when stored at compression humidity below 85% RH. Fragmentation is limited, and plastic deformation is believed to be the dominating volume reduction mechanism for MCC (Rees and Rue, 1978) with the main binding force attributed to intermolecular forces formed directly during compaction (Karehill and Nyström, 1990). Our data for the binary mixtures of MCC and PVP shows identical compaction properties to that of MCC with no change in tensile strength during storage. This indicates that plastic deformation is also the dominating volume reduction mechanism for the binary mixtures.

The tensile strength of tablets of MCC and the dry blend compressed at 85% RH was significantly reduced during storage at unchanged humidity. This reduction might be explained by the further moisture sorption that was observed and probably explained by the evaporation of moisture during the compaction. The moisture sorption during storage of tablets based on a dry blend was 0.6%. At other relative humidities, the moisture sorption was less than 0.2% for both MCC and the binary mixtures. No significant change of the tablet dimensions was observed on any of the samples during storage.

3.7. Storage of tablets at another RH than that used during compression

The tensile strength for tablets compressed at 85% RH and stored for 2 weeks at 11% RH were found to be more than 10 MPa. This is to be compared to 6.25 MPa (dry blend) and 6.12 MPa (MCC) when tablets are both compressed and stored at 11% RH. This increase in tensile strength for tablets of MCC may be explained by the formation of intermolecular forces during the removal of absorbed water vapour. Tablets of the dry blend, however, hardened more probably due to formation of solid bridges during the transition of PVP from a rubbery to a glassy state, i.e. when the water activity is reduced below this specific value for RH at room temperature (70% RH).

When tablets compressed at 11% RH were stored at 85% RH, they showed significantly lower values for tensile strength relative to when both stored and compressed at 85% RH. The values for the dry mixture is 1.4 MPa when compressed at 11% RH and stored at 85%, and 2.9 MPa when compressed and stored at 85% RH; for tablets of MCC, the values are 1.6 MPa and 4.8 MPa, respectively.

Consequently, both the conditioning humidity prior to compression and the storage humidity after compression will significantly affect the tensile strength. The effect of the storage humidity after compression might even have a more profound influence on the compact strength than the conditioning humidity prior to compression.

3.8. Moisture-solid interactions of MCC

The effect of moisture on the properties of MCC has been investigated by several groups. Zografi et al. (1984) and Khan and Pipel (1986) used moisture sorption isotherms to describe the interaction between the two materials. The latter group (1987) combined the sorption isotherms with the dielectric response compared to Fielden et al. (1988) and Blair et al. (1990) who used calorimetric methods. All these investigations give support to the conclusion that moisture is sorbed into the amorphous part of MCC. Several steps are involved, i.e. one water molecule binding between two anhydroglucose units, followed by the binding of one water molecule to each anhydroglucose unit. Finally, a sorption of more loosely bound water will occur as described by Khan and Pipel (1987). This latter structure increases the molecular mobility of MCC and may be the explanation why water could act as a plasticiser of the amorphous parts of MCC.

The upward shift seen for the sorption isotherm for MCC at about 70% RH (Fig. 2) may be explained by such an increase in molecular mobility or a transition from a glassy (< 70% RH) to a rubbery (> 70% RH) state and may thus be related to T_g. Similar relationships between sorption isotherms and T_g have been reported for other materials by several authors (Oksanen and Zografi, 1993; Hancock and Zografi, 1993; Kaki-

vaya and Hoeve, 1975). We tried to verify such a change in the internal structure related to the moisture sorption characteristics and to T_g by using DSC and a special DSC utilizing oscillating frequencies (ODSC, Seiko, Japan). However, thermal changes reflecting a glass transition could not be observed with the applied techniques. The reason is, most probably, an insufficient sensitivity of the measuring techniques in combination with the low content of amorphous structure in the sample. Our observed decrease in tensile strength of compacts of MCC (Fig. 4) further indicates that a plasticising effect of water, which is related to T_g , takes place. Consistently, Radebaugh et al. (1989) and Amidon and Houghton (1995) have reported that moisture may change the viscoelastic properties and act as a plasticizer for MCC. The latter group have further shown that at a moisture content above a certain level consistent with a transition from a glassy to a rubbery state, significant changes in the mechanical properties will occur.

Faroongsarng and Peck (1994) have reported the T_g for dry MCC (Avicel PH 102), determined by DSC, to be 142.5°C with a decrease to 135.1°C for wet material (100% RH). This is a lower decrease than what is expected from the plasticizing effect of water. The reliability of these data is therefore questionable. We were not able to reproduce the results.

4. Conclusions:

The tensile strength of tablets of MCC depends upon the relative humidity, RH, prior to compaction. At an RH of about 70%, a decrease is observed corresponding to an upward shift for the moisture sorption isotherm, indicating that a glass transition in the amorphous structure of MCC takes place.

For a dry blend of MCC and PVP, as well as for a granulation, the tensile strength is determined by the properties of MCC at RH values below 70%. At RH above 70%, a reduction of the glass transition temperature, T_g , of PVP below the operating temperature (20°C) is the dominating factor determining the tensile strength of these

tablets. Thus, the tensile strength decreases markedly at humidities above 70% RH.

The results illustrate the importance of a thorough characterization of materials used in pharmaceutical products with regard to the effects of water content. The relationship between operating temperature and relative humidity should be taken into consideration during formulation work and production. For instance, during tableting for extended time periods an increase in temperature may occur inducing phase transitions. Another example is where a transition from a glassy to a rubbery state occurs resulting in chemical instability and a changed in vitro dissolution.

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