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Predictive Milling of Pharmaceutical Materials Using Nanoindentation of Single Crystals

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Abstract:

Five pharmaceutical materials, including two salts and three neutral compounds, have been subjected to nanoindentation analysis on a single-crystal scale. The nanoindentation experiments were used to calculate a brittleness index for each of the five materials. These results were compared to the size reductions that were obtained on a pilot-plant scale mill. A good correlation between single crystal and large pilot-plant scale results was obtained for the range of materials studied.

Introduction

The milling of an active pharmaceutical ingredient (API) is often employed to control/increase dissolution and promote homogeneity when the drug is mixed with excipients during solid-dosage form development. Information about milling propensity of a new candidate is generally obtained from milling trials during scale-up of the API process. This approach can potentially lead to high demands on API when experiments with different mill types have to be carried out. The approach that Pfizer is taking at Sandwich, with respect to this issue, is to build up a correlation between small- and large-scale milling behaviour so that, in the future, milling can be predicted from small-scale tests and potentially a single-crystal test. The Pfizer approach is summarised in Figure 1. In this contribution, data from nanoindentation studies (the single-crystal test) and from pilot-plant milling trials (typically 10−30 kg) are reported.

From our development experience we knew that sildenafil citrate[1] is a very fragile material and easy to mill, whereas voriconazole[2] is a very plastic material which is difficult to mill. Three other compounds were selected for study. These compounds were expected to be intermediate between sildenafil citrate and voriconazole. The structures of the compounds selected for study are shown in Figure 2.

A common approach in calculating the brittleness of materials is to use indentation. Lawn and Marshall[3] proposed that the brittleness of a material is related to the ratio of indentation hardness to fracture toughness. The majority of indentation fracture toughness calculations have been performed with ceramics. Little work has been reported previously using pharmaceutical materials. This is due to the difficulties of indenting small crystals.

The breakthrough in assessing pharmaceutical materials with this technology came with the development of nanoindentation using sharp indenters.[4] Using these indenters, the nanoindentation process forms cracks in the crystal. The lengths of these cracks are measured and used to calculate the fracture toughness of the materials. The hardness can be calculated from the depth of the indentation. The brittleness index (BI) is then calculated by dividing the hardness (H) by the fracture toughness (K_c).

$$\mathrm{BI} = \frac{H}{K_c}$$

The objective of this report was to measure the brittleness index for five APIs and then to compare these values with the degree of size reduction that occurred during milling.

Methods and Equipment

(i) Nanoindentation.[5] Light microscopy was used to select crystals for mounting. For four of the five compounds, the crystals which were tested were obtained directly from large-scale batches. For one compound, slightly larger crystals were prepared by slow cooling and stirring in a computer-controlled laboratory reactor.

After selection, these crystals were transferred to a glass slide using a very thin tungsten needle. Selection was based on size and quality of crystals, with the aim of using only single crystals and not agglomerates or aggregates of material. The crystals were held in place with a nonviscous adhesive (Permabond). This was achieved by placing a minute quantity of glue near a crystal and then drawing out a very fine trail of liquid using a tungsten needle. Glue was taken up to the edge of a crystal and drawn underneath the

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(1) Dale, D. J.; Dunn, P. J.; Golightly, C.; Hughes, M. L.; Levett, P. C.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* **2000**, *4*, 17−22.

(2) Butters, M.; Ebbs, J.; Green, S. P.; Macrae, J.; Morland, M. C.; Murtiashaw, C. W.; Pettman, A. *Org. Process Res. Dev.* **2001**, *5*, 28−36.

(3) Lawn, B. R.; Marshall, D. B. *J. Am. Ceram. Soc.* **1979**, *62*, 347−350.

(4) Harding, D. S.; Oliver, W. C.; Pharr, G. M. *Mater. Res. Soc. Symp. Proc.* **1995**, *356*, 663−668.

(5) For a more complete discussion of nanoindentation results see: Taylor, L. J.; Papadopoulos, D. G.; Dunn, P. J.; Bentham, A. C.; Mitchell, J. C.; Snowden, M. J. *Powder Technology*, submitted for publication.

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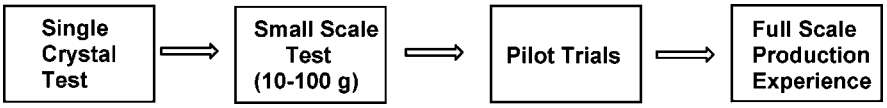

Figure 1. **Science of scale approach to milling.**

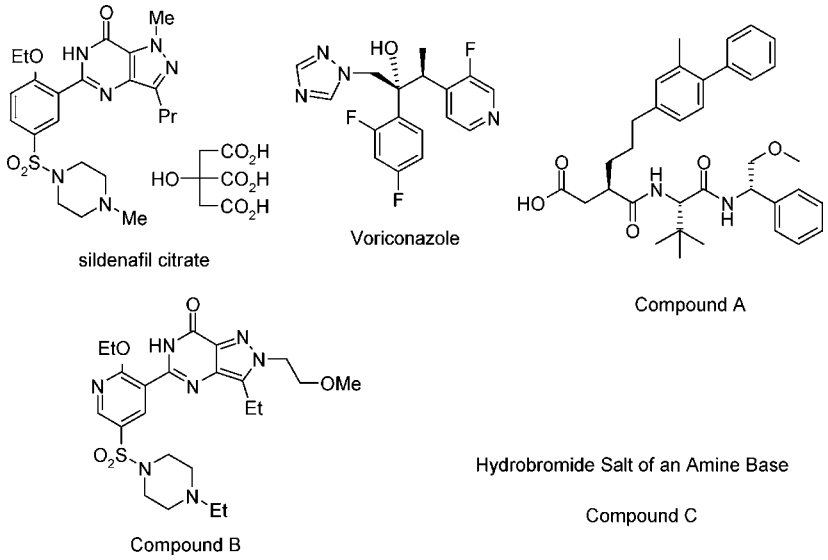

Figure 2. **Compounds selected for study.**

particle by capillary action. The glass slide was then attached to a Nanotester sample holder using a small amount of the adhesive. A small quantity of glue was used to enable the removal of the slide after indenting to use for further analysis. Crystal orientation was always in the same direction with respect to the indenter, with indentation only on the predominant face. Orientation of the crystal with respect to the indenter can influence the mechanical properties evaluated.[6]

Nanoindentation was carried out using a Nanotester 600 (Micro Materials Ltd, Wrexham, UK). This works on the principle of continuous recording of the penetration depth of the sharp indenter as a function of the applied force throughout a loading−unloading experiment. A schematic diagram of the instrument is shown in Figure 3.

A diamond three-sided pyramid (Berkovich) indenter is attached to a pendulum, which is able to move freely around an essentially frictionless pivot. The indenter is loaded against the sample by passing a current through the coil, which is drawn to the permanent magnet. The load applied (P) is controlled by the amount of current passed through the coil. As the current increases, the force of the indenter on the sample increases. Displacement of the indenter into the sample is measured by the variation in voltage between the capacitance plates. The load may range between 0.05 and 500 mN and the depth between 20 and 5000 nm, while typical resolution for the instrument is 100 nN and 0.1 nm for load and depth, respectively. The sample holder is aligned with the indenter by means of three DC motors that run XYZ micrometer stages. This arrangement is mounted on a separate stage, which allows movement between the indenter

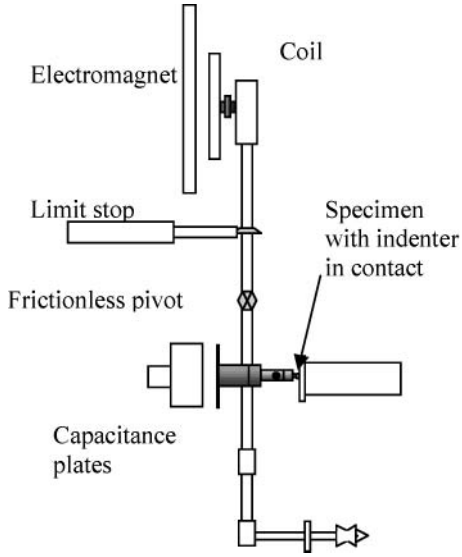

Figure 3. **Schematic of Nanotester 600.**

and a high-resolution zoom microscope. The zoom microscope can be used to select areas for indentation on the crystals with high precision. The software package enables the programming of multiple indentations over a number of crystals using the microscope.

Nanoindentations were carried out at 40 mN for all the materials tested. The loading rate was set at 0.37 mN s^{-1}. A minimum distance of 50 μm was set between each indent. For very fragile crystals, such as sildenafil citrate only one indent per crystal was carried out. All nanoindentation measurements were carried out at 28 °C and 40% relative humidity.

Statistical analysis of hardness and Young's modulus data indicated that, in most cases, a minimum sample size of five crystals provided reasonable confidence limits. Increasing

(6) Duncan-Hewitt, W. C.; Mount, D. L.; Yu, A. *Pharm. Res.* **1994**, *11*, 616−623.

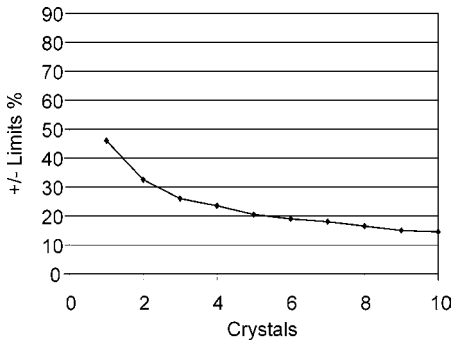

Figure 4. **Error limits of single-particle hardness as a function of the number of crystals tested.**

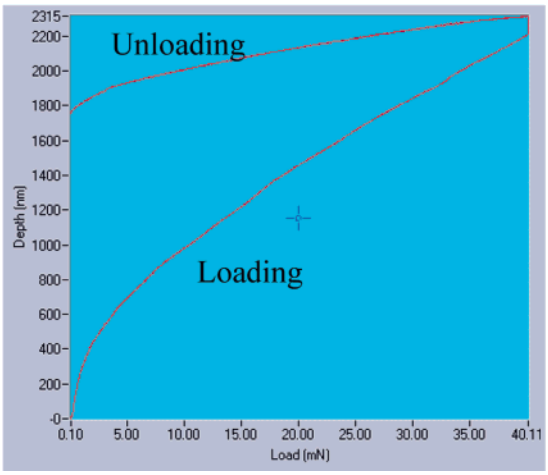

Figure 5. **Hysteresis curve for sildenafil citrate (suitable for data generation).**

the test sample size beyond five crystals did not lead to significant improvement in confidence (Figure 4).

The indenter was cleaned in 2-propanol between tests on different samples and viewed under the microscope to ensure that the tip was clear of debris. The orientation of the indenter with respect to the pendulum was kept the same, since angle of indenter in relation to the crystal face can influence the measurement of hardness.[7]

After indentation, scanning electron microscope (SEM) images were taken of the crystals. The indent diagonals (α) and the crack length (c) were measured and used to calculate fracture toughness as outlined overleaf.

(ii) Milling Trials. Milling trials were performed on an Apex 314 hammer mill operating at 7000 rpm with hammers forward. The screen size was a 0.027 in. (0.69 mm) round hole. The mill was hand fed. The measurements were taken from routine preparations during development.

Results

(i) Hardness and Young's Modulus. Figure 5 shows a typical load-displacement curve generated by nanoindentation for sildenafil citrate. A smooth load-displacement curve like this is ideal to generate nanoindentation data. In some cases anomalies are observed, such as in Figure 6. These steps, highlighted by arrows, are believed to correspond to crack

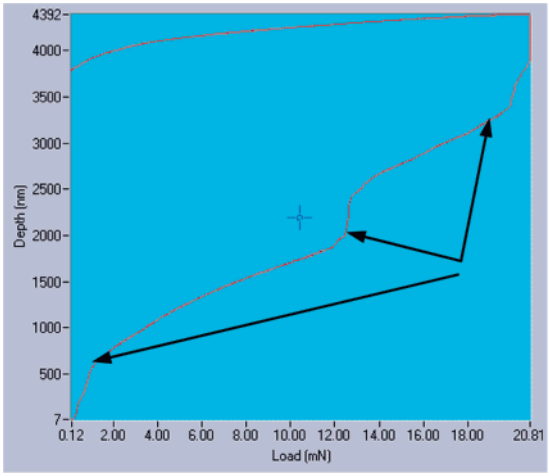

Figure 6. **Hysteresis curve where arrows show rapid cracking (unsuitable for data generation).**

Table 1. **Mechanical properties of the test compounds**

material	H (GPa) ± sd	E (GPa) ± sd
sildenafil citrate	0.52 ± 0.06	13.9 ± 1.5
compound C	0.43 ± 0.07	14.9 ± 1.3
compound B	0.39 ± 0.05	7.6 ± 0.5
compound A	0.10 ± 0.02	2.9 ± 0.4
voriconazole	0.13 ± 0.01	3.7 ± 0.4

development. This type of curve is generally discarded from the analysis of mechanical properties as the materials have cracked too quickly and the influence of this rapid cracking on hardness and Young's modulus (E) is not known.

Young's modulus and hardness analysis was carried out by the Oliver and Pharr method[8] and used data from the unloading curve in Figure 5 or similar curves for other materials. The mechanical properties of the compounds investigated are listed in Table 1. In addition to the hardness data, the values for the Young's modulus (E) are also shown for information; these values are also used to calculate fracture toughness. The values shown are average values based on a sample size of a minimum of five crystals per material.

Good reproducibility of results was observed for all the compounds investigated for both hardness (H) and Young's modulus (E). The results indicate that voriconazole is a very plastic and elastic compound when compared to the other materials. Sildenafil citrate is the hardest of the five materials tested. The standard deviations in Table 1 indicate that both hardness and Young's modulus are very reproducible. The range of values and the reproducibility of the mechanical properties indicate that it is possible to distinguish between pharmaceutical materials using nanoindentation.

(ii) Fracture Toughness. Scanning electron microscope (SEM) images for some of the compounds examined are shown in Figures 7−9. Sildenafil citrate (Figure 7) was found to readily form cracks around indents. Once these cracks were initiated, the material appeared to fracture very easily. In contrast, voriconazole does not form cracks at this load, as Figure 9 indicates. This suggests that the cracking

(7) Arteaga, P. A.; Ghadiri, M.; Lawson, N.S.; Pollock, H. M. *Tribol. Int.* **1993**, *26*, 305−310.

(8) Oliver W. C.; Pharr, G. M. *J. Mater. Res.* **1992**, *7*, 1564−1568.

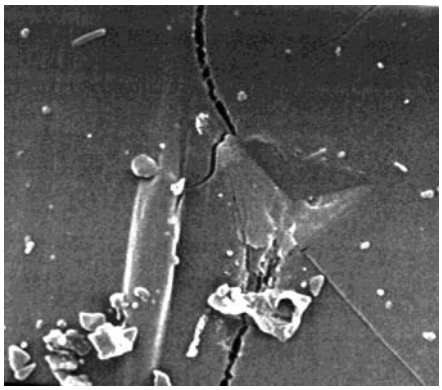

Figure 7. **SEM of sildenafil citrate.**

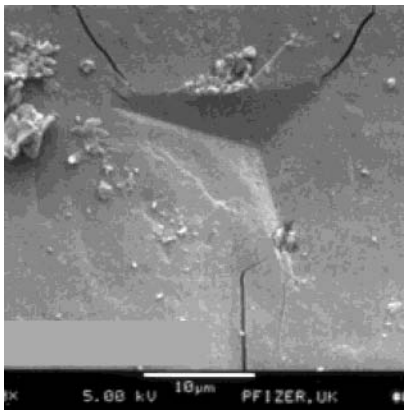

Figure 8. **SEM of compound C.**

Figure 9. **SEM of voriconazole.**

threshold for voriconazole must be greater than 40 mN. Voriconazole is so plastic that measurement of its fracture toughness was not feasible within the load range of interest.

The diagonals and the cracks emanating from the indent were measured. These were used to calculate the fracture toughness, K_c.[9] The calculation of K_c is dependent on the assumption that $P/c^{3/2}$ is constant, which is true for ceramics.[10] Figure 10 shows a plot of crack length as a function of load for compound A. The graph indicates that $P/c^{3/2}$ is indeed constant for pharmaceutical materials.

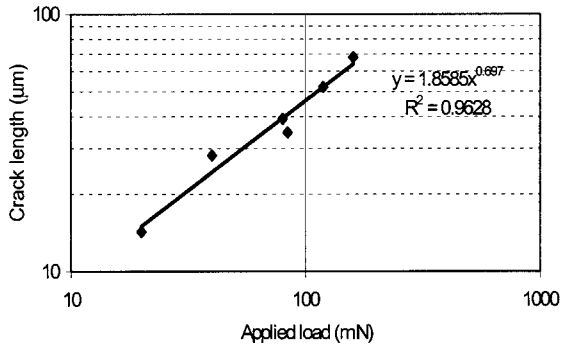

Figure 10. **Crack length as a function of load for compound A.**

Table 2. **Fracture toughness for the test compounds**

material	K_c (MPa m$^{1/2}$) ± sd
sildenafil citrate	0.02 ± 0.01
compound C	0.05 ± 0.01
compound B	0.04 ± 0.01
compound A	0.06 ± 0.00
voriconazole	unmeasurable

Table 3. **Summary of mechanical properties of the test compounds**

material	hardness (H) in GPa	fract. toughness (K_c) in MPa m$^{1/2}$	brittleness index in km$^{-1/2}$
sildenafil citrate	0.52	0.02	27.8
compound C	0.43	0.05	9.5
compound B	0.39	0.042	9.0
compound A	0.1	0.06	1.7
voriconazole	0.13	unmeasurable	<1

The fracture toughness for the five materials (where measurable) are shown in Table 2.

The standard deviations for fracture toughness are much higher than for hardness and are the main source of variation when calculating the brittleness index.

(iii) Brittleness Index. The brittleness indices were determined as described previously[3] and are summarised in Table 3.

By expressing the brittleness index values in units of km$^{-1/2}$, the values show a convenient range for the process chemist and engineer. Materials that are very plastic such as voriconazole have a brittleness index of <1, whereas very brittle materials such as sildenafil citrate have a brittleness index of around 30.

(iv) Milling Trials. The results from the milling trials are summarised in Table 4. The volume mean diameter (VMD), which is often referred to as D[4,3] or volume weighted mean diameter, provides a measure of where a given size distribution is centered, on the basis of the volume of material within each size class. It is a number which describes a particle size distribution and is calculated by

(9) Calculated using the following equation:

$$K_c = x_b(a/l)^k(E/H)^n(P/c^{*3/2})$$

K_c denotes fracture toughness, x_b is a calibration constant for the Berkovich indenter, a the indent diagonal, l the length of a crack, E the Young's modulus, H the hardness, P the load, c^* the crack length given by $a + l$ and k and n power indices. For further information see Dukino, R. D.; Swain, M. V. *J. Am. Ceram. Soc.* **1992**, *75*, 3299−330.

(10) Lawn, B. R.; Evans, A. G.; Marshall, D. B. *J. Am. Ceram. Soc.* **1980**, *63*, 574−581.

Table 4. **Results of milling trials**

cmpd	brittleness index ($\times 1000\ m^{-1/2}$)	milling results: input size VMD (μm)	input size D_{90} (μm)	output size VMD (μm)	output size D_{90} (μm)	% size reduction ratio VMD	% size reduction ratio D_{90}
sildenafil citrate	27.8	173[c]	402[c]	47[a]	94[a]	73%[f]	77%[f]
compound C	9.5	157−405[a] (Table 5)	285−666[a] (Table 5)	47[a] (Table 5)	95−193[a] (Table 5)	69%[g]	71%[g]
compound B	9.0	approximately 200[d]	470[a]	70[a]	141[a]	−	70%
compound A	1.7	88[b]	155[b]	55[b]	114[b]	27%	36%
voriconazole	<1		250[a]		250[a]		0%[e]

[a] Measured by Malvern Mastersizer (wet dispersion). [b] Measured by Sympatec. [c] Measured by Sympatec using a cuvette dispersion unit. [d] Estimated by microscopy [e] No reduction below D_{90} < 250 μm using repeated hammer milling runs. [f] It is possible that the % size reduction is actually higher than this for sildenafil citrate. It is very hard to measure the input size (see text). [g] Average of six milling runs (see Table 5).

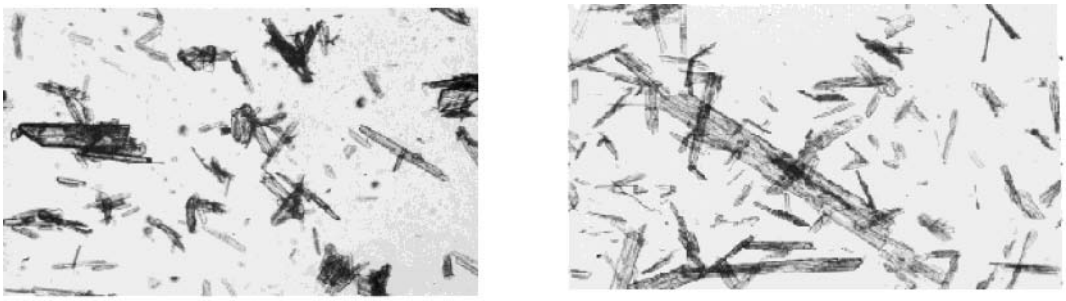

Figure 11. **Photomicrographs of sildenafil citrate crystals; a 100 μm particle longest dimension in this photomicrograph is equivalent to 5 mm.**

multiplying each particle diameter by the total volume occupied by particles of that size and summing across the entire distribution. This is then divided by the total particle volume. Similarly, D_{90} is defined as the size below which 90% of the weight of the particle lies.

The % size reduction ratio is calculated using the following formula:

$$\frac{(\text{input size} - \text{output size}) \times 100}{\text{input size}}$$

As can be seen, there is a good correlation between the brittleness index and the % size reduction ratio. Sildenafil citrate is the most brittle material and could be milled on any of the standard mill types. Voriconazole is the most plastic material, and no size reduction below 250 μm could be obtained. For voriconazole, a more energetic milling process was required.

In all cases, there is some concern about the absolute value of the particle size results before milling, as the analytical methodology employed is more suited to analysis of materials post milling. However, Table 5 summarises the results from 6 different batches of compound C, and the results show a good degree of consistency. In addition, in all cases the data pre-milling were reality checked using microscopy. Table 5 also shows that the size reduction ratio for compound C is the same, irrespective of whether the volume mean diameter (VMD) or D_{90} is used in the calculation. A similar trend was observed with the other test compounds.

For sildenafil citrate, the material which has the highest brittleness index, the crystals were so fragile that obtaining particle size data pre-milling was a real challenge. The data for sildenafil citrate presented in Table 4 were measured using cuvette dispersion. In addition to having a high brittleness index, the sildenafil citrate crystals also had a high aspect ratio (see Figure 11) and this also contributed to their fragility. For sildenafil citrate, the size reduction results given in Table 4 are very much an estimate and could well be higher due to the analytical challenges of measuring the unmilled material. It was also noted that different size inputs always gave very consistent output material (with respect to particle size).

Table 5. **Apex hammer milling results for compound C**

input size[a] VMD (μm)	input size[a] D_{90} (μm)	output size (one pass)[1] VMD (μm)	output size (one pass)[1] D_{90} (μm)	% size reduction ratio VMD	% size reduction ratio D_{90}
405	666	85	193	71%	71%
170	334	65	140	58%	62%
312	618	80	178	71%	74%
231	500	76	170	66%	67%
300	609	63	144	76%	79%
157	308	47	95	69%	70%
average size reduction				**69%**	**71%**

[a] Using Malvern Mastersizer (wet dispersion).

In Table 4, it can be seen that compounds B and C have very similar brittleness indices, and it is encouraging to see that their size reductions, when subjected to Apex hammer milling trials, are also similar. These two compounds were also subjected to milling trials using an air classifier mill (a 50ZPS mill ex Hosokawa). By using input materials of similar size (approximately D_{90} < 450 μm) very similar size reduction ratios were also obtained on this type of mill. This

confirms the importance of the brittleness index as a pertinent guiding tool. The brittleness index may be relevant to many different types of mill.

Conclusions

There are many factors which impact on the ability to predict milling data, for example the morphology of the crystal, aspect ratio, feed size distribution, and mechanical properties. Hence, these results, on a small number of compounds, must be treated with caution. Nevertheless, the correlation obtained is impressive, and a rank order correlation assessment of brittleness (and hence "millability") can be established from a single-crystal test. These data can also be used as part of the process to assess which types of mill should be used. In addition, expressing the brittleness index in $km^{-1/2}$ is a convenient, easy-to-remember scale for process chemists and engineers. We have recently measured an API with a brittleness index of around 100 $km,^{-1/2}$ and this is the most brittle compound that we have studied.

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