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Research Paper

Influence of Crystal Structure on the Compaction Properties of *n*-Alkyl 4-Hydroxybenzoate Esters (Parabens)

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Purpose. The aim of the study is to examine the influence of slip planes on the nanoindentation hardness and compaction properties of methyl, ethyl, *n*-propyl, and *n*-butyl 4-hydroxybenzoate (parabens).
Methods. Molecular modeling calculations, embodying the attachment energy concept, were performed to predict the slip planes in the crystal lattices, whereas the nanoindentation hardness of the crystals and the tensile strength of directly compressed compacts were measured.
Results. Unlike the other three parabens, methyl paraben has no slip planes in its crystal lattice, and its crystals showed greater nanoindentation hardness, corresponding to lower plasticity, whereas its tablets exhibited substantially lower tensile strength than those of ethyl, propyl, or butyl paraben.
Conclusions. The nanoindentation hardness of the crystals and the tensile strength of directly compressed tablets were each found to correlate directly with the absence or presence of slip planes in the crystal structures of the parabens because slip planes confer greater plasticity. This work presents a molecular insight into the influence of crystal structural features on the tableting performance of molecular crystals in general and of crystalline pharmaceuticals in particular.

KEY WORDS: attachment energy; compaction; crystal structure; nanoindentation; paraben; slip plane; tableting; tensile strength.

INTRODUCTION

The tablet is the most widely administered pharmaceutical dosage form. Pharmaceutical tablets are usually made by compaction of powders to achieve specific dimensions and to possess a certain coherent strength. Properties of the powders, such as polymorphism (1), moisture content (2,3), particle shape (4), particle size (5,6), and surface roughness (7), may affect the mechanical properties of the tablets. Crystal structure is one of the most important intrinsic features of a compound. Under defined environmental conditions (pressure, temperature, and the absence of impurities), the crystal structure represents the packing of molecules in the crystal lattice, which, in turn, affects the solid-state properties of the crystals and hence greatly influences the compaction properties of the solids.

During the compaction of a tablet formulation, drug particles undergo elastic and plastic deformations to accommodate the volume reduction. During the compaction process, particles rearrange in the initial stage of compression, which is followed by elastic deformation for further reduction of volume. Beyond the yield point of the particles, they plastically deform. Fragmentation of the particles because of their brittle fracture propensity forms new particles with new contact areas between them. Interparticulate bonds form on the contact areas between particles and contribute to the coherent strength of the tablet.

Elastic deformation is reversible upon the release of the compaction load. The elastic recovery of the particles in the post-compaction stage may lead to fracture problems of the compact, such as lamination and capping. However, the elastic modulus does not significantly influence tablet strength (8). On the other hand, plastic deformation is an irreversible process, which contributes to the formation of interparticulate bonds and hence reinforces tablet strength (9). Therefore, plastic deformation is usually desirable to produce a strong tablet. The ease of plastic deformation of crystals is strongly influenced by the crystallographic features of the crystal structure and the presence of crystallographic defects in the crystal (10). The plasticity of a crystal is indicated by its indentation hardness. The greater the plasticity of the crystal, the lower is its indentation hardness.

The plastic movement of the line defects in the crystal is termed *slip*. Slip may occur preferentially along certain planes in the crystal structure, which are called *slip planes*. The slip planes comprise close-packed molecules within parallel planes and weak interplanar interactions between the parallel planes. Slip planes in the crystal lattice allow easier slip motion, enabling greater plasticity, and hence may produce stronger tablets. For example, the existence of slip planes (in the form of sheets of carbon atoms) in the crystal

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structure of graphite allows much easier plastic deformation than for diamond. Among these two polymorphs, only graphite can form coherent compacts.

Molecular modeling has been used to predict the most likely slip planes in pharmaceutical compounds (11). In the crystal structure, the planes whose attachment energy has the smallest absolute value will have the least resistance to cleavage and hence will most likely serve as slip planes. The attachment energy E_{att} is defined as the energy released on attachment of a growth slice (a new layer) to a growing crystal face. E_{att} was calculated as the difference between the lattice energy of the crystal ($E_{lattice}$) and the energy released on formation of a growth slice of thickness equal to the interplanar *d*-spacing of the crystallographic plane that represents a face (E_{slice}).

$$E_{att} = E_{lattice} - E_{slice} \quad (1)$$

Previous studies with polymorphic forms I and II of sulfamerazine have probed the effect of slip planes on tableting performance (1). The absence of interlayer hydrogen bond explains the existence of slip planes in form I, whereas form II has hydrogen-bonded layers that are zigzag-shaped. Translational slip can therefore occur with greater ease in form I than in form II. Under identical compaction pressures, form I gives a much higher tensile strength and a significantly lower porosity. The results are explained by the existence of slip planes in the crystal structure of form I crystals. The greater plasticity because of slip planes in the crystal structure of form I provides greater compressibility (porosity *vs.* compaction pressure) and greater tabletability (tensile strength *vs.* compaction pressure).

The model compounds selected for this study were the following *n*-alkyl 4-hydroxybenzoate esters (parabens), namely, methyl, ethyl, propyl, and butyl parabens. Parabens are antimicrobial preservatives that are widely used in pharmaceutical formulations (12), as well as in cosmetics and food products. The crystal structures of the four parabens have been determined by Giordano *et al.* (13). Methyl paraben shows no slip planes in its crystal structure (Fig. 1A), whereas ethyl, propyl, and butyl paraben all show slip planes in their crystal structures (Fig. 1B–D). The ethyl and propyl parabens are isostructural because they crystallize in the same space group with very similar unit cell dimensions and atomic coordinates of the common atoms. Methyl and butyl parabens have crystal structures that are different and distinct from those of ethyl and propyl parabens. Table I summarizes the unit cell parameters of the crystal structures of the parabens.

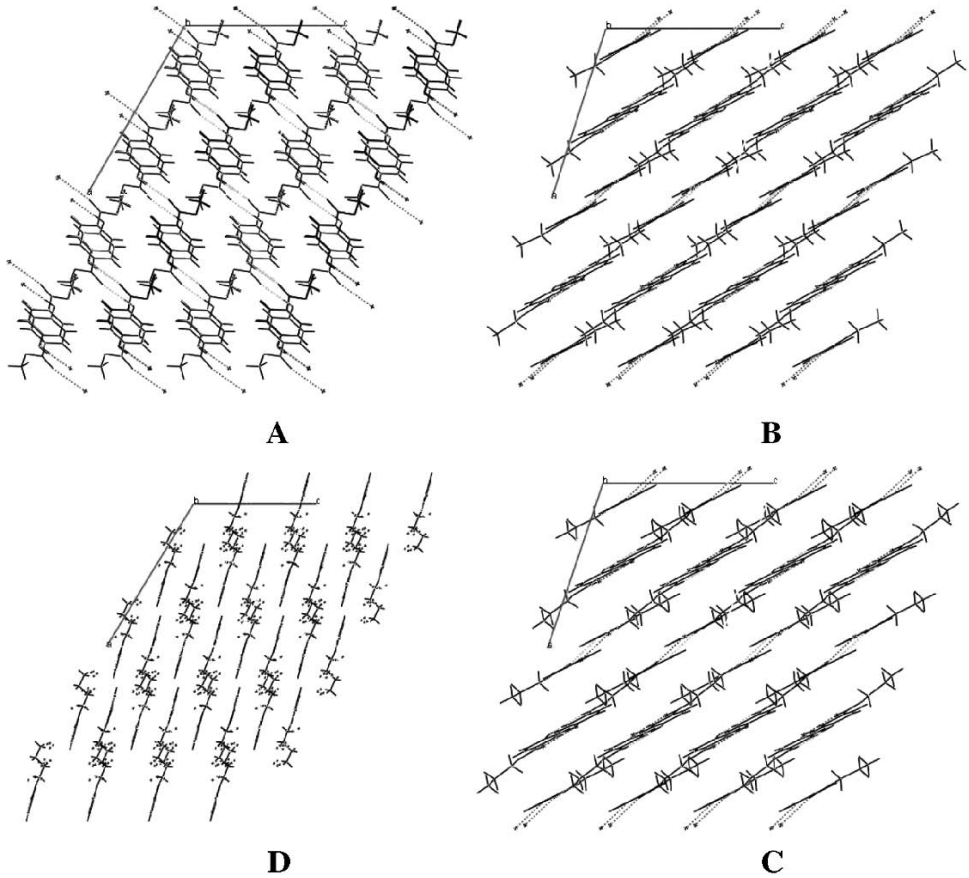

Fig. 1. Crystal structures of (A) methyl, (B) ethyl, (C) *n*-propyl, and (D) *n*-butyl 4-hydroxybenzoate (parabens) showing hydrogen bond (13). Methyl paraben does not show slip planes, and the molecules are connected by a network of hydrogen bonds. Ethyl, propyl, and butyl parabens show slip planes, with hydrogen bonds connecting the molecules within the slip planes, but not between the slip planes. Ethyl and propyl parabens are isostructural, and their structures are presented on the right-hand side.

Table I. Summary of the Unit Cell Parameters of Methyl, Ethyl, *n*-Propyl, and *n*-Butyl 4-Hydroxybenzoates (Parabens) (13)

Paraben	Methyl	Ethyl	Propyl	Butyl
Formula	$C_8H_8O_3$	$C_9H_{10}O_3$	$C_{10}H_{12}O_3$	$C_{11}H_{14}O_3$
Crystal class	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Z	12	8	8	8
Space group	CC	$P2_1/C$	$P2_1/C$	$C2/C$
a	13.5720	11.8030	12.0435	20.0870
b	16.9780	13.2140	13.8292	8.2182
c	11.0270	11.6060	11.7847	14.7136
β	120.09	107.67	108.63	121.39
Density (g/cm^3)	1.3791	1.2799	1.2871	1.2444
Slip planes	No	Yes	Yes	Yes

MATERIALS AND METHODS

Materials

The model compounds, methyl, ethyl, *n*-propyl, and *n*-butyl 4-hydroxybenzoate esters (parabens) were purchased from Sigma-Aldrich Company (St. Louis, MO, USA).

Experimental Methods

Molecular Modeling

Molecular modeling employed Cerius$^{2,\text{TM}}$ software, version 4.9, (Accelrys Inc., San Diego, CA, USA) with the force field Dreiding 2.21. Point charges for individual atoms were assigned using the charge equilibration method. Structural minimizations were iterated before and after charge assignments for optimal structure–charge relations.

Nanoindentation Hardness Measurements

To measure the hardness of parabens crystals, nanoindentation hardness measurements were performed on surfaces of single crystals grown by slow evaporation from ethyl acetate solutions. Fine-quality transparent crystals with typical habit, smooth surfaces were picked for measurements. X-ray microdiffraction (Bruker-AXS Rapid XRD Microdiffractometer, Bruker AXS Inc., Madison, WI, USA) was used to identify the index of the faces. There was one index identified for each face of the crystal. Hardness measurements were performed using a triboscope (Hysitron, Minneapolis, MN, USA) and probe (Berkovich diamond indenter) mounted on a Nanoscope III AFM (Digital Instruments, Santa Barbara, CA, USA). The surface was scanned before indentation to examine the surface smoothness and after indentation to ensure satisfactory indentation and the absence of cracks. In this method, hardness is calculated as the maximum force divided by the maximum area following correction for elastic recovery. The hardness H is determined from the partial unloading segment of the force-displacement curve.

$$H = \frac{P_{\max}}{A(h)} \tag{2}$$

where $P_{\max}$ is the maximal force and $A(h)$ is the corrected area function (14). The indentation starts with a 1-s holding, followed by a 10-s linear load increase. After 2-s holding at maximum load, the unloading segment is a 10-s linear load decrease. A typical force-displacement curve in the nanoindentation hardness measurements is shown in Fig. 2.

Because the nanoindentation tests are performed on single crystals, they exclude many factors present in large-scale compaction tests, such as particle size and particle

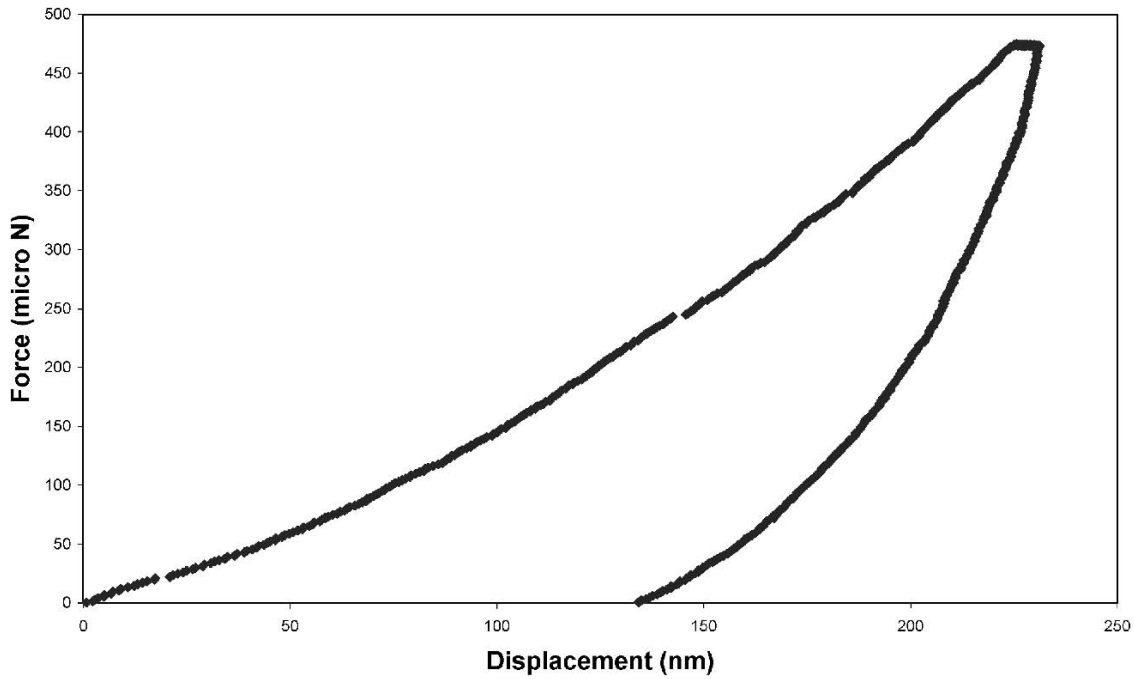

Fig. 2. A typical force-displacement curve in the nanoindentation hardness measurements. The unit for force in y-axis is μN.

shape. The index of the faces, on which the indentation was performed, was identified using X-ray microdiffraction. Powder X-ray diffractometry (PXRD, Cu Kα radiation generated at 40 mA and 45 kV, Model D5005, Siemens, Hamburg, Germany) and Raman spectroscopy (RAM II, Bruker Optics Inc.) showed that the parabens crystals, on which the nanoindentation hardness was measured, were of the same crystalline phase as in the corresponding parabens powders.

Preparation and Characterization of the Parabens Powders

The parabens powders were sieved (USA standard testing sieve, W.S. Tyler, Inc., Cleveland, OH, USA) to obtain 150 to 250 μm fraction for preparing tablets. The sieving process was sufficiently mild that any mechanical damage to the crystals was insignificant. The powders were stored in desiccators over drierite (13001, W.A. Hammond Drierite Company, Xenia, OH, USA) for 1 week before compaction. The powders were found to be crystalline by means of PXRD. Crystallinity was confirmed by differential scanning calorimetry (DSC, at 10°C/min under nitrogen purge at 70 mL/min, Model 2920, TA Instruments, New Castle, DE, USA) and by birefringence under an optical microscope (Wild Heerbrugg M3Z, Heerbrugg, Switzerland). The parabens powders contained negligible water by thermal gravimetric analysis (Q50, TA Instruments) and Karl Fischer titrimetry (Model CA-05, Mitsubishi Chemical Industries Ltd., Tokyo, Japan). The parabens powders sorbed negligible moisture under ambient conditions (25°C and 35% RH) by dynamic vapor sorption (DVS-1000, Surface Measurement Systems, Allentown, PA, USA). All processing and compaction of powders were conducted in an environmentally controlled room at 25°C and 35% RH.

Preparation of Tablets

Tablets of methyl, ethyl, propyl, and butyl parabens were prepared for studies of tableting properties. To exclude particle size effects, paraben powders were sieved, and the size range 150–250 μm was used. The sieved powders of parabens were compacted to make square compacts of dimensions $19 \times 19 \times 9$ mm. Compaction was performed using a uniaxial hydraulic press and split die to allow triaxial decompression to prevent mechanical failure (15). The die walls and punch surfaces were lubricated with a suspension of magnesium stearate (5% w/v) in ethanol before pouring powder into the die. The dwell time at maximum load was set at 10 min, and the compaction pressure was 42 MPa. During the first 1–2 min of the compression stage, the pressure drops by about 1.5–2 MPa because of viscoelastic effects. The compaction pressure is defined as the constant pressure following this initial pressure reduction. The tablets were equilibrated in desiccators for 72 h before mechanical testing.

Tablet density was determined by accurate measurement of the weight and volume of the square tablets. Tablet porosity is calculated from the tablet density and the true density data read from single crystal structure files. The single crystal structures of parabens were determined at room temperature.

The tablet porosities of methyl, ethyl, propyl, and butyl parabens were 0.17, 0.03, 0.06, and 0.03, respectively. No significant variation of tablet porosity was observed at compaction pressures of 21–63 MPa. Under compaction pressures that are normally applied in tablet manufacture, it was not possible to reduce the porosity of methyl paraben tablets to the same values as for tablets of the other parabens. High particle hardness of the methyl paraben crystals might contribute to this effect.

Polymorphism of the Paraben

As a test for polymorphism, the melt of each paraben was fast cooled down to 25°C. On fast cooling the melt of methyl paraben, hot-stage microscopy (Mettler thermosystem FP800, Mettler Instrument Corporation, Hightstown, NJ, USA) and DSC revealed a hitherto unknown metastable polymorph that melted at about 108°C, in contrast to the originally purchased stable form that melted at about 125°C. The nature of this new form is under investigation. On fast cooling the melt of the other three parabens, no polymorphic transitions were detected. Furthermore, PXRD and Raman spectroscopy showed no evidence of polymorphic transformation on the surfaces and in the interior of all the paraben tablets, both before and after compaction or subsequent mechanical tests.

Tensile Strength Measurements of Paraben Tablets

The tensile strength of the paraben tablets was determined using a compressive tensile test (14) in a material testing machine (model 1485, Zwick/Roell, Atlanta, GA, USA). The orientation of the tablets was identical in these measurements, five of which were performed for each paraben. The tablets were diametrically fractured between two padded platens, each 7.8 mm wide (about 0.4 times the width of the tablets), under a constant rate of displacement of 0.01 mm/s. The tensile strength of the tablets was then calculated as 0.16 times the maximum force reached in the tensile strength failure test (14).

The strength determined by this method is indeed the compression strength of the tablet. In the field of pharmaceutical practice, this strength is often called *tensile strength*, which has fully different meaning in mechanics. In this article, the authors use the term tensile strength to denote the strength determined by the above-described test to follow conventional pharmaceutical practice.

RESULTS AND DISCUSSION

Crystal Structures of Parabens

Figure 3 shows the asymmetric units of the various parabens. Methyl paraben has three molecules in the asymmetric unit (Fig. 3A). The angles between the three aromatic ring surfaces are 74.20°, 74.78°, and 0.58°. Hence, two of the aromatic ring surfaces are almost parallel to each other (angle = 0.58°), but display a significant angle with the third ring. In addition, when considering the hydrogen bonds connecting the molecules in three dimensions, methyl paraben

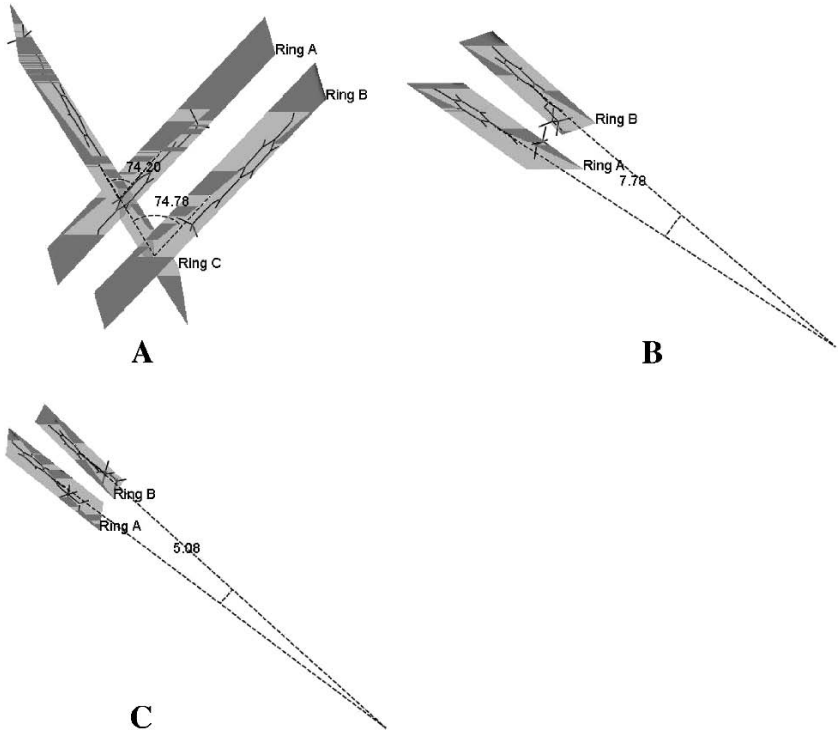

Fig. 3. Asymmetric units of the crystal lattices of (A) methyl, (B) ethyl, and (C) *n*-propyl 4-hydroxybenzoate (parabens). The angles between the planes of the aromatic rings are also shown. (Butyl paraben has only one molecule in the asymmetric unit. The aromatic rings in its crystal lattice are parallel to each other.)

molecules form a three-dimensional network in the crystal lattice that has hydrogen bonds in the directions of all three axes. The lattice of the methyl paraben is strengthened by the "three-dimensional" hydrogen bonds, which explains the increase in resistance to plastic deformation, corresponding to reduced plasticity. This situation does not apply to ethyl, propyl, and butyl parabens. Ethyl paraben has two molecules in the asymmetric unit (Fig. 3B). The angle between the two aromatic ring surfaces is 7.78°. Hydrogen bonds exist only inside the slip planes and hence serve as intraplanar strengthening factors. The interplanar interactions are relatively weak because of lack of hydrogen bonds. The isostructural propyl paraben also has two molecules in the asymmetric unit (Fig. 3C). The angle between the two aromatic ring surfaces is 5.08°. Hydrogen bonds exist only inside the slip planes, not between them. Butyl paraben has only one molecule in the asymmetric unit. The aromatic rings in its crystal lattice are parallel to each other. Again, hydrogen bonds exist only inside the slip planes, not between them. Summarizing the hydrogen bond patterns in the paraben structures, the hydrogen bonds serve as three-dimensional strengthening factors of the network in the methyl paraben lattice, but as an intraplanar strengthening factor inside the slip planes of the ethyl, propyl, and butyl parabens lattices.

Molecular Modeling

In Cerius^{2,TM}, the morphology calculation has two main steps: first, a set of stable surface configurations for each set of (*h k l*) plane indices is generated; second, the crystal growth rate according to each surface configuration is estimated. The software has two methods for calculating attachment energy. The growth morphology method generates flat surfaces by cleaving the crystal along a crystal plane. The Hartman-Perdok method constructs connected nets to explore a much larger variety of surface configurations. These two methods use the same attachment energy principle to determine the growth rate from its most stable surface configurations and hence to predict the morphology. When the Hartman-Perdok theory also generates flat surface configurations, the results from the two methods are the same, as is the case for the paraben series. Although the lattice energy values generated by the two methods differ, they have the same rank order in both approaches. The attachment energy values generated are virtually identical. Table II summarizes the results of the calculations using the Hartman–Perdok method. The attachment energy value for methyl paraben corresponds to the plane with the smallest absolute value in its crystal structure. The attachment energy values for ethyl, propyl, and butyl parabens correspond to the planes with the smallest absolute value in their crystal structures, which are (1 0 0), (1 0 0), and (0 0 2), respectively (Table II).

In morphology calculations from Cerius^{2,TM}, the growth rate of an individual plane is assumed to be proportional to the attachment energy of that plane. Hence, when the crystal lattice has one set of planes with a significantly lower absolute value of attachment energy than the other planes, the face represented by this set of planes will likely be a slow-growing face, corresponding to a predominant face in the crystal morphology. This situation applies to ethyl and propyl parabens, both of which have plate morphology (the second

Table II. Summary of the Attachment Energy Calculations of Methyl, Ethyl, *n*-Propyl, and *n*-Butyl 4-Hydroxybenzoates (Parabens)

Miller indices of the planes			Attachment energy	
h	*k*	*l*	E_{att} (kcal/mol)	*d*-spacing (Å)
Methyl				
1	1	−1	−115	9.3
1	−1	0	−123	9.4
2	0	−2	−159	6.4
Ethyl				
1	0	0	−55	11.0
1	−1	0	−78	8.5
1	1	−1	−84	8.0
Propyl				
1	0	0	−64	11.2
1	−1	0	−90	8.8
0	1	−1	−104	9.0
Butyl				
0	0	2	−89	6.6
2	0	−2	−98	6.9
2	0	0	−99	8.7

set of E_{att} values in Table II is more than 40% greater than the first set). Methyl paraben, with octahedral crystal morphology, possesses no predominant face in its crystal, reflecting the fact that it does not have slip planes in its crystal lattice (the second E_{att} value in Table II is only 7.5% greater than the first set). For butyl paraben, the second E_{att} value in Table II is about 11% greater than the first set, indicating possible multiple slip planes in its crystal lattice.

Values of the attachment energy indicate the relative strength of bonding between the corresponding planes. Hence, the higher the absolute value of the attachment energy, the less mobile are the corresponding planes. When the attachment energy reaches a certain value, it is unlikely that slip planes are present in the crystal lattice. Based on the molecular modeling calculation, the (1 1- 1), (1 0 0), (1 0 0), and (0 0 2) planes, which have the smallest absolute value of attachment energy in the respective paraben structures, are identified as the most likely slip planes in the crystal lattices of methyl, ethyl, propyl, and butyl parabens, respectively. However, methyl paraben has the highest absolute value of E_{att}=−115 kcal/mol, which suggests that it is the least likely among the paraben series to possess slip planes. This deduction is consistent with the fact that Fig. 1A shows no slip planes in the crystal structure of methyl paraben. Ethyl and propyl parabens have similar attachment energy values (E_{att} = −55 and −64 kcal/mol), presumably because of their isostructurality (Fig. 1B and C). Among these two parabens, the higher absolute value of the attachment energy in propyl paraben suggests that the slip plane in its lattice is less mobile than that in ethyl paraben. Butyl paraben has a slightly higher absolute value of attachment energy (E_{att} = −89 kcal/mol), which may result from the longer alkyl chain and the smaller *d*-spacing (Fig. 1D).

As described in last session, hydrogen bonds serve as one factor that holds all molecules in methyl paraben lattice in a three-dimensional matrix, as well as the molecules in ethyl, propyl, and butyl parabens lattices in their slip planes. There might have been other factors, such as intermolecular distance and molecular conformation, that contribute to the attachment energy values calculated. Therefore, the attachment energy values could not be viewed as a direct representation of the hydrogen bond patterns.

The free volume in the unit cells indicates the ease of movement of planes of molecules along each other. The available volume in the unit cells of the parabens was calculated using Cerius^{2,TM} (Table III). Ethyl, propyl, and butyl parabens are compared directly because they all have eight molecules in each unit cell as well as slip planes in their crystal structures. The total volume of the unit cell increases accordingly. Although propyl paraben has a slightly higher *d*-spacing of its slip planes than ethyl paraben, the longer side chain makes the free volume/total volume ratio lower than that of ethyl paraben, indicating less mobility of the slip planes in propyl paraben than those in ethyl paraben. This effect is further illustrated by the experimental results, namely, nanoindentation hardness and tensile strength, described below.

Nanoindentation Hardness Measurements

Nanoindentation hardness tests were performed on the predominant face of single crystals of methyl, ethyl, propyl, and butyl parabens (Fig. 4). The morphologies of the methyl,

Table III. Summary of the Results Obtained for Methyl, Ethyl, *n*-Propyl, and *n*-Butyl 4-Hydroxybenzoates (Parabens): Slip Planes, Attachment Energies, Nanoindentation Hardness of Single Crystals, and Tensile Strength of Paraben Compacts

Paraben	Methyl	Ethyl	Propyl	Butyl
Molecular modeling				
Slip planes	No	Yes	Yes	Yes
Indices of slip planes (*h k l*)	–	(1 0 0)	(1 0 0)	(0 0 2)
Lowest attachment energy (kcal/mol)	−115	−55	−64	−89
d-spacing (Å)	9.3	11.0	11.2	6.6
Total available volume V_{avail} (Å^3/unit cell)	612	498	530	574
Total volume of cell V_{total} (Å^3/unit cell)	2198	1725	1860	2074
V_{avail}/V_{total}	0.2784	0.2885	0.2852	0.2767
Mechanical data				
Nanoindentation hardness (GPa)[a]	1.41 ± 0.44	0.312 ± 0.089	0.452 ± 0.105	0.514 ± 0.068
Tensile strength of compacts (MPa)[a,b]	0.10 ± 0.02	1.11 ± 0.13	0.43 ± 0.05	0.84 ± 0.03

[a] Mean ± standard deviation.
[b] Methyl paraben compacts were prepared with a dwell time of 24 h; ethyl, propyl, and butyl parabens compacts were prepared with a dwell time of 10 min.

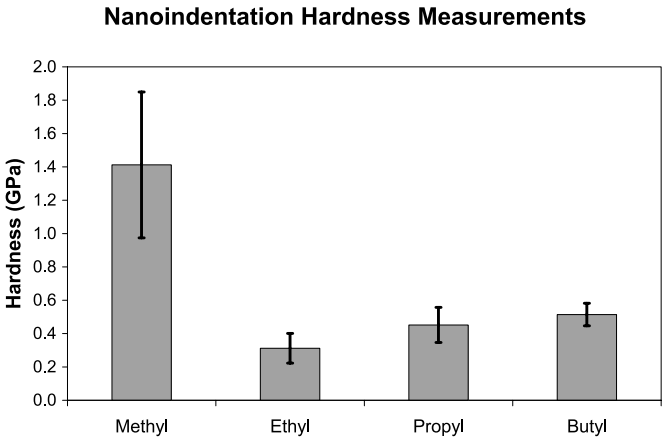

Fig. 4. Nanoindentation hardness (mean ± standard deviation) of crystals of methyl, ethyl, *n*-propyl, and *n*-butyl 4-hydroxybenzoate (parabens) grown by slow evaporation of solutions in ethyl acetate.

ethyl, propyl, and butyl parabens crystals grown from ethyl acetate are octahedral, plate, plate, and blade, respectively. From the morphology predictions, described above, these faces are (1 1 -1), (1 0 0), (1 0 0), and (0 0 2) for methyl, ethyl, propyl, and butyl parabens, respectively. Because methyl paraben has the highest hardness value among the parabens, it has the least flexibility to undergo plastic deformation under stress, which is consistent with the absence of slip planes. Ethyl, propyl, and butyl parabens have slip planes in their structures, which facilitate plastic deformation of their crystals under stress, resulting in lower values of nanoindentation hardness. The highest *d*-spacing associated with the slip planes of ethyl paraben enables its slip planes to glide more easily along each other, providing even lower values of nanoindentation hardness than the isostructural propyl paraben. In butyl paraben, the longer and more bulky alkyl chain provides greater friction that hinders the gliding process of the crystallographic slip planes, reduces plastic deformation, and increases nanoindentation hardness above that of the ethyl and propyl parabens (Fig. 4).

Tensile Strength Measurements of Paraben Tablets

Because of the absence of slip planes, tablets of methyl paraben exhibited a lower mechanical strength than those of the other three parabens, such that methyl paraben tablets crumbled before the tensile tests. To produce coherent tablets of methyl paraben, which would withstand handling in the experiments, appreciably longer dwell times (24 h) were employed for methyl paraben tablets (as compared with 10 min for ethyl, propyl, and butyl parabens tablets). Figure 5 shows the tensile strengths of paraben tablets. The tensile strengths of methyl and ethyl parabens tablets are comparable with those of Pedersen and Kristensen (16). The tablets

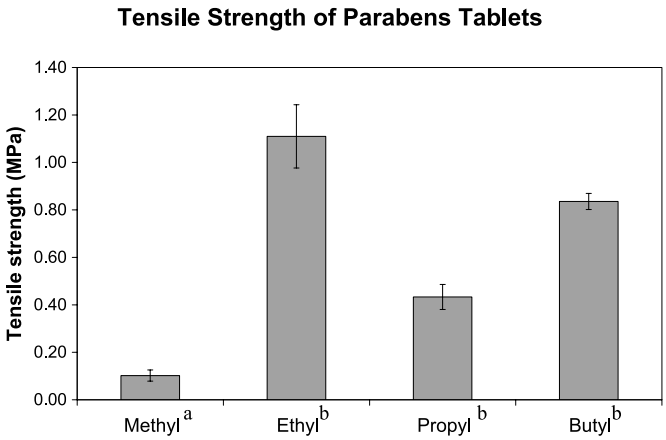

Fig. 5. Tensile strength (mean ± standard deviation) of compacts made by compressing powders of methyl, ethyl, *n*-propyl, and *n*-butyl 4-hydroxybenzoate (parabens) at 42 MPa. (a) Methyl paraben compacts were prepared with a dwell time of 24 h. (b) Ethyl, propyl, and butyl parabens compacts were prepared with a dwell time of 10 min.

of methyl paraben have the least tensile strength among the series, which is consistent with the absence of slip planes in the crystal structures. The data in Fig. 5 refer to a dwell time of 24 h for methyl paraben. Without the help of a substantially longer dwell time, methyl paraben tablets would possess extremely lower tensile strength than those of ethyl, propyl, or butyl parabens, as a result of the absence of slip planes in the crystal structure of methyl paraben. The tablets of propyl paraben showed a lower tensile strength than those of isostructural ethyl paraben, possibly because of the smaller free volume ratio in the unit cell of propyl paraben as a result of the extra methene (methylene) group. The smaller free volume between the slip planes as a result of the more bulky side chain provides more friction in motion and hence less flexibility for the planes to slide along each other. This slip leads to lower plasticity for propyl paraben and thus provides weaker tablets than does ethyl paraben. In the crystal structure of butyl paraben, however, the disorder in the side chain affords a higher degree of flexibility in the structure. Hence, butyl paraben has greater plasticity and so provides tablets with greater tensile strength than those of propyl paraben.

The mechanical properties of the parabens have been studied previously by Newton *et al.* (17) using four-point beam bending, which showed that beam compacts of methyl paraben have the greatest tensile strength. However, the four-point beam bending experiments were performed on (1) beam compacts made from powders of significantly different median particle size, namely, 70, 240, 370, and 250 μm for methyl, ethyl, propyl, and butyl parabens, respectively, and (2) beam compacts of similar solid fractions for all four parabens. In contrast, the present experiments were performed on (1) square compacts made from powders of similar mean particle sizes about 200 μm for all four parabens and (2) square compacts of solid fraction 0.83, 0.97, 0.94, and 0.97 for the methyl, ethyl, propyl, and butyl parabens, respectively. The work of Newton *et al.* could serve as an example in using substantially lower particle size, higher compaction pressure, and longer dwell time to overcome the effects of absence of slip planes to produce strong tablets. Our work shows that the absence of slip planes in methyl parabens explains the differences between its compaction behavior and that of the other three parabens under similar compaction conditions. We also correlated these differences in tableting behavior with the mechanical strength of the single crystals of parabens. Moreover, we found granulation as another effective approach to overcome the effects of absence of slip planes (manuscript in preparation).

CONCLUSIONS

The compaction properties of methyl, ethyl, propyl, and butyl parabens were found to correlate with the absence of slip planes (methyl) or presence of slip planes (ethyl, propyl, and butyl) in their crystal structures. This link is further confirmed by measurements of nanoindentation hardness of single crystals as an indication of the plasticity of the paraben crystals. The presence of slip planes in the crystal structures of three parabens (ethyl, propyl, and butyl) provides easier plastic deformation of the crystals during compaction and hence produces compacts of greater tensile strength. These examples provide molecular insight into the relationship between the tableting properties of pharmaceutical powders and features of their crystal structures.

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