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X-ray and Crystallographic Applications in Pharmaceutical Research III. Crystal Habit Quantitation

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It is customary practice when describing the crystal habit of a given compound to make use of qualitative terms, such as "needles" or "plates." These terms are useful in describing crystal habit as it relates to some important pharmaceutical characteristics, such as suspension stability and syringeability, but inadequate for the more involved processes in which crystal habit affects tableting ability. In this paper a method is presented for describing the crystal habit of a given compound in quantitative terms which may be used, in some instances, to predict tableting behavior and to serve as specifications for tableting materials.

THE SYMMETRY of a crystal is fixed by the crystal system and class to which it belongs. Its relative dimensions, however, are independent of its symmetry. As a crystal grows from solution, a variety of factors, notably crystallization rate and the presence of impurities, tend to influence the amount of growth on each of the possible faces. Extremes of the possible conditions result in acicular, or needle-shaped crystals as a consequence of unidimensional growth (bidimensional retardation) and tabular, or plate-shaped crystals, as a consequence of bidimensional growth (unidimensional retardation). Terms such as acicular, equant, and tabular describe crystal habit in a qualitative manner.

Crystal habit often exerts a dominant influence on some important pharmaceutical characteristics, such as suspension stability, suspension syringeability, and the behavior of powder mixes during a tablet-compressing process. In the case of suspension syringeability, the influence is mostly mechanical. A suspension of plate-shaped crystals, for instance, may be injected through a small needle with greater ease than one with needle-shaped crystals of the same overall dimensions.

In the case of tableting behavior, however, the influence of the crystal habit of the active ingredient is more involved. The mechanical influence of crystal shape just mentioned is one factor, but there is another, sometimes dominant one, which results from the anisotropy of cohesion and of hardness which is possessed by organic (low symmetry) crystals and, therefore, of most pharmaceutically important compounds. It is significant that this anisotropy bears a fixed relation to the fundamental crystallographic directions. Therefore, as crystal habit varies, the dominant faces may vary in their relation to this anisotropy, and it is the influence of the dominant faces which tends to orient the crystals during a packing or compression process. Thus, major habit variations of an active ingredient can influence greatly the ease or the difficulty of making satisfactory compressed tablets. This is particularly true when the active ingredient makes up a large portion of the total tablet mass.

In order to evaluate tableting behavior as influenced by crystal habit, the habit must be expressed in quantitative terms which reflect some relationship between the dominant faces and the principal crystallographic directions. Qualitative terms describing shape are, in some instances, not sufficient.

Relating the Dominant Faces to the Crystallographic Directions.—An ideal situation exists when the crystals are less than about 0.2 μ in size, for in this range there is measurable "line-broadening" in the X-ray powder diffraction pattern, and the average crystal sizes in each of the crystallographic directions can be measured directly. Thus, needle-shaped crystals elongated along the c axis show sharp (001) reflections, and broadened (hk0) reflections. The actual dimensions can be measured from the width of each of the appropriate peaks at half maximum height. However, most crystalline preparations for pharmaceutical use are out of the X-ray line-broadening range, being larger, usually, than one micron, and this procedure cannot be applied.

For a typical pharmaceutical composition, it has been found that a quantitative description of crystal habit as it affects tableting behavior can be based upon measurements of preferred orientation. After relating habit extremes to tableting behavior by experimentation, optical and X-ray crystallographic studies on representative single crystals allow the designation of the dominant faces by their Miller indexes. An X-ray powder diffraction

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pattern is then measured for crystals of each habit extreme on specially prepared samples. The samples are prepared in such a manner that preferred orientation effects are maximized. A ratio of the relative peak intensities of critical lines in this diffraction pattern serves to indicate the average habit of the crystals. The ratio is useful in predicting tableting behavior, as well as serving, when desired, as a manufacturing specification.

General Illustrative Example.—In the preparation of compressed tablets of a specific drug, it has been found that some lots of bulk material vary in their ability to compress readily into satisfactory tablets. Although the pure crystalline drug in the various lots displayed no variation in measurable physical constants, examination with a petrographic microscope has disclosed a crystal habit variation. Crystals from lots with histories of good tableting behavior exhibited an acute bisectrix interference figure as the most common orientation, and crystals from lots with bad tableting behavior histories exhibited obtuse bisectrix figures most commonly. A consideration of the optic orientation (a = Y, b = X) and optic sign (positive) of single crystals indicated that the c crystallographic axis was coincident with the acute bisectrix direction, and the b axis with the obtuse bisectrix direction. Thus, it followed that "poor lot" crystals tended to lie on their 010 face, and "good lot" crystals tended to lie on their 001 face. Figure 1 shows orthogonal and clinographic projections of the crystal. The projections do not show the 001 face, although this face sometimes is present from growth, and often from cleavage, resulting in crystals with favorable tableting ability.

Using single crystal X-ray data,[1] an X-ray powder diffraction pattern was partially indexed. This allowed the choosing of powder pattern peaks whose intensities would most likely be influenced by crystals changing from 001 orientation to 010 orientation. These peaks were found in the diffraction pattern at 2 θ values of 8.72° (intensity indicates 010 orientation) and 12.09° (intensity indicates close to 001 orientation). (The 001 reflection itself is extinct.[2])

Samples for analysis were prepared so that all crystals had the best chance to orient preferentially on their most prominent faces. To accomplish this the sample was dusted onto a petrolatum-smeared glass microscope slide, and the excess shaken off. The essentially monolayered sample was placed directly in a diffractometer (General Electric XRD-5) and the intensities of the peaks at 8.72 and 12.09° were determined from the recorder tracing.

TABLE I.—CORRELATION OF TABLETING ABILITY OF VARIOUS LOTS OF BULK DRUG WITH CRYSTAL HABITS

Order of Tableting Ability of Lots		Intensity at 12.09°/Intensity at 8.72°
A		3.60
B		2.36
C		2.43
D	decreasing	1.50
E	tableting	2.00
F	ability	1.40
G		1.25
H		1.15
I	↓	1.12

[1] The orthorhombic unit cell dimensions are: a = 9.07 A; b = 20.14 A; c = 7.78 A.

[2] Corresponding d spacings for these 2 θ values are: 10.13 A for 8.72°; 7.31 A for 12.09°.

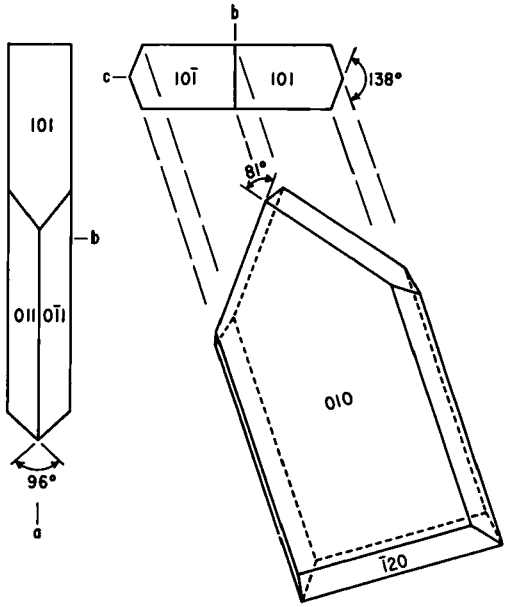

Fig. 1.—Orthogonal and clinographic crystal projections.

Since the intensity of the 12.09° peak is proportional to the mass of crystalline material with 001 orientation (good tableting ability) and that of the 8.72° peak proportional to the mass with 010 orientation (poor tableting ability), the ratio of intensities of these two peaks is a very sensitive measure of the average crystal habit represented, as it relates to tableting ability.

Table I shows a comparison of nine sample lots of bulk drug. In the left-hand column the designations are listed in decreasing order of acceptability, as determined by actual observation during the tableting process by experienced personnel. In the right-hand column are listed the intensity ratios for each sample designation as determined by the method described above. Although the averaging of multiple samplings of each lot gives better correlation, the measured values of Table I, representing single determinations, show good correlation with observed tableting behavior and indicate the validity of the method. The results reported are from a blind study.

As the method employs the use of measured ratios, it is independent of the total amount of sample taken for each determination. The validity is increased, however, by taking as large a sample as is practical and, for this reason, it has been found advisable to employ large X-ray beam and detector slits in order to scan larger sample areas. The attendant loss of resolution when large slit values are employed is not important for these studies.

A total time of approximately 5 minutes is required for sample preparation, X-ray scanning, and ratio calculations.