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The Impact of Shear Stress on Compression-nduced Polymorphic Transformation in Tablets and the Creation of Strategies to Minimize It

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A B S T R A C T

We set out to determine how the polymorphic transformation (form C / A) of chlorpropamide, a model medication, was impacted by (i) hydrostatic pressure alone and (ii) hydrostatic pressure in conjunction with shear stress during compaction. Both hydrostatic pressure in a pressure vessel and tablet pressing were used to submit the powder to pressures between 25 and 150 MPa. Powder X-ray diffractometry was used to find the total amount of phase transformation, whereas 2D-XRD was used to quantify the distribution of phase composition in tablets. The amount of transformation that occurred after compaction was more than what would have been expected from hydrostatic pressure alone; this disparity was explained by the fact that shear stress was also present during compaction, regardless of the pressure. The degree of phase change varied significantly between the radial tablet surface and the core when subjected to a compression pressure of 25 MPa. As the compression pressure increased, this gradient diminished. A site-specific lubricant, a viscoelastic excipient, a ceramic-lined die, and a cavity tablet were the four methods that were tried to lessen the impact of compression-induced phase transition. To reduce the amount of compression-induced phase change, the ceramic-lined die in conjunction with site-specific lubrication worked well.

Introduction

The physical properties of an active pharmaceutical ingredient (API) in a solid dosage form, such as its polymorphic shape, solvation state, and degree of crystallinity, might impact the final product's performance.Given that it is anticipated to undergo the least amount of changes while scaling up, processing, and storage, the thermodynamically stable physical form of the API is selected when bioavailability is not an issue.2 Nonetheless, Ostwald's rule makes it clear that a pharmacological substance's manufacturing procedure might influence the development of kinetically stable but thermodynamically metastable forms.

3Several processing processes may be applied to the API during the fabrication of a solid dosage form, such as tablets. These procedures include milling, wet/dry granulation, drying, compression, and coating. Various solvents (such as granulating fluid or coating solution) and extremes of temperature and water vapor pressure may be encountered by the API during these manufacturing steps. Phase transitions (from amorphous to crystalline, from anhydrous to hydrate, and back again), as well as metastable to stable polymorph, may occur depending on the processing stages and environmental factors. Phase changes caused by processing may significantly impact the final product's performance in many cases.4

This study is devoted to the topic of compression-induced phase transformation. When compressing a tablet, an upper and lower punch apply axial pressure on a porous powder mass that is contained in a die. A stress (sij) with normal and shear components better describes this load.5 The presence of a fluid around a finite stress element causes all of its

surfaces to undergo normal loads of the same magnitude. In this particular instance, where -s11 ¼ -s22 ½ -s33 and all other.Therefore, there is no resolved shear component, and sij (is j) is equal to zero.
Hydrostatic pressure is one possible name for this (Fig. 1a).

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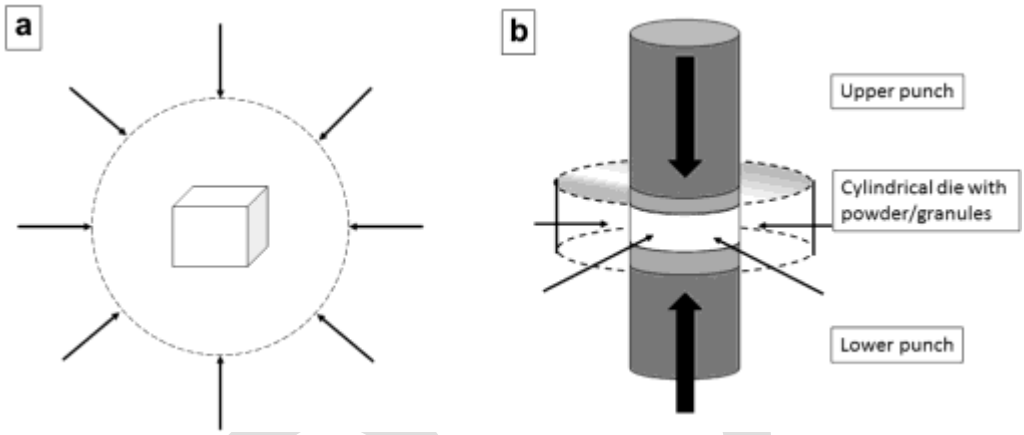

Figure 1. Difference between hydrostatic pressure and tablet compression. (a) a pressure is applied to a fluid in which particle is suspended. Resolved stresses on a finite element within the particles are all normal and equal. (b) a pressure is applied to powders/granules in a cylindrical die. Stress is applied axially via upper and lower punches, whereas normal stresses are resolved radially as particles deform against the die walls. Shear stresses are resolved throughout as particles deform and rearrange. (Source Wildfong 2009[5] copyright 2009, Redrawn Figure 11, with permission of Taylor and Francis Group LLC Books).

of molecules in a unit cell.[13] Form B of sulfabenza- mide, when compressed at 50 MPa, extensively converted to
stable form A. The extent of transformation increased as a function of compression pressure.[14] Pressure-induced polymorphic

In a processing step causing deformation, such as during compression, in addition to hydrostatic stress states, shear based deviatoric component will always occur.[5] Hence, shear state applied for consolidation includes significant resolved shear stresses, s_{ij} (i s j) (Fig. 1b), which occurs as particles rearrange anddeform during consolidation.

—s11 —s12 —s13
. .
—s31 —s32 —s33

Compared to simply hydrostatic applied states, these shear states with shear components may induce phase change at much lower loads.6
The compression force produced by the top punch and the force communicated to the

bottom punch is significantly different. The force needed to release the tablet upon compression is a good indicator of this variation.7 For tablet manufacturing, the compression pressure is usually applied for brief periods (about 1 second) and ranges from 40 to 200 MPa. For many pharmaceuticals, these circumstances do not cause a phase transition. On the other hand, compression is known to alter a small but significant subset of pharmaceuticals. At compression pressures typical of commercial tablet manufacturing, theophylline, nitrofurantoin, and amlodipine besylate tablets showed signs of partial amorphization.8 Conversely, crystallization of amorphous medicines such indomethacin, sucrose, and celecoxib occurred upon compression.9-11 Because it is in direct touch with the die wall, the radial tablet surface exhibited the highest degree of crystallization, which was explained by the friction between the two surfaces.10

Additionally, there are other instances when compression has caused

metamorphoses between crystalline and non-crystalline states. When combined with excipients and compressed at 70-170 MPa, caffeine in its first form converted into its stable second form.12 The detailed study focused on the polymorphic change of fluconazole from form I to form VIII at a pressure of around 800 MPa. Although their lattice parameters were different, forms I and VIII were both triclinic. Compression was thought to have an impact because transformations have been extensively investigated in chlorpro- pamide (CPM). On compression, the metastable form C consis- tently converted to stable form A.[6,15-17] Interestingly, partial reverse transition under pharmaceutically relevant compression pressures, that is, conversion of form A to C, has been observed only by some investigators.[17,18]

The factors influencing compression-induced phase trans- formations, in complex multicomponent pharmaceutical systems (e.g., tablet dosage forms), have not been comprehensively inves- tigated. This can be accomplished by taking a two-pronged approach: (i) modulate the processing conditions and (ii) system- atically evaluate the effect of formulation components. In this context, it is instructive to review the effect of compression con- ditions. Physical transformations that are kinetically retarded or have an induction period under hydrostatic conditions may be accelerated under compression, a process considered to be non- hydrostatic or quasi-hydrostatic in nature.[19] Thus a compression- induced phase transformation of an API observed in a die cavity may be delayed or absent under hydrostatic conditions. Wildfong et al.[6] observed no phase transformation in CPM, when subjected to hydrostatic pressure of 11.7 MPa, while compaction at pressures exceeding ~10.5 MPa caused polymorph A ⇄ C interconversion. The authors determined that the observed transition is facilitated by shear stress at interparticulate contacts and not hydrostatic pressure.

An analytical method that can (i) quantify the reactant and product phases at the same time and (ii) provide spatial resolution for the phase composition will be a huge help in understanding the mechanisms behind processing-induced phase transformations in tablets. In order to get mechanical understanding of the transformation process, the geographical information is essential. The detection of polymorphic changes is facilitated by spectroscopic methods such as solid-state nuclear magnetic resonance (NMR), infrared spectroscopy, and X-ray powder diffractometry. However, these

methods' main drawback is that they only provide you the "average" data from the whole sample. If shear stress facilitates the polymorphic transformation, as stated by Wildfong et al.6, then monitoring the phases at the die wall-powder interface may reveal the influence of friction. In the event that the phase transition does begin (especially

We may see the transformation's propagation toward the tablet core at the die wall-powder contact, where it is metastable or stable. Keeping an eye on the phase composition in various parts of the tablets will allow you to do this. We accomplished this by measuring the transformation in several tablet sections using two-dimensional X-ray diffractometry (2D-XRD), starting from the radial surface and working our way to the core. Aside from giving a two-dimensional picture, 2D-XRD allows for quick data gathering, improved signal intensity, and the possibility of error reduction due to preferred orientation by capturing a large portion of each diffraction ring.20 Overarchingly, we want to learn more about the mechanisms that cause phase transitions when we compress powders into tablets. Extending the principles to other compression-induced phase changes (amorphous/crystalline [and vice versa]; stable/metastable polymorph) is possible, even though we concentrate on a particular polymorphic transition. Our specific goals are as follows: (i) Using a hydrostatic pressure bottle free of die and punch friction effects, distinguish and quantify (delineate) the transformation caused by hydrostatic pressure and shear stress during tableting. (ii) While making tablets, we want to know how compression pressure affects the polymorphic phase change of active pharmaceutical ingredient (API). With the use of 2D-XRD, we can determine the thickness of the trans-formation in relation to the depth (spatial data). (iii) Discover ways to lessen the impact of compression-induced phase transition. A ceramic-lined die, (c) external or site-specific lubrication, (d) "cavity tab-lets" to reduce the impact of compression-induced phase change, and (a) the use of viscoelastic excipients were the four distinct approaches taken.

This model molecule is based on CPM, a sulfonylurea that is used to treat type 2 diabetes mellitus. The stable polymorph "A" has a real density of 1.461 g/cm3, while the high temperature polymorph "C" has a genuine density of 1.317 g/cm3. These two polymorphs have been extensively described. Many studies have focused on CPM, and its polymorphic transition (C / A) is extensively recorded.6, 15–17

Experimental Section

Materials

Powder X-ray diffractometry (PXRD) and differential scanning calorimetry were used to demonstrate that the CPM that was acquired from Sigma-Aldrich Co. (St. Louis, MO) was pure polymorph A (CPM- A). According to Simmons et al. (21), CPM polymorph C (CPM-C) was created by dividing 5 g of CPM-A into thin layers and placing them in glass petri dishes. The dishes were then heated in an oven at 115 ◦C for three hours. Form C's phase purity was validated by PXRD. Experiments and analyses performed within 24 hours after phase preparation do not reveal any discernible transformation since the retransformation kinetics of form C/A held at ambient conditions are sufficiently slow. Corn starch from National Starch Food Innovation, microcrystalline cellulose from DFE Pharma, hydroxypropyl methylcellulose from Methocel® K4M, PVP from Kollidon® 30 at BASF, and magnesium stearate from Fisher Scientific were all used in their original forms.

Transformation Under Hydrostatic Pressure

A latex filler pellet containing about 1 g of CPM-C was placed in a flexible lamination pouch and then vacuum sealed using a FoodSaver® vacuum sealer. Antifreeze liquid, air, and the hydrostatic pressure vessel's sample chamber (CPP35-200B; Supplementary Fig. S1) were all filled. was extracted and then put into the sample bag. It was sealed with a piston lid. A Carver® press (Fred S. Carver Inc.) was used to pressurize the chamber and hold the whole assembly. The sample bag was exposed to consistent pressure from all directions as it is entirely surrounded by liquid. There was an absence of shear stress due to die wall or punch friction, in contrast to tablet compaction. Before being immediately exposed to PXRD, samples were treated to hydrostatic pressures of 25, 50, 100, or 150 MPa for a dwell duration of 5 minutes.

Preparation of Tablets

We used a universal material testing equipment (Zwick/Roell; Zwick GmbH & Co., KG, Ulm, Germany) that came with flat-faced punches that measures 8 mm in diameter. The 200 mg tablets were subjected to compression at 25, 50, 100, or 150 MPa for 5 minutes in an ambient environment with 45% relative humidity (see Supplementary Materials for further information). There was no dwell period when 150 MPa tablets were made either.
The inner die wall and the faces of the upper and lower punch tips were greased with a magnesium stearate slurry (1% w/v in ethanol) prior to crushing each tablet for site-specific lubrication. A fine brush was used to apply the suspension, and then it was let to dry. In the die cavity and on the faces of the punch tips, a thin film of magnesium stearate was produced.

Tensile Strength

A texture analyzer (TA-XT2i; Stable Micro System), at a test speed of 0.01 mm/s with a maximum force of 480 N was used.

Powder X-Ray Diffractometry

Stainless steel X-ray holders were used to retain the powder specimens while they were subjected to CuKa radiation in a powder X-ray diffractometer (Bruker D8 Advance) at room temperature (1.54 Å; 45 kV × 40 mA). Scan speeds of 0.5 s per step and step sizes of 0.02 ◦ 2q were usually used to create XRD patterns ranging from 3 to 30◦ 2q. The integrated intensities of the lines with d-spacings of 5.89 Å and 7.49 Å, respectively, were used to determine the amount of transformation (form C /A). (See Supplementary Material for details) A standard curve was created to represent the relationship between the weight fraction of form C/A and the integrated intensity of the 5.89/7.49 Å peak.
An agate pestle and mortar were used to delicately ground the compressed pills. For comparison, CPM-C powder was similarly triturated in an agate pestle and mortar and then put via PXRD. Trituration prevented us from seeing any polymorphic change of CPM-C.

X-Ray Spectroscopy in Two Dimensions

The tablets were either whole or broken and then placed in a two-dimensional X-ray diffractometer (D8 Discover 2D, Bruker with a 140-mm diameter window VÅNTEC-500 detector) and exposed to CoKa radiation (1.79 Å; 35 kV 40 mA) at room temperature. XRD patterns were collected, using
a 0.8 mm collimator set at 8° angle of incidence and an area de-

tector (angular range 36°) set at an angle of diffraction at 16° 2q. The irradiated area can be described by an ellipse with a major axis of 6.97 mm and minor axis of 0.97 mm. For depth profiling, tablets were split into two halves, and the split surface was analyzed (Supplementary Fig. S2). NIST 1976a disc was used as reference standard. Data analyses were performed using commercially available software (JADE 2010).

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Using ICP-MS to Analyze Material

utilizing inductively coupled plasma mass spectrometry (ICP-MS), the magnesium stearate content was assessed in tablets that were manufactured utilizing both internal and external lubrication. The Supplementary Materials provide more information.

Finding out how much magnesium stearate was used as an external lubricant on the die wall and punches was also important. After washing the lubricated die wall and punches with ethanol, the concentration of magnesium stearate in the ethanol was measured using ICP-MS.

Results and Discussion

How Hydrostatic and Shear Stress Are Described

Our primary objective was to identify the ways in which hydrostatic and shear stresses affect phase change in compression. This was made possible by compressing the sample in a hydrostatic chamber where the antifreeze liquid surrounded it, eliminating shear stress. CPM-C did not undergo any polymorphic transition, according to PXRD data, when subjected to 25 MPa hydrostatic pressure for 5 minutes. Previous experiments with CMP-C at a hydrostatic pressure of 11.7 MPa did not reveal any transformation.6 But when CPM-C was exposed to 50, 100, and 150 MPa for 5 minutes at a greater dwell period, it changed dramatically to CPM-A. Figure 2a shows that the amount of transformation increased as the pressure rose. We can't rule out the possibility that, as the hydrostatic pressure increases, the shear stress and interparticulate friction would also rise.

Even at a compression pressure of 25 MPa, a noticeable polymorphic transition (C/A) was seen when exposed to uniaxial compaction (Fig. 2a; left y-axis). The degree of transformation was greater at 50, 100, and 150 MPa compression pressures compared to the equivalent hydrostatic pressures (Fig. 2a; left y-axis). Friction between the tablet surfaces and the die wall or punches may create shear stress, which in turn causes a greater transformation after uniaxial compression.

Subtracting the percentage change owing to compression from the percent change due to hydrostatic pressure allowed us to determine the role of shear stress in phase transition (Fig. 2a; right y-axis). It is assumed in this computation that there are no water-induced rubbing between particles. As the compression pressure increased, the shear stress's role in the polymorphic transition diminished, which went counter to expectations.

Friction between the powder and the die wall causes a portion of the applied force to be lost as radial stress during compression.22 The amount of force needed to release the tablets upon compression is an indicator of this.23 For a given tablet weight, a reduction in die wall friction is caused by an increase in compression pressure, as the ejection force is directly proportional to the area of the tablet in contact with the wall.24,25 Recall that when compression pressure increased, the role of shear stress in polymorphic transformation decreased (Fig. 2a). Because the die wall friction decreases as compression pressure increases, this phenomenon makes sense.

Additionally, CPM-C was compressed at 150 MPa of hydrostatic pressure for a brief period of time (hence referred to as 0 min) in an attempt to mimic the conditions seen in commercial tablet production. Regardless of the stay length, there was a significant difference in the amount of polymorphic transformation (C / A; % w/w) caused by

hydrostatic and compression pressures ($p < 0.05$; paired t-test (2-tailed); Fig. 2b).

Phase Transformations in Tablets dSpatial Heterogeneity

Compression of a tablet does not result in a uniform distribution of pressure throughout the powder. The "middle region" of the tablet is often less dense than the radial portions because of this trend.26, 27 An impact on the degree of phase transition may result from the resulting unequal shear stress. The 2D-XRD analysis was performed immediately upon compression on the tablets subjected to varying pressures in an unslubricated die. We plotted the polymorphic transformation (C/A) across the tablet by tracking the CPM-A percent vs distance (radially). Careful measures were made to maintain a consistent irradiation area when various parts of the tablets were exposed to X-rays, due to the large spot size (an ellipse with a minor axis of 0.97 mm and a major axis of 6.96 mm) and the 0.8 mm collimator.

As seen in Figure 3, there was a clear variation in the amount of transformation over the fractured radial surface.

Following compression at 25 MPa, while the radial surface exhibited pro- nounced phase transformation, the tablet no changes were made to the central area. There was an increase in radial surface transformation when compressed at 150 MPa. Nevertheless, there is a gradient in the amount of

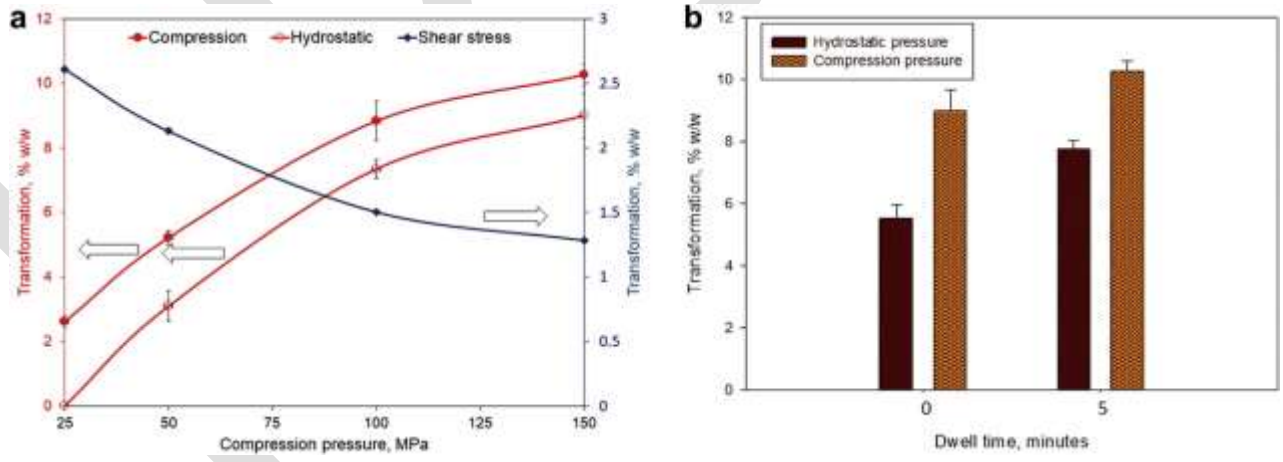

Figure 2. Extent of polymorphic transformation (C⁄A; % w/w) of CPM upon compaction at different compression pressures. (a) Left y-axis: the effect of hydrostatic and compression pressures (n ¼ 3; mean ± SD). Right y-axis: contribution of shear stress in the phase transformation. It is assumed that there is no interparticulate friction at low hydrostatic pressures. We recognize that the assumption may not be valid at higher pressures. (b) The combined effects of dwell time and hydrostatic/compression pressure (150 MPa) on the extent of polymorphic transformation. The results were significantly different (details in the text).

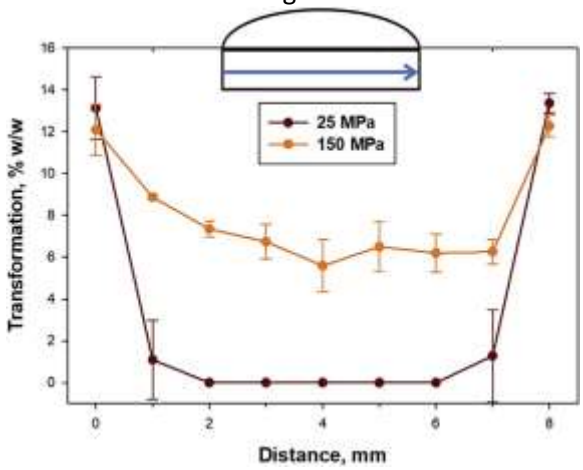

Figure 3. Spatial pattern of polymorphic transformation in split surface of tablets. CPM-C tablets were compressed at either at 25 or 150 MPa using an unlubricated die. Tablets were split and subjected to 2D-XRD, across split surface (inset).

There was significantly reduced, but not abolished, transition between the surface and core. This radial tension (shear stress) causes the tablet and die wall surfaces to rub against one other, which may be seen as a more polymorphic surface due to the increased density of the tablet.

When applied to solids, pressure may significantly damage their surfaces, resulting in the heterogeneous nucleation of new stable phases near grain boundaries. The creation of nuclei of critical size may be facilitated by the energy linked to crystal imperfections.

28 Similarly, shear stress may cause crystal defects to form in certain areas, which can then give rise to the formation of a new phase. Although the polymorphic transformation is caused by pressure, our data show that shear stress enhanced the amount of change during compression. This agrees with the impact of shear stress on ice Ih / II that has been shown to promote polymorphic transition.29 The change happened at 195 K with a shear stress of 50 MPa and a confining pressure of 170 MPa. At pressures greater than 250 MPa, the transition took place under hydrostatic conditions, meaning that shear stress was not present.30

Polymorphic transformation in dies is caused by pressure as well as shear stress from friction between the die walls.

CPM. The former would be in charge of transformation on the whole tablet, while the latter is thought to be mostly in charge of transformation on the radial surface.

First Strategy for Mitigation: Use of External Lubricants

Pressure and shear stress were attempted to be reduced by means of a number of methods. Using magnesium stearate (MgSt) as a lubricant was the first step. Mixing the granules with the lubricant, typically in a concentration range of 0.1% to 1% w/w, is standard procedure.31 "Internal lubrication" describes this process. Because of its hydrophobic properties, MgSt cannot be concentrated in formulations without running the danger of "over-mixing." Dissolution, hardness, and friability are some of the inter- and intra-batch characteristics that may be affected by these.ages 32–35 The use of external spray

lubrication was a common solution to several of these issues; it increased tablet hardness while preventing sticking and picking on the tooling and tablet face.36

We previously noted that site-specific external lubrication of the die wall significantly reduced compression-induced crystallization on the radial surface.10 Prelubricating the die wall and punch tip faces with MgSt had a comparable impact on the polymorphic transformation of CPM. Figure 4 shows how different types of lubrication affect the transformation profile in 25 or 150 MPa crushed tablets. The radial surface (~11%) of internally lubricated systems had a noticeable phase transition when subjected to compression at 25 MPa, although the core remained unaffected. At a compression pressure of 150 MPa, the radial surface and core regions showed comparable levels of transformation (~11%) and somewhat greater levels (~6%), respectively. As a result, increasing the compression pressure decreased the gradient in the amount of transformation between the radial surface and the core.

Specific to the location (external) at a pressure of 25 MPa

Lubricating the die wall significantly decreased the amount of transformation on the surface of the radial tablet (Fig. 4a). Figure 4b shows that at a greater compression pressure of 150 MPa, this technique of lubrication was much less successful in avoiding phase transitions.

An extremely low lubricant concentration is required for the die wall-powder/tablet contact in the external lubrication method, which seeks to specifically reduce friction there. But, a large concentration of lubricant on the radial tablet surface might result from MgSt being transported from the die wall to the tablet surface.

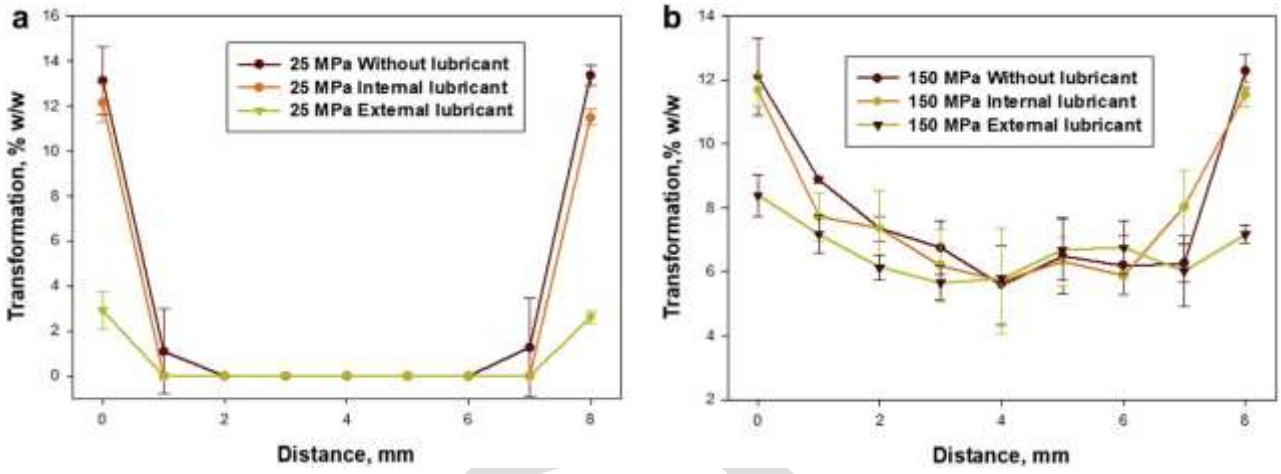

Figure 4. Spatial pattern of polymorphic transformation in split tablets. Tablets were analyzed using 2D-XRD, across split tablet surface. CPM-C tablets were compressed either at
(a) 25 MPa or (b) 150 MPa. The compression conditions were (i) no lubricant (control), (ii) internal lubricant (1% w/w), and (iii) external (site specific) lubricant.

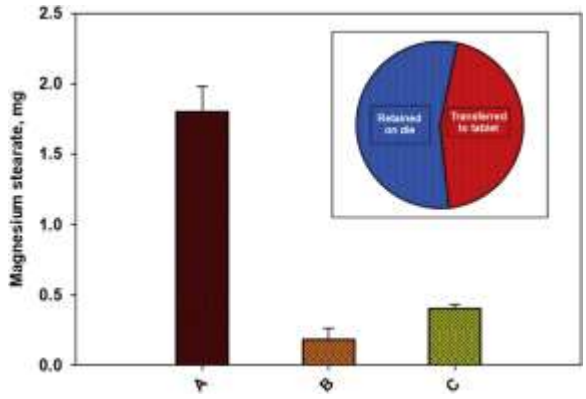

Figure 5. Magnesium stearate (MgSt) content in tablets compressed at 150 MPa with internal (a) or external (b) lubrication. (c) MgSt content in die wall following application of MgSt slurry. The inset shows the distribution of MgSt following external lubrication. Blue: fraction retained in the die (0.22 mg); Red: fraction transferred to tablet (0.18 mg).

After both procedures were used to lubricate the tablets, the MgSt content was measured using ICP-MS. The nominal quantity of magnesium strontium in the internally lubricated tablets was 2.0 mg/tablet, however the actual content was 1.8 ± 0.18 mg/tablet. The MgSt content was 0.18 ± 0.08 after external lubrication. So, the MgSt content of the tablet was significantly reduced due to the site-specific lubrication.
The quantity of MgSt that was transported from the die wall to the tablet surface was another area of interest for us. The lubricant concentration was found to be 0.4 ± 0.3 mg when the die wall was treated with MgSt slurry (see experimental section for details). Based on the fact that the pill contained 0.18 mg of MgSt per tablet, it may be inferred that about 0.22 mg of MgSt remained in the die wall. Figure 5 (inset) shows that this was also confirmed experimentally. The MgSt contents after internal and external lubrication were found to be significantly different ($p < 0.05$; Fig. 5), according to one-way analysis of variance (ANOVA) and Tukey's multiple comparison test.

Strategy 2 for Mitigation: Utilization of Viscoelastic Excipients

Tablets that have been crushed must be strong enough to endure the stressors that follow (such as coating, packing, and transportation). Compression testing may determine a tablet's mechanical strength by determining its radial tensile strength from its diameter breaking force.37 The general guideline is that tablets should have a tensile strength between 1.5 and 2.5 MPa. Factors such as compaction pressure and compaction duration, as well as the viscoelastic characteristics of the deforming particles, impact the

contact area, which in turn affects the tensile strength of the tablet.

38 We already know that pressure increases the amount of transformation (Fig. 2a). We intended to lower the compression pressure without lowering the tablets' tensile strength as a secondary mitigating technique. The use of viscoelastic excipients, which are characterized by a combination of elastic and viscous properties, may accomplish this. The compact is made stronger with the help of excipients that have plasticity.39 Compacted viscoelastic excipients such as starch, PVP K30, MCC, and HPMC were tested for their tensile strength in relation to compression pressure (Supplementary Fig. S3). The MCC compacts had the greatest tensile strength across the board for all compression pressures. Intramolecular hydrogen bonding40 and mechanical interlocking of fiber particles may explain why MCC has a greater tensile strength.41 Compressing CPM-C at 250-300 MPa is necessary to achieve an ideal tensile strength of around 2 MPa, as shown in Supplementary Figure S3. According to Table 1, the amount of transformation was about 12% when CPM-C was crushed independently at 300 MPa. To achieve the required tensile strength at reduced compression pressures of 100 MPa, a mixture of CPM-C and MCC (50/50 w/w) was used. Although the impact was not strong, the presence of MCC reduced the magnitude of phase transformation.

Mitigation Strategy 3: Use of Ceramic-Lined Dies

The force required to expel the tablet from the die is less with ceramic-lined dies due to the reduced friction between the powder and the die wall.42 A ceramic-lined die was found to reduce the degree of polymorphic phase change on the radial tablet surface while compressing powder at 25 MPa in the absence of lubrication, compared to a normal die. No phase transition was seen when the die was externally lubricated (Fig. 6a). Figure 4a shows that typical die external lubrication was not able to entirely prevent phase transition. Thus, the tablet was entirely shielded from phase change at a modest compression pressure of 25 MPa thanks to external lubrication and a ceramic-lined die.

Nevertheless, radial tablet surfaces still underwent polymorphic phase change when the compression pressure was raised to 150 MPa, even with a reduction in the usage of a ceramic-lined die in conjunction with external lubrication (Fig. 6b).

Mitigation Strategy 4: "Cavity" Tablet

Coating an API-containing tablet (the core tablet) with a different powder by compression creates an envelope around the core tablet; this process is called compression coating.43 Commonly, a core transfer assembly will connect two separate machines to complete the coating. Part of the process involves compressing the core tablet and then moving it to another machine with a

Table 1

Influence of Compression Pressure on Extent of Transformation (CPM-C / CPM-A) and the Tensile Strength of the CPM Tablets

Compression Pressure (MPa)	Extent of Transformation (C⁄A; % w/w)		Tensile Strength of Tablets (MPa)	
	CPM Alone	CPM	CPM Alone	CPM

		þ MCC		þ MCC
25	2.6 (±0.2)	ND	0.2	0.8
50	5.2 (±0.2)	1.9 (±0.8)	0.4	1.0
75	7.5 (±0.4)	4.3 (±0.4)	0.8	1.6
100	8.8 (±0.6)	6.9 (±1.2)	1.3	2.2
150	10.3 (±0.3)	[a]	1.7	[a]
300	12.1 (±0.3)	[a]	2.3	[a]

ND, not detectable.

[a] As the required tensile strength could be achieved at 100 MPa, higher compression pressures were not studied.

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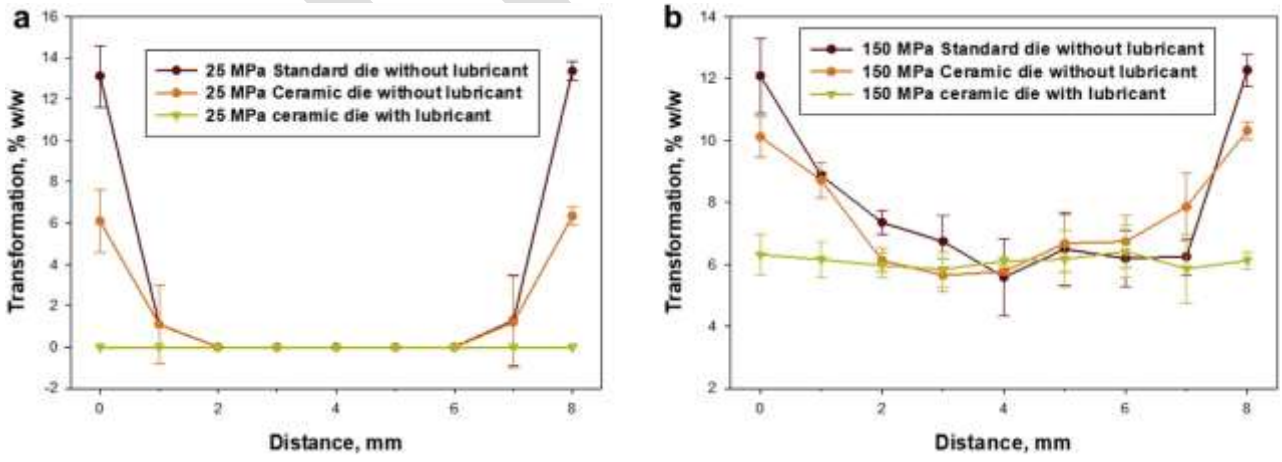

Figure 6. Spatial pattern of polymorphic transformation in split CPM tablets compressed with ceramic-lined die, without or with lubrication. Compression with unlubricated standard die served as the control. Compression pressures were (a) 25 MPa and (b) 150 MPa.

the coating powder into a bigger die, and then crush it again to create a "dry coat" around the core. Ozeki created a dry coated tablet manufacturing process that only required one step.44 First, the lower outer layer is formed. Then, the core is compressed. Finally, the whole outer layer is compressed. This is the method's three-stage process. The core touches the die wall and the upper punch directly during compression in both procedures.

A novel method for compression coating called a "cavity tablet" has been invented by us. In this method, the core material is kept away from the die and punches (Supplementary Fig. S4). This "stress" (Fig. 2) should have no impact on the powder's transformation as it won't encounter die wall friction. In this process, there are three steps (Supplementary Fig. S4): (i) using a 10-mm die and lower punch and an 8-mm upper punch to create a "cavity tablet" out of the coat material (MCC in this example); (ii) filling the cavity with the API; and (iii) adding more coat material to the die before finally compressing it with a 10-mm upper punch. The fact that the API will not come into touch with MgSt is an additional benefit of the design, allowing it to be utilized for pharmaceuticals like hydrochloride salts that are incompatible with MgSt.45

Figure 7a shows the results of evaluating the amount of API transformation after compressing these tablets using MCC as the covering material and CPM-C as the core. Both the unlubricated and externally lubricated dies were used to crush the tablets, and the outcomes were compared. Cavity tablets showed a much lower degree of phase transition compared to the other two methods.

The level of change in the cavity tablet did not show any spatial variability when exposed to 2D-XRD (Fig. 7b). Crucially, compared to the surface of the tablets made using an unlubricated die (~11% transformation), the radial surface had a far lesser degree of alteration at about 6%. Therefore, the amount of transformation was significantly reduced when die wall friction was not present.

Significance and Conclusions

The metastable (form C) / stable (form A) change of CPM was observed upon compression at pharmaceutically relevant pressures. Because of the greater amount of friction between the radial surface and the die wall, the degree of change was consistently greater at the radial surface. In the case of indomethacin, compression had a comparable effect, leading to the formation of amorphous/crystalline

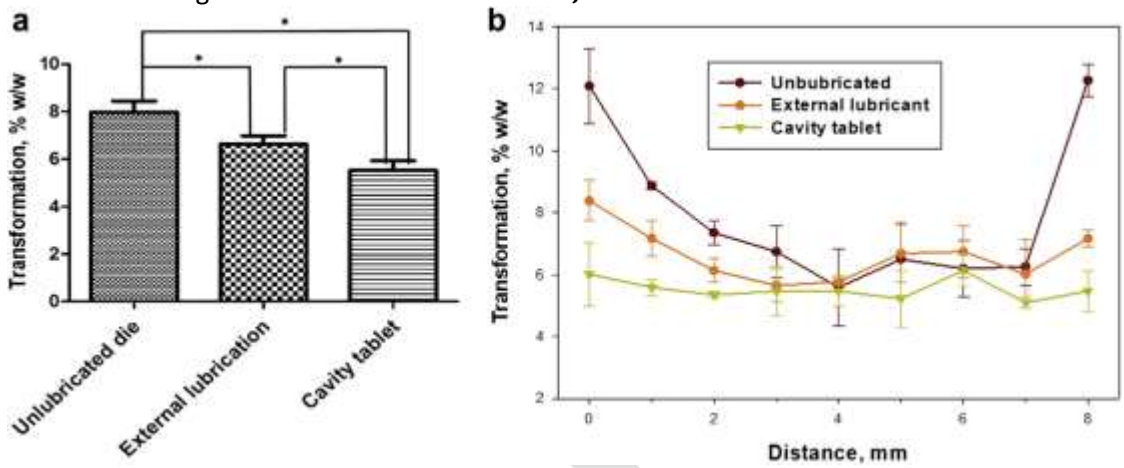

Figure 7. (a) Extent of polymorphic transformation (C⁄A), in tablets compressed at 150 MPa, using unlubricated or externally lubricated die and punches, and in "cavity tablets." The extent of transformation was found to be statistically significant, using one way ANOVA. * Tukey's multiple comparison test indicating $p < 0.05$. (b) Spatial pattern of poly- morphic transformation in split tablets.

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phase change on the surface of the tablet was not prevented by site-specific lubrication, even if it did reduce the impact of compression. So, to reduce the impact of compression, we used a multi-pronged strategy to reduce radial surface-die wall friction. The formulation method achieved the target tensile strength with a reduced compression pressure by using a viscoelastic excipient (MCC). Table 1 further shows that the amount of transformation was somewhat reduced. Reduced phase transition on the radial surface was the result of the second strategy, which included switching from inter-nal to site-specific lubrication; this change was most noticeable at low compression pressures (Fig. 4). The amount of transformation at the surface of the tablet was decreased with a change in tablet tooling from a stainless steel die to one lined with ceramic (Fig. 6). At a modest compression pressure of 25 MPa, the compression-induced transformation was entirely avoided by using a ceramic-lined die in conjunction with site-specific lubrication. Figure 6 shows that the amount of transformation was significantly reduced at a higher pressure of 150 MPa. Fig. 7 shows that the amount of surface change was significantly reduced when using a cavity tablet, which incorporates the API within the core tablet and prevents it from coming into direct contact with the die wall. The pharmaceutical community is interested in preventing phase transition at compression pressures of 150 MPada, however so far no mitigation method has been fully successful.

Because of its tendency to undergo polymorphic phase transitions, CPM transformation, was chosen as the compound to serve as a model. The significance of radial surface-die wall friction should be thoroughly examined if an API is known to undergo compression-induced phase shift. Other compression-induced phase changes (such as amorphous/crystalline and crystalline/amorphous polymorph) may also be mitigated using these methods.

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