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Plasticity and Slip System of Plate-Shaped Crystals of L-Lysine Monohydrochloride Dihydrate

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Purpose. To identify the slip system of L-lysine monohydrochloride dihydrate (LH) and to relate it to the deformation behavior under uniaxial compression.

Methods. The indentation hardness of the {100} face and the indentation moduli of the {100} and {011} faces of plate-shaped single crystals of LH (LHP) were determined using Knoop and Berkovich indenters, respectively. The deformation behavior during uniaxial compression was studied by the punch-stress vs. punch-displacement profile and by electron microscopy of the deformed crystals within cracked compacts.

Results. The different indentation (elastic) moduli of the {100} and {011} faces of the crystals are consistent with the molecular packing density along these planes and suggest anisotropy. The existence of the {001} <100> slip system is proposed based on the pattern of changing indentation hardness with varying orientation of the Knoop indenter. A jagged uniaxial compression profile suggests deformation by mechanical twinning and not simple slip. The hypothesis of deformation by mechanical twinning is supported by the appearance of twin bands along the crystal faces as observed by electron microscopy of the cracked compacts.

Conclusions. During compression, most LHP crystals have their {100} faces oriented normal to, or inclined to, the compression axis, thereby facilitating plastic deformation along the {001} <100> slip system by mechanical twinning. Due to the low attachment energy between them, the {001} planes can also act as cleavage planes. This study demonstrates that knowledge of the crystal structure and slip systems can be used to model the tableting and compaction behavior of molecular crystals, such as LH.

KEY WORDS: compaction; L-lysine monohydrochloride dihydrate; mechanical twinning; microindentation; plastic deformation; plate morphology; slip system.

INTRODUCTION

Prediction of the tableting properties of the bulk powder from the molecular or crystal structure and from the mechanical properties of single crystals may greatly benefit the formulation of solid dosage forms. Mechanical properties are influenced by molecular or crystal structure. For example, a definite correlation was found between the chain length of a homologous series of benzoic acid esters and the mechanical properties of the compressed polycrystalline mass (1,2). Several previous studies have attempted to predict tableting properties from the mechanical properties of single crystals (3–6) and from the cohesive energy density of molecular crystals (7–10). For example, Roberts *et al.* (9) proposed that plastic deformation of pharmaceutically important organic crystals primarily results from slip. However, little is known about the mechanical twinning of pharmaceutically important molecular crystals and its influence on tableting.

Because almost 80% of organic crystals belong to the monoclinic and triclinic classes (11) and hence possess low symmetry while exhibiting anisotropy, the relative orientation of the crystallites during compression may also significantly influence the overall mechanical properties of the compact. Microindentation studies have demonstrated the anisotropy that is associated with organic crystals (12). Because the shape (habit) of the crystallites often influences their orientation, models for predicting tableting properties should ideally consider their shape and the packing orientation (with respect to the compression axis), in addition to the mechanical properties of the crystals.

Intuitively, if the dimension of any one edge (or even two) is considerably smaller than the others, most of the crystals may pack in a similar orientation. Hence, plate-, rod-, or needle-shaped crystals may pack preferentially with their longer dimension(s) oriented normal to the compression axis. In contrast, more rounded or more equidimensional crystals will orient randomly and will demonstrate overall reduced anisotropy during compression. Hence, attempts to relate the crystal structure of organic crystals to their overall mechanical behavior and tableting properties will definitely benefit from a consideration of crystal habit.

The mechanical properties of a crystal may be estimated from the indentation hardness of the various faces of the crystal. Indentation hardness provides a measure of the propensity for elastic/plastic deformation of these faces. The tableting properties of any given crystalline powder will depend, to a large extent, on the ability of the crystals to undergo plastic deformation, because plastic deformation results in the permanent change in particle shape that increases interparticulate contact area and promotes binding. In contrast, crystals that neither yield nor undergo plastic deformation may store considerable elastic energy during compression that may be released during decompression, producing cracks within the tablet.

The plastic deformation of crystals can be attributed to glide (or slip), twinning, and kinking, all in simple shear (13). Plastic deformation by slip occurs along a specific crystallographic plane when sheets of molecules glide across one another similar to a stack of playing cards in a deck of cards. Slip occurs along specific planes in the crystal, called slip planes, and along specific directions. Any given slip plane (*hkl*) and the associated slip direction *<h'k'l'>* then constitute a complete slip system. In simple translational slip, the orientation of the slip planes is unaffected even after such lateral displacement. Plastic deformation is more likely due to twinning for crystals with low symmetry and few slip systems or when plastic deformation is hindered due to unfavorable alignment and under high loading (compression) rates. In twinning, successive slip planes are displaced about a mirror plane (the twin plane) such that the lattices above and below the twin plane are mirror images of each other. Unlike slip, the deformation in twinning is homogenous over the entire lattice and

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displacement of the lattice planes is not restricted to multiples of the lattice parameter. Crystals that undergo twinning demonstrate a discontinuity or bending of the crystal surface with the discontinuity tracing a so-called twin-band on the surface. The deformation in twinning is polar, such that a reversal of stress direction could theoretically reverse the deformation direction of a crystal. Translational slip and mechanical twinning are schematically represented in Fig. 1.

During tableting, the orientation of the slip plane with respect to the applied compressive stresses would affect the resolved shear stress available for slip. In molecular crystals of low symmetry, slip systems are uncommon. Hence, the identification of potential slip systems (slip planes and the associated slip directions) within the crystal lattice, and knowledge of their orientation with respect to the crystal packing direction facilitate the prediction of plastic deformation characteristic and tablet quality. Frequently, the slip plane is also the one with the least attachment energy, and may be manifested as the largest face within the crystal habit. The influence of such large crystal faces on the overall mechanical properties of the compressed tablet can also be of prime importance.

The objective of this study is to use single crystal microindentation to identify the possible slip system(s) in crystalline L-lysine monohydrochloride (LH) dihydrate. LH dihydrate is a molecular ferroelectric crystal, such that the polar water molecules in the crystal lattice are ordered in an already polarized unit cell (14). Because of its crystallochemical nature, LH dihydrate is used as a dielectric and in nonlinear optics (14). From a pharmaceutical and nutritional perspective, L-lysine (1,6-diaminohexanoic acid) is a basic amino acid and an essential nutrient, and is sometimes used for the enrichment of protein quality and supplementation of wheat-based foods to improve human growth and tissue synthesis. The shape and the various faces of the thin plate shaped crystals (LHP) is illustrated in Fig. 2a. In a subsequent report, knowledge of the mechanical properties of a single crystal will be applied to model the compression characteristics of the bulk powder.

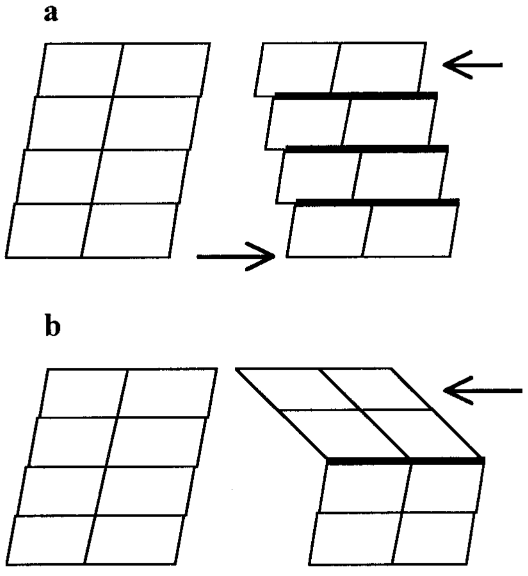

Fig. 1. Schematic representation of crystal deformation by (a) slip and (b) twinning. The thick lines represent the relative positions of the slip planes in (a) or the twin band in (b). The arrows indicate the directions of the applied stress.

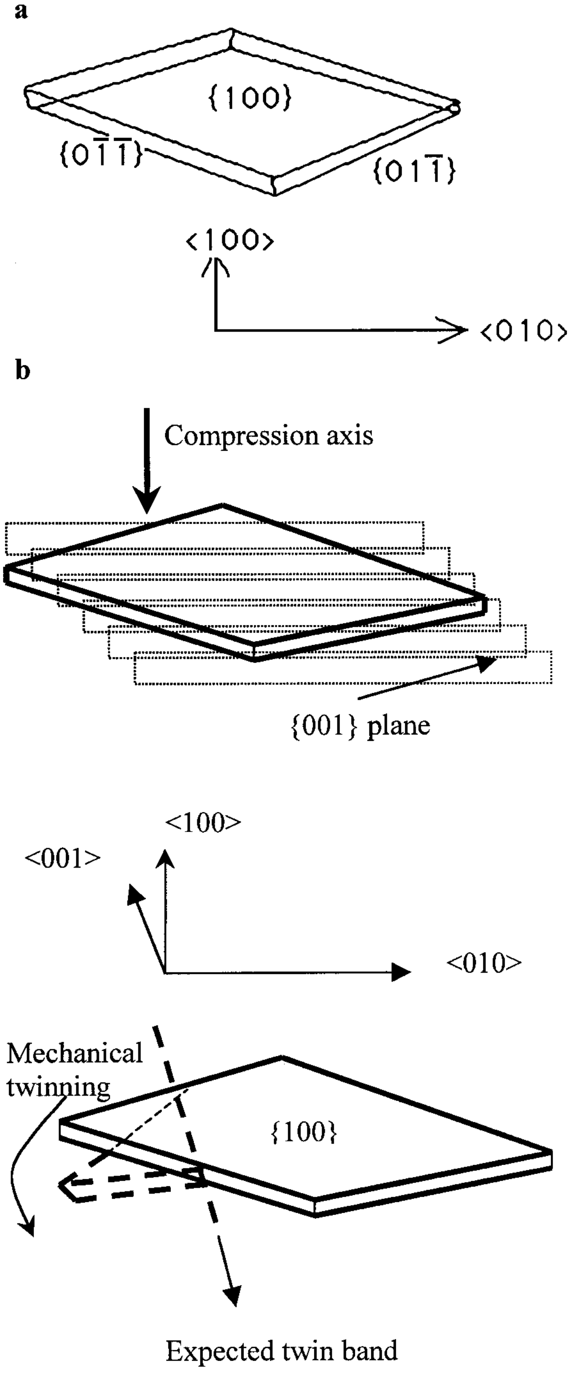

Fig. 2. (a) Sketch of a thin plate-shaped crystal of L-lysine monohydrochloride dihydrate showing the Miller indices for the various crystal faces. (b) A schematic representation of twinning of the plate shaped crystals of L-lysine monohydrochloride demonstrating the relative orientation of the slip planes and the twin band with respect to the crystal faces.

MATERIALS AND METHODS

Crystallization of L-Lysine Monohydrochloride Dihydrate

Saturated aqueous solutions of anhydrous LH (Aldrich Chemical Co., Milwaukee, WI) were prepared at 45°C in glass flasks, transferred to the 6 L crystallizer, and allowed to equilibrate. The crystallization vessel was maintained at a slightly higher temperature (47–50°C) to redissolve any nucleation seeds generated during the transfer. The initial pH of the saturated aqueous solution was adjusted to 9.6, the isoelectric point of L-lysine, with sodium hydroxide (Fisher Scientific, Fair Lawn, NJ). The crystallization medium was cooled linearly at 0.56°C/min from 50°C to 5°C over a period of 80 min. The addition of a small proportion of acetone (50 mL/L of crystallization medium) during cooling resulted in thin plate-like crystals with a diamond shape. In general, these plate shaped crystals were obtained in low yield, which increased somewhat after addition of a few seed crystals of L-lysine (Aldrich Chemical Co., Milwaukee, WI) to the crystallization medium. The crystals, so obtained, were filtered under vacuum, because the thin plates blocked the filter paper and slowed down the process of filtration. The crystals were characterized as L-lysine monohydrochloride dihydrate by direct analysis using single-crystal X-ray crystallography.

Electron Microscopy

To study the effect of compaction pressure on crystal morphology and on the cracking behavior of the compacts, the compacts were split under tension in a tensile stage and observed by environmental scanning electron microscopy (ESEM, Electroscan, Wilmington, DE). The water-vapor pressure of the sample chamber was adjusted close to ambient (30–50% RH) to prevent the loss of the water of crystallization during electron microscopy. Unlike conventional scanning electron microscopy, ESEM does not require the samples to be coated with a conducting surface. The edges of the compacts were clamped to the tensile stage using sliding calipers that were tightened carefully by hand so as not to introduce any local damage. Once inside the observation chamber, the stage was operated remotely at predetermined speeds. These observations were complemented by direct observation of the cracked surfaces of the compacts.

Mechanical Properties of Single Crystals

Carefully grown LHP single crystals were used for microindentation studies. The micromechanical tester used in this study has been described in detail by Wu (15) and was built indigenously by the Characterization Facility at the Center for Interfacial Engineering, University of Minnesota. The indentation hardness of the {100} face, which dominates this crystal habit, was measured at several orientations of the Knoop indenter around the <100> axis. The variation of the hardness, as measured by the asymmetric Knoop indenter, was used to identify the operative slip system(s) responsible for plastic deformation. To demonstrate anisotropy, the reduced elastic moduli and the hardness of the {100} and {011} faces were calculated from plots of load vs. depth-of-penetration of a Berkovich three-sided pyramidal indenter. The unloading portion of the load-penetration profile was used to calculate the elastic moduli using the approach of Doerner and Nix (16). In brief, the reciprocal of the unloading curve, dh/dP, is related to the reduced elastic modulus, E', thus:

$$\frac{\mathrm{d}h}{\mathrm{d}P} = \frac{1}{2h_{\mathrm{p}}}\left(\frac{\pi}{24.5}\right)^{1/2}\frac{1}{E'} \quad (1)$$

where h is the depth of penetration of the indenter in μm, P is the force in mN, and h_{p} is the plastic depth in μm, evaluated as the intercept on the depth-axis in the linear fit over the top one-third of the unloading profile. The Berkovich indenter had the same ratio of cross sectional area to depth as the Vickers Indenter. The maximum rate of indentation was gradually decreased with increasing depth of penetration into the crystal surface by the indenter from a maximum rate of about 60 nm/s.

MOLECULAR MODELING

Attachment Energy Calculations

The attachment energy, E_{att}, is defined as the energy released on the attachment of a growth-slice to a growing crystal face (17,18). E_{att} is calculated as

$$E_{\mathrm{att}} = E_{\mathrm{lattice}} - E_{\mathrm{slice}} \quad (2)$$

where E_{lattice} is the lattice energy of the crystal, and E_{slice} is the energy released on the formation of a growth-slice of a thickness equal to the interplanar *d*-spacing for the crystallographic plane that represents a face. The Dreiding 2.21 force field (19) was used to calculate the attachment energies of the various crystal faces of LH dihydrate using commercial software (Property Prediction module of Cerius$^{2\mathrm{TM}}$, version 3.0, Accelrys Inc., San Diego, California).

Simulated Powder X-Ray Diffraction Pattern

The powder X-ray diffraction patterns of the plate-shaped LH dihydrate were generated from their crystal structures using commercial software (Analytical Instruments module of Cerius$^{2\mathrm{TM}}$, version 3.0, Accelrys, San Diego, California) and compared with the experimental data. The simulated pattern was predicted for crystallites with hypothetical dimensions of 0.1 × 0.1 × 0.1 μm using Cu Kα radiation with a polarization factor of 0.5. The calculated patterns were used to identify the interplanar *d*-spacing of the various crystallographic planes.

RESULTS AND DISCUSSION

Identification of the Crystal Faces

Changing the unit cell of LH dihydrate to the conventional right-handed coordinate system resulted in an interchange of the *a* and *c* dimensions (Table I) from those reported earlier (20) and also changed the Miller indices assigned to the various crystal faces. Kravchenko *et al.* (14) reported the predominance of the {110} and {001} faces in crystals of LH dihydrate, which correspond to the {100} and the {011} faces in the present frame of reference. The {100} and {011) family of faces also predominate in the thin plate-shaped crystals obtained in this study. The primary slip plane is frequently the plane with the lowest attachment energy and can also turn out to be the cleavage plane for the crystals. The attachment energies of some relevant faces of the present crystal structure are listed in Table II, and the {001} plane can be identified as the one having the lowest absolute value of the attachment energy. The presence of glide-symmetry over the {001} plane satisfies the crystallographic requirements for slip along {001}. Taking the interchange of cell dimensions into account, Kravchenko *et al.* (14) identified this same crystallographic plane as the cleavage plane.

Table I. Lattice Dimensions and Other Crystallographic Parameters of Freshly Grown Thin Plate-Shaped Crystals of L-Lysine Monohydrochloride Dihydrate (LHP) Compared with Those Reported by Wright and Marsh (20)

	LHP crystal	LH dihydrate from ref 20
Study temperature	173 (2) K	Not reported
X-ray wavelength	0.71073 Å	1.54051 Å
Crystal system	monoclinic	monoclinic
Space group	$P2_1$	$P2_1$
a	5.8803(1) Å	7.492(1) Å
b	13.2676(3) Å	13.320(4) Å
c	7.4458(2) Å	5.879(1) Å
β (α = 90°, γ = 90°)	97.902(1)°	97.79(1)°
Unit cell volume	575.39(2) Å^3	581.3(1) Å^3
Density (calculated)	1.262 g/cm^3	1.259 g/cm^3
R-factor	0.0312	0.057

Note. The a and c crystallographic dimensions are interchanged between the two structures.

From microindentation measurements using a Berkovich pyramidal indenter on thin plate-shaped crystals of LH, the reduced elastic modulus, E', and the indentation hardness, H, of the more important planes and family of planes are: {100} E' = 20.6 (2.2) GPa, H = 680 (130) MPa; {011} E' = 12.9 (1.3) GPa, H = 719 (66) MPa. (The standard deviations for n = 4 are in parentheses.)

The elastic modulus is a measure of rigidity of the crystal lattice. Due to elastic rigidity, if an applied stress slightly displaces the atoms and molecules within the crystal lattice from their equilibrium positions, the intermolecular (or interatomic) forces will restore them to the equilibrium position on removal of the applied stress (21). If we assume that the nature of the interatomic forces are similar along the <100> or the <011> directions, then the elastic moduli in these two directions would be directly related to the displacement from the equilibrium position of the atoms. Hence, the lower elastic modulus for {011} can probably be attributed to the higher interplanar *d*-spacing in this direction as compared to the *d*-spacing between the {100} planes. The mean hardness of the {100} face was found to be slightly lower than that of the {011} faces.

The deformation stress during microindentation is parallel to the line of steepest slope on the individual indenter facets (12,22). The slip planes are constrained elastically during indentation such that, as indentation proceeds, the material is displaced from within the bulk to the specimen surface by rotation of the slip plane around an axis parallel to an adjacent indenter facet. The resolved shear stress, τ, necessary for plastic deformation by slip (22) may be expressed as:

$$\tau = (F/A)\cos\lambda\,\cos\phi\,\cos\psi \tag{3}$$

where F is the applied force, A is the area of indentation, λ is the angle between the stress axis (parallel to the long axis of a Knoop indenter) and the slip direction, ϕ is the angle between the stress axis and the normal to the slip plane, and ψ is the angle between the stress axis and the axis of rotation for the slip planes (Fig. 3). The rotation of the slip planes is constrained by the cosine of the angle ψ between an adjacent indenter facet and the rotational axis of any given slip system. When the axis is parallel to the indenter facet, constraint is minimal ($\psi = 0$, $\cos\psi = 1$) and the maximum resolved shear stress necessary for the rotation is available. When the axis of rotation is normal to the facet, the constraint is maximal (ψ = 90°, $\cos\psi = 0$, resolved shear stress = 0) and rotation of the slip plane is prevented. Figure 4 shows the variation of hardness of the {100} face with indenter orientation. (In general, a lower indentation hardness is attributed to increased plasticity—compliance to the deforming stress—that results from slip, twinning, or movement of the molecules associated with the dislocations.) The hardness of the {100} face is minimal when the long axis of the Knoop indenter is parallel (orientation angles = 0° and = 180°) to the <001> direction, i.e., <001> coincides with the axis of rotation. Hence, the existence of the {001} <100> slip system (meaning slip along the {001} plane, in the <100> direction) can be established clearly.

The large variability in the Knoop hardness when measured by microindentation is not uncommon. Apart from control of the instrument and sensitivity of the measurements, slip planes frequently have the least attachment energy and can also act as cleavage planes. Some cleavage (as cracks) may occur to varying degrees during indentation. In fact, microscopic examination of the indentations on {100} frequently revealed cracks along the proposed slip plane. Such complexity of crystal deformation for low symmetry crystals adds to the challenges of modeling bulk compaction behavior. Crystallographic planes consisting of large molecules do not glide

Table II. The Calculated Attachment Energies of Various Crystallographic Planes in Plate-Shaped Crystals of L-Lysine Monohydrochloride Dihydrate (LHP)

Miller indices of planes	Attachment energies of lattice planes for LH dihydrate (kJ/mol)	Interplanar *d*-spacing (Å)
(100)	−55.2	5.8
(011)	−62.1	6.4
(020)	−103.8	6.6
(111)	−96.1	4.1
(110)	−78.6	5.3
(101)	−95.3	4.3
(001)	−27.2	7.4

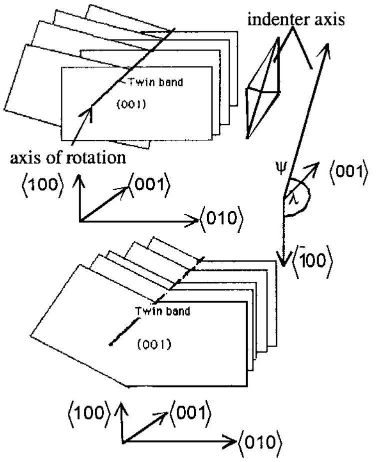

Fig. 3. Schematic representation of the relative orientation of the axes of a Knoop indenter with respect to the slip planes, and the expected rotation of the slip planes during indentation.

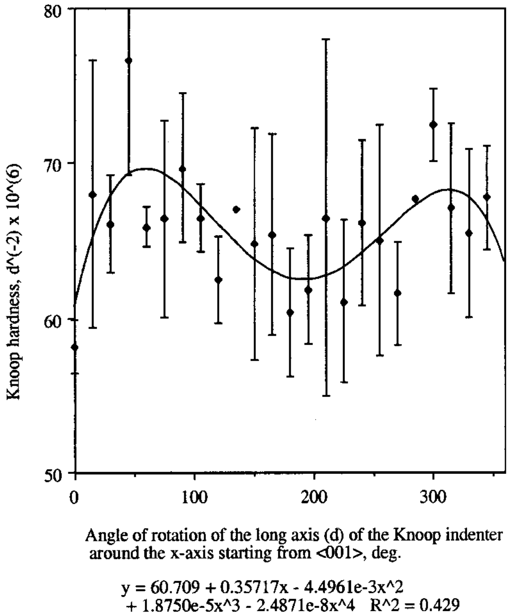

Fig. 4. The variation in hardness, y, of the {100} face of plate-shaped crystals of L-lysine monohydrochloride with varying indenter orientation, x. The given profile of hardness vs. indenter-orientation was fitted to a fourth order polynomial, thus: $y = 60.71 + (0.36)x - (0.005)x^2 + (1.9 \times 10^{-5})x^3 - (2.5 \times 10^{-8})x^4$

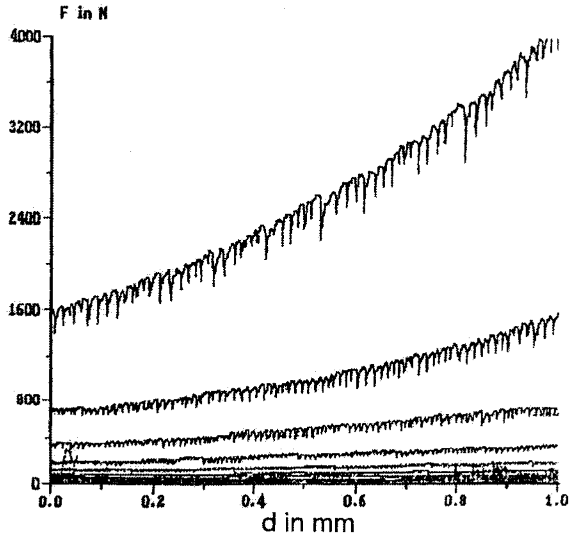

Fig. 5. Typical profiles of axial load, F in N, vs. compression depth profile, d in mm, generated by uniaxial compression of a powder bed consisting of plate shaped crystals (355–595 μm) of L-lysine monohydrochloride. The punch diameter was 10.0 mm, the punch speed was 1.0 mm/min, and the die wall was lubricated with magnesium stearate.

past one another easily, even if such an operation is permitted without affecting crystal symmetry. Steric hindrance through peripheral side chains and functional groups may be the major limitation to such shear deformation, and can be a major factor in explaining the tendency of the crystals to cleave at these planes rather than to undergo slip. Moreover, the propensity for slip or twinning depends significantly on the dislocation density and the ease of movement of such dislocations. Because of the finite time for movement of these dislocations, crystals comprising molecules of low symmetry may appear brittle under relatively fast compression.

The jagged compression profile of stress vs. strain for LHP is typically associated with twinning (Fig. 5). The sudden release of stress due to twinning of a subset of crystals undergoing compression gives rise to the jagged appearance of the stress vs. strain (or displacement) profile. The slippage of individual particles (grains) or build-up of static charge and its dissipation during compression can also cause a sudden release of stress to produce a similar jagged compression profile. However, likelihood of twinning in this case is supported by (a) visual observation of the twinned crystals, (b) the broad range of compaction pressures and compact porosity over which the jagged profile is displayed, and (c) additional observations to be reported separately, which show the jagged profile only at orientations that are favorable for slip/mechanical twinning. Moreover, given the restricted slip system in LH, under favorable alignment during compression, LHP crystals are expected to undergo twinning, not simple slip. Twinning along the {001} <100> slip system is schematically illustrated in Fig. 2b along with the expected position of twin bands on the {100} face. The photomicrographs of the cracked compact surfaces demonstrate some twinning on the {100} faces that are exposed (Fig. 6). The deformed crystals appear continuous and homogenous up to the twin band where the orientation of the crystal suddenly changes. It is not uncommon for cracks to appear along the twin bands (23). ESEM photomicrographs also confirm that most crystals pack with their larger {100} faces parallel to the punch faces during compaction (Fig. 6). Accordingly, the {001} plane is oriented parallel to the compression axis, maximizing the resolved shear stress along this plane. Mechanical twinning along this {001} <100> slip system can also explain the appearance and the orientation of the twin bands on the {100} face of LH dihydrate (Fig. 6). The similarity of the {001} plane to a cleavage plane can also give rise to cleaved crystals under compression.

We are extending this study to other pharmaceutical crystals with restricted slip systems. For crystalline powders that are capable of slip/twinning, compaction characteristics can be favorably modulated to increase plastic deformation and tablet integrity.

CONCLUSIONS AND IMPLICATIONS

These observations with a typical molecular crystal of monoclinic symmetry, LH, demonstrate that mechanical twinning can induce plastic deformation. During compression, most of the plate-shaped crystals of LH have their {100} faces oriented normal to, or inclined to, the compression axis, thereby facilitating plastic deformation along the {001} <100> slip system by mechanical twinning. Due to the low attachment energy between them, the {001} planes can also act as cleavage planes. Mechanical twinning usually occurs under impact loading conditions that are very likely, when a crystalline pharmaceutical powder is compacted in a high-speed tableting machine. Twinning and slip help release the internal stresses within the crystals, and may cause residual stresses to develop at the twin boundaries. If the residual stresses are large, twinning can result in rupture and can impart brittle characteristics to the crystals, as reported previously (23).

In a polycrystalline mass, such as a compact, the cumulative mechanical properties of the constituent crystals are a

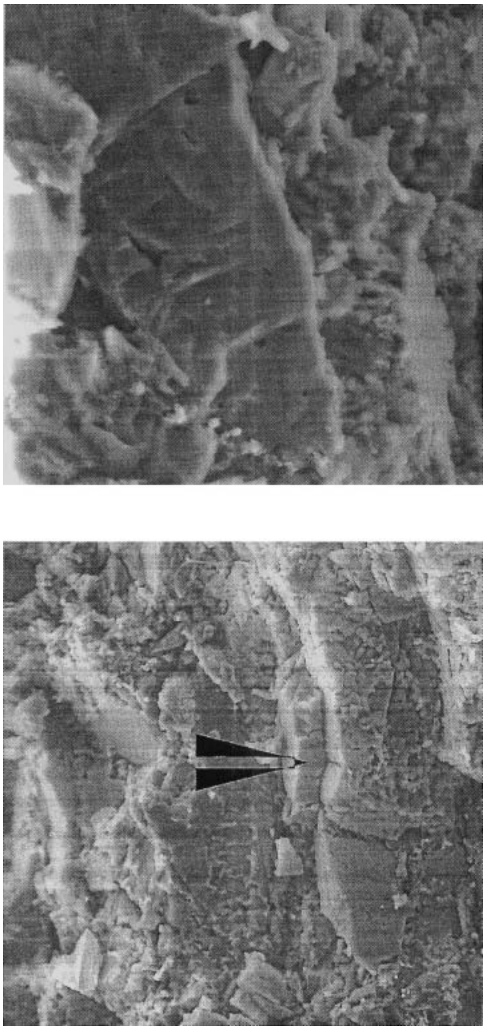

Fig. 6. Predominant packing direction of the plate shaped crystals of L-lysine monohydrochloride as observed with environmental scanning electron microscopy. The appearance of the broad deformation bands on the {100} faces is demonstrated (top). From the side view, the large arrow specifies the direction of uniaxial compression and mechanical twinning of the plate shaped crystals.

function of some statistical weighting factor characteristic of the packing orientation of the crystals. Hence, it is important to understand the packing orientation of the crystals with respect to the compression axis. Ideally, the compaction properties of bulk crystalline solids can be predicted *a priori* from indentation studies of well-grown single crystals, and from their crystal shape and structure.

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