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RESEARCH PAPER

Understanding the Effect of Environmental History on Bilayer Tablet Interfacial Shear Strength

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ABSTRACT

Purpose To understand the effect of post production environmental conditions on the interfacial strength of bilayer tablets.

Methods Bilayer tablets of microcrystalline cellulose/dicalcium phosphate were exposed to several humidity conditions higher/lower than production conditions and tested in shear to assess interfacial strength. Specific failure mechanisms were observed using x-ray microtomography and scanning electron microscopy.

Results Transients in moisture diffusion of bilayer tablets with significant differential moisture absorption characteristics are responsible for the reduction of strength in both high and low moisture environments. X-ray microtomography and SEM experiments have shown that two different mechanisms of interfacial crack formation are present. For low moisture exposure, interfacial cracks close to the surface were produced, whereas at high moisture conditions, internal interfacial cracks were created. In both cases the fracture modes are consistent with the tensile stresses that develop locally due to the volumetric strains induced by moisture absorption.

Conclusions The insight gained from this work will be useful for material selection and packaging of bilayer tablet systems. While additional work is needed to develop specific guidelines for the optimization of bilayer strength, the results presented here provide a rational basis upon which such work can be conducted.

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KEY WORDS bilayer tablets · cracking · humidity · interfacial strength · transient diffusion

INTRODUCTION

Since the early development of a sustained-release aspirin tablet (1), bilayer tablets have proven to be an effective method to more efficiently deliver one or more therapeutics over a prolonged period of time as opposed to the conventional single layer tablet (2–4). Despite clinical benefits of administering bilayer tablets, production, physical stability, and mechanical integrity are nontrivial issues which must be better understood. To date very few studies exist on the mechanical characterization of bilayer tablets. An early study in 1990 performed by Karehill *et al.* showed a decrease in axial tensile strength of bilayer tablets with increasing first layer compaction pressure (tamping pressure) for several mechanically different materials, e.g. plastically deforming materials and brittle fragmenting materials (5). The observed decrease in axial strength was attributed to the reduction of bonding surface area and adhesion between the layers (5). Inman *et al.* in two complementary studies found similar results for bilayer tablets made of two layers of microcrystalline cellulose (6,7). More recently, Wu and Seville measured the diametrical strength of bilayer tablets made of lactose and microcrystalline cellulose with that of tablets made from a powder mixture of the two materials (8). Anuar and Briscoe evaluated the interfacial relaxation of bilayer tablets upon die ejection and found increased interfacial bonding at higher compaction pressures allows for more robust tablets (9). More recently Podczeck reported on the delamination tendencies in bilayer tablets system. Podczeck suggested that thermal stresses caused from compaction and elastic material mismatch between layers can

result in tablet delamination. In addition, a fracture toughness test was utilized to examine the fracture behavior of the bimaterial interface (10).

All prior work has focused on the strength of bilayer tablets immediately after compaction and ejection. An important aspect which has not attracted any attention yet is the effect of moisture absorption on the strength of bilayer tablets due to the exposure to varying moisture environments. The effect of humidity on pharmaceutical materials in general has been copiously examined within the literature and several phenomena have been recognized such as, changes in the flowability of powders (11), changes in the compressibility and tensile strength of powders exposed to elevated humidity prior to compaction (12–15), and changes of the mechanical integrity of the tablets stored at various humidity conditions over a prolonged period of time (16).

The goal of this study is to understand the effect of post-production environmental conditions on the interfacial strength of bilayer tablets. Bilayer tablets were exposed to several humidity conditions higher and lower than the production conditions. In this paper, we present experimental results of the evolution of shear strength of bilayer tablets exposed to different humidity environments. *In situ* experiments in x-ray computed tomography and scanning electron microscope provide information on failure mechanisms. We put forward the hypothesis that transients in the moisture diffusion in and out of bilayer tablets with significant moisture absorption characteristics are at least partially responsible for the reduction of bilayer tablet strength in both high and low moisture environments. The goal of this paper is to develop a mechanistic understanding of bilayer tablet strength reduction as a result of post-production environmental conditions. Such understanding provides the basis for the evaluation of accelerating testing techniques and provides some insight in material selection and packaging of bilayer tablet systems.

MATERIALS AND METHODS

The work presented here is based on a model bilayer tablet system that consists of a hygroscopic material, microcrystalline cellulose, Avicel PH102 – (MCC) (12–15), and a non-hygroscopic material, dibasic calcium phosphate anhydrous with 1% by weight magnesium stearate lubrication (DCP1MgSt) (17). Bilayer tablets were produced on a fully instrumented Huxley-Bertram compaction simulator. Relative humidity during production was controlled at approximately 25%RH. Flat faced bilayer tablets were produced in a 9.525 mm diameter die at 20 MPa tamping pressure and 200 MPa main compaction pressure. The tamping and main compaction pressures were chosen to represent production parameters that provide sufficient interfacial strength without defects such as visible interface cracking. Microcrystalline cellulose was the first layer filled *via* a gravity hopper and was subsequently tamped *via* the upper punch. Then, dibasic calcium phosphate anhydrous was filled *via* a stirred gravity hopper, thus comprising the second layer. A linear compaction profile with a punch velocity of approximately 120 mm/min per punch, or 240 mm/min relative punch velocity, was used for all tablets. The use of dual action compaction (both punches moving) had two main goals: (a) to maintain the interface flat which improves the reliability and objectivity of the shear test as discussed below and (b) to reduce the effect of tablet/die wall friction (18). The relatively low speed was also chosen by design because it reduces frictional effects on the die wall (19). The displacement of each punch was estimated based on the expected relative density of MCC and DCP1MgSt at 200 MPa. Compaction profiles were executed to maintain constant dimensions for the second layer (2 mm), and total tablet thickness (4 mm). For the geometry and conditions described here, finite element simulations using the Drucker-Prager Cap model show that the relative density at the interface within each layer are minimal with a range of 88%RD-91%RD for MCC and 52%RD to 53%RD for DCP1MgSt (unpublished work).

To assess the interfacial strength of the bilayer tablets a shear testing device was used, see Fig. 1. The device is a variation of the shearing device of Dietrich, *et al.* in which the tablet was held in the axial direction during shearing (20). Such axial constraint affects the measured strength. In this study each layer of the tablet is held diametrically and is forced into motion in opposite directions subjecting the interface to shear. Interface alignment along the shear axis can be achieved by looking through a small window on the device. The samples were loaded until failure in a CT5 diametrical compression (Engineering Systems Inc.)

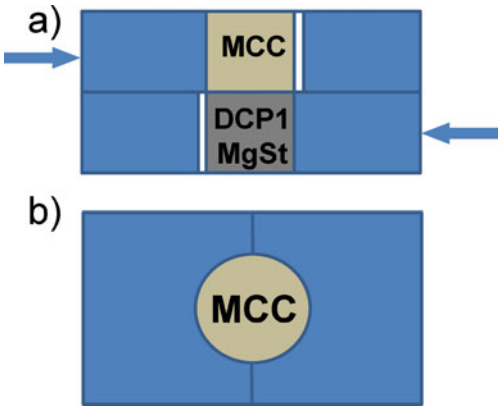

Fig. 1 Schematic drawing of bilayer shear testing device, (**a**) plane cut through center of device showing side view of tablet orientation and (**b**) top view of device.

machine with a resolution of 0.1 N and a loading rate of 2.5 mm/s. Shear strength (σ_{ss}) was calculated by

$$\sigma_{ss} = \frac{P}{\pi r^2} \quad (1)$$

where P was the load to failure and r was the radius of the die, 4.7625 mm.

The sensitivity of the measured shear strength on the exact placement of the bimaterial interface in the shear device was examined in (21). Misalignments in which the shear plane was biased into the MCC layer by 100–200 microns were shown to result in a slight increase in shear strength, approximately 10%, whereas a misalignment into the brittle DCP1MgSt layer showed a negligible effect on interfacial strength.

In order to examine the effect of environmental history on bilayer interfacial shear strength four different history conditions were examined and are listed in Table I. Prior to environmental exposure tablets were allowed to equilibrate at 25%RH for 2 days to ensure that complete relaxation had been achieved. Tablets were weighed using a microbalance with 0.1 mg resolution and measured for thickness and diameter of both layers with a micrometer of 1 μm resolution. The diameters were measured close to the free end of each layer. Tablets were then placed within an environmental chamber where humidity and temperature were maintained at constant set points of 30°C and 55% or 75%RH within variation of +/−2.5%RH and +/−1°C. In addition a set of tablets were exposed to extremely low relative humidity, ~2%RH, which was created by placing a container of anhydrous calcium sulfate in the chamber throughout the exposure time. After each testing point, tablets were removed from the environmental chamber, reweighed, measured, and immediately tested in shear. Specific attention was made to minimize time in which tablets were outside the controlled environment.

RESULTS AND DISCUSSION

Strength Measurements

The bilayer interfacial strength at equilibrium is plotted in Fig. 2 against the external relatively humidity. The strength of the tablets after production is also included in this diagram with a relative humidity of 25%, which corresponds to the controlled humidity of the lab where the compaction (and the storage of the powders before the compaction) took place.

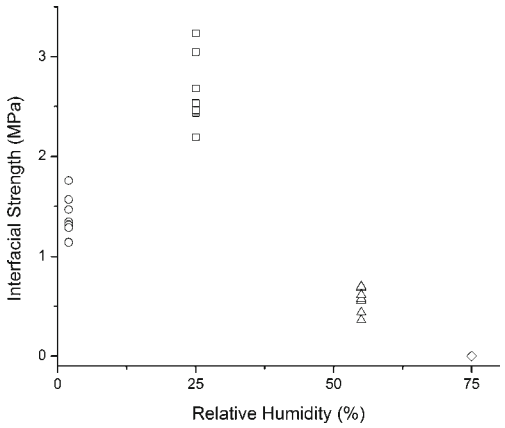

Fig. 2 Bilayer interfacial strength for each testing conditions, $n = 8$ samples (the variation in the %RH signal was +/−2.5% at the constant set points of 55%RH and 75%RH).

The bilayer tablets exposed for 2 days at 75%RH showed a large interfacial crack upon removal from the chamber. In this case, upon handling the tablet split into two. The MCC layer had residual DCP1MgSt on the interface but coverage was minimal, not forming a continuous layer. For the remaining environmental conditions examined, there was no visual sign of interfacial cracking or cracking within an individual layer after exposure. However, upon testing in shear the tablet broke cleanly along the interface and in each case there was residual DCP1MgSt on the MCC layer, similar to that previously mentioned for 75%RH.

These results show that the shear strength of bilayer MCC/DCP1MgSt tablets is reduced from its level after production both for tablets exposed to high relative humidity and for tablets exposed to a near dry atmosphere. Although it is not possible to claim that the maximum of the strength is exactly at the conditions of production of the tablets, it is very clear that either higher or lower relative humidity atmospheres lower the shear strength of the tablets. In order to understand the effect of the relative humidity on the strength of bilayer tablets, we need to understand the parameters that affect their strength and the effects of relative humidity on the tablet.

Table I Environmental History Testing Conditions

Testing I.D.	Condition
Initial	Post production – no prior exposure
75%RH	30°C and 75%RH for 2 days
55%RH	30°C and 55%RH for 2 days
Drying	30°C and ~1–2%RH for 2 days

Differential Diametrical Expansion from Die Size

Mismatch in elastic properties coupled with differences in radial wall stress result in differential expansion from die size for each layer of the bilayer tablet. Figure 3 shows an x-ray backshadow of a bilayer tablet after production along with a

Fig. 3 Geometry of MCC- DCP1MgSt bilayer tablet after ejection.

magnified detail of the edge to emphasize the difference in diameter of the two layers. It is evident from the x-ray backshadow that the DCP1MgSt has a larger diameter compared to the MCC layer. Measurement of the two layers close to the free end with a precision micrometer gave an expansion from die size on the order of 0.9% for DCP1MgSt, while only 0.2% for microcrystalline cellulose. Experiments in single layer tablets of MCC and DCP1MgSt exhibited similar levels of diametrical expansion (0.4% and 1.0% respectively). This comparison indicates that the strain differential between the two layers results in the development of residual stresses, mostly close to the interface. The DCP1MgSt layer, which expands more than the MCC layer, is in a state of compression whereas the MCC layer is in a state of tension as expected by the diametrical strain differential of the two layers. Also, as it is typical in mechanical problems involving interfaces between dissimilar materials, higher stresses are expected at the interface on the surface. The magnitude of these stresses is difficult to quantify because of local plastic deformation and microcracking. Furthermore the stresses in MCC may be further reduced after ejection by viscoelastic relaxation. At this point, it is important to keep in mind that there are residual stresses that exist in these tablets and any additional stresses from subsequent exposure to moisture will be superimposed.

The Effect of Differential Moisture Absorption on Diametrical Strains of Each Layer in the Bilayer

Moisture pick up by MCC results in significant swelling of the material, while the opposite effect occurs if the tablet is subjected to a dry environment. Figure 4 shows the axial and radial strain increment for the MCC layer after equilibration at different levels of external relative humidity. The reference state for the strain increment is the side of the MCC layer in the bilayer tablet after production. Swelling equilibrium was confirmed by exposing MCC single layer tablets to identical conditions and it was determined that the characteristic time of moisture diffusion was 14 h, well within the time of 2 days allotted to reach equilibrium. Figure 4 shows only results for the MCC layer because the DCP1MgSt layer exhibited negligible change upon exposure. It was assumed that the initial amount of moisture within the MCC layer corresponds to equilibrium of the tablet at 25%RH, which is confirmed by the interpolation of the results. Exposure to different humidity conditions resulted in significant swelling and shrinkage anisotropy. The axial to radial strain ratio was approximately 4 for each of the different humidity conditions. The origin of the observed swelling and shrinking anisotropy arises from a combination of particle orientation during the compaction process and the specific sites of water adsorption as described in (13).

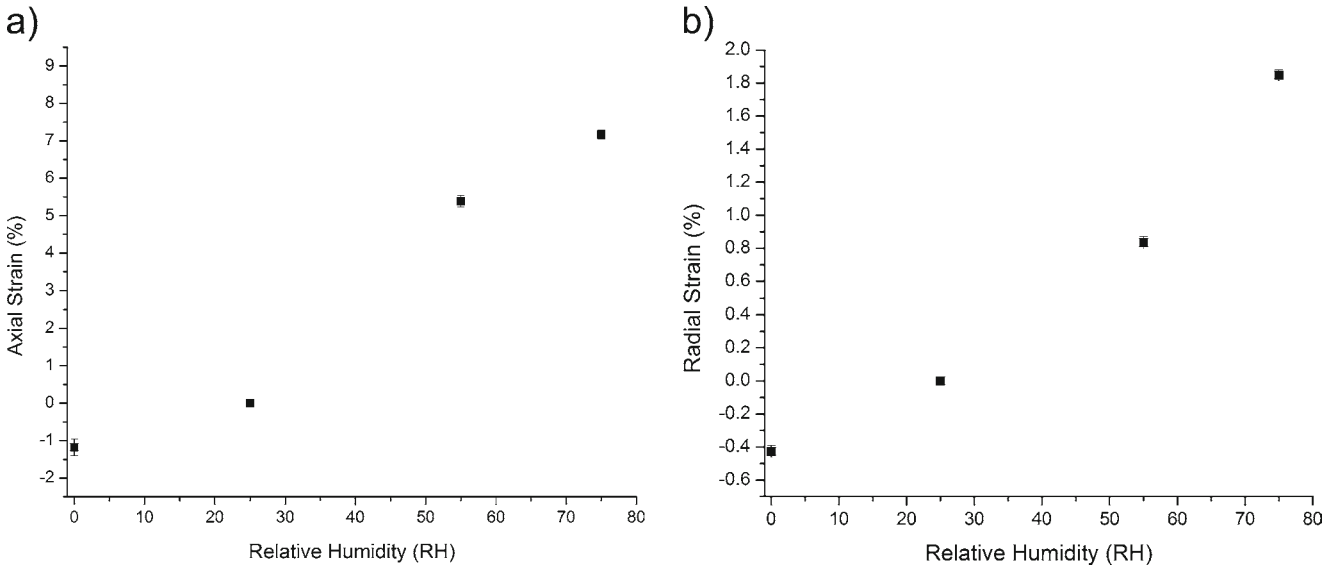

Fig. 4 Equilibrium (**a**) axial and (**b**) radial strain of the MCC layer within bilayer tablets at 30°C and different exposure humidity.

The strain increment from exposure to different humidity conditions is superimposed to the initial strain state of the tablet. Therefore drying of the tablet exaggerates the differential expansion from die size between the MCC and DCP1MgSt layers, while exposure to higher humidity reduces the differential and at very high values of relative humidity reverses the sign of the diametrical strain differential. Figure 5 shows the interfacial strength *versus* the final diametrical strain differential upon completion of environmental testing, calculated by:

$$\Delta\varepsilon_{diametrical} = \frac{\left(d_{DCP1MgSt} - d_{MCC}\right)}{d_{die}} * 100 \qquad (2)$$

For this result the reference point is the size of each layer within the die before ejection (i.e., the diameter of the die). From a purely geometrical point of view, an increase in the diametrical strain differential, as seen in drying, should increase the level of residual stresses and should decrease the strength of the tablet, in agreement with the experimental observations of Fig. 4. The opposite is expected when the tablet is exposed to humidity higher than the one characteristic of the production. Swelling of the MCC will initially decrease the diametrical strain differential between the two layers, until a level of humidity is reached for which the diameters of the two layers become equal in size, indicated as the "best" case scenario in Fig. 5. For a relative humidity higher than this level, the swelling of the MCC is so large, that the diametrical strain differential changes sign (MCC diameter is larger than the diameter of DCP1MgSt). It appears that if swelling negates the differential expansion from die size, it should be beneficial to the strength of the tablet. This concept, however, is not confirmed by the experiments. There are many possible effects that need to be considered in order to explain this discrepancy among which: (a) the effect of moisture on the elastic properties of the two layers (b) the effect of viscoelastic relaxation, (c) a direct effect of moisture on the strength of MCC and (d) the possibility that the transient rather than the equilibrium of moisture absorption plays a role in the determination of the strength.

The direct effect of moisture on the viscoelastic properties of MCC has been examined in (22). It was reported that the storage modulus was constant up to 5%w/w water content (equivalent to MCC in equilibrium at RH = 50%) and then drops to 40% of the original value at a moisture content of 7%w/w (equivalent to MCC in equilibrium at RH = 70–75%).

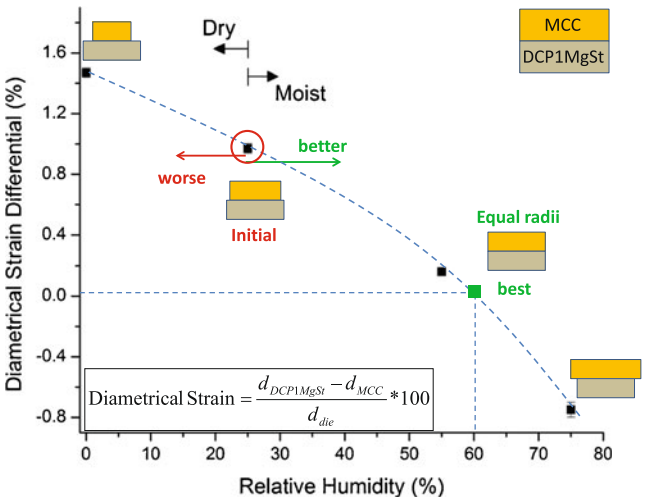

Fig. 5 Diametrical strain differential upon equilibration to different levels of relative humidity. An "ideal" condition would correspond to no diametrical stress differential and is marked with a *square* in the graph above.

In addition to the direct reduction of modulus, increased water content may affect the viscoelasticity of MCC. Results from the literature (23,24) indicate that characteristic relaxation time for MCC is on the order of seconds. Any relaxation of the internal stresses due to viscoelasticity will be realized effectively immediately for the range of experiments performed here. Therefore, moisture uptake is limited only by diffusion and there is no constraint by the viscoelasticity of the material on swelling. Furthermore the stresses that exist before or develop during moisture absorption are affected by the fully relaxed viscoelastic properties of MCC. Intuitively, both the reduction of modulus and viscoelastic relaxation should decrease the level of residual stresses at high humidity, a tendency that is not in line with the experimental observations.

The Effect of Transient Moisture Absorption upon Exposure to High Relative Humidity

To ensure that the bilayer tablets had reached equilibrium, a series of experiments were performed in which the weight of MCC single layer tablets (9.525 mm diameter and 4 mm thick) were measured throughout the time to reach equilibrium upon exposure to 30°C and 75%RH. Figure 6 shows the transient uptake of MCC single layers for 90%RD tablets which correspond to the density of the MCC layer in the bilayer tablets. The same trend was observed in the single layer tablets, as with the bilayer tablets, in which the time to reach equilibrium was approximately 2000 min which lies within the 2 days (2880 min) time that the bilayers were exposed. The transient measurements provide insight into the time constant of moisture diffusion into the porous tablet.

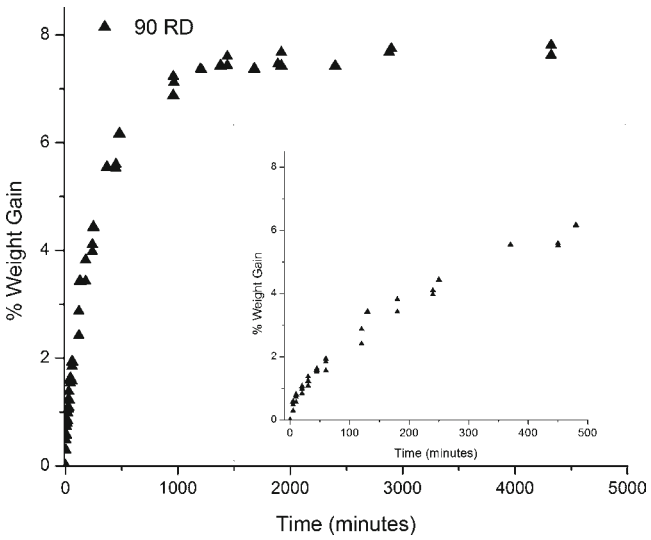

Fig. 6 Transient weight gain of MCC single layer tablets exposed to 30°C and 75%RH (inset shows the initial stages of weight gain).

Parallel work (25) has shown that the time constant for moisture diffusion in a low aspect ratio tablet may be related through the following equation:

$$\tau = \frac{\tau_{non-absorbing}}{(1-RD)}\left(1+\frac{RD}{\beta(1-RD)}\right) \tag{3}$$

where $\tau_{non-absorbing}$ is the time constant for moisture diffusion in a non-absorbing porous medium, RD is the tablet relative density, and β is the partition coefficient dictating the amount of moisture absorbed within the material. Using equation 3, an effective diffusivity may be established for the bilayer tablet system where D_{eff} is defined through equation 4.

$$D_{eff} = D_{non-absorbing}\frac{1}{\left(1+\frac{RD}{\beta(1-RD)}\right)} \quad where\ D_{non-absorbing} \sim D_{air}^{H_2O}(1-RD) \tag{4}$$

Within equation 4 it is important to note that the non-absorbing diffusion coefficient has an inherent dependency on porosity, as shown it is related to the diffusivity of water vapor in air and the relative density of the tablet. For example, at a relative density equal to one the effective diffusivity of water vapor would be zero. Using the effective diffusion coefficient defined through equation 4, the transient moisture gradients within the MCC layer may be estimated. For instance, after just 5 min of exposure the distance in which moisture has traveled within the tablet is on the order of several hundred microns. However, after 500 min of exposure moisture has traveled approximately 1 mm into the tablet thus creating a large moisture gradient which spans from the surface of the tablet to the center. Consequently, a volumetric strain gradient develops within the tablet. Diffusion anisotropy may also be taken into consideration through equation 4. Therefore, in calculating the estimated diffusion distance after a given time it should be expected that moisture will travel less in the axial direction then the radial due to direction dependent tortuosity (26). In addition DCP1MgSt has a larger partition coefficient, β, than MCC, indicating that it absorbs very little moisture at 75%RH. As a result, moisture diffusion through DPC1MgSt will be faster than MCC and similar to diffusion through a non-absorbing porous material.

The experimental observation of mass pickup of MCC at RH=75% (see Fig. 6) indicates that the characteristic diffusion time is of the order of 10^5s, or a diffusivity of 10^{-10}m^2/s. During the two day exposure of our experiments, the bilayer tablets spend a significant fraction of time under conditions that the moisture has only partially penetrated into the MCC layer. Therefore significant gradients of water concentration, swelling strain, and associated stresses exist during this period of time within the MCC layer. A schematic shown in Fig. 7 attempts to provide a qualitative picture of these transients during moisture uptake. Upon absorption of moisture within

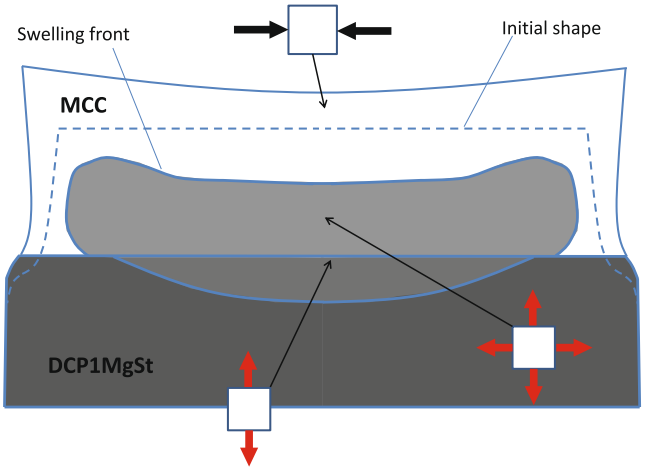

Fig. 7 Stresses generated upon swelling of the MCC layer (*red arrows* indicate tensile stresses and *black arrows* indicate compressive stresses).

the MCC layer, the surface layer exposed to moisture will swell and expand almost instantaneously whereas the center of the MCC layer is still not subjected to increased moisture and will not swell. At the same time, moisture will diffuse into the DCP1MgSt layer (faster than it will diffuse into MCC), which does not swell. The swelling of the surface of the MCC layer reduces the difference in diameter between MCC and DCP1MgSt, and thus it reduces any residual stresses associated with this geometric issue. The partial penetration of the swelling front, however, induces additional stresses within the MCC layer. The MCC material close to the outer surface attempts to swell but it is constrained by the unchanged core where the moisture retains its original level. This constraint results in compressive stresses close to the surface with a direction parallel to the free surface. These stresses are balanced by corresponding tensile stresses in the core of the MCC layer. At the interface close to the axis of rotational symmetry of the tablet, the tensile stress is normal to the interface and increases the potential for mode I failure (tensile opening) of the interface.

The magnitude of the internal tensile stresses is a function of the material properties upon absorption and the degree of swelling. Noting that in general bimaterial interfaces are weaker in mode I *versus* mode II (shear loading) (27), it is conceivable that the internal tensile stresses result in internal cracks that effectively reduce the strength of the bilayer tablet. To explore this hypothesis, tablets were imaged during moisture uptake within a x-ray computed microtomography machine (Skyscan 1172).

Figure 8 shows a sequence of x-ray images of the bilayer tablet exposed to 75%RH and ambient temperature. The DCP1MgSt layer appears as the darker grayscale material and the MCC layers appears as the lighter grayscale material due to different levels of x-ray absorption. Initially, as shown in Fig. 8a, b, there is no evidence of cracking throughout the tablet or along the interface. A clear boundary exists between the MCC and DCP1MgSt layer. After 17.5 min of exposure at 75%RH a crack opens along the interface of the bilayer tablet, see Fig. 8c. The crack is very subtle but the arrows indicate the opening of the crack. The crack expands along most of the interface but does not extend through to the exterior surface of the tablet. The opening of the crack took shorter than 1 min which was the interval between images at that time of the experiment. After 3 h of exposure the crack has opened approximately 50 microns as shown in Fig. 8d. At this point the crack has propagated closer to the interface but instead of following the interface to the edge of the table, the crack has deflected into the DCP1MgSt layer. Upon 24 h of exposure the crack has opened such that the interface is no longer in contact at the left edge of the tablet shown in Fig. 8e, f.

These observations are fully consistent with the idea that moisture diffusion gradients contribute to the reduction of strength. Initial internal crack opening occurs after a rather short time when moisture has diffused approximately 200 microns into the tablet and a swelling strain gradient is established. The fact that the crack opens in the center and not at the surface is also consistent with the concepts shown in Fig. 7. Notable is also the fact that tablets removed from the high moisture conditions around 20 min of exposure did not show visual evidence of a crack along the interface. Therefore unbeknown to the observer a crack may develop within a bilayer tablet system upon swelling which may not be detectable from traditional visual observations.

The Effect of Transients During Drying of Bilayer Tablets

An analogous situation occurs when bilayer tablets are subjected to drying environments. During exposure to low humidity, the surface of the MCC layer will lose moisture and shrink. Figure 9 depicts the situation where moisture is lost from the MCC layer and the resulting stress state is developed within the bilayer tablet. As a result of the loss of water, the dimensions of the MCC layer will decrease both in the axial and radial directions. The diametrical strain differential between the two layers will further increase and create a shear stress state close to the bimaterial interface on the surface of the tablet, which is more severe than that of the original state of the tablet. In addition, the drying front, which advances into the MCC layer, separates MCC into two regions, a shrinking region close to the surface and an intact region in the core of the tablet. The internal region opposes the shrinking of the outer layers creating a state of tension within the partially dried region with a direction parallel to the surface. As in the previous case these tensile stresses are balanced by compressive stresses in the center of the tablet.

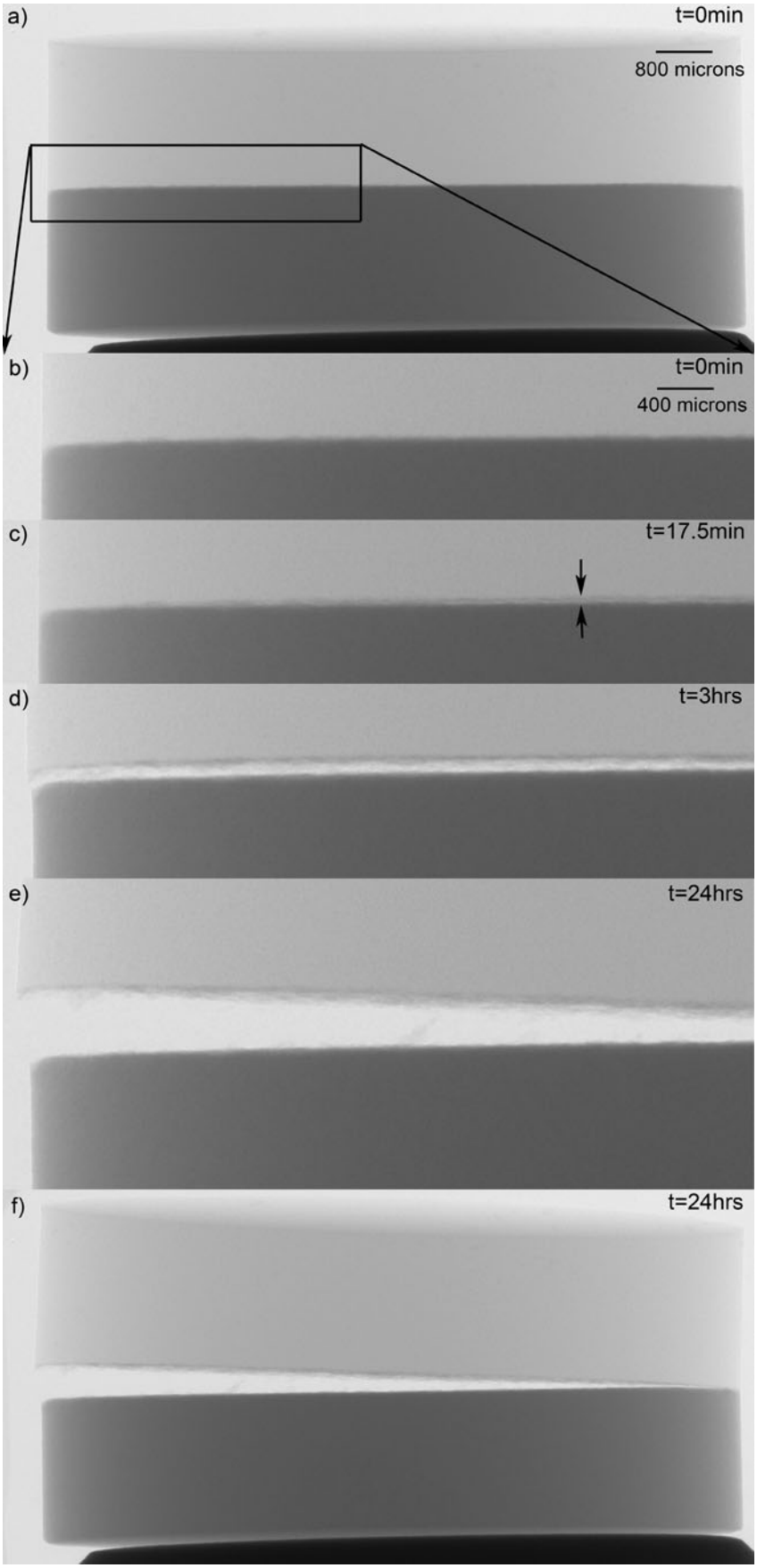

Fig. 8 Crack development upon exposure to 75%RH (**a, b**) 0 min exposure, (**c**) 17.5 min exposure, (**d**) 3 h exposure, (**e, f**) 24 h exposure. (Scale bar is the same for images **a, f, b,** and **e**. Please see Supplementary Material for transient movie of the swelling process.)

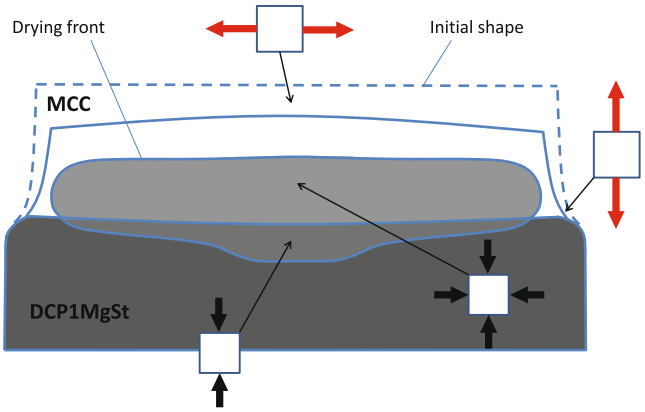

Fig. 9 Stresses generated upon drying of the MCC layer (*red arrows* indicate tensile stresses and *black arrows* indicate compressive stresses).

The interface fracture is caused by a combination of the increased shearing (mode II) of the bimaterial interface on the surface due to the enhanced diametrical strain differential and the superimposed tensile stresses in the same area due the transient state of drying of the MCC layer. To confirm the location of cracking upon drying, bilayer tablets were examined within the scanning electron microscope (SEM). Due to the high vacuum conditions within the chamber, moisture is lost by the MCC material resulting in shrinking. Note that drying experiments were attempted within the microcomputed tomography machine but lack of spatial resolution limited the early detection of cracking. Figure 10 shows the progression of the interfacial crack opening along the radial edge of the bilayer tablet due to the loss of moisture. Initially a very small crack opening may be seen which travels along the entire interface. It is possible that this crack appears within the time interval between the placement of the sample in the SEM and the beginning of the observation. After several minutes the MCC layer starts to shrink in the radial direction and the crack opens further in a mode II manner. However, after an hour of drying the two materials separate significantly resulting in a large crack opening along the interface in a mode I fashion. The crack penetrates through the tablet and along the interface. The presence of the crack on the interface and the combined mode I and mode II of the crack opening are in full agreement with the suggested hypothesis, discussed above.

DISCUSSION

The results presented here clearly show that exposure to high or low moisture results in a reduction of the interfacial strength of bilayer MCC/DCP1MgSt model tablets. Factors associated with internal stresses in bilayer tablets, such as (1) differential expansion from die and its subsequent evolution upon exposure to high or low moisture environments, (2) viscoelasticity of MCC, and (3) gradients in moisture and swelling strains, were examined to pinpoint the factors that cause this behavior. While (1) and (2) both certainly affect the internal stress state, it is the effect of moisture transients that is consistent with the *in-situ* observations, e.g. the mode of failure and the location of the cracks, as well as the fact that these cracks may appear relatively early and grow with continuous exposure to high or low moisture. As in any fracture problem, failure occurs when the stress field is such that a critical material property is exceeded. It is, therefore essential to consider the direct effect of moisture on the strength of the interface. A direct assessment of this effect is very difficult since all the other factors mentioned above are unavoidably present. Thus, this aspect of the problem can only be conceptually examined. While the overall variation of strength (shown in Fig. 2) with the relative humidity may be consistent with a hypothetical non-monotonic dependence of interface strength on the relative humidity with a maximum at RH=~25%, such hypothesis is inconsistent with the *in-situ* observations of crack development in bilayers exposed to RH=75%. Given that the external surface of the bilayer is first exposed to and quickly reaches the external humidity level, if the failure of the tablet was due to the degrading effect of moisture on the interfacial strength, then the failure should initiate on the surface, and not internally as observed and discussed previously. Therefore this hypothesis needs to be rejected unless somehow moisture arrived quickly into the inner core of the tablet from the DPC1MgSt side. This is possible as DCP1MgSt does not pick up any appreciable amount of moisture and its relative density is sufficiently low (~55%) at 200 MPa so that the diffusion of moisture is substantially faster than in MCC (100 times faster).

To exclude this possibility, a series of experiments were conducted with bilayer MCC/MCC tablets. MCC bilayer tablets made to the same conditions and dimensions as the MCC-DCP1MgSt bilayers were exposed to 75%RH within the microCT. In this situation moisture diffusion will be slow in both layers because of MCC's ability to absorb moisture. It was found that crack formation within the MCC bilayer tablets was identical as in the MCC/DCP1MgSt tablets and the time to reach crack initiation was equivalent. This result demonstrates that although a direct contribution of moisture on the interfacial strength cannot be excluded, the *in-situ* observations can only be justified by the consideration of the transient moisture diffusion and the associated strain and stress gradients.

CONCLUSIONS

We presented experimental results on the variation of interface strength of bilayer tablets consisting of a highly absorbing layer (MCC) and an non-absorbing layer (DCP1MgSt)

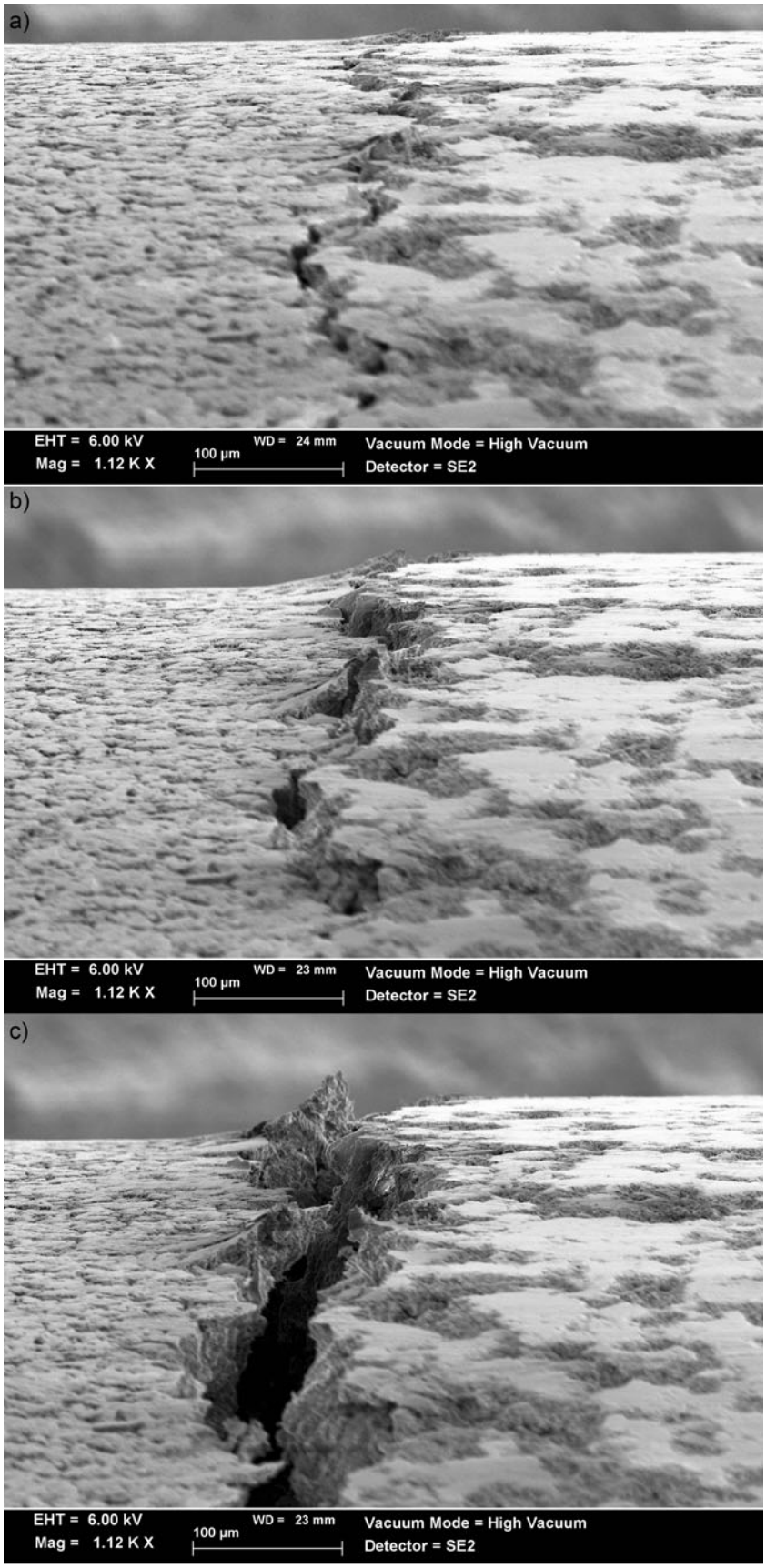

Fig. 10 Drying of bilayer tablet examined through SEM (**a**) t = 0 min, (**b**) t = 30 min, and (**c**) t = 55 min. MCC layer is on the left and DCP1MgSt layer on the right. (Please see Supplementary Material for transient movie of the drying process.)

that were initially produced and stored at RH=~25% and were subsequently exposed to relative humidity higher and lower than RH of 25%. The presented results demonstrate that in either case (higher or lower RH) the bilayer tablet interfacial strength was reduced. Since the consideration of the equilibrium swelling of the hygroscopic MCC layer is not consistent with this results, it was concluded that transient stresses due to partial diffusion of moisture in and out of the MCC layer are responsible for the reduction of strength. Consistent with this idea are the results of x-ray microtomography and SEM experiments which showed, that two different mechanisms of interfacial crack formation were present. For low moisture exposure, interfacial cracks close to the surface were produced, whereas at high moisture conditions, internal interfacial cracks were created. While a direct contribution of the moisture on the reduction of the bilayer strength is possible, in both cases the fracture modes are consistent with the tensile stresses that develop locally due to the volumetric strains induced by transient moisture absorption or reduction. While much more work is needed to develop general guidelines for the optimization and the long term performance of bilayer strength, the results presented here provide a rational basis upon which such work can be conducted.

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