CRYSTAL GROWTH & DESIGN
2008
VOL. 8, NO. 5
1575–1579

Improving Mechanical Properties of Caffeine and Methyl Gallate Crystals by Cocrystallization

Changquan Calvin Sun* and Hao Hou

Materials Science Laboratory, Small Molecule Pharmaceutics, Amgen Incorporated, Thousand Oaks, California 91320

Received September 4, 2007; Revised Manuscript Received December 21, 2007

ABSTRACT: By the formation of a 1:1 cocrystal of caffeine and methyl gallate, we demonstrated that powder compaction properties could be profoundly improved. The selection criterion for cocrystal exhibiting superior compaction properties was the presence of slip planes in crystal structure. Bulk cocrystal was prepared by suspending powders of the two pure compounds in ethanol. Fine powders of similar particle size distribution were compressed. Within the whole range of compaction pressure, the tablet tensile strength of methyl gallate was very poor (<0.5 MPa) and severe lamination and sticking occurred in almost all tablets. Tabletability of caffeine was acceptable at <150 MPa. However, at >180 MPa, severe lamination of caffeine tablets suddenly occurred. Tablet tensile strength dropped sharply at >240 MPa. In contrast, the tabletability of the cocrystal was excellent over the entire pressure range. Tablet tensile strength of the cocrystal was ~2 times that of caffeine at <200 MPa, and the ratio gradually increased with increasing pressure, e.g., ~8 fold at 350 MPa. Poor tablet tensile strength was always associated with high elastic recovery and low plasticity. The good plasticity and tabletability of the cocrystal validated the selection criterion, i.e., the presence of slip planes in crystal structure.

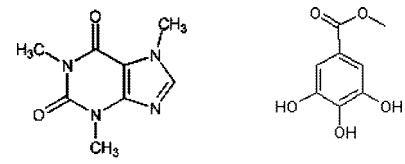
Introduction

Propelled by the recent understanding of the role of weak molecular interactions in directing the process of crystallization, where the making and breaking is noncovalent bonds, crystal engineering has emerged as a maturing field of chemistry.[1] Through crystallization, molecules may be assembled into crystals of different structures, known as polymorphs. The identical molecular composition but different packing motifs in the solid state make it possible to probe how weak interactions, those other than traditional chemical bonds (ionic and covalent), can affect a range of physical properties of molecular crystals.[2,3] Recent studies on relationship between crystal structure and mechanical properties of organic crystals showed the potential of engineering crystals of fine chemicals for superior physicomechanical properties.[4–6]

The successful development and commercialization of any drug requires adequate manufacturability, stability, and bioavailability. However, organic compounds with desired biological activities hardly exhibit adequate physical properties to meet all of the requirements. Some compounds lack adequate aqueous solubility and in vivo dissolution rate, some show high hygroscopicity, others exhibit poor compaction properties. One persistent challenge in the development and manufacturing of promising drugs is the poor mechanical properties. Difficulties often arise during the processes of milling, filling, and compaction because of poor mechanical properties of powders. Crystal engineering is a tool of ever increasing importance in pharmaceutical discovery and development because it can modify physical properties of a drug while maintaining its pharmacological activities.

To deliver life-saving medicines to needing patients, pharmaceutical scientists have taken advantages of crystal engineering to remedy deficiencies of different nature. For ionizable molecules, salt formation can often be successfully used to modify properties such as solubility and dissolution rate, solid-state stability, ease of crystallization, chemical stability, hygroscopicity, and mechanical properties.[7–9] Similar to what salts can deliver, cocrystals can also effectively modify physical properties of a drug.[10–12] Many advantageous pharmaceutical properties of cocrystals have been demonstrated in the literature. However, it remains to be shown that cocrystal can be used to improve mechanical properties, e.g., tabletability, of a drug. It has been established that, among polymorphs, crystals exhibiting flat layers that are hydrogen-bonded correspond to better plasticity and tabletability.[4] These layers serve as slip planes in crystals to promote plasticity that benefits the process of powder compaction. The same also holds true for chemically different molecular crystals. For example, among the homologous series of parabens, crystals with slip planes exhibit better plasticity and tabletability.[13,14] It was also demonstrated that water of crystallization could significantly improve powder compaction properties by facilitating the formation of slip planes in the hydrate crystal.[15] We postulate that the presence of slip planes in crystal structure may also be used to guide the search for cocrystals with superior mechanical properties.

Scheme 1. Chemical Structure of (a) Caffeine and (b) Methyl Gallate



a) b)

Caffeine is one of the most frequently studied drug molecule in cocrystallization research.[16] A search of caffeine cocrystals in the Cambridge Structural Database (CSD)[17] returned multiple hits. Visualization of these crystal structures showed the 1:1 cocrystal between methyl gallate and caffeine (Scheme 1) exhibits the desired feature of flat hydrogen bonded layers, i.e., slip planes, in its structure (Figure 1).[18] In the cocrystal, each of the three phenolic groups of methyl gallate is connected to a different caffeine molecule via a hydrogen bond. Two of the

* Corresponding author. Address: One Amgen Center Dr. 21-2-A, Thousand Oaks, CA 91320-1799. E-mail: ccsun@amgen.com; sunx0053@yahoo.com. Tel: (805) 313-5581. Fax: (805) 447-3401.

10.1021/cg700843s CCC: $40.75
Published on Web 04/10/2008

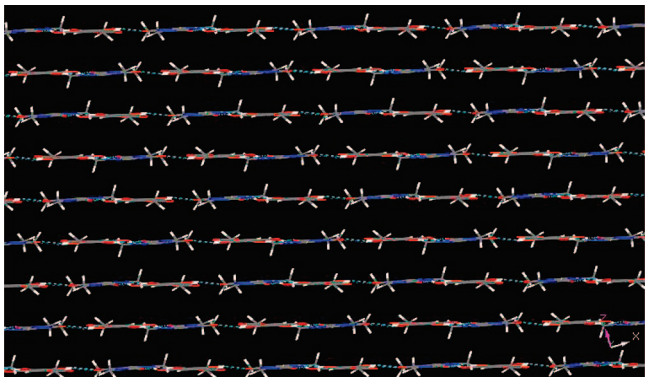


Figure 1. Crystal structure of caffeine−methyl gallate cocrystal. Broken lines indicate hydrogen bonds. The flat molecule layers correspond to (0 0 2) crystallographic planes.

Table 1. Summary of Key Particle Size Distribution Parameters of Caffeine, Methyl Gallate, and Their 1:1 Cocrystal (standard deviations are in parentheses (n = 3))

powders	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)
caffeine	1.60 (0.01)	12.02 (0.99)	51.07 (2.02)
methyl gallate	2.03 (0.05)	17.35 (0.91)	81.39 (9.87)
1:1 cocrystal	1.07 (0.05)	11.89 (2.91)	87.04 (21.0)

hydrogen bonds are between two phenolic groups (methyl gallate) and keto-amide groups (caffeine) with bond lengths of 2.744 and 2.774 Å, respectively. One hydrogen bond is formed between one phenolic group and one basic nitrogen (caffeine), with a bond length of 2.870 Å. This gives rise to extended two-dimensional hydrogen-bonded layers in the cocrystal.[19] The rings in both types of molecules are in plane leading to a smooth topographic feature of each layer (Figure 1). The mean separation between two adjacent parallel layers is 3.37 Å.[19] This type of laminar structure is analogous to that of graphite. It is therefore a suitable model system to test our hypothesis.

Materials and Methods

Materials. Caffeine (low melting temperature form II) was purchased from Alfa Aesar (Ward Hill, MA) with a purity of 99%. Methyl gallate with ≥98% purity and ethanol (200 proof, USP/NF) were purchased from Sigma-Aldrich (St Louis, MO). All materials were used as received. To prepare bulk 1:1 cocrystal of caffeine and methyl gallate, we suspended 0.3 mol of the two materials (56.7 g of caffeine and 53.7 g of methyl gallate) in ~500 mL of ethanol in a 1 L glass beaker. The suspension was stirred by the means of a magnetic stirring bar to maintain a stable vortex. The beaker was wrapped by a layer of aluminum foil to exclude light and left in a fume hood undisturbed. The suspension was vacuum-filtered after 10 days. The filtered powder was spread on a flat surface to allow air-dry. As the drying proceeded in the first 2 h, agglomerates were manually broken to facilitate drying. The powder was then air-dried overnight. Before compaction, all powders were passed through a 500 μm sieve.

Particle Size Analysis. The volume-based particle size distribution (PSD) of dry powders was obtained using a laser scattering particle size analyzer (Sympatec Helos, Sympatec Inc., Princeton, NJ). After a pressure titration step, the dispersing pressure of 3 bar was chosen for replicating PSD measurements. Three measurements were made on each powder. The resulting particle size distributions were averaged and standard deviations were calculated.

Powder X-ray Diffraction (PXRD). Powder X-ray diffraction was performed using a Phillips X'PERT Pro diffractometer (PANalytical, Almelo, The Netherlands). The system used a copper X-ray source (45 kV and 40 mA) to provide Cu Kα1 emission of 1.5406 Å and an X'Celerator RTMS detector. The beam aperture was controlled using tube divergence and antiscatter slits of 1/4° and 1/2°. A nickel filter of 0.02 mm thickness was used in the diffracted beam path. The opening

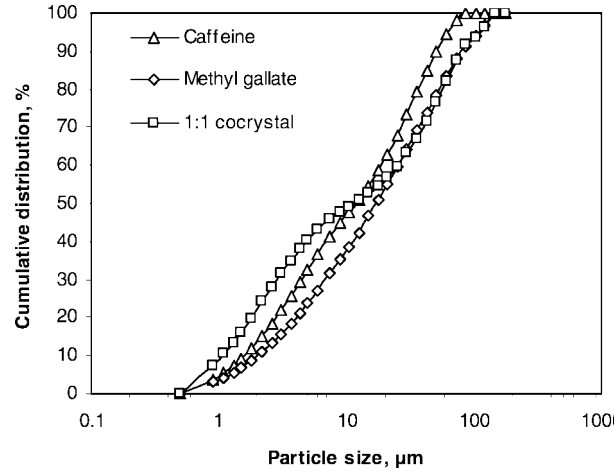


Figure 2. Cumulative particle size distributions of caffeine, methyl gallate, and the 1:1 cocrystal are similar.

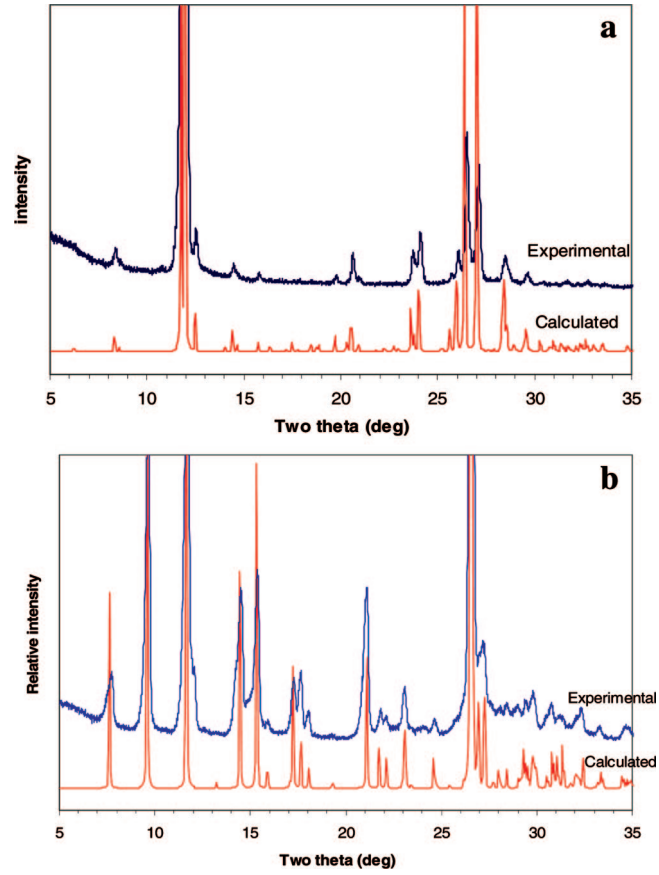


Figure 3. Excellent agreement between experimental the calculated PXRD patterns of (a) caffeine (form II) and (b) 1:1 cocrystal.

of the parallel plate collimator was 0.09°. Each powder was packed into a round top loading sample holder and gently pressed using glass slides to ensure coplanarity between the sample surface and the surface of the sample holder. During data collection, the sample holder kept spinning. Data was collected from 5 to 35° 2θ using a continuous scan mode corresponding to a step size of 0.0084° with a counting time of 0.13 s per step.

Thermal Analysis. Differential scanning calorimetry (DSC) experiments were conducted using a calorimeter (Q1000, TA Instruments, New Castle, DE). The temperature was calibrated using three-point method with indium, tin and lead standards. Approximately 2 mg of powder was placed in hermetically sealed aluminum pan. During measurement, the cell was purged by a stream of dry nitrogen at 50

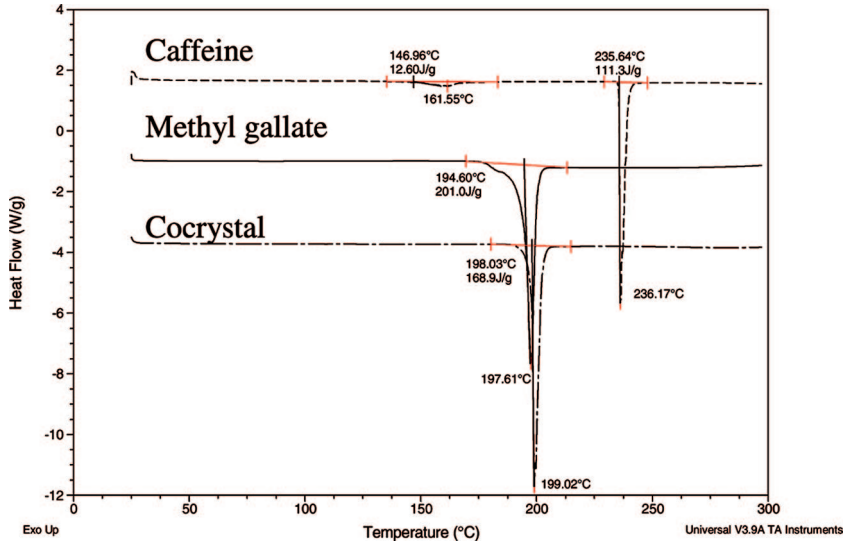


Figure 4. DSC thermograms of caffeine (form II), methyl gallate, and their 1:1 cocrystal.

mL/min. Data were analyzed using the Universal Analysis 2000 software (TA Instruments). The sample was heated at a rate of 10 °C/min from room temperature to 300 °C. Thermogravimetric analysis (TGA) was performed on a TA-Q500 (TA Instruments). Samples (~10 mg) were analyzed in an open aluminum pan under nitrogen purge (40 mL/min) from 25 to 300 °C at a heating rate of 10 °C/min.

Powder Compaction and Tablet Characterization. Powder compaction was carried out using a compaction simulator (Presster, Metropolitan Computing Corporation, East Hanover, NJ), simulating a Korsch XL100 running at 120 rpm (linear speed of 0.741 m/s), corresponding to a production speed of 72 000 tablets per hour. The compaction rolls were 250 mm in diameter. Flat round toolings with a diameter of 8.00 mm were used to make tablets. Tablet toolings were coated using a 5% (w/v) suspension of magnesium stearate in ethanol and dried prior to each compaction,. This was followed by filling the die with 200–240 mg of powder. The compaction profile of force vs in-die tablet thickness was recorded for each tablet.

Tablet weight, dimensions, and breaking force were measured immediately after ejection. Each tablet was accurately weighed to 0.01 mg using an analytical balance. The diameter and thickness of each tablet were measured to 0.01 mm using a digital caliper. Loose particles on tablet surfaces were gently removed, and flashing on the edge of each tablet, if present, was removed to obtain more accurate measurements of tablet dimensions. Tablet breaking force was measured using a texture analyzer (HD model, Texture Technologies Corp., NY) at a test speed of 0.01 mm/s. Tensile strength, σ, in MPa was calculated using eq 1.

$$\sigma = \frac{2F}{10^6 \pi D T} \tag{1}$$

where F is the breaking force (N), D is the tablet diameter (m), and T is the thickness of tablet (m).[20,21]

Elastic recovery (ER) is related to amount of elastic energy stored during compaction that is released during decompression.[22] ER may be calculated using eq 2.

$$\mathrm{ER}\% = 100(h - h_0)/h_0 \tag{2}$$

where h is the height of tablet after compaction stress reaches zero at the end of the decompression phase and h_0 is the height of tablet under maximum compaction pressure.

Results and Discussion

Particle Size Distribution. All three powders comprised fine particles (Table 1). Average particle size distributions of the three powders ($n = 3$) are shown in Figure 2. Although differences are present, overall particle size distributions were similar.

Powder Phase Purity. PXRD of all powders showed intense sharp diffraction peaks without amorphous halo observed. PXRD pattern of the caffeine powder matched well with the calculated pattern from the crystal structure of form II (Figure 3a). Similarly, PXRD of the cocrystal powder also matched well with that of the calculated PXRD pattern based on single crystal structure (Figure 3b). Single crystal structure of the methyl gallate is not available. However, only one crystalline form of methyl gallate has been observed so far.

DSC traces of all three powders were characterized by flat baselines and sharp melting peaks (Figure 4). This is consistent with the high crystallinity of the powders suggested by PXRD. A single endothermal peak, corresponding to melting of crystals, was present for both methyl gallate (197.6 °C, peak temperature) and the cocrystal (199 °C, peak temperature). For the DSC trace of caffeine, the endothermal event at ~147–170 °C corresponded to form II to I transition.[23] This was followed by the melting of Form I caffeine at 236 °C (peak temperature). The DSC traces were consistent with the high phase purity in the three powders suggested by PXRD. TGA data showed negligible weight loss of the three powders up to 120 °C (0.24, 0.06, and 0.001% for caffeine, methyl gallate, and the cocrystal powders, respectively).

Tabletability. Figure 5 shows tabletability of the three powders. Extremely poor tabletability of a powder is generally indicative of a lack of plastic deformation during compaction. This is often accompanied by high elastic recovery because a large fraction of work done by punches is elastic and elastic moduli of organic powders are low. Upon the removal of compaction pressure, the stored elastic energy is released to result in volume expansion of individual particles and the tablet. This process can break bonds, i.e., contacting surfaces at atomic distance, formed during compression. Consequently, the tablet is porous and weak in strength.

Compaction properties of methyl gallate were extremely poor. Methyl gallate tablets in the whole pressure range were low in strength and exhibited severe lamination. Tensile strength of most tablets could not be measured because of lamination upon ejection from tablet die. Clearly, plasticity of methyl gallate crystals is low. This is supported by the relatively high elastic recovery (ER) of methyl gallate during decompression, e.g., ~32% at 420 MPa (Figure 6). The structural origin of the low plasticity in molecular crystals is likely a lack of flat slip planes.[4,14] Crystal structure of methyl gallate is not yet available.

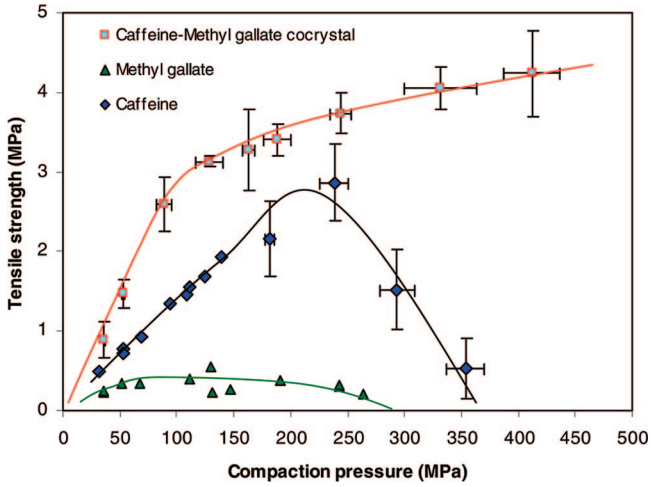


Figure 5. Tabletability plots of caffeine (form II), methyl gallate, and their 1:1 cocrystal.

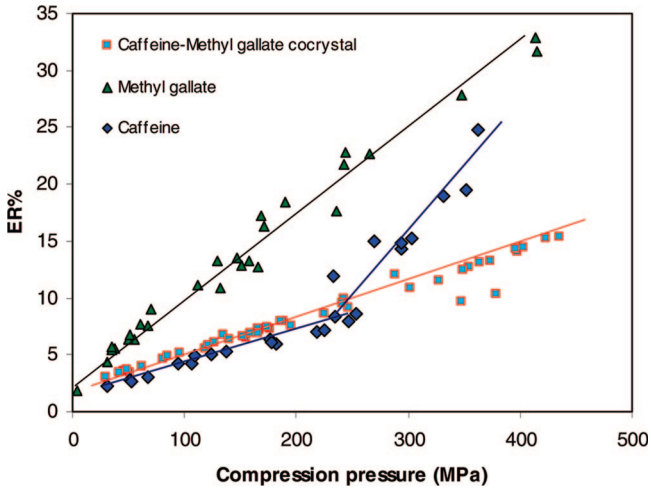


Figure 6. Elastic recovery of caffeine (form II), methyl gallate, and their 1:1 cocrystal as a function of compaction pressure.

Efforts are being made to elucidate crystal structure of methyl gallate for gaining molecular insights to its poor compaction properties.

Tabletability of the form II caffeine was interesting. In the low pressure range of <150 MPa, intact tablets could be made. Tensile strength of these tablets was reasonable and was substantially higher than that of methyl gallate. At pressure >180 MPa, severe lamination of tablet was observed and tablet strength was highly variable. At >~240 MPa, a sharp reduction in tablet tensile strength occurred with increasing pressure (Figure 5). The detrimental effect of compaction pressure on tablet mechanical strength and severe lamination are common signs of overcompaction. Similar to the mechanism of poor tabletability of methyl gallate, the overcompaction may be caused by extensive elastic deformation of the caffeine powder. Corresponding to the acceptable tabletability of caffeine at <150 MPa, ER was low in this pressure range (Figure 6). However ER suddenly rose at above ~240 MPa roughly corresponding to the profound reduction in tabletability (Figure 5). This suggests detrimental effect of elastic recovery on tablet strength outplayed bonding strength gained due to elevated pressure. It has been known that compaction can induce polymorph conversion of caffeine crystals.[24] Work is ongoing to check whether the sudden change in elastic property may correspond to pressure induced crystal form change. Overall, the compaction properties of caffeine are problematic.

In contrast to poor tabletability of caffeine and methyl gallate, the cocrystal exhibited excellent tabletability (Figure 5). Under identical compaction pressure at <150 MPa, tablet tensile strength of the cocrystal was approximately 2 times that of caffeine. At >150 MPa, the tensile strength of cocrystal tablet continued to increase with increasing pressure. This was in contrast to the sharp drop in strength observed for caffeine tablets. No tablet lamination was observed even at the highest compaction pressure. The tabletability profile of the cocrystal is typical of plastic tablet excipients, e.g., microcrystalline cellulose. The apparently good plasticity is consistent with the presence of slip planes in its structure (Figure 1). These layers are characterized by large *d*-spacing and interactions between two adjacent layers are mainly nonspecific weak van der Waals interactions. When sheared, the adjacent layers can slide over each other easily, because of the low energy barrier, to render crystals superior plasticity, which in turn results in superior tabletability of the cocrystal.

Conclusion

Phase-pure 1:1 cocrystal of caffeine and methyl gallate was prepared in bulk quantity. Using the caffeine−methyl gallate system, we demonstrated that compaction properties of organic powders could be dramatically improved by forming cocrystals exhibiting flat slip planes in their structures. The presence of slip planes can be an effective criterion in selecting cocrystals with superior mechanical properties a priori. Crystal engineering can be an effective means in rectifying, among many other properties, poor mechanical properties of a drug for smooth development of tablet dosage forms.

References

(1) Desiraju, G. R. Chemistry beyond the molecule. *Nature* **2001**, *412*, 397–400.
(2) Grant, D. J. W. Theory and Origin of Polymorphism. In *Polymorphism in Pharmaceutical Solids*; Brittain, H. G., Ed.; Marcel Dekker: New York, 1999; pp 1–33.
(3) Berstein, J., *Polymorphism in Molecular Crystals*, ed. Oxford University Press: New York, 2002; pp 188–239.
(4) Sun, C. C.; Grant, D. J. W. Influence of crystal structure on the tableting properties of sulfamerazine polymorphs. *Pharm. Res.* **2001**, *18* (3), 274–280.
(5) Reddy, C. M.; Basavoju, S.; Desiraju, G. R. Sorting of polymorphs based on mechanical properties. Trimorphs of 6-chloro-2,4-dinitroaniline. *Chem. Commun.* **2005**, *19*, 2439–2441.
(6) Reddy, C. M.; Padmanabhan, K. A.; Desiraju, G. R. Structure-Property Correlations in Bending and Brittle Organic Crystals. *Cryst. Growth Des.* **2006**, *6* (12), 2720–2731.
(7) Stahl, P. H.; Nakano, M., Pharmaceutical aspects of the drug salt form. In *Handbook of Pharmaceutical Salts−Properties, Selection, and Use*; Stahl, P. H., Wermuth, C. G., Eds.; Wiley-VCH: New York, 2002; pp 82–116.
(8) Bowker, M. J., A procedure for salt selection and optimization. In *Handbook of Pharmaceutical Salts−Properties, Selection, and Use*; Stahl, P. H., Wermuth, C. G., Eds.; Wiley-VCH: New York, 2002; pp 161–190.
(9) Sun, C. C.; Grant, D. J. W. Compaction properties of L-lysine salts. *Pharm. Res.* **2001**, *18* (3), 281–286.
(10) Jones, W.; Motherwell, W. D. S.; Trask, A. V. Pharmaceutical cocrystals: an emerging approach to physical property enhancement. *MRS Bull.* **2006**, *31* (11), 875–879.
(11) Rodríguez-Hornedo, N.; Nehm, S. J.; Jayasankar, A., Cocrystals: design, properties and formation mechanisms. In *Encyclopedia of Pharmaceutical Technology*, 3rd ed.; Swarbrick, J., Ed.; Deeker Encyclopedias from Taylor & Francis Books: London, 2007; pp 615–635.
(12) Vishweshwar, P.; McMahon, J. A.; Bis, J. A.; Zaworotko, M. J. Pharmaceutical Co-Crystals. *J. Pharm. Sci.* **2006**, *95* (3), 499–516.

(13) Feng, Y.; Sun, C. C.; Grant, D. J. W. Influence of crystal structure on the tableting properties of n-alkyl 4-hydroxybenzoate esters (Parabens). *J. Pharm. Sci.* **2007**, *96*, 3324–3333.

(14) Pedersen, S.; Kristensen, H. G. Compaction behavior of 4-hydroxybenzoic acid and two esters compared to their mechanical properties. *Eur. J. Pharm. Biopharm.* **1995**, *41* (5), 323–328.

(15) Sun, C. C.; Grant, D. J. W. Improved tableting properties of *p*-hydroxybenzoic acid by water of crystallization: a molecular insight. *Pharm. Res.* **2004**, *21* (2), 382–386.

(16) Bučar, D. K.; Henry, R. F.; Lou, X.; Duerst, R. W.; Borchardt, T. B.; MacGillivray, L. R.; Zhang, G. G. Z. Co-crystals of caffeine and hydroxy-2-naphthoic acids: unusual formation of the carboxylic acid dimer in the presence of a heterosynthon. *Mol. Pharm.* **2007**, *3*, 339–346.

(17) Allen, F. H. The Cambridge structure database: a quarter of a million crystal structures and rising. *Acta Crystallogr., Sect. B* **2002**, *58*, 380–388.

(18) Crystal data for the methyl gallate. $M = 378.34$, monoclinic, space group $P21/a$, $a = 24.14$ (5) Å, $b = 10.057$ (20) Å, $c = 7.005$ (4) Å, $\beta = 106.55(11)°$, $V = 1630.19$ Å^3, $Z = 4$, $D_c = 1.542$ g cm^{-3}, Mo-Kα radiation, $F(000) = 792$, $R = 0.0551$.

(19) Martin, R.; Lilley, T. H.; Bailey, N. A.; Falshaw, C. P.; Haslam, E.; Magnolato, D.; Begley, M. J. Polyphenol-caffeine complexation. *J. Chem. Soc., Chem. Commun* **1986**, *2*, 105–106.

(20) Fell, J. T.; Newton, J. M. Determination of tablet strength by the diametral-compression test. *J. Pharm. Sci.* **1970**, *59*, 688–691.

(21) Sun, C. C. A material-sparing method for simultaneous determination of true density and powder compaction properties - Aspartame as an example. *Int. J. Pharm.* **2006**, *326*, 94–99.

(22) Sun, C. C.; Grant, D. J. W. Influence of crystal shape on the tableting performance of L-lysine monohydrochloride dihydrate. *J. Pharm. Sci.* **2001**, *90*, 567–577.

(23) Cesaro, A.; Starec, G. Thermodynamic properties of caffeine crystal forms. *J. Phys. Chem.* **1980**, *84*, 1345–1346.

(24) Pirttimäki, J.; Laine, E.; Ketolainen, J.; Paronen, P. Effects of grinding and compression on crystal structure of anhydrous caffeine. *Int. J. Pharm.* **1993**, *95*, 93–99.

CG700843S