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Micro-scale measurement of the mechanical properties of compressed pharmaceutical powders. 2: The dynamic moduli of microcrystalline cellulose

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Abstract

The use of two 'micro-scale' dynamic mechanical testing techniques for determining the viscoelastic properties of very small microcrystalline cellulose compacts (~ 20 mg) is reported. The first method is a simple tensile 'stretching' test, and the second is a dynamic version of the three-point beam-bending technique. For both approaches the storage (elastic) and loss (viscous) moduli could be readily determined for compacts of a wide range of porosities. The experimentally determined storage moduli were consistently one order of magnitude greater than the corresponding loss moduli indicating a dominating elastic response for the microcrystalline cellulose compacts. The moduli determined using the oscillating three-point beam-bending technique were slightly lower than expected and this was attributed to sample anisotropy and imperfect sample alignment/friction during testing. The moduli obtained using the simple dynamic tension tests were practically identical to complex moduli values reported for much larger specimens, and it appears that this technique is well suited to measuring the dynamic mechanical properties of very small pharmaceutical powder compacts. © 2001 Published by Elsevier Science B.V.

Keywords: Microcrystalline cellulose; Three-point beam-bending; Young's modulus; Dynamic mechanical spectrometer; Thermomechanical analyzer; Storage modulus; Loss modulus; Damping; Elasticity

1. Introduction

The dynamic mechanical properties of compressed pharmaceutical powders are of great interest to scientists engaged in the formulation of tablet dosage forms. Since drug supplies are often limited during the early stages of formulation development there is a particular interest in developing very small scale testing techniques that can be used to determine such properties. In this work we report the evaluation of two micro-scale dynamic mechanical testing techniques for determining the viscoelastic properties of very small powder compacts (~ 20 mg). The first method is a simple dynamic tensile 'stretching' test similar to that commonly used with polymeric films (Ferry, 1980). The second technique is a dynamic version of the three-point beam-bending technique which

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has previously been used to determine the elasticity and fracture behavior of pharmaceutical powder compacts at low strain rates (Rowe and Roberts, 1995).

2. Materials and methods

2.1. Specimen size considerations

Microscopic modulus measurements may be successfully made on single particles (e.g. single crystals) provided they are free from significant defects (e.g. Haussuhl and Jiyang, 1999). For compressed powder samples significantly larger specimens are required due to the inherent heterogeneity and porosity of the samples. The minimum specimen size that can be successfully used for mechanical property testing of powder compacts is determined by the sample microstructure. The specimen must be of a sufficient size that the cross section is representative of the bulk material, thus ensuring that during testing reproducible and equilibrium strain conditions can be readily achieved. The model material selected for use in this study was microcrystalline cellulose (Avicel PH101, FMC Corp., PA, USA). This material is amenable to the formation of compacts of a range of porosities without the need for special preparative conditions. It is also probably the most widely studied of all pharmaceutical powders and this permits the comparison of our results with already published data. For the particular grade of microcrystalline cellulose selected, the primary particles are fibers with a nominal size of 50 μm. It can be readily appreciated that the compact dimensions selected (length = 8.0 mm, width = 4.5 mm, thickness $\approx$ 0.4 mm) probably represent the minimum size that can be successfully used with this type of material since the sample thickness is just one order of magnitude greater than the nominal particle size.

2.2. Specimen preparation

Approximately, 20.0 mg portions of the 'as-received' powder were compacted into rectangular specimens by uniaxial compression/decompression using an 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 ($\sim$ 151, 302, 454, 726 and 1361 kg) were used to form specimens of varying porosities. All the samples were equilibrated at $\sim$ 0% relative humidity by storing them in a glass desiccator over a desiccant for a minimum of 10 days. Their weights and dimensions were then measured and the porosities (P) of the compacts calculated using the following equation:

$$P = 1 - \frac{m}{\rho V} \quad (1)$$

where m is the weight of the compact, V is the volume of the compact, and ρ is the true density of microcrystalline cellulose (1.56×10^3 kg/m^3, as determined by helium pycnometry).

2.3. Dynamic mechanical testing

A dynamic mechanical spectrometer (DMS) (Haake-Seiko, DMS 200, Paramus, NJ) was used to determine the steady state moduli of the compacts under dynamic tension at nine frequencies from 0.05 to 20 Hz and at 21 ± 0.5 °C/ $\sim$ 0% RH (Fig. 1) (ASTM, 1994a,b). The instrument was calibrated for temperature and modulus using a standard poly(methyl methacrylate) plate supplied by the instrument manufacturer. The instrument compliance and spring constant, bias in detection circuitry, and effects due to acceleration and deceleration of the clamping assembly were accounted for by blank measurements with rigid metal samples, as recommended by the instrument manufacturer. The compacted powder specimens

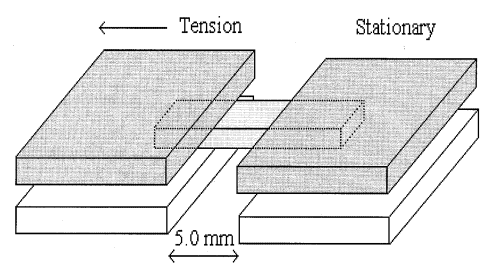

Fig. 1. Experimental configuration for dynamic tension experiments (using the DMS).

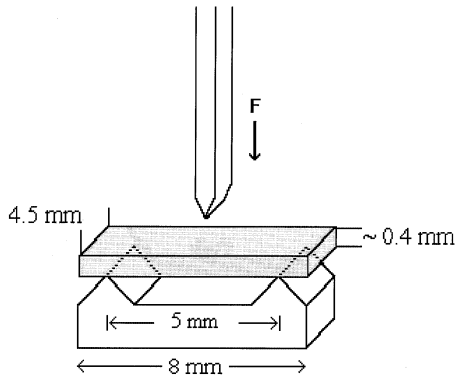

Fig. 2. Experimental configuration for dynamic three-point beam-bending experiment (using the TMA).

were fixed horizontally with the separation between the clamps equal to approximately 5 mm. One clamp was fixed while the other oscillated sinusoidally in tension at the required frequency with a maximum force of ~ 100 g, sufficient to achieve measurable but low sample strains. These conditions were selected so that all testing occurred within the linear viscoelastic region for the samples. Careful clamping of the samples was necessary to prevent damage or slipping at the clamping points. These events could be easily detected by microscopic examination of the samples after testing or from apparent changes in sample length during testing. The dimensions of each sample were determined before and after testing using a handheld digital micrometer and the storage and loss moduli were obtained directly using the proprietary instrument software. Typically triplicate determinations were made at each porosity.

A thermomechanical analyzer (TMA) (Haake-Seiko, 120C, Paramus, NJ) was used for the three-point beam-bending experiments (Fig. 2) (ASTM, 1994a,b). The instrument was calibrated for force using a series of standard weights (1–100 g) and for displacement using several standard shims provided by the instrument manufacturer. Corrections for instrument compliance and bias were made in an analogous way to those described above for the DMS experiments. A dry atmosphere was maintained during the experiments by placing desiccant in a small test tube within the sealed TMA furnace chamber and by purging with dry nitrogen gas. All experiments were carried out at a controlled temperature of 21 ± 0.5 °C. The samples were stressed by applying a sinusoidal load of up to 100 g (65 ± 35 g) at a frequency of 0.05 Hz. This loading procedure produced sample deformations of less than 0.1 % (in the linear viscoelastic region for the samples). Each experiment consisted of at least 15 complete loading cycles (depending upon the time taken to reach steady state conditions), and the absence of damage to the samples during testing was confirmed by microscopy. The load and displacement of the sample were recorded as a function of time and converted into stress and strain using the following equations:

$$\text{Stress}(\sigma) = \frac{3Fl}{2wc^2} \tag{2}$$

$$\text{Strain}(\varepsilon) = \frac{6cd}{l^2} \tag{3}$$

where 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 c is the thickness of the beam. The absolute modulus (E^*) was then determined from the stress and strain values according to the appropriate ASTM methods (ASTM, 1994a,b). Typically triplicate determinations were made at each porosity.

For both DMS and TMA experiments the mean phase lag (δ) was determined from:

$$\delta = 2\pi f \Delta t \tag{4}$$

where $\pi = 3.14159$, f is the experimental frequency, and Δt is the average time delay between the applied load and resulting displacement. The time delay was resolved to better than 0.01 s using the proprietary instrument software. The storage and loss moduli (E' and E'') were then calculated using following equations:

$$E' = |E^*| \cos \delta \tag{5}$$

$$E'' = |E^*| \sin \delta \tag{6}$$

The storage (E') and loss moduli (E'') describe the elastic and viscous properties of the material, respectively (Craig and Johnson, 1995).

3. Results and discussion

3.1. Force–porosity relationship

Fig. 3 shows the decrease in mean porosity with increasing compaction force for the small microcrystalline cellulose beams used in these experiments. As previously reported microcrystalline cellulose powder is very compactable (Doelker, 1987) and thus a wide range of sample porosities could be achieved. The porosity versus force relationship was very reproducible and thus results could be averaged across several specimens if so desired. The results presented in the remainder of this report were not averaged since this was not necessary for the data manipulation.

3.2. DMS measurements

The storage and loss moduli determined for the microcrystalline cellulose compacts at 0.05 Hz using the simple dynamic tension experiment are shown in Fig. 4, as a function of the specimen porosity. Very similar results were obtained at all the experimental frequencies used (0.05–20 Hz). The magnitudes of the storage and loss modulus values varied approximately logarithmically with the specimen porosity and were similar to those determined for much larger compacts of microcrystalline cellulose and potato starch using a dynamic flexure testing technique (Radebaugh et al., 1989; Van der Voort Maarschalk et al., 1996).

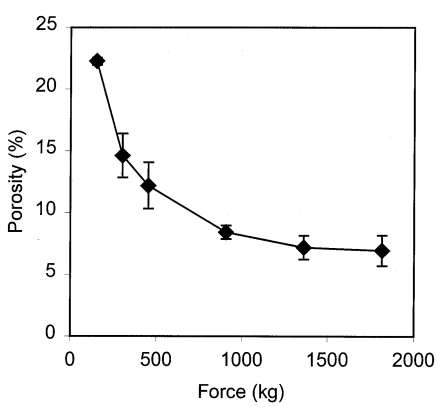

Fig. 3. Variation of the porosity of the microcrystalline cellulose specimens with applied compaction force.

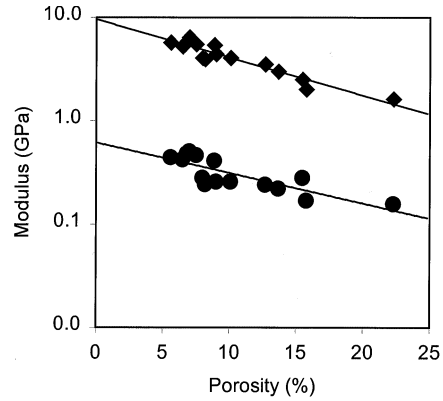

Fig. 4. Variation of the storage (◆) and loss (●) moduli of the microcrystalline cellulose compacts with sample porosity (determined by simple dynamic tension experiments at 0.05 Hz).

The storage modulus values for the current samples were approximately one order of magnitude greater than the loss modulus values at all porosities indicating that the balance of viscous and elastic properties was not affected by the microstructure of the compacts. The difference in magnitude of the storage and loss moduli indicates that the microcrystalline cellulose compacts deformed primarily as if they were elastic bodies and thus their storage moduli values should be approximately equal to their absolute moduli values. It is also true under these circumstances that each of these values should be very similar to literature values for Young's moduli that have been determined at low strain rates.

In order to be able to compare the current data to published data it is necessary to determine the moduli at a common porosity condition. Usually this is achieved by an extrapolation of the data to the theoretical zero porosity point (the y-axis) by using the Spriggs equation (Spriggs, 1961; Rowe and Roberts, 1995)

$$E = E_0 e^{-bP} \tag{7}$$

where E_0 is the modulus at zero porosity and b is a constant. Since there are no previous reports of dynamic modulus values for microcrystalline cellulose compacts at zero porosity (E'_0) it is necessary to compare our current data with literature values for the Young's modulus (E_0) determined at low strain rates. The values for E'_0 in this work

ranged from 9.3 GPa at 0.05 Hz to 11.1 GPa at 20 Hz and these results compare very well with the range of published E_0 values determined at low strain rates (6.3–10.3 GPa) (Rowe and Roberts, 1995). The absolute moduli values at zero porosity determined in this work (9.4–11.1 GPa) were also very similar to the literature values. These results are particularly striking since less than 350 mg of powdered material was required for the determination of E_0^*, E_0' and E_0'' using the micro-scale dynamic mechanical testing technique described herein.

The effect of measurement frequency on the storage and loss moduli extrapolated to zero porosity is shown in detail in Fig. 5. There was a significant increase in the storage modulus with increasing frequency indicating that the molecular rearrangement processes during testing become more and more restricted with increasing measurement frequency. At higher frequencies a limiting storage modulus value would be expected to be achieved. The loss modulus changed with experimental frequency in a similar fashion to the storage modulus and thus the ratio of the two parameters (known as the damping coefficient, or $\tan\delta$) was approximately constant over the frequency range studied (0.064–0.069 at 0.05–20 Hz).

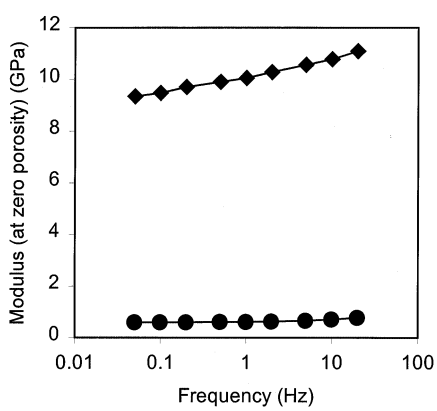

Fig. 5. Variation of the storage (◆) and loss (●) moduli of the microcrystalline cellulose compacts at zero porosity with test frequency (determined by simple dynamic tension experiments).

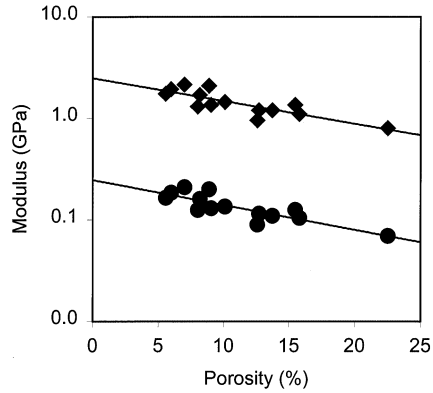

Fig. 6. Variation of the storage (◆) and loss (●) moduli of the microcrystalline cellulose compacts with sample porosity (determined by dynamic three-point beam-bending at 0.05 Hz).

3.3. TMA measurements

The storage and loss moduli determined for the compacted microcrystalline cellulose samples using the dynamic three-point beam-bending technique are plotted in Fig. 6 as a function of the specimen porosity. As previously noted for the DMS data the storage modulus was about one order of magnitude greater than the loss modulus at all porosities indicating that the deformation of the microcrystalline cellulose compacts was primarily elastic. Both of the moduli increased approximately logarithmically with decreasing compact porosity as expected.

Compared with the results of the DMS measurements the storage and complex modulus values at zero porosity determined by dynamic three-point beam-bending were slightly lower (Figs. 4 and 6). This difference cannot easily be attributed to non-uniform density of the samples or the presence of small defects (cracks) in the specimens since none of these problems were encountered when identical samples were tested using the same test configuration at a low constant strain rate (Hancock et al., 2000). The mode of loading the samples is different for the two test configurations (DMS and TMA), but in theory each should result in tensile loading parallel to the longest dimension of the sample if the samples are perfectly isotropic. It has been demonstrated that the assumption of isotropy may not be valid for

compacted pharmaceutical powders (including microcrystalline cellulose) in some circumstances (Nebgen et al., 1995; Moe and Rippie, 1997). It is also possible that the assumptions of perfect sample orientation and zero friction between the sample and the supports required for the three-point beam-bending analysis may have started to break down under the conditions selected for dynamic testing with the TMA. None of these potential explanations for the slightly lower modulus values from the three-point beam-bending experiments could be easily verified experimentally.

Despite the apparent slight bias in the results from the micro-scale three-point beam-bending technique the data appeared to indicate the expected trends in the dynamic mechanical properties of the microcrystalline cellulose compacts. Hence, this technique may still be useful for rank ordering the properties of small compressed powder samples. It might also be possible to provide results, which are comparable to those from other experimental techniques if different sample loading and orientation approaches were developed. It is notable that the results of the current work with two different dynamic testing techniques show a similar scatter to data reported in the literature for low shear rate techniques (primarily 3- and 4-point beam bending experiments) using much larger and presumably more 'ideal' specimens. The variation in published values for these systems has been attributed to slight variations in sample preparation conditions, specimen geometry, storage conditions, and test procedures between different laboratories (Bin Baie et al., 1996). The current work suggests that some dynamic testing configurations may be more susceptible to these types of effects than others, and that miniaturization of mechanical testing techniques can result in an acceptable degree of accuracy and precision provided the experimental procedures are carefully chosen and developed.

4. Conclusions

The suitability of utilizing very small (~ 20 mg) samples for the determination of the dynamic mechanical properties of compressed pharmaceutical powders was evaluated using a simple dynamic tension technique and an oscillating three-point beam-bending method. With both techniques the storage and loss moduli could be easily measured as function of sample porosity, and for the former technique a wide range of loading frequencies could be employed. The experimentally determined storage moduli were consistently one order of magnitude greater than their corresponding loss moduli and thus could be compared directly with Young's modulus values measured using low shear rate techniques. The storage moduli determined by the oscillating three-point beam-bending technique were slightly lower than the expected values and this was attributed to sample anisotropy and imperfect sample orientation during the dynamic testing procedure. The complex moduli of beams of microcrystalline cellulose recorded using the simple dynamic tension test were extremely close to values reported in the literature and it appears that this technique is well suited for the determination of the viscoelastic properties of very small powder compacts. It should be noted that difficulties with reproducibly making, presenting and holding very small compressed powder samples are real and extreme care will always be needed when performing micro-scale mechanical property testing. Despite this caveat the possibility of determining the viscoelastic properties of such small compacts is extremely attractive and the techniques described herein could enable the dynamic mechanical properties of pharmaceutical materials to be determined at the early stages of the drug development process.

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