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International Journal of Pharmaceutics 241 (2002) 73–85

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Comparison of the mechanical properties of the crystalline and amorphous forms of a drug substance

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Received 8 November 2001; received in revised form 9 April 2002; accepted 9 April 2002

Abstract

Purpose: To better understand the influence of long-range molecular order on the processing characteristics of an active pharmaceutical ingredient (API). *Methods:* Crystalline and amorphous samples of a model drug substance were isolated and their ''true'' density, crystallinity, melting point, glass transition temperature, particle size distribution, and powder flow characteristics determined. Compacts of a standard porosity were manufactured from each form and their dynamic indentation hardness, quasi-static indentation hardness, tensile strength and ''compromised tensile strength'' determined. X-ray powder diffraction was used to confirm that no changes were induced by compact formation or testing. *Results:* The crystalline and amorphous forms of the drug substance had relatively high melting and glass transition temperatures (approximately 271 and 142 °C, respectively) and were physically and chemically stable under the conditions of the testing laboratory. Consistent with this there was no evidence of crystallinity in the amorphous samples or vice versa before, during or after testing. The two API lots were effectively equivalent in their particulate properties (e.g. particle size distribution), although differences in their particle morphologies were observed which influenced powder flow behavior. The compacts of the bulk drug samples exhibited moderate ductility, elasticity, and strength, and high brittleness, in keeping with many other drug substance samples. A significantly greater compression stress was required to form the compacts of the crystalline material, and these sample materials were more ductile, less brittle and less elastic than those made from the amorphous API. There were no major differences in the tensile strength or the viscoelasticity of the compacts made from the crystalline and amorphous samples. *Conclusions:* The mechanical properties of compacted amorphous and crystalline samples of a drug substance have been measured and the contributions due to the molecular ordering of the crystalline form proposed. Small but significant differences in the mechanical properties were noted which could potentially affect the processing performance of API. © 2002 Published by Elsevier Science B.V.

Keywords: Amorphous; Crystal; Mechanical

1. Introduction

Differences in the physical and chemical properties of various drug substance forms (e.g. crystal

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0378-5173/02/$ - see front matter © 2002 Published by Elsevier Science B.V.

PII: S0378-5173(02)00133-3

polymorphs) are well documented, and the properties of ''families'' of such materials can be related to their known molecular, crystal and particulate property variations (e.g. crystal lattice energy) (Byrn et al., 1999). Indeed, the discipline of ''particle engineering'' has grown up based on the premise that the properties of a drug substance can be purposefully manipulated through an understanding of molecular structure-processing performance relationships (York, 1992). Unfortunately, studies of the mechanical properties (e.g. powder flow, powder compressibility) of various drug forms are complicated by the difficulty of de-coupling the particulate properties of a powdered sample (such as particle size and shape) from the molecular properties of the material (such as crystal lattice energy or molecular conformation). Hence, no general rules have been developed to guide the selection of the drug substance's physical form based on reaching some desired mechanical property target. Most work in this area has focused on the study of crystalline polymorphs (Summers et al., 1977; Roberts and Rowe, 1996; Roberts et al., 2000), and there has been only sparse attention paid to the mechanical properties of non-crystalline drug substances (Kopp et al., 1989; Andronis and Zografi, 1997; Hancock et al., 1999). This is probably because even further complications are added to an already complex experimental situation by the introduction of a molecularly disordered amorphous material. Potential complications include, but are not limited to, physical or chemical instability of the pure amorphous material under normal laboratory testing conditions, and a lack of sufficient quantities of amorphous material for conducting the most common macroscopic mechanical testing procedures.

One might expect that the complete absence of long-range three-dimensional inter-molecular order associated with amorphous materials might significantly modify the mechanical properties of a powdered amorphous drug substance (Kopp et al., 1989; Andronis and Zografi, 1997; Hancock et al., 1999). This in turn could have a profound impact upon the approach taken for the development of solid dosage forms from such a material and on the selection of appropriate manufacturing unit operations and processing conditions. Hence, the ability to understand and potentially manipulate the mechanical properties and performance of amorphous materials is an extremely important, albeit highly challenging, area of research. In the work reported in this article, we set out to determine the mechanical properties of compacts made from crystalline and amorphous forms of a model drug substance which have similar particulate properties. A direct comparison of the mechanical properties was then performed with a view to determining the potential differences in the pharmaceutical processing characteristics of those materials and the possible molecular level source(s) of those differences.

2. Materials and methods

2.1. Materials

The model drug substance selected for study was 3-[(4-*O*-[4,6-bis(fluorophenylcarbomyl)]-β-D-glucopyranolsyl-)β-D-flucopyranosyl]oxy-(3β, 5α, 25R)-spirostan-12-one (Fig. 1). This compound was developed as a cholesterol-absorption inhibitor for the potential treatment of hypercholesterolemia (DeNinno et al., 1997, 1998). The pure anhydrous crystalline drug substance was supplied by the chemical R&D department of Pfizer Inc. The amorphous form was produced by careful spray-drying from acetone using a Niro laboratory scale spray dryer (Niro Inc., Columbia, MD) fitted with a 1.0 mm two-fluid nozzle and oper-

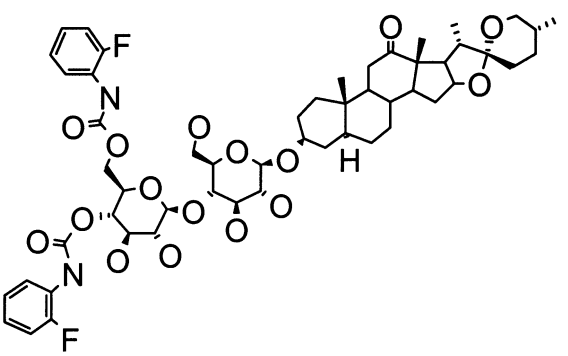


Fig. 1. The molecular structure of the model drug substance.

ated at 170 °C inlet and 50 °C outlet air temperature. These spray-drying conditions were selected to provide the material with an equivalent particle size distribution to the crystalline drug substance (see later) and comparable levels of residual solvent and non-volatile impurities. The two forms of the model drug substance were subjected to a comprehensive stability challenge test and were shown to be chemically and physically stable ($< 1\%$ change from initial) for at least 8 weeks when stored at high stress International Conference of Harmonization (ICH) conditions (unpublished data). The samples used in this work were stored and tested together in a controlled room temperature environment (approximately 20 °C and 40% RH).

2.2. Characterization of the powdered crystalline and amorphous drug samples

Powder samples of 10–15 mg were analyzed by differential scanning calorimetry (DSC) (Perkin–Elmer, Norwalk, CT) at a heating rate of 10 °C/min. A dry nitrogen purge of 25 ml/min was employed and samples were heated from room temperature to approximately 300 °C. Calibration of the instrument with respect to temperature and enthalpy was achieved using high purity standards of indium and tin. Sample pans were made of aluminum, and the mean results of three replicate determinations are reported.

X-ray powder diffraction measurements were used to confirm the crystalline or amorphous nature of the starting materials and to determine if any change in their form occurred as a result of their testing. A Siemens D500 instrument (Siemens, Munich, Germany) was used and scans were taken between 4 and 40° 2θ. Samples were presented as lightly pressed powder disks. The compacts used for mechanical property testing were very lightly crushed using an agate pestle and mortar prior to analysis.

The particle size distributions of the powdered drug samples were determined using a Sympatec HELOS laser diffraction instrument (Sympatec, Princetown, NJ) fitted with a RODOS dry powder dispersion accessory. An air pressure of 1.0 bar and a vacuum of 35 mbar were used to produce a uniform powder dispersion for each sample. These conditions were optimized to achieve a complete dispersion of the primary particles without causing significant particle attrition. The measurement duration was approximately 100 ms, and the mean results of concordant duplicate measurements are reported.

Photomicrographs were taken with a Jeol JSM-5800 scanning electron microscope (Jeol USA Inc., Peabody, MA). Samples were prepared by mounting on aluminum stubs and sputter-coating in a vacuum with a gold–palladium alloy. A working distance of 10 mm and an accelerating voltage of 5–25 kV were used.

The "true" densities of powder samples (approximately 1 g) were determined with a helium pycnometer (Quantachrome Instruments, Boynton Beach, FL) operated according to the manufacturer's recommended procedures. Calibration was performed using standard stainless steel spheres, and the mean value of triplicate determinations is reported.

Powder flow was assessed using a custom-built simple shear cell that has previously been described (Hiestand and Wilcox, 1968). A two-point determination of the effective angle of internal friction (EAIF) was performed at 20 °C and 50% RH using normal stresses of 0.00741 and 0.01029 MPa. All determinations were made in duplicate and mean values are reported.

2.3. Compact mechanical property measurements

The compact mechanical testing approach taken in this work was a pragmatic one. The properties of compacts of a fixed and finite porosity were determined using several standardized and well-controlled empirical tests and then compared. The mechanical testing methods were selected because other commonly used approaches (e.g. three- or four-point beam bending experiments) were found to be unworkable for the particular materials of interest. Alternate approaches, such as tableting experiments with a compaction simulator, were also attempted but again did not work for the materials in question. The techniques used were found to work well with the chosen materials, and despite some limitations they provided reliable and badly needed comparative data regarding the me-

chanical properties of crystalline and amorphous forms of the model active pharmaceutical ingredient (API). Some authors have advocated using mechanical property data collected over a range of compact solid fractions to extrapolate to a theoretical value of each property for the solid sample at zero porosity. Whilst being valid in many instances, there are some disadvantages to this approach which need to be considered, primarily the empirical nature of the extrapolation procedures and the significant raw material requirements. Because of the difficulty of making compacts of the model bulk drug and its limited availability, the mechanical property comparisons in this work were performed at a single reference compact porosity (15%). This porosity is representative of many real compressed pharmaceutical powder systems (e.g. roller-compacted ribbons, immediate-release tablets), and is directly experimentally accessible so that no empirical data extrapolation procedures are required.

Determinations of the indentation hardness and tensile strength of carefully prepared compacts of the crystalline and amorphous drug substance were performed according to the methods described by Hiestand and Smith (1984) (Fig. 2). At least two replicate determinations were performed for each mechanical testing procedure and mean values are reported. Compacts for mechanical testing were approximately 5 g rectangular compacts measuring $1.9 \times 1.9 \times 1.0$ cm. They were carefully formed by slow (approximately 1 mm/min; 5 min dwell time) uniaxial compression using a custom-built hydraulic press that permitted gradual triaxial decompression of the samples and minimized the residual internal stresses in the compacts. The punch and die surfaces were sparingly lubricated with magnesium stearate suspended in methanol (approximately 5% w/w). The mass and dimensions of each compact and the associated compression forces were closely controlled and recorded, and the compacts were permitted to equilibrate with their surroundings for at least 24 h prior to testing. Previous work in this laboratory has shown that this is sufficient time for most compacted pharmaceutical materials to show constant mechanical properties. The compact porosities were calculated from the external dimensions and mass of the compacts and the "true" densities of the powdered drug samples. Indentation hardness determinations were performed in "dynamic" mode (approximately 1500 mm/s impact speed) using a pendulum impact device and in "quasi-static" mode (approximately 0.008 mm/s impact speed) with a custom-built indentation tester (Hiestand and Smith, 1984). The spherical indentors were of 2.54 cm diameter and 65.6 g mass, and the pendulum length was 92.3 cm with a release angle of 30°. Quasi-static indentation forces were selected to produce indentations of a similar size to the dynamic indentation test (approximately 1.5–2 mm diameter). The compact indentations were measured using a stylus-type profilometer (Mahr Federal Inc., Providence, RI), and the dent depth, dent diameter, apparent radius of curvature and rebound height were used to calculate the indentation hardness and elastic modulus of the compacts (Hiestand and Smith, 1984). The tensile strength of the compacted samples was determined with a custom-built tensile tester (Hiestand and Smith, 1984). Tensile failure was observed for all the rectangular compacts when compressed between flat-faced platens at a speed between 0.041 and 0.002 mm/s. Specially modified punch and die sets permitted the formation of square compacts with a centrally located hole (0.11 cm diameter) which acted as a stress concentrator during testing. This capability permitted the determination of a "compromised" compact strength and thus facilitated an assessment of the defect sensitivity of each compacted material.

3. Results

3.1. Characterization of powdered crystalline and amorphous drug samples

The melting point of the crystalline drug was determined to be approximately 271 °C using DSC. Melting of the samples was accompanied by the onset of decomposition. Upon heating the spray-dried material, a glass transition event was clearly observed at a temperature of approximately 142 °C, and this was followed by the exothermic crystallization of the supercooled liq-

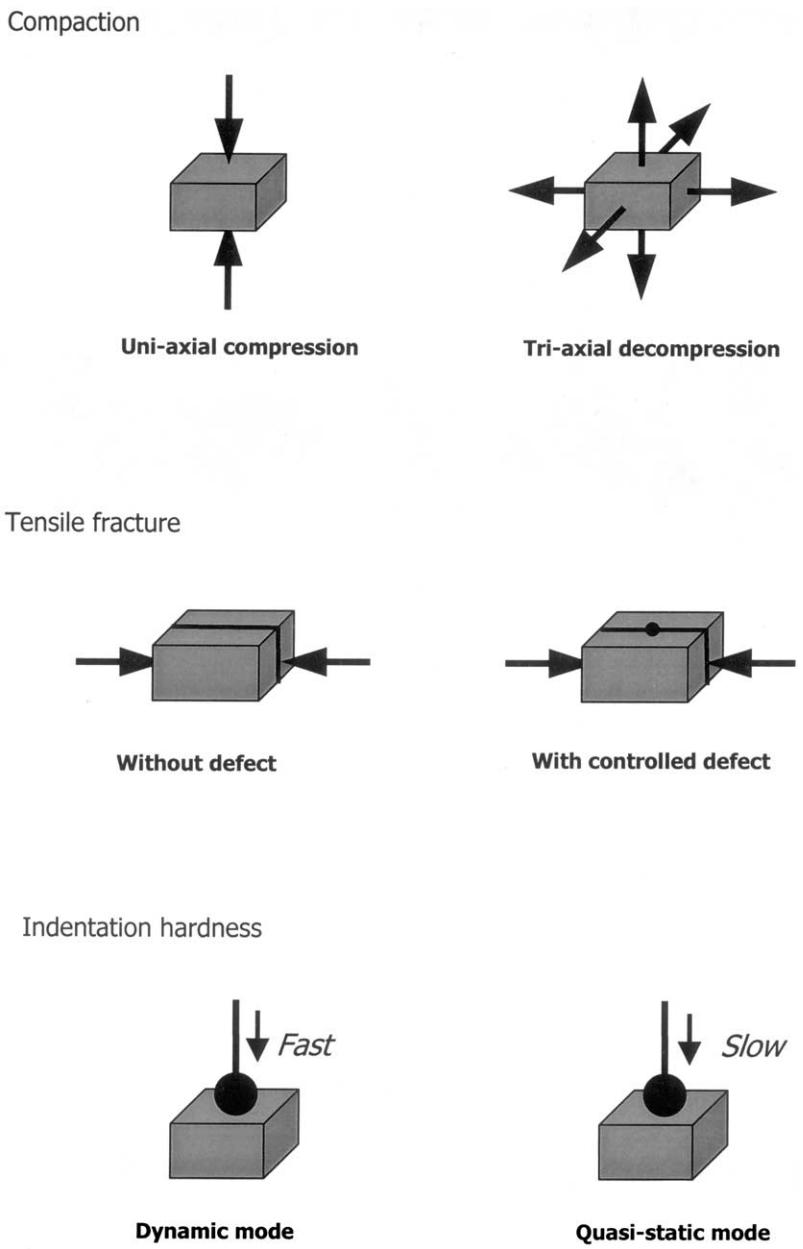


Fig. 2. Schematic of the compact formation and testing procedures.

uid at temperatures greater than 160 °C. There was no evidence of a glass transition event in the DSC trace for the crystalline material. The physical nature of the starting materials was confirmed by X-ray powder diffraction measurements, as shown in Fig. 3. The particle size distributions of the crystalline and amorphous samples are compared in Fig. 4, and the median particle sizes were found to be 6.1 and 5.8 μm. Examination of the two powder samples by scanning electron microscopy yielded the images shown in Fig. 5. The "true" densities of the samples and the effective

angles of internal friction (which indicate the flow properties of the bulk powder samples) are reported in Table 1.

3.2. Compact mechanical property measurements

Formation of intact compacts of pure bulk drug substance which contain no significant flaws is normally a significant challenge and has severely limited the number of reports of this type of work. By adopting the procedures outlined in Section 2, compacts of both crystalline and amorphous API could be produced in sufficient quantity for mechanical property testing using a limited amount of the starting materials (50 g). The mechanical properties of these compacted bulk drug samples are summarized in Tables 1–3. Specifically, the compact preparation conditions are compared in Table 1, the tensile strength determination data are provided in Table 2, and the results of the indentation testing are summarized in Table 3. After testing, each compact was analyzed using optical and scanning electron microscopy and X-ray powder diffraction to look for any signs of physical change. Particle breakage occurred in both samples upon compaction (Figs. 5 and 6), and there was no detectable change in the molecular order of the samples induced by the compaction process (Fig. 7).

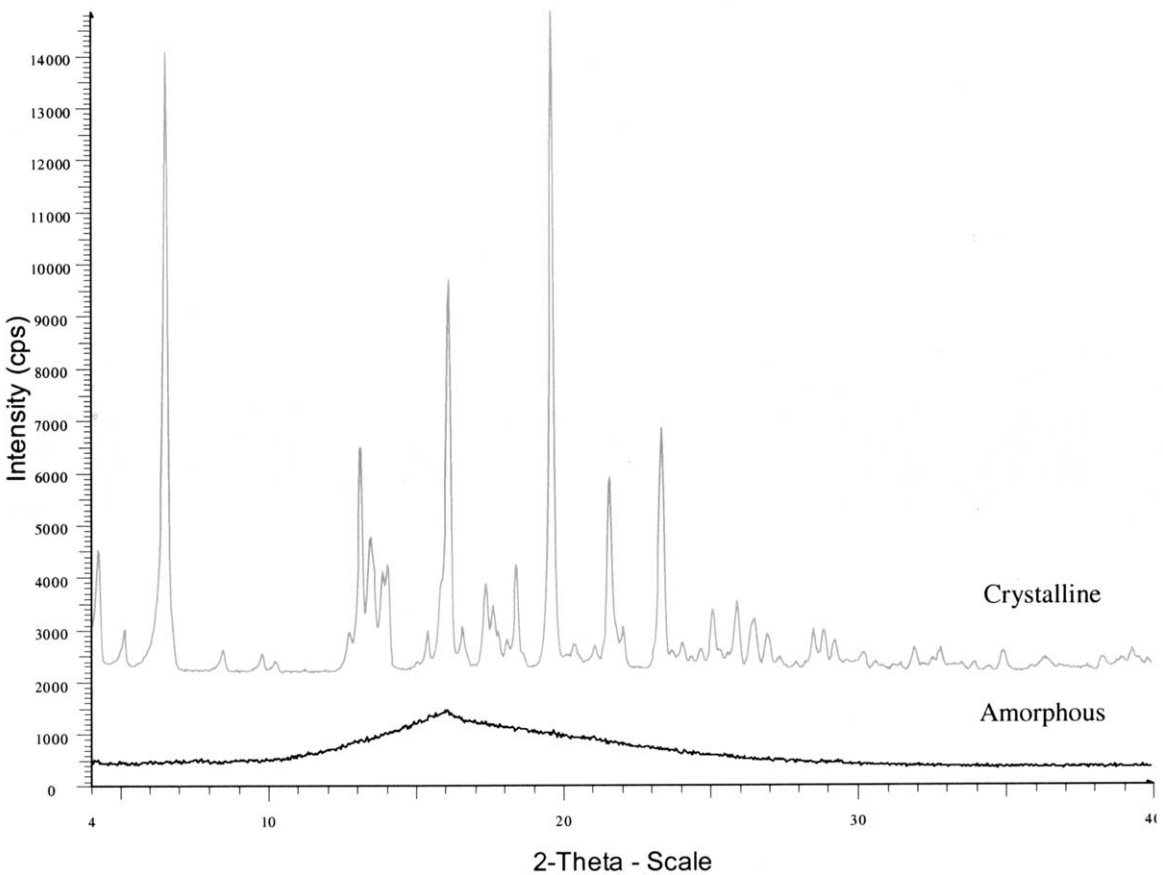


Fig. 3. Powder X-ray diffractograms for the crystalline and amorphous forms of the drug substance.

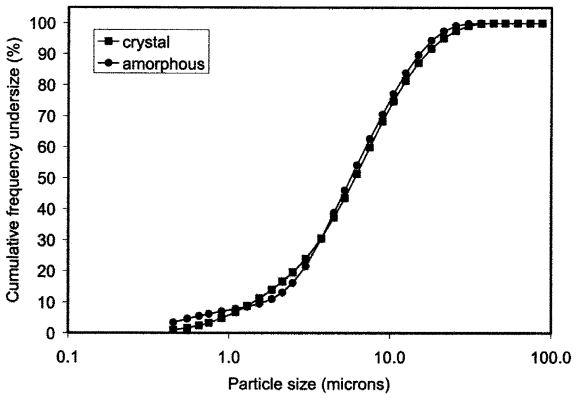


Fig. 4. Particle size distributions for the crystalline and amorphous forms of the drug substance.

4. Discussion

By the use of thermal analytical and spectroscopic methods, the practically complete crystalline and amorphous nature of the starting materials was confirmed (e.g. Fig. 3). The ratio of the melting temperature to the glass transition temperature (in Kelvin) was 1.3, which is typical of the behavior of many other pharmaceutical materials (Hancock and Zografi, 1997). The drug substance had both a high melting point ($>>$ 200 °C) and a high glass transition temperature ($>>$100 °C), and thus it was expected to be physically and chemically stable in both the amorphous and crystalline states. This was confirmed by the storage of these drug substance forms under ICH stress conditions and testing using standard analytical techniques (unpublished data). Consistent with this, the physical form of the samples was also unchanged to any measurable degree following the formation of the compacts and their subsequent mechanical property testing (e.g. Fig. 6).

The equivalent volume particle size distributions of the samples were indistinguishable by all standard measures (Fig. 4). The ''true'' densities of the crystalline and amorphous samples were within 5% of each other, and as expected the more ordered crystalline sample had the slightly higher density (Table 1). The morphological properties of the crystalline and amorphous drug substance particles were quite different, as indicated by the scanning electron micrographs (Fig. 5). The crystalline sample comprised agglomerates of elongated prisms with distinct angular features, whereas the amorphous sample comprised more equant but less uniform primary particles. This is probably a direct result of the different degrees of molecular ordering in the two samples, with the repetitive molecular packing of the crystalline material resulting in a regular particle habit, and the more random arrangement of molecules in the amorphous sample leading to less reproducible particle shapes. Such differences in particle morphology are expected (and an underlying sign of normalcy) when studying the properties and per-

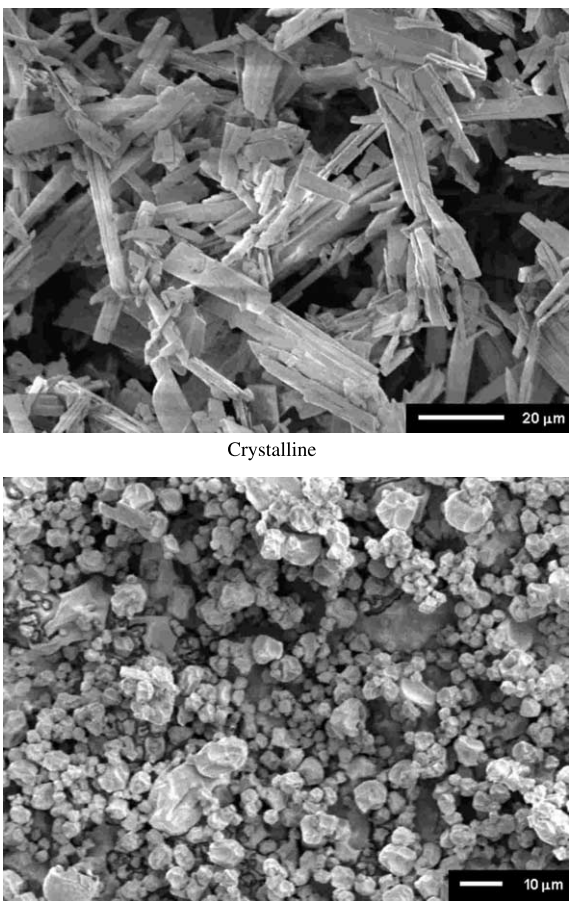


Fig. 5. Scanning electron micrographs for the crystalline and amorphous forms of the drug substance.

Table 1
Powder density, flow and compact preparation data for the crystalline and amorphous forms of the drug substance (mean ± range)

Property	Crystalline sample	Amorphous sample
"True" density (g/ml)	1.33 (0.00)	1.31 (0.00)
Effective angle of internal friction	42.0 (0.0)	30.8 (0.0)
Compact compression stress (MPa)	61 (0.6)	45 (1.5)
Compact porosity (%)	15 (0.0)	15 (0.0)

formance of crystalline and amorphous samples of the same chemical entity. One clear impact of the difference in the morphological characteristics of the bulk drug samples was on their powder flow characteristics. The spray-dried material gave a notably lower EAIF in the shear cell test than the crystalline material (Table 1). This result indicates an increased ease of powder flow for the amorphous particles under the moderately compressive conditions of this test. Neither of the drug substance samples could be described as a free flowing powder sample when compared to common pharmaceutical excipients; however, the observed behavior was quite typical of other bulk drug substances studied in this laboratory (i.e. mean EAIF = 33, range = 18–45).

There was no significant difference in the compression stress required to form the "standard" and "compromised" compacts within each sample

Table 2
Tensile strength testing data for the crystalline and amorphous forms of the drug substance (mean ± range)

Property	Crystalline sample	Amorphous sample
Tensile strength (MPa)	1.66 (0.42)	1.63 (0.23)
Compromised tensile strength (MPa)	0.63 (0.02)	0.43 (0.06)
Ratio of tensile strength values	0.38	0.26

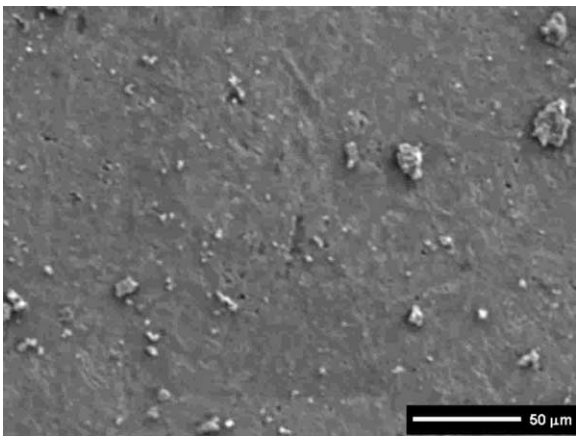
Table 3
Indentation hardness testing data for the crystalline and amorphous forms of the drug substance (mean ± range)

Property	Crystalline sample	Amorphous sample
Dynamic indentation hardness (MPa)	178.4 (13.8)	230.3 (2.3)
Quasi-static indentation hardness (MPa)	43.0 (2.2)	55.2 (1.5)
Ratio of indentation hardness values	4.1	4.2
Elastic modulus (GPa)	2.5 (0.0)	4.1 (1.2)

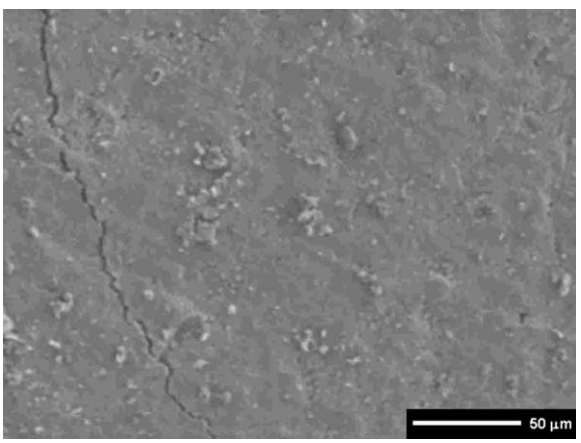
type. However, the crystalline material observed required an approximately 30% greater compression stress than the amorphous sample to form compacts of the desired porosity. This greater resistance to compact formation by the crystalline material suggests that stronger inter-particle and/or inter-molecular forces have to be overcome to reach the target porosity. This is consistent with the broad expectation that crystalline materials have a lower free energy than amorphous materials at equivalent temperature and pressure conditions (Hancock and Parks, 2000). The mechanisms of powder consolidation may have been different for the two sample types, and this could also have influenced the compression stress required to form the compacts. Following compact formation, inspection of the exterior and interior surfaces of the compacts by scanning electron microscopy indicated that the primary particles of both the crystalline and amorphous powders samples were destroyed by the compaction process (e.g. Fig. 6). That is, the different particle morphologies were not preserved in either case and the micron scale structures of the compacts were indistinguishable from one another. It was thus concluded that it was valid to directly compare the mechanical properties of the equally porous compacted crystalline and amorphous samples.

The tensile strength of the compacts made from the crystalline and amorphous samples was in the middle of the range historically recorded in this

laboratory for bulk drugs and excipients (approximately 1–10 MPa) (unpublished data), and thus these materials may be described as forming compacts with a moderate tensile strength (Table 2). When a controlled flaw was introduced into the compacts prior to tensile testing, the effect on the apparent strength was marked, with reductions in the compact strength of 62 and 74% for the crystalline and amorphous materials, respectively. It can be said that both materials formed compacts that were very "brittle", i.e. they had a pronounced sensitivity to the presence of flaws and were considerably weakened by such flaws (Hiestand and Smith, 1984). In the terminology of classical fracture mechanics these samples would both be likely to have very low critical stress intensity factors (K_{IC} values). The compacts of the amorphous drug substance were even more brittle than those of the crystalline sample and even more susceptible to failure induced by the presence of flaws. This is in keeping with the well-documented brittle nature of many "glassy" amorphous materials at temperature well below their calorimetric glass transition temperatures (T_g—120 K in this instance) (Brungs, 1995). Detailed inspection of the failure surfaces of the compacts formed from the crystalline and amorphous samples revealed that there were subtle differences which might reflect the differences in their brittleness. In the crystalline samples there appeared to be striations running parallel to the failure plain, whereas this feature was not so prominent for the amorphous material compacts which had a more isotropic appearance (Fig. 8). Such features could reflect differences in the mechanisms by which the samples accommodate mechanical stresses, and possibly they indicate somewhat different crack propagation events immediately prior to sample breakage.



Crystalline



Amorphous

Fig. 6. Scanning electron micrographs of the compact surfaces for the crystalline and amorphous forms of the drug substance.

The dynamic and quasi-static indentation hardnesses of the compacts of the model drug indicated that the material formed moderately hard compacts relative to other bulk drugs and excipients. Notably, the indentation hardness values for the amorphous drug substance were both significantly higher (approximately 30%) than those of the crystalline drug substance (Table 3). This type of behavior is opposite to that reported for solid discs of amorphous and crystalline phenobarbitone made by a melt–solidification–aging technique (Kopp et al., 1989), but is not necessarily unexpected. The indentation behavior of the amorphous API sample was characteristic of a typical inorganic glass, with a marked tendency for the samples to shatter into many pieces during testing. At the mechanical property testing temperature (controlled room temperature) the amorphous drug was approximately 120 K below its glass transition temperature and therefore existed in a truly "glassy" state. Presumably at temperatures near and above its glass transition temperature, the amorphous drug substance would show

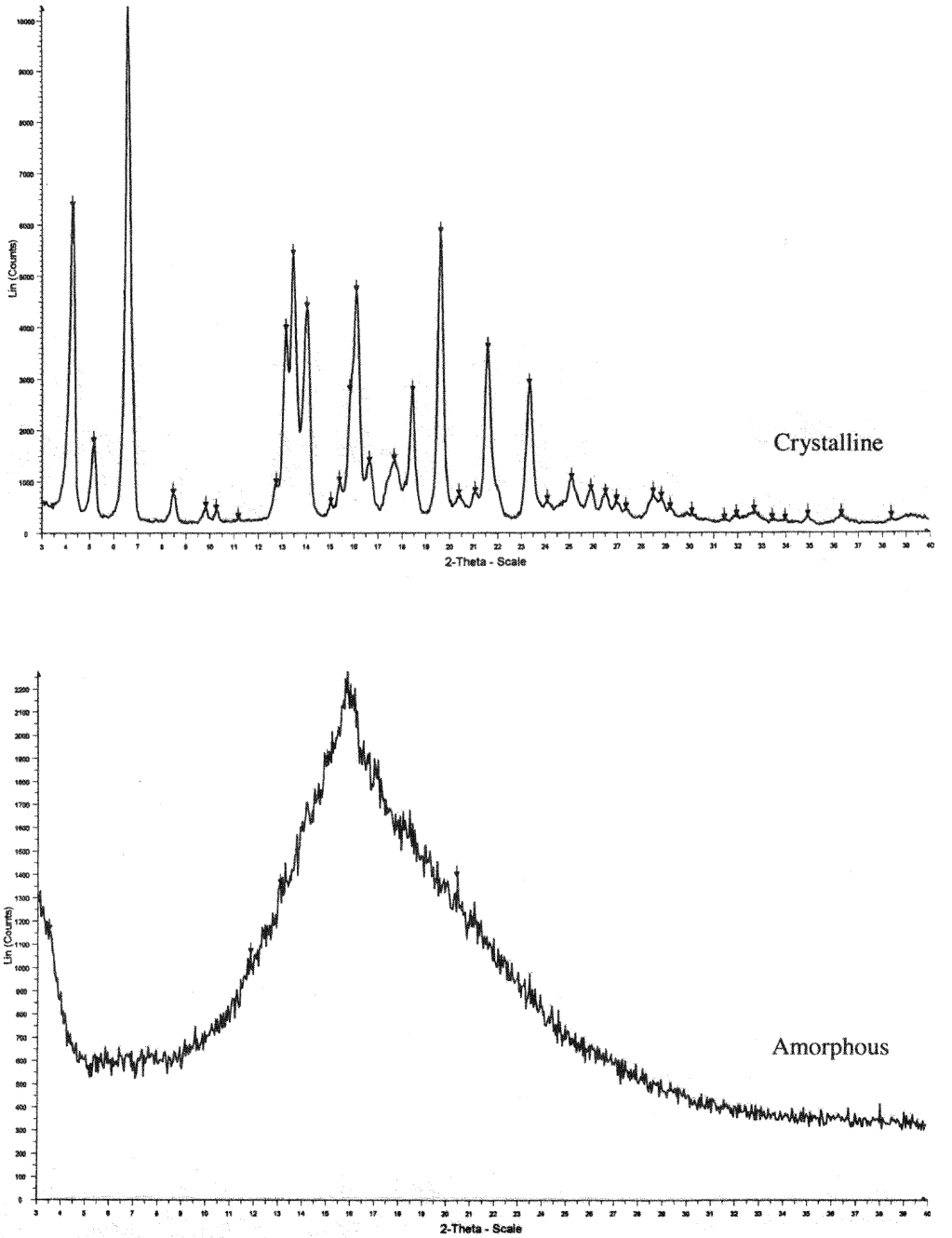


Fig. 7. Powder X-ray diffractograms for compacts of the crystalline and amorphous forms of the drug substance after mechanical property testing.

a change in its behavior with a marked increase in ductility (Hancock et al., 1999), whereas the indentation hardness of the crystalline material would not change anywhere near as markedly with temperature. The glass transition temperature of phenobarbitone is approximately 100 °C closer to ambient temperature (Kerc and Srcic, 1995), so it would be expected to have been more ductile relative to its corresponding crystalline form. This observation highlights an important difference in the mechanical properties of crystalline and amorphous pharmaceutical materials, which is the temperature dependence of their response to mechanical stresses. Since it would have required significant modification of the current testing equipment to permit data to be collected at elevated temperatures, this phenomena could not be explored in detail as part of the current work.

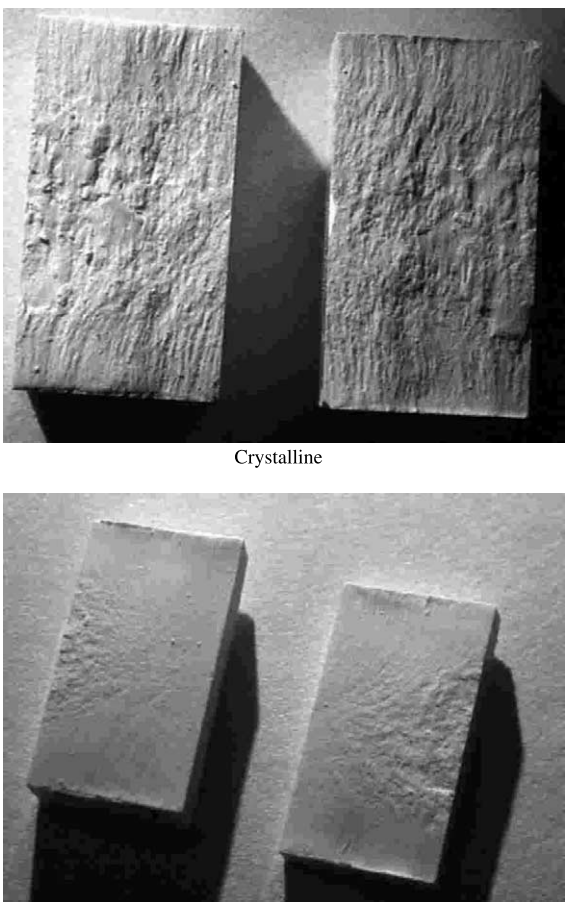


Fig. 8. Photographs of the compact fracture surfaces for the crystalline and amorphous forms of the drug substance.

The ratio of the dynamic and quasi-static indentation values can provide a rough indication of the viscoelasticity of each compacted material. In this attribute the compacts of the crystalline and amorphous drug substance were essentially equivalent to each other (Table 3) and in the middle of the normal range for other bulk drugs and excipients (approximately 1–65). The elastic modulus of the compacts (calculated from the results of the quasi-static indentation hardness measurements) indicated that the amorphous drug formed somewhat stiffer compacts than the crystalline material (Table 3). In many instances amorphous materials, such as polymers, are found to be more viscoelastic than their crystalline counterparts, but this particular drug substance does not appear to follow this pattern of behavior at the chosen testing conditions. This observation may also be attributable to the high glass transition temperature of the amorphous drug relative to the testing temperature. The amorphous material at approximately 20 °C is at over 100 °C below its glass transition temperature and thus it would be expected to exist in a very rigid glass-like state.

Based on the analysis of over 1500 APIs, excipients and tablet formulations by the authors (unpublished data), some general comments can be made regarding the mechanical properties of the current samples. Overall, the mechanical properties of the crystalline and amorphous model drug substance were typical of many APIs, and thus not particularly well suited to direct manufacture into pharmaceutical solid dosage forms by conventional tableting operations. It would certainly be necessary to mix and co-process either form of this API with a significant proportion of excipients in order to achieve a robust tablet manufacturing procedure. Both the crystalline and amorphous samples would require improvements in their compact ductility, tensile strength, brittleness and their powder flow prior to being able to identify a viable commercial tablet manufacturing process. By comparing the attributes and inadequacies of the two forms of the model drug substance, it can be concluded that the amorphous drug substance would provide the

biggest formulation challenge since it was the least ductile (highest indentation hardness values), and formed compacts with the lowest tensile strength and the highest brittleness, even though it required a lower compression stress to form compacts, and its flow properties were somewhat better than the crystalline material. These differences are broadly consistent with those which would be expected between a spray-dried glassy amorphous material and its crystalline counterpart, based on basic principles of physical chemistry and chemical engineering. There are, however, some notable exceptions to the expected behavior, and some unanswered questions regarding the importance of the operational temperature relatively to the glass transition temperature and the role of particulate and molecular structure. These unanswered questions present some exciting avenues for further work in this area.

5. Conclusions

By very careful sample selection, preparation and testing, it has been possible to directly compare the mechanical properties of compacts made from the glassy amorphous and crystalline forms of a model drug substance. Physically and chemically stable samples of both forms with near identical particulate properties were produced and used to prepare practically equivalent compacts of 100% drug substance. The tensile strength, indentation hardness, brittleness and viscoelasticity of the these compacts were then carefully determined. The mechanical properties of the compacts of the two physical forms of this API were similar to those of many other bulk drug substances, and they differed from each other primarily in terms of their sensitivity to small flaws (''brittleness'', or fracture propensity) and their ductility or plasticity (measured as their indentation hardness). These differences in mechanical properties were consistent with the known differences in the molecular order of the samples, and would be expected to affect the ultimate processing performance of each physical form. No difference in the viscoelasticity of the compacts formed from the crystalline and amorphous drug samples was detected, and further work is needed to elucidate the reason for this behavior.

Acknowledgements

Ravi Shaker, and Ivan Samardjiev of Pfizer Inc. are thanked for their contributions to this work. The assistance from Brenda Simpson, Marshall Crew, Heather Melcher, Doug Lorenz and many others at Bend Research Inc. is also gratefully acknowledged.

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