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Micro-scale measurement of the mechanical properties of compressed pharmaceutical powders. 1: The elasticity and fracture behavior of microcrystalline cellulose

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Abstract

The feasibility of using very small compacts ($\sim 8.0 \times 4.5 \times 0.4$ mm; ~ 20 mg) to determine the elasticity and fracture behavior of compressed pharmaceutical powders using the three-point beam-bending technique was evaluated. Compacts of microcrystalline cellulose with a range of porosities were tested using a thermomechanical analyzer and values for the Young's modulus and critical stress intensity factor at zero porosity (E_0 and K_{IC0}) were determined by extrapolation. The value of E_0 measured at ambient relative humidity on un-notched beams was found to be in close agreement with that reported for much larger samples, and the value of K_{IC0} for the small notched compacts was at the lower limit of the accepted range of values for microcrystalline cellulose. The fracture toughness (R) and total energy of fracture (U) for the notched specimens were also determined and used to estimate the apparent surface energies for crack initiation (γ_i) and for total fracture (γ_f). To further probe the utility of the micro-scale mechanical testing techniques, the effects of humidity on the various mechanical properties of the small microcrystalline compacts were examined and it was found that E_0, K_{IC0}, R_0, γ_{i0} and γ_{f0} each decreased as the surrounding humidity (and water content of the samples) increased.

Keywords: Microcrystalline cellulose; Three-point beam-bending; Young's modulus; Critical stress intensity factor; Fracture toughness; Surface energy; Moisture content; Relative humidity

1. Introduction

The mechanical properties of compressed powder specimens are of interest to pharmaceutical scientists because an appreciation of these properties can help in understanding the behavior of tablet dosage forms. The Young's modulus (E) (i.e. the stiffness, or elasticity) and the critical stress intensity factor (K_{IC}) (i.e. resistance to crack

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propagation) are both important parameters for characterizing the physical behavior of pharmaceutical compacts (Rowe and Roberts, 1995). Likewise, the fracture toughness (R) and surface energy for fracture (γ) can be useful for describing the failure behavior of compressed powder samples (Davidge and Tappin, 1968; Rowe and Roberts, 1995). The objective of the work described herein was to evaluate the use of very small compressed powder compacts (~ 20 mg) for determining these properties of pharmaceutical materials using the three-point beam-bending technique. The three-point beam-bending technique is a test in which a beam (un-notched or notched) is stressed (bent or broken) by applying a force on a probe at a fixed rate (Fig. 1). To date the smallest beam size that has been used to evaluate these mechanical properties of compressed pharmaceutical materials has been $20 \times 7 \times \sim 3.5$ mm (~ 200 mg) (Rowe and Roberts, 1995). The specimens used in the current experiments were designed to be as small as practically possible ($\sim 8.0 \times 4.5 \times 0.4$ mm; ~ 20 mg) in order to minimize the amount of material required for testing. The applicability of the small scale testing techniques was further investigated by determining the relationship between the humidity surrounding the test specimens and their mechanical properties using the micro-scale three-point beam-bending method. The effects of the environmental conditions on compact mechanical properties are of interest because water content has been observed to affect the durability of pharmaceutical tablets (Nyqvist et al., 1981). The micro-scale mechanical testing technique used in this work allowed the sample temperature and humidity to be precisely controlled throughout testing as well as minimizing the amount of material required for each test.

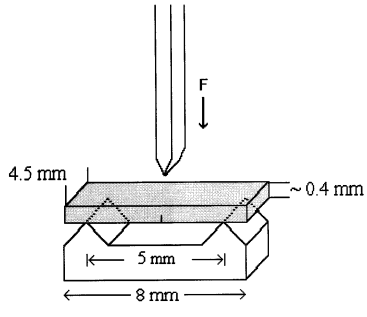

Fig. 1. Experimental configuration for three-point beam-bending using the thermomechanical analyzer.

1.1. Sample size considerations

The minimum specimen size that can be successfully used for mechanical property testing of compressed powder samples is principally determined by the microstructure of the compacted material. The specimen must be of a sufficient size that its cross-section at any point is representative of the bulk structure, and for fracture mechanics experiments ('beam-breaking') the artificially introduced crack must extend over multiple particle diameters. These features ensure that during sample bending and fracture an equilibrium stress condition can be readily achieved.

Empirical lower limits on the width, thickness and crack depth of compressed powder samples used for fracture mechanics experiments have been proposed based on experience with a range of ceramic, polymeric and metallic materials (Bansal and Duckworth, 1979; Hashemi and Williams, 1984). Based on these criteria minimum specimen dimensions for microcrystalline compacts have been estimated (Rowe and Roberts, 1995) (thickness and crack depth ~ 0.6 mm, and sample width ~ 1.2 mm). To our knowledge no theoretical or empirical restrictions on specimen size have been proposed for the determination of the elastic modulus of compressed powder specimens by three-point beam-bending. It has been pointed out by several authors that appropriate mechanical testing conditions will vary between materials and test configurations and thus there can be no pre-set universal criteria for specimen dimensions (Bansal and Duckworth, 1979). The sample dimensions selected for use in this work (length $= 8.0$ mm, width $= 4.5$ mm, thickness ≈ 0.4 mm, crack depth $= 0.15$ mm) were principally dictated by the capabilities of the measuring instrument and were of the same order as the lower limits estimated for measuring the fracture behavior of microcrystalline cellulose samples. Hence, this work should allow the validity of these minimum dimensions to be experimentally evaluated.

2. Materials and methods

2.1. Beam formation

Beams comprising approximately 20 mg of microcrystalline cellulose (Avicel PH101, FMC Corp., PA; ~50 μm nominal particle size) were made by uniaxial compression/decompression using a flat-faced 8.0 × 4.5 mm punch and die set (Elizabeth Carbide, NC) and a hydraulic press (Fred S. Carver Inc., NJ). Loads of 333, 666, 1000, 1600 and 3000 pounds (~151, 302, 454, 726 and 1361 kg) were used to form beams of varying porosities. When required a small sharp V-notch (0.15 mm depth; 60° internal angle) was incorporated into the bottom surface of the beams by using a specially designed lower punch with a raised 'knife-edge' across its centre. This method of introducing a pre-defined crack is very reproducible, and represents the normal way in which surface flaws are introduced into pharmaceutical tablet surfaces during manufacture (i.e. by embossing).

2.2. Beam pre-conditioning and storage

The beams were equilibrated at humidities of ~0, 22, 53 and 75% RH by sealing them in glass desiccators over a desiccant or saturated salt solution for a minimum of 10 days. The salt solutions used were potassium acetate (22% RH), magnesium nitrate (53% RH) and sodium chloride (75% RH) (Rockland, 1960). Drierite™ and a vacuum were used to obtain the ~0% RH atmosphere. The dimensions of the beams (±1 μm) were measured with a micrometer after 10 days equilibration. The average weight of the beams during the experiments was evaluated by weighing the beams immediately before and after the experiment and determining the mean value ('wet-weight'). The water content of the beams was determined by subtracting the dry weight of the beams (measured after the beams were dried under vacuum at 105°C for 24 h) from the wet weight. The porosities (P) of the beams were calculated using the following equation which takes into account the water content of the specimens

$$P = (1 - (m/(w_1\rho_1 + w_2\rho_2)\cdot V)) \times 100, \quad (1)$$

where m is the wet-weight of the beam, V is the volume of the beam, w_1, w_2, ρ_1 and ρ_2 are the weight fractions and densities of water and microcrystalline cellulose respectively.

2.3. Beam testing

The mechanical properties of the microcrystalline cellulose compacts were determined by the three-point beam-bending test using a Seiko thermomechanical analyzer (TMA 120C, Haake-Seiko, Paramus, NJ) with a quartz probe and sample stage (Fig. 1). The appropriate relative humidity was maintained during the experiment by placing an appropriate salt solution or desiccant in a small test tube within the sealed TMA furnace chamber. At least three compacts were tested at 21.0 ± 0.5°C for each humidity/porosity/parameter combination and the individual results typically agreed within ±5%. The beams were first allowed to equilibrate in the TMA and then a load was applied at a fixed linear rate (10 g min^{-1}). For the beam-bending determinations a maximum load of 50–100 g was applied (according to the porosity of the sample), whereas for the beam-breaking determinations the beams were loaded until failure. In all cases the displacement of the sample was measured every 0.1 s to an accuracy of ±1 μm.

2.4. Calculations

The Young's modulus was determined from the linear region of the force-displacement curves for both the notched and un-notched specimens. Specifically, the modulus was obtained from the slope of the stress versus strain plots where

$$\text{Stress } (\sigma) = 3Fl/2wt^2, \quad (2)$$

$$\text{Strain } (\varepsilon) = 6td/l^2, \quad (3)$$

d is the vertical displacement of the beam, F is the force applied to the beam, l is the distance between the supports, w is the width of the beam and t is the thickness of the beam. The critical stress intensity factor was calculated from the results of the beam-breaking experiments (Rowe and Roberts, 1995) using

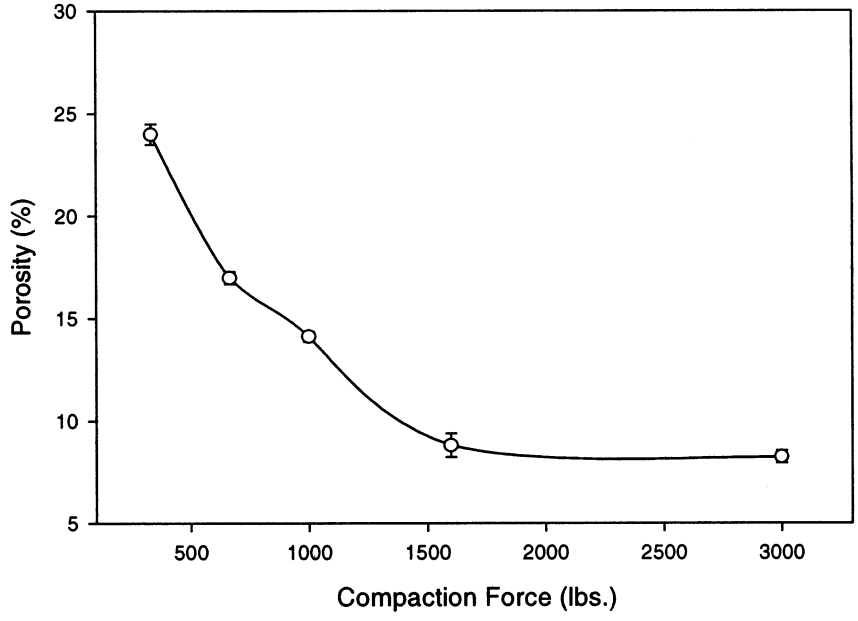

Fig. 2. Porosity of beams as a function of compaction force (at 22% relative humidity).

$$K_{IC} = Y(3F'lc^{0.5}/2wt^2), \quad (4)$$

where F' is the force at failure, c is the notch depth, and Y is a polynomial expression incorporating the dimensions of the specimen

$$Y = 1.96 - 2.75(c/t) + 13.66(c/t)^2 - 23.98(c/t)^3 + 25.22(c/t)^4. \quad (5)$$

The total energy consumed during fracture (U) was determined by integrating the area under the load-displacement curve for the fracture mechanics ('beam-breaking') experiments (Davidge and Tappin, 1968; Bansal and Duckworth, 1979). In all instances a range of forces were used to produce beams with varying porosity and the experimentally determined values for E, K_{IC} and U could be extrapolated to zero porosity (E_0, K_{IC0}, U_0) to permit comparison to previously published results.

The fracture toughness (R) and the apparent surface energy for crack initiation (γ_i) at zero porosity were estimated from E_0 and K_{IC0} (Davidge and Tappin, 1968; Bansal and Duckworth, 1979; Rowe and Roberts, 1995)

$$R_0 \approx (K_{IC0})^2/E_0, \quad (6)$$

$$\gamma_{i0} \approx R_0/2, \quad (7)$$

and the apparent surface energy for fracture at zero porosity (γ_{f0}) was calculated from U_0

$$\gamma_{f0} = U_0/(2w(t-c)), \quad (8)$$

3. Results and discussion

3.1. Force-porosity relationship

Fig. 2 shows the decrease in porosity with increasing compaction force for the small microcrystalline cellulose beams used in these experiments. The results were practically identical for the notched and un-notched beams stored at each of the different relative humidities.

3.2. Young's modulus

There was a clear increase in the measured Young's modulus as the porosity of the beams decreased, as illustrated in Fig. 3. This trend is identical to that observed by other workers using much larger beams, both with the three and four point beam bending methods (Rowe and Roberts,

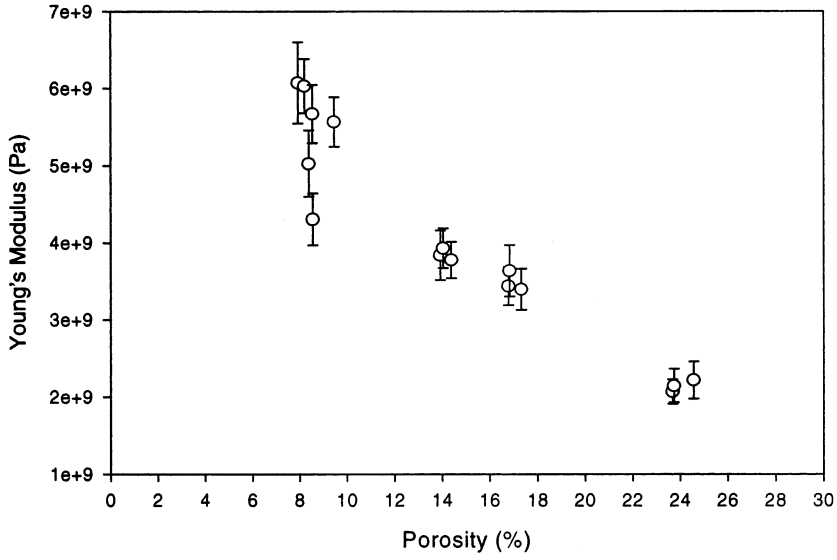

Fig. 3. Mean Young's modulus of the un-notched beams as a function of porosity (at 22% relative humidity).

1995). The trend was preserved at each relative humidity of storage examined. It is likely that the mechanical stiffness of powder compacts is related to the number and intimacy of inter-particle contacts and these would be expected to increase as the compact porosity decreases. Another way to view the system is as a solid body containing microscopic voids or flaws which weaken the specimen. These defects are effectively squeezed out as the porosity of the compact increases and thus the stiffness and resilience of the sample increases.

Previous workers have advocated the use of the empirical Spriggs equation to describe the variation of the Young's modulus with specimen porosity

$$E = E_0 \cdot e^{(-b \cdot P)}, \quad (9)$$

where E_0 is the modulus at zero porosity and b is a constant (Spriggs, 1961; Rowe and Roberts, 1995). Fits of the data obtained with the un-notched beams at 22% and 75% relative humidity to the Spriggs equation are shown in Fig. 4, and equally good fits were obtained for all the data sets (r^2 values between 0.9443 and 0.9698). The modulus values at zero porosity (E_0) for the un-notched samples at normal ambient humidities (e.g. 22% and 53% RH) obtained from this curve fitting procedure (Table 1) were very close to published values for much larger beams (7.5–10

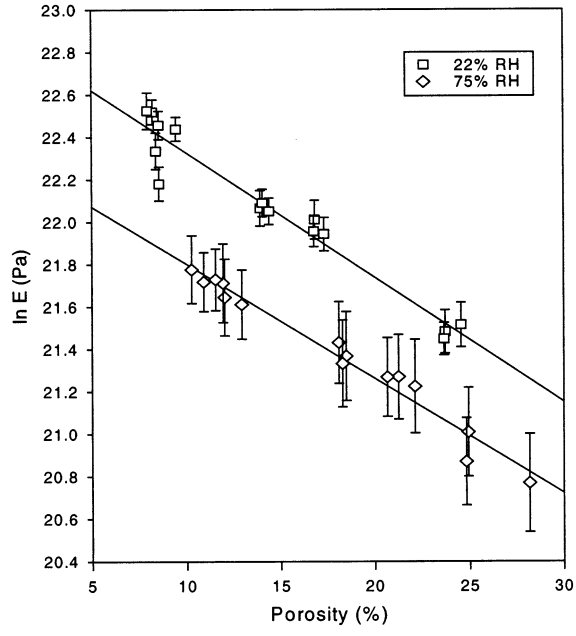

Fig. 4. Natural log of the mean Young's modulus of the un-notched beams as a function of porosity (at 22% and 75% relative humidity).

Table 1
Mean mechanical property values at zero porosity for small microcrystalline cellulose beams stored at different humidities

Relative humidity (RH)	Mean water content	Young's modulus (un-notched beams) (E_0)	Young's modulus (notched beams) (E_0)	Critical stress intensity factor (K_{IC0})	Fracture toughness (R_0)	Total energy consumed during fracture (U_0)	Surface free energy for crack initiation (γ_{i0})	Surface free energy for fracture (γ_{f0})
(%)	(% $^{w}/_{w}$)	(GPa)	(GPa)	(MPa.m$^{0.5}$)	(Jm^{-2})	(J$\times 10^{-6}$)	(Jm^{-2})	(Jm^{-2})
~0	0.7	9.2	5.7	0.67	49	61	24	27
22	3.7	9.0	5.1	0.60	40	51	20	23
53	5.6	6.5	4.2	0.46	33	36	16	16
75	7.7	5.1	3.2	0.31	19	28	9	12

GPa (Rowe and Roberts, 1995)). This indicates that the ~20 mg un-notched compacts of microcrystalline cellulose are suitable for modulus determinations using the three point beam bending method. This is a particularly notable result since less than 350 mg of powdered material was required for the entire determination of E_0 using the micro-scale mechanical testing technique.

Modulus values are not typically determined from the results of beam-breaking experiments on notched beams, however, if the initial bending behavior prior to failure were reproducible and unaffected by the presence of the notch this might provide a valuable means of obtaining additional data from fracture mechanics experiments (Personal communication: R.J. Roberts). Davidge and Tappin have investigated the effect of notch depth on the stiffness of glass specimens subjected to three-point beam-bending and reported that sample stiffness decreased measurably as the notch depth to thickness ratio increased (Davidge and Tappin, 1968). The moduli of the notched microcrystalline cellulose samples at zero porosity determined from the initial force-displacement profiles were approximately 40% lower than those for the un-notched samples (Table 1), in close agreement with the results reported for the glass specimens at equivalent notch depth to thickness ratios (Davidge and Tappin, 1968). It appears that the initial elasticity of notched microcrystalline cellulose compacts is significantly reduced by the presence of surface defects (cracks). Clearly such modulus results cannot be used for the comparison of different systems (e.g. different materials) because of the likelihood of their strong dependence on the sample characteristics (e.g. crack depth). However, these results are useful in a practical sense since they very clearly demonstrate the effect of surface flaws or cracks on the modulus of 'real' compressed powder specimens (e.g. pharmaceutical tablets).

3.3. Critical stress intensity factor

The relationship between the critical stress intensity factor and the porosity of the small microcrystalline cellulose beams was practically identical to that reported previously for larger specimens (i.e. log-linear) (Rowe and Roberts, 1995). Hence, a modified form of the Spriggs equation was used to estimate the K_{IC} values at zero porosity (by substituting K_{IC} for E) (Table 1). The K_{IC0} values obtained at ambient humidities were equivalent to the lowest values reported for microcrystalline cellulose compacts in the literature (Rowe and Roberts, 1995). The K_{IC} values for small samples would be expected to be slightly reduced compared to larger specimens if alignment of the testing apparatus was not quite perfect resulting in uneven stress distributions, or if the crack depths were somehow slightly enlarged, for example, by the presence of micro-flaws within the compacts. The beam and crack dimensions used in this work were approaching the size of the microstructural features within the compact, with the theoretical crack depth only three times greater than the nominal size of the particles and the sample thickness only 8-fold larger, so the observed level of agreement is in fact very good. Notably the reproducibility of the determinations did not appear to be reduced by the very small sample dimensions. Data for solid samples of several synthetic homopolymers have been shown to demonstrate a slight decrease in the K_{IC} with decreasing sample size (Hashemi and Williams, 1984) and consideration of the literature data for microcrystalline cellulose compacts in combination with the current data shows a similar small decrease in K_{IC0} with specimen size (Rowe and Roberts, 1995). It therefore appears that the current sample size (~20 mg) probably represents the practical lower limit for fracture mechanics experiments with this material and type of testing apparatus.

3.4. Fracture toughness, total energy consumed during fracture, surface energy for crack initiation, and surface energy for fracture

The fracture toughness at zero porosity was determined from the E_0 and K_{IC0} values using Eq. (6). Since the K_{IC0} values were at the lower extreme of the published range the fracture

toughness values followed the same trend (Table 1). Despite this the fracture toughness results from this work were sufficiently accurate to confirm that microcrystalline cellulose compacts can be classified as 'semi-brittle' specimens (Rowe and Roberts, 1995).

The total energy consumed during fracture (U) was determined at each porosity and observed to increase with decreasing porosity (data not shown). The U vs. porosity plots were extrapolated to zero porosity in the same way as for E and K_{IC} and values for U_0 were obtained (Table 1). Values for the limiting apparent surface free energies of crack initiation (γ_{i0}) and total failure (γ_{f0}) were estimated from the fracture toughness and total energy of failure at zero porosity using Eq. (7) and Eq. (8) (Table 1). Theoretically these parameters represent the energy consumed during crack initiation and total sample failure in order to create new material surfaces. The values reported in Table 1 are quite similar to each other under similar experimental conditions which suggests that for this material the fracture behavior is dominated by the energy requirement for initiation of crack growth. The apparent surface free energy values were however several orders of magnitude greater than the surface free energy value for microcrystalline cellulose measured using other techniques and this indicates that during the cracking of the microcrystalline cellulose compacts a significant amount of energy is required for processes other than the creation of new surfaces (e.g. for plastic deformation) (Davidge and Tappin, 1968). This is consistent with the mechanical properties of microcrystalline cellulose (e.g. yield pressure) reported in the literature.

3.5. Effect of specimen storage at different relative humidities

Table 1 indicates the range of water contents that was produced by the equilibration of the microcrystalline beams at various relative humidities. It should be noted that there was some overlap of the individual sample water contents at the chosen relative humidities. There was a distinct decrease in the modulus, K_{IC}, fracture toughness, and surface free energies of the microcrystalline cellulose compacts with increasing storage humidity and water content (Table 1). The decrease in elasticity with increasing water content was most pronounced after the water content reached approximately 3% w/w, and this trend is identical to that reported by other workers for microcrystalline cellulose compacts (Khan et al., 1988; Radebaugh et al., 1989; Malamataris et al., 1991; Amidon and Houghton, 1995). Notably the moisture induced shifts in the mechanical properties were all within one order of magnitude and thus can be considered to be moderate changes comparable in significance to those due to differences in specimen porosity (e.g. see Fig. 3 and Fig. 4). It should also be noted that the current microscale testing technique was very well suited to establishing trends in mechanical properties with water content since its small, sealed, temperature controlled sample chamber allowed very close control of the environmental conditions around the test specimens.

A plausible and consistent explanation for the observed trends in mechanical properties with changing compact moisture content is not easy to pinpoint. Previous authors have speculated about the effects of adsorbed surface layers of water, plasticization of the amorphous regions of the cellulose, and disruption of inter- and intra-molecular hydrogen bonding within the cellulose structure. As shown by Radebaugh and co-workers (1989) even the method of introducing water into microcrystalline cellulose compacts influences the measured mechanical properties. Intuitively it seems most likely that water taken up by a compact formed under ambient conditions will exert its major influence by disrupting and weakening the interparticle interactions. When a microcrystalline cellulose compact bends or breaks it is most likely to fail at these interparticle contacts since they will include some of the weakest links between molecules. This mechanism for the effect of water on the properties of microcrystalline cellulose compacts is consistent with the observed reductions in each of the mechanical properties measured in this work.

4. Conclusions

The suitability of utilizing very small compacts for the determination of the mechanical properties of compressed pharmaceutical powders using the three-point beam-bending method was evaluated. The moduli of un-notched beams of microcrystalline cellulose recorded at ambient humidities and extrapolated to zero porosity were extremely close to values reported for larger specimens. Therefore such small beams appear to be quite suitable for the determination of Young's modulus using this method. The critical stress intensity factor, fracture toughness, total energy of failure, and surface free energies of crack initiation and failure could also be determined using the micro-scale three-point beam-bending techniques, albeit with a slightly lower degree of accuracy. To further evaluate the micro-scale mechanical testing approach the effects of humidity on each of the mechanical properties were determined and it was found that all of the properties decreased with increasing water content.

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