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RESEARCH PAPER

Overcoming Poor Tabletability of Pharmaceutical Crystals by Surface Modification

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ABSTRACT

Purpose To test the hypothesis that coating particles with a highly bonding polymer is effective in improving tabletability of poorly compressible drugs.

Methods Micronized acetaminophen ($d_{90} < 10$ μm, Form I) was coated with 1%–10% (wt%) hydroxypropyl cellulose (HPC) by spray-drying. Phase nature of acetaminophen powders was identified using powder X-ray diffractometry, SEM, and thermal analysis. Powder tabletability was evaluated on a compaction simulator. Mechanical properties of acetaminophen and HPC were determined by nanoindentation.

Results Spray-drying successfully produced acetaminophen particles enveloped with a layer of HPC but did not cause any detectable phase change of acetaminophen. At 200 MPa, physical mixtures containing up to 40% HPC could not be compressed into intact tablets. In contrast, acetaminophen coated with 1% to 10% HPC could form strong tablets (tensile strength was 1.9–7.0 MPa) at 200 MPa. Under a given compaction pressure, tablet tensile strength increased sharply with the amount of HPC coating. The profoundly improved tabletability of acetaminophen confirmed the effectiveness of the particle coating approach in improving tableting performance of drugs.

Conclusions HPC coating by spray-drying profoundly enhances tabletability of acetaminophen. This strategy is expected to have transformative effects on formulation development of poorly compressible drugs.

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INTRODUCTION

Optimizing powder mechanical properties is critical for achieving robust manufacturing processes in many industries, including pharmaceutical, nutraceutics, detergents, energy, powder metallurgy, and ceramic, where powder compaction is involved (1–3). This especially pertains to pharmaceutical development and manufacturing of tablet dosage forms (3–6).

Many active pharmaceutical ingredients (APIs), such as acetaminophen (ACM, Form I), phenacetin, sulfamerazine (Form II), piroxicam, and ascorbic acid, exhibit poor mechanical performance and cannot be directly compressed into intact tablets with sufficient strength (7–10). This problem has been traditionally addressed by mixing drugs with highly compressible excipients. This method is, however, not efficient, and sometimes more than 40% highly bonding excipients is required to attain sufficient powder tabletability (11–14). Besides the cost from the use of large amounts of excipients, this approach also leads to problems such as large tablet size, poor content uniformity, and sensitivity to variations in physiochemical properties of excipients. More recently, crystal engineering (e.g., by forming salts, hydrates, and cocrystals) emerged as an effective approach to enhance compaction properties of drugs (9,15–18). This process, however, has its limitations. First, poor tableting properties of APIs are typically observed during a later stage of product development; therefore, it is time-consuming and cost-prohibitive to switch to a new crystal form. Since a new crystal must be treated as a new chemical entity, commercialization is likely

delayed. Second, only a limited number of solid forms can be made for each drug molecule, and there is no guarantee that the new crystals exhibit satisfactory tableting behavior (19). Moreover, a new crystal form with superior mechanical properties may be associated with other problems, such as poor stability and solubility. Finally, salts or cocrystals are less potent than crystals of the parent drug alone. To deliver the same amount of active molecule for treating diseases, more of these crystals will be needed.

We have demonstrated that surface coating with a highly bonding polymer can effectively transform non-compressible sand into strong tablets by compaction (11). The basis for this approach is the formation of a continuous three-dimensional bonding network within a tablet during compaction without the need of bond percolation. Recently, it was shown that flow and compaction properties of MCC microfibers can be simultaneously improved by a layer-by-layer coating process (13). The formation of core/shell structure by surface coating holds the potential to be a universal strategy for solving the problems presented by poorly compressible drugs without drawbacks in other approaches outlined in the preceding paragraph. The keys to the successful implementation of this strategy in pharmaceutical industry are (1) the ability to coat powders using an industrial process and (2) the availability of more than one polymer to minimize the possible problem of drug-excipient incompatibility.

In this context, we use ACM (Form I), a widely used analgesic and antipyretic drug with well-known poor tableting performance, as model drug and hydroxylpropyl cellulose (HPC) as a bonding polymer to show that the drug compaction properties can be significantly enhanced by surface modification.

MATERIALS AND METHODS

Materials

ACM (Form I, Johnson & Johnson Company, NJ, USA) and HPC (Klucel HXF Pharm grade, Hercules Inc., DE, USA) were used as model compounds. Distilled water was used to dissolve HPC and disperse micronized ACM (Form I) crystals.

Preparation of HPC-Coated ACM Powders by Jet-Milling and Spray-Drying

Commercial ACM consisted of large crystals. To avoid jamming the nozzle of spray-dryer, commercial ACM was micronized using a laboratory jet mill (Glen Mills Inc, NJ, USA). Size reduction was achieved by employing two opposing jets, with respective gas pressures of 80 and 100 psi, which collided to create a turbulent air flow inside of the milling chamber.

1%, 2.5%, 5%, and 10% (wt%) of HPC-coated ACM samples were prepared using a spray-dryer (Mini B-191, Buchi, Flawi, Switzerland). A total of 20 g of micronized ACM was suspended in 1 L of HPC aqueous solution with appropriate concentration. As the suspension was vigorously stirred by a magnetic stirring bar, it was delivered to the spray-dryer using a peristaltic pump at a rate of 5 mL/min. Inlet temperature, aspiration, and pump were set at 85°C, 100% of capacity, and 10% of capacity, respectively. As a control, corresponding physical mixtures of jet-milled ACM and HPC (10 g batch size) were also prepared by manually mixing two powders in a glass bottle for ~5 min.

Preparation of ACM (Form I) Single Crystals and HPC Films

The single crystals of ACM (Form I) were grown by slow evaporation of an acetone solution (10 mL of 56.7 mg/mL solution in a 20 mL glass vial) at ambient conditions. The HPC films were prepared by drying an HPC aqueous solution on a silicon wafer at ambient conditions (22±5% relative humidity and 23±1°C) for 2 days.

Physicochemical Characterization of Powders

The crystallinity of powder materials was measured using powder X-ray diffractometry (PXRD, Bruker AXS D5005, WI, USA) with a Cu X-ray source operated at 45 kV and 40 mA. Data were collected between 5° and 35° two theta angles, with a step size of 0.04°. The dwell time at each step was 1 s.

The thermal properties of powder samples were examined using differential scanning calorimetry (DSC, model 2920, TA Instruments, DE, USA) operated in standard mode. Samples, placed in hermetically sealed aluminum pans, were heated from 20°C to 180°C (heating rate of 10°C/min, with nitrogen gas purge of 50 mL/min). After performing baseline calibration, indium standard was used to calibrate temperature and cell constant.

Particle morphology was investigated by scanning electron microscopy (SEM, JEOL 6500, MA, USA) operated at accelerating voltage of 5 kV. Before SEM experiments, samples were sputter-coated with platinum (~50 Å thickness) using an Ion Beam Sputterer (IBS/TM200S, VCR Group Inc., CA, USA).

Mechanical Properties of ACM Form I Single Crystals and HPC Films

Nanoindentation is a technique that may be used to characterize the mechanical properties, including

reduced elastic modulus, E_r, and hardness, H, of materials at the submicron scale (20,21). In this work, we characterized mechanical properties of ACM and HPC using a nanoindenter (TriboIndenter TI-900, Hysitron Inc., MN, USA) fitted with a Berkovich diamond indenter tip. Before nanoindentation testing, the tip area function was derived from a series of indentations on a fused quartz standard with a known E_r of 69.6 GPa. The nanoindentation experiments were performed under the displacement control mode, which is more sensitive than force control mode (22,23), at the loading and unloading rate of 100 nm/s. A 10 s holding was applied at the maximum indentation depth of 500 nm to allow stress relaxation, if any. During nanoindentation test, force and displacement were recorded simultaneously as the indenter tip was pressed into the test material's surface with resolution of 1 nN and 0.2 nm, respectively. A total of 16 indentations were performed on each sample. E_r and H were determined using unloading force-displacement curves according to the method described by Oliver and Pharr (20), where detailed information about the operation and mechanisms of nanoindentation can be found.

Powder Compaction Behavior

A linear compaction simulator (Presster, Metropolitan Computing Company, New Jersey, NJ) was used to perform tableting experiments simulating a rotary tablet press (KORSCH XL100, 10-station). Cylindrical tablets were made using round (9.5 mm diameter), flat-faced tooling under different pressures. Before compaction, about 250 mg sample was manually transferred into the die. The linear speed, dwell-time, and tableting speed during the compaction were 0.65 m/s, 20 ms, and 61,600 tablets/h, respectively. These compaction parameters allowed us to assess tableting performance of powders under realistic manufacturing conditions.

Tablet weight, tablet diameter and thickness, and diametrical breaking force were immediately measured after ejection. Breaking force was determined using a texture analyzer (TA-XT2i, Texture Technologies Corp., Scarsdale, NY) at a speed of 0.01 mm/s with a 5 g trigger force. Tablet tensile strength was calculated from the maximum breaking force and tablet dimensions (16,24). The in-die elastic recovery (ER) of tablet was calculated using Eq. 1 (16):

$$ER = 100\% \cdot (h - h_0)/h_0 \quad (1)$$

where h_0 was the thickness of tablet under maximum compaction pressure and h was the thickness of tablet at the end of unloading phase.

RESULTS AND DISCUSSION

Effect of Jet-Milling and Spray-Drying on Particulate Morphology

As expected, jet-milling results in significant particle size reduction and changes in crystal morphology (Fig. 1). While the commercial ACM crystals are elongated, large crystals (up to several hundreds of microns) with sharp edges and large flat faces, jet-milled ACM crystals appear to be much smaller (<10 μm) and equi-dimensional.

The spray-dried powders consist of aggregates, ranging from 10 μm to 30 μm in size. When 1% HPC coating is used, sharp edges of crystals can still be easily observed, suggesting the coating layer is thin. With 2.5% HPC, no obvious particle edges can be observed, while shape of coated particles resembles that of the uncoated particles. With 5% HPC, a large fraction of particles without sharp edges are observed. For all of the particles, the sharp edges disappeared when 10% HPC coating was applied (Fig. 1).

ACM Phase Stability During Jet-Milling and Spray-Drying Processes

The starting ACM crystals are the poorly compressible Form I, which is also the stable crystal form at room temperature. Processes, such as milling, spray-drying, and compaction, may lead to phase change of organic solids (25–29). We therefore examine materials after both jet-milling and spray-drying to ensure phase stability of ACM.

PXRD pattern of the jet-milled ACM shows neither new diffraction peaks nor disappearance of existing peaks (Fig. 2). We attribute changes in PXRD peak intensity to the effects of preferred orientation because most of the particles in the starting ACM powder are large and elongated crystals (Fig. 1). In contrast, jet-milled ACM consists of fine and more equi-dimensional particles with smooth surfaces and no obvious edges. Consequently, any preferred orientation of crystals during PXRD experiments is expected to be minimized. The melting point and enthalpy of fusion of starting and jet-milled ACM are identical, being 171.2°C and 193.3 J/g, respectively (Fig. 3). This confirms that jet-milling does not induce detectable form change for ACM Form I.

Similarly, PXRD results show no evidence for phase change after spray-drying, since HPC-coated materials show neither appearance of new peaks nor disappearance of existing peaks (Fig. 2). However, peak intensity of coated ACM is lower than that of jet-milled ACM (Fig. 2). Melting point of 10% HPC-coated ACM, 170.15°C, is 1°C lower than that of pure ACM (Fig. 3). The onset of the melting endotherm is not as sharp as that of pure ACM, which may be attributed to the dissolution of ACM crystals into HPC before melting commences. Both PXRD and DSC results show that ACM

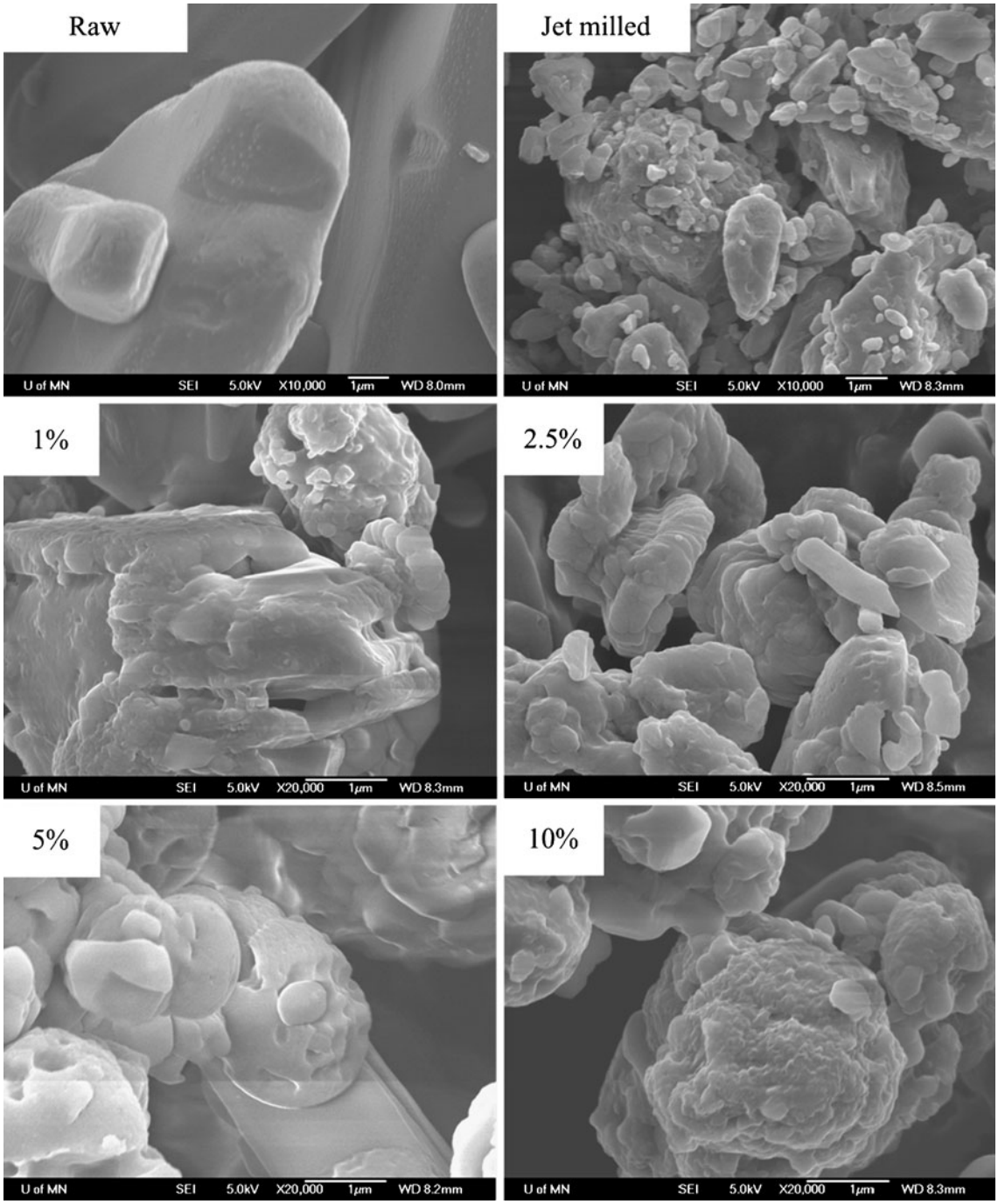

Fig. 1 Morphology of starting ACM, jet-milled ACM, and HPC-coated ACM.

Form I is stable during both jet-milling and spray-drying processes. At this point, we rule out the possibility of crystal form changes that might contribute to the enhanced tabletability of HPC-coated ACM powders.

Plasticity of ACM (Form I) Crystals and HPC

Powder compaction is a complex physical process. A clear understanding of powder tableting performance requires simultaneous consideration of multiple material properties, including particle size distribution, particle morphology, porosity, composition, crystal structure, elasticity, and plasticity. Among these properties, plasticity plays a central role (30).

A material yielding to a lower stress is softer and therefore more plastic. Yield strength is typically calculated as one third of the indentation hardness (31). The mechanical properties of organic crystals may vary with

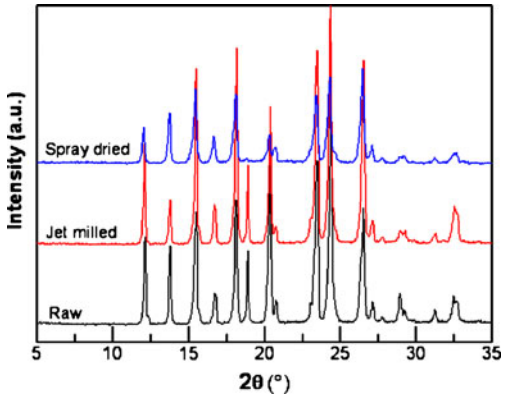

Fig. 2 X-Ray diffraction patterns of commercial ACM, jet-milled ACM, and spray-dried ACM containing 10% HPC. Jet-milling and spray-drying do not lead to phase change of ACM.

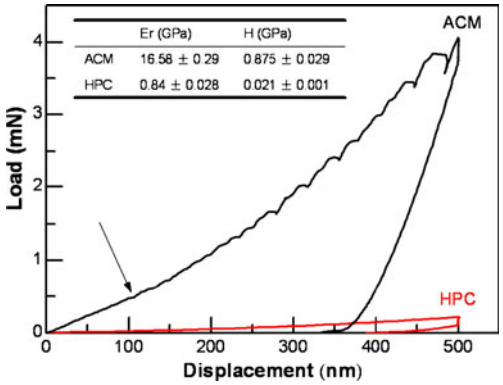

Fig. 4 Load-displacement curves of nanoindentation performed on (011) face of ACM Form I single crystal and HPC film. The first yielding event of ACM crystal is indicated by an *arrow*.

crystal face because of the anisotropic nature of organic crystals (32,33). However, such variations are small for ACM crystals (34). Therefore, we only performed nano-indentation testing on (0 1 1) face of ACM crystals. The indentation hardness of ACM is 0.875 ± 0.029 GPa on (0 1 1) crystal face and that of HPC is 0.021 ± 0.001 GPa (Fig. 4). Correspondingly, yield strengths of ACM and HPC are approximately 300 and 7 MPa. HPC is therefore much more plastic (~41-fold) than ACM crystal. In addition, at a fixed 500 nm penetration depth, maximum loads applied by the diamond tip on HPC and ACM crystal are 0.22 mN and 4.06 mN, respectively (Fig. 4). This also suggests HPC is significantly softer than ACM crystal.

The load-displacement curves for ACM single crystal contain a series of sudden force drops (yielding event) due to dislocation burst activities (Fig. 4). The high load (>0.5 mN) at the first yielding event corresponds to a high yield strength and thus low plasticity for ACM (35). Furthermore, the indentation force of ACM, during the 10 s relaxation period, decreases slowly from 4.06 mN to 3.73 mN, corresponding to 8.1% loss in load (Fig. 4). However, during the same holding period, the indentation force applied to HPC drops sharply from 0.22 mN to 0.11 mN, corresponding to 50% loss in load (Fig. 4). The more profound stress relaxation in HPC also confirms its higher plasticity than ACM crystal.

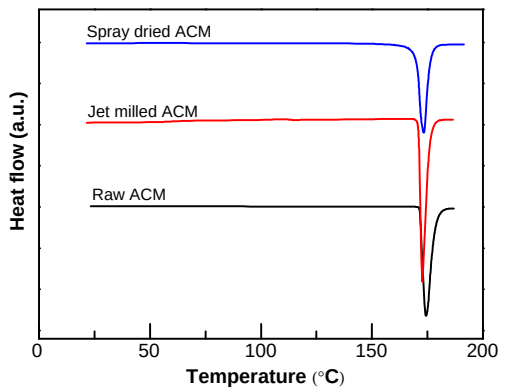

Fig. 3 DSC thermograms of commercial ACM, jet-milled ACM, and spray-dried ACM containing 10% HPC. No phase change is detected after jet-milling and spray-drying.

Tableting Performance

Under compaction pressures up to 400 MPa, jet-milled ACM powders cannot form intact tablets. Thus, changes in particle size and morphology do not lead to noticeable enhancement in powder tableting performance of ACM powders. Having shown the phase stability of ACM after both jet-milling and spray-drying, we are now ready to study effectiveness of surface coating on powder tabletability.

A physical mixture containing 20% HPC or less does not show observable improvement in tabletability. Tablet lamination and capping are always observed (Fig. 5). Under compaction pressures higher than 200 MPa, physical mixtures containing 40% HPC can be made into intact tablets after ejection. However, these tablets are extremely weak in strength and do not survive the stresses experienced when measuring tablet weight and dimensions. Moreover, obvious capping and lamination occur after those intact tablets are stored at ambient environment for 24 h. Tabletability of these physical mixtures is therefore considered negligible.

This behavior agrees well with the common observations that for physical mixtures containing a compressible powder and a non-compressible powder, strong tablets could be made only when a significant amount (e.g., >40%) of the compressible component is present in the mixture. These observations indicate that simply blending with excipients is ineffective for addressing poor tabletability of drugs. This phenomenon is well explained by the percolation

Fig. 5 Tablets prepared with physical mixture (20% HPC) and coated powders (1% PHC) under compaction pressure of 150 MPa.

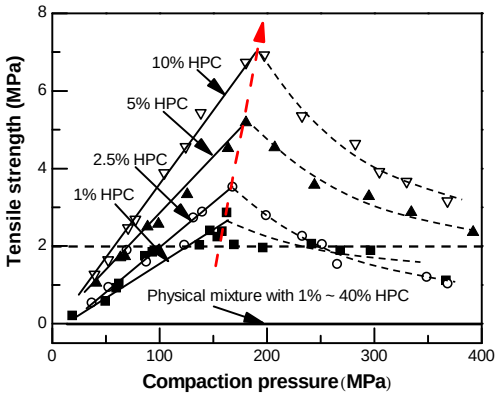

Fig. 6 Tabletability of HPC-coated ACM powders and simple blends of ACM and HPC.

theory, which predicts that a three-dimensional continuous bonding network consisting of the compressible excipient must be present in the tablet in order for it to show appreciable mechanical strength (12,36). The appearance of this bonding network thus corresponds to a critical threshold in compositions. Tablets of appreciable strength are attained only when the critical threshold is exceeded.

In contrast to the poor compaction performance of physical mixtures, HPC-coated ACM powders exhibit excellent tableting behavior. For example, intact tablets can be made from ACM coated with 1% HPC under a pressure as low as 20 MPa. All of its tablets remained intact after 24 h of relaxation with no detectable evidence of capping or lamination. One tablet compressed at 150 MPa is shown in Fig. 5. Under the same compaction conditions, the tablet tensile strength increases sharply with increasing amount of coated HPC. For example, at 100 MPa, the tensile strengths of tablets made from 1%, 2.5%, 5%, and 10% HPC-coated ACM powders are 1.51, 1.95, 2.84, and 3.57 MPa, respectively (Fig. 6). This effect is understandable because a higher amount of available HPC around the contact point between two adjacent ACM particles forms a larger interparticulate bonding area during compaction. In addition, the bonding strength of HPC–HPC or HPC–ACM may also be higher than that of ACM-ACM. Both effects lead to stronger tablets (30). Since tablets with tensile strength >2 MPa can be made using all four batches of HPC-coated ACM powders (Fig. 6), their tabletability is considered excellent (37). Coated ACM powders are therefore suitable for being used in a direct compression process in terms of powder tabletability.

Tabletability of HPC-coated ACM powders may be divided into two distinct zones (Fig. 6). With increasing compaction pressure, tablet tensile strength initially increases linearly up to a critical point and then decreases. For example, the tensile strength of tablets of 5% HPC-coated ACM powders increases linearly to 5.2 MPa at the pressure of 179 MPa and then drops to 2.8 MPa at 400 MPa pressure. The compaction pressure corresponding to maximum tablet tensile strength shifts to higher values with increasing amount of HPC. For example, compaction pressures corresponding to the maximum tablet tensile strength are 160 MPa, 167 MPa, 179 MPa, and 193 MPa for 1%, 2.5%, 5%, and 10% HPC-coated ACM powders, respectively. It should be noted that tensile strength remains sufficiently high, even though it has decreased at elevated pressures.

The phenomenon of deteriorating tablet tensile strength with increasing pressure is known as overcompaction. This phenomenon occurs when, above a critical pressure, higher pressure causes more elastic deformation of the particles without leading to significantly larger interparticulate bonding area (38). During the unloading phase of compaction, particle elastic recovery leads to rupture of bonding area between adjacent particles (16). More extensive elastic recovery causes more rupture of bonds, which weakens the three-dimensional bonding network in the tablet and deteriorates tablet strength. A thicker layer of HPC on ACM crystals may have two effects that alleviate the overcompaction problem: (1) more HPC fills the space between ACM particles during compaction, which leads to larger contact area; (2) the larger bonding area between adjacent particles leads to stronger bonding network, which is more resistant to elastic recovery. In this work, elastic

recovery is independent of amount of HPC coating within the 1%–10% loading range studied (Fig. 7). This observation suggests that elastic deformation during compaction is largely contributed by ACM but not HPC. This can happen only when ACM particles are always in contact during compaction, which is possible when the soft HPC around contact points is pushed out of the contact point between two ACM crystals during compression and thus does not contribute to elastic deformation and subsequent elastic recovery of the overall powder. We have so far mainly focused on roles of elastic recovery to explain the complex phenomenon of overcompaction. Additional considerations of other material deformation mechanisms, such as brittle fracture and viscoelastic deformation, may also assist its understanding. For HPC-coated ACM, the overcompaction phenomenon is present even for the sample with 10% HPC coating (the highest amount of HPC coating in this study). However, we expect the overcompaction phenomenon will eventually disappear above a certain level of coating HPC. This is similar to the compaction behavior of PVP-coated sand, where the overcompaction problem disappeared when >5% PVP was used (11).

The elastic modulus of ACM Form I is 16.58± 0.2869 GPa, which is about 25% that of silica (E= 70 GPa), a very hard material (Fig. 4). In this work, elastic recovery increases approximately linearly with increasing compaction pressure for both simply blended and coated samples (Fig. 8). For example, the elastic recovery of ACM coated with 1% HPC increases from 1.5% to 12.8% when compaction pressure is increased from 19 MPa to 360 MPa. HPC-coated ACM samples have lower elastic recovery when compared to physical mixtures at the same compaction pressure (Fig. 8). This difference is the same as the observation in the PVP-sand system and may be explained from the different distributions of HPC in the two types of powders (11).

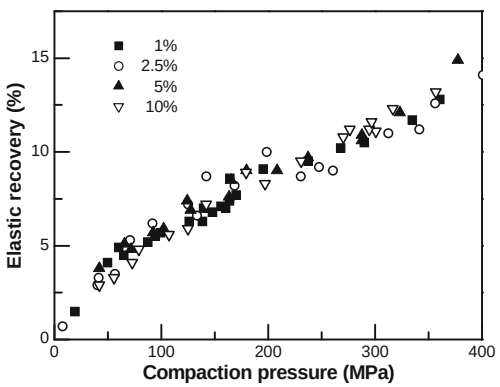

Fig. 7 Within 1%–10% loading range, HPC shows negligible effect on the elastic recovery of HPC-coated ACM.

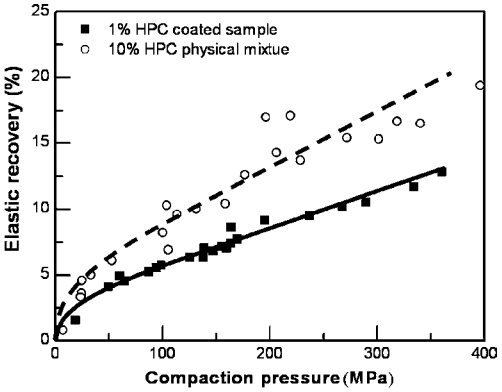

Fig. 8 Elastic recovery profiles of a physical mixture (90% ACM + 10% HPC) and ACM coated with 1% HPC.

The results have clearly shown that delivering excipients to the right place in tablets, coating layer in this case, using an appropriate process is critical for effective problem-solving in product development. A key benefit of the surface-coating strategy is its potentially universal applicability in solving manufacturing problems presented by poor mechanical properties of drugs. That is, solving powder tabletability problems can be readily achieved without the need of changing crystal structure, which will trigger extensive research and development efforts. However, despite the effectiveness of this strategy in enhancing powder compaction properties, its broad industrial application requires overcoming limitations in scalability of spray-drying process and the potential problems of process-induced phase transformation.

CONCLUSIONS

We have shown that the poor compaction properties of an organic crystal, ACM Form I, can be profoundly improved by coating it with a small amount of HPC. 1% HPC coating transforms the non-compressible ACM into a highly compressible powder suitable for direct compression. This is in stark contrast to the lack of observable improvement when up to 40% HPC was used in physical mixtures. The strategy of surface coating is valid and highly effective for addressing problems caused by poor tabletability of drugs. This strategy holds potential to be universally applicable for solving problems of poor tabletability of drugs, since polymer coating can be readily achieved using many common industrial processes, including spray-drying and fluid-bed-coating. An immediate impact of this strategy is to enable the successful reformulation of products containing a high dose of drugs and nutritional supplements for more economical and robust commercial manufacturing.

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