5 Using crystal's morphology to predict the hardness of active pharmaceutical ingredients

Abstract

The pharmaceutical area, both the scientific and industrial, increasingly needs very small particles. A common method to produce such particles is milling or micronisation. The hardness of particles is a critical parameter for assessment of the right size reduction conditions. The purpose of this study is to predict the hardness of (pharmaceutically important) crystals based on particle morphology and crystal structure. The study defines the slip system of a crystal. Based on theoretical considerations and experimental tests a correlation between particle morphology and the slip system of crystals has been established. This relation, combined with data of the unit crystal and the cohesive energy density of the molecule make it possible to calculate the particle's hardness. To check the validity of the model the hardness of four other compounds was predicted based on the correlation established in this study. Subsequently, the predicted hardness was compared with the experimentally determined hardnesses as reported in literature. There was reasonable agreement. Consequently, the hardness of crystals can be predicted using the morphology of the particle, the crystal's unit cell dimension, and the cohesive energy density of the molecule.

5.1 Introduction

Crystallization is a key unit-operation in the development and manufacturing of active pharmaceutical ingredients (API's) and is widely used in the pharmaceutical industry for purification and final crystal form selection (1). Frequently, pharmaceutical applications require smaller particles than those obtained by crystallization. There are several ways to produce small particles but micronization by (jet) milling is still preferred as there are no moving parts and jet mills are easy to clean (2). Unfortunately, batch-to-batch variations in terms of particle size are frequently encountered during milling, even when the same processing conditions are employed. The conclusion is that alterations in mechanical material properties must play a role because generally, milling conditions are kept constant (3). Earlier research on this topic clearly revealed that the hardness of particles is of utmost importance for the size reduction behaviour of particles (4, 5). Hardness has been defined as "the resistance offered by a given material to external mechanical action endeavouring to scratch, indent or in any other way affect its surface" (6). Essentially, the hardness gives a quantitative value to the material's ability to resist local deformation (7) and is a useful parameter in predicting breakage behaviour of solids. However, in view of the complexities of the crystal structure of organic solids, prediction of the hardness is a challenge. Roberts and Rowe (8) developed a model to predict the material hardness. Unfortunately, the prediction of the hardness sometimes fails since the hardness depends heavily on the presence of so-called slip planes in the crystals (8). Slip planes are specific planes in a crystal which frequently coincide with the major cleavage plane, i.e. the plane along which the crystal fractures more easily (8, 9). Therefore, if slip systems (slip planes and the associated slip directions) are identified within the crystal lattice, it should be possible to determine the hardness of crystals. As far as the authors know, a prediction of the slip system based on crystal morphology has not been

performed before. The objective of this study is to identify slip planes based on crystal morphology and, subsequently, to predict the hardness of pharmaceutically important organic crystals.

5.2 Materials and methods

5.2.1 Materials

Several pharmaceutically active compounds and one undisclosed heterocyclic compound A were used. All materials were from Organon N.V., Oss, The Netherlands.

5.2.2 X-ray powder diffraction

The unit cell dimensions of the pharmaceutical compounds have been determined using X-ray powder diffraction. The X-ray powder diffractograms (XRPD) were recorded with a Panalytical XPert Pro diffractometer using monochromatic Cu-K_α radiation. Generator settings were 40 kV and 50 mA. The measuring conditions: 2 Θ =5 – 35°, step size 0.02°, time per step 5 s.

5.2.3 Scanning electron microscopy

Scanning electron microscopy (SEM) micrographs were taken of all crystals. A high resolution scanning electron microscope (LEO, type Gemini) equipped with energy dispersive analysis (EDX, Oxford, type INCA) was used.

5.2.4 Aspect ratio

The least bounding rectangle length (LBRL) and the least bounding rectangle width (LBRW) of the crystals were determined using SEM micrographs of the crystals. The LBRL is defined as the length of the smallest rectangle that encloses the image as has been illustrated in Figure 5-1. The LBRW is defined as the width of the smallest rectangle that encloses the image.

Subsequently, the aspect ratio (A_r) was calculated as the length-to-width ratio of that rectangle (10).

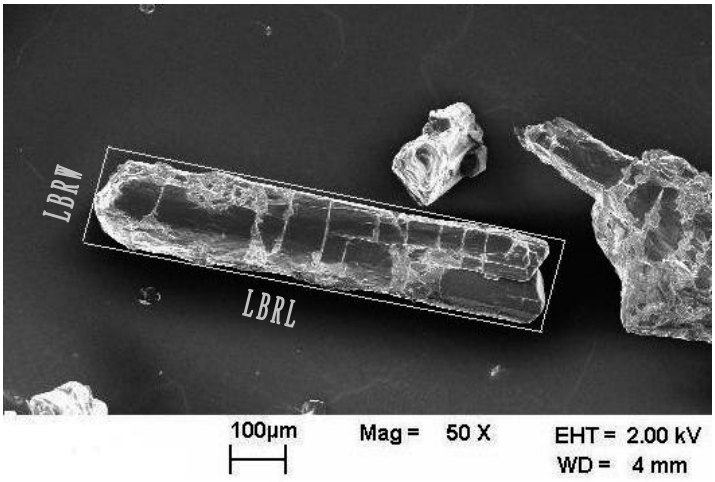

Figure 5-1 Determination of the aspect ratio defined as the ratio of the least bounding rectangle length (LBRL) to the least bounding rectangle width (LBRW).

5.2.5 Determination of crystal hardness

The crystal hardness was determined as proposed by Heckel (11). The porosity-pressure relation of the compounds was investigated using a high speed compression simulator (ESH, Brierley Hill, UK). This compression simulator enables the assessment of compaction behaviour with single tablets. A powder sample of 500 mg was compressed into a cylindrical compact with a diameter of 13 mm. Compression load and compact volume with time were recorded. The average punch speed was 3 mm/s. The compression profile was sinusoidal. Heckel (11) suggested to linearise the porosity (ε)-pressure (P) relation of powders:

$$-\ln(\varepsilon) = K.P_c + A \qquad (1)$$

The symbol *A* is a constant which is thought to be a measure of the relative density of the powder bed after particle rearrangement (12). The linear part of the curve has slope *K* and this slope is related to the yield strength (σ_c) by:

$$\sigma_c = \frac{1}{3.K} \tag{2}$$

It is known that the yield pressure of a material is equal to 3 times the yield strength. Hence, the reciprocal of *K* can be regarded as numerically equal to the mean yield pressure (13):

$$P_y = 3 \cdot \sigma_c \tag{3}$$

The next step is to determine the hardness (*H*) of the material under investigation. Following Roberts and Rowe (13) it is assumed that the hardness of a material is equal to 3 times the yield pressure.

5.3 Results and discussion

5.3.1 Crystal characterization and determination of slip ratio

Table 5-1 lists the basic data of the crystals. The parameters *a*, *b*, and *c* represent the dimensions of the unit cells. The angle between the axes *a* and *c* is given by *β* (8) and *Z* is the number of molecules in a unit cell. The cohesive energy density (*CED*) is a thermodynamic parameter that represents the amount of energy which is necessary to remove a molecule from the lattice in which it is placed. The *CED* was determined using the group contribution method as proposed by Hansen (14). The last columns give the aspect ratios (A_r) and the hardnesses (*H*) of the crystals which were obtained as discussed in the materials and methods section.

Table 5-1 Crystallographic data, hardness and aspect ratio of the APIs.

Compound	*a* (nm)	*b* (nm)	*c* (nm)	*β* (°)	*Z*	*CED* (MPa)	A_r (-)	*H* (MPa)
Androstenolone	0.6641	1.14423	2.2085	90	4	493	2.6	157
Bepridil	3.0106	1.4017	1.1725	100.78	8	405	7.0	43
Buprenorphine	1.151	1.151	3.4	90	8	625	1.9	64
Danazol	0.6601	1.053	2.6177	90	4	581	2.5	64
Dexamethasone TBA	1.6278	2.3252	1.0447	90	8	548	5.9	208
Etonogestrel	0.6653	1.841	0.797	107.49	2	493	2.6	183
Medroxy prog. acetate	1.1078	1.05	0.927	103.23	2	388	1.4	74
Mestranol	0.6998	3.9737	0.6871	117.58	4	511	4.6	114
Mianserine HCl	0.9014	1.4917	1.2412	108.84	4	441	4.4	163
Mirtazapine	0.983	1.732	0.888	106.47	4	562	2.5	81
Norethindrone	2.0803	1.2185	0.6542	90	4	497	1.3	54
Norethindrone acetate	0.683	1.2164	2.3846	90	4	396	1.6	78
Progesterone	1.2568	1.3819	1.0363	90	4	388	2.4	110
Rimexolone	1.176	1.175	0.7596	98.85	2	462	3.3	343
Testosterone	0.794	1.3632	1.5952	90	4	493	1.7	125
Compound A	1.555	0.7748	1.1314	124.81	1	664	2.2	215

Roberts and Rowe (8) developed a model which allows prediction of the indentation hardness of organic molecular solids based on their cohesive energy densities, the weakest planes from the crystal structures, and crystal structural parameters. Reworking their model results in:

$$S_r = \sqrt[3]{\frac{c_1\ c_2\ \sin\beta\ 2\ N_a\ CED}{R_c^2\ Z\ H}} \tag{4}$$

where S_r is defined as the slip ratio, C_1 and C_2 are unit cell constants being either the cell dimensions *a*, *b*, or *c* depending on the choice of the reference unit cell axis (8), N_a is Avogadro's number, and finally, $\boldsymbol{R}_c$ is the length of the reference unit cell axis. This study assumes that the length of the reference unit cell axis is equal to the largest unit cell axis. The slip ratio is defined as the ratio of the Burgers vector $\boldsymbol{b}$ over the reference cell vector $\boldsymbol{R}_c$ (8). The Burgers vector is a measure of the magnitude and direction of a crystal dislocation. In this study we use the notation slip system rather than slip ratio which is to be more consistent with other references (9, 15). Consequently, based on the crystallographic data of Table 5-1 and using equation 4 the slip system of the compounds can be determined corrected for the extinction conditions of the space group (16). Screw axes can introduce systematic extinctions into various classes of reflections in X-ray patterns (18). This means that a crystal grows in reality one layer, whereas X-ray pattern suggests growth of two complete layers. This phenomena is referred to as extinction conditions for X-ray diffraction (16,19). To check whether a compound is subject to extinction conditions two criteria had to be fulfilled. First, the compound contains a screw axis and second, after halving the length of the reference unit cell axis its length had to be larger than the length of any of the other two unit cell axes. Consequently, the slip system was calculated of the compounds which fulfil both criteria by halving the length of the reference unit cell axis. These are listed in Table 5-2.

Table 5-2 Slip system of the pharmaceutical materials.

Compound	Slip system
Androstenolone	0.53
Bepridil	0.63
Buprenorphine	0.55
Danazol	0.65
Dexamethasone TBA	0.50
Etonogestrel	0.62
Medroxy progesterone acetate	1.34
Mestranol	0.33
Mianserine HCl	0.73
Mirtazapine	0.83
Norethindrone	0.798
Norethindrone acetate	0.606
Progesterone	0.90
Rimexolone	0.80
Testosterone	0.796
Compound A	1.03

The next step is to correlate the slip system with the morphology of a particle. A common assumption is that the dominant slip plane is the plane with the lowest attachment energy ($E_{att,}$ which is the energy released when a new layer is added to the surface (16)). Moreover, Hartman and Bennema (20) demonstrated that the relative growth rate (R) is proportional with the attachment energy. The ratio of growth rates in the different directions determines the crystal's morphology (16). Considering the two dominant faces of a crystal implies that the aspect ratio of a crystal is basically proportional to the ratio of growth rates and hence the ratio of attachment energies:

$$A_r = \frac{LBRL}{LBRW} \div \frac{R_2}{R_1} \div \frac{E_{att2}}{E_{att1}} \tag{5}$$

Following from this discussion it is reasonable to assume that aspect ratio and slip system are correlated. Furthermore, a common approach (8, 9) assumes that slip occurs in the planes with

the largest interplanar distance. Because the interplanar distance is known to be inversely proportional with the relative growth rate (21) it is reasonable to assume that aspect ratio and slip system are inversely related. This will be investigated in the next section.

5.3.2 Relation between slip system and aspect ratio

The previous section shows that a relation may be expected between the crystal morphology and the slip plane. Figure 5-2 shows the relationship between the slip system of the compounds (Table 5-2) and the reciprocal of the aspect ratio (Table 5-1).

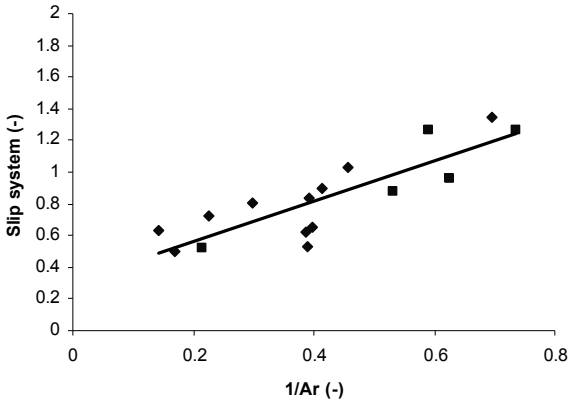

Figure 5-2 Slip system as function of the reciprocal of the aspect ratio of the compounds. (Slope is 1.2784±0.2114 and the intercept is 0.3091±0.0956 with a 95% confidence interval, correlation coefficient R^2= 0.72). The compounds which are subject to extinction conditions are marked with the symbol (■).

The results show that the slip system is inversely proportional to the aspect ratio. Moreover, it can be concluded that crystal symmetries play an important role too. Linear regression analysis has been performed to calculate the relationship between the slip system and the crystal's aspect ratio. Hence, the crystal's slip system can be estimated by:

$$S_r = 1.2784 \frac{1}{A_r} + 0.3091 \quad (6)$$

It is likely that this relationship is valid for a limited range of aspect ratios. For instance, for elongated particles like needle-shaped particles which have a very high aspect ratio it is likely that the propensity to break radially will increase. However, there is no evidence for this suggestion. The next step is to check the validity of the model by means of predicting the hardness of four arbitrary pharmaceutical active compounds which is addressed in the next section.

5.3.3 Checking the validity of the model

In order to check the validity of the model, the hardness of some other compounds were predicted and compared with the hardness values reported in literature. Table 5-3 shows the crystallographic data of these compounds.

Table 5-3 Crystallographic data of reference compounds.

Compound	Source	*a* (nm)	*b* (nm)	*c* (nm)	*β* (°)	*Z*	Space group
Ibuprofen	8	1.467	0.789	1.073	99.36	4	$P2_1/c$
Adipic acid	8	1.001	0.515	1.006	136.75	2	$P2_1/c$
Paracetamol	24	0.71	0.938	1.17	97.82	4	$P2_1/a$
Salicylamide	8	1.292	0.498	2.104	91.8	8	$P2_1/a$

The slip system was determined using equation 6. Subsequently, the crystal hardness of these compounds was calculated using equation 4. Table 5-4 shows the values of the aspect ratio, the slip system, the predicted hardness, and the experimentally determined crystal hardness of four compounds.

Table 5-4 Comparison between predicted hardness and the experimentally determined hardness of reference compounds (sources are in brackets).

Compound	A_r (-)	S_r (-)	*CED* (MPa)	Predicted hardness (MPa)	Experimental hardness (MPa)
Ibuprofen	*2.4* (22)	0.83	416	85	35-166 (8)
Adipic acid	*1.6* (23)	1.10	615	98	123 (8)
Paracetamol	*1.5* (24)	0.75	762	419	235-456 (26)
Salicylamide	*2.8* (25)	0.76	979	197	123-151 (8)

The data in Table 5-4 show that the predicted hardness coincides reasonably well with the experimentally determined hardness. It should be noted that deviations of the predicted hardness might occur when the crystals are not at equilibrium during crystallization since the resulting crystal morphology is influenced by many factors like temperature, rate of cooling, supersaturation, solvent, and impurity concentration (16, 17). However, although there are some deviations the order of magnitude predicted seems acceptable and it is concluded that the proposed method is able to predict the hardness of pharmaceutical active ingredients. This study shows that crystal morphology is correlated with the slip system and hence correlates with crystal hardness. Since it is known that crystallization conditions influences crystal morphology (16) heavily it can be concluded that crystallization conditions affects the breakage behaviour of materials during milling.

5.4 Conclusions

In this study an inverse correlation between crystal morphology represented by the aspect ratio and the crystal's slip system has been demonstrated. Using this correlation it is possible

to estimate the slip system of pharmaceutical active ingredients using the crystal's morphology. Consequently, the hardness of crystals can be predicted, reducing time and material consumption during micronization trials. Furthermore, since it is known that crystallization conditions influences crystal morphology heavily it can be concluded that crystallization conditions affects the breakage behaviour of pharmaceutical materials during milling.

5.5 Appendix 1: Nomenclature

A	Constant	[-]
A_r	Aspect ratio	[-]
a,b,c	Unit cell dimensions	[m]
$\boldsymbol{B}$	Burgers vector	[-]
C_1,C_2	Constants	[-]
CED	Cohesive energy density	[Pa]
D	Relative density	[-]
E_{att}	Attachment energy	[J/mol]
H	Hardness	[Pa]
K	Constant	[-]
N_a	Avogadro number	[mol^{-1}]
P	Pressure	[Pa]
P_y	Yield pressure	[Pa]
R	Growth rate	[s^{-1}]
$\boldsymbol{R}_c$	Reference unit cell vector	[m]
S_r	Slip system	[-]
Y	Young's modulus of elasticity	[Pa]
Z	Number of molecules for unit cell	[-]
β	Angle	[°]
ε	Porosity	[-]
σ_y	Yield strength	[Pa]

5.6 References

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