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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

Our objective was to ascertain the effects of (i) hydrostatic pressure alone and (ii) hydrostatic pressure combined with shear stress during compaction on the polymorphic transformation (form C / A) of chlorpropamide, a generic drug. The powder was subjected to pressures ranging from 25 to 150 MPa using a combination of hydrostatic pressure in a pressure vessel and tablet pressing. The overall quantity of phase change was determined using powder X-ray diffractometry, and the distribution of phase composition in tablets was quantified using 2D-XRD. Due to the presence of shear stress during compaction, which was independent of pressure, the quantity of transformation that took place after compaction exceeded expectations based on hydrostatic pressure alone. When compressed to 25 MPa, the radical tablet surface and the core showed vastly different degrees of phase shift. This gradient became smaller with increasing compression pressure. To mitigate the effects of compression-induced phase change, four different approaches were considered: a cavity tablet, a ceramic-lined die, a site-specific lubricant, and a viscoelastic excipient. The ceramic-lined die and site-specific lubrication effectively decreased the amount of compression-induced phase shift.

Introduction

Product efficacy may be affected by the physical characteristics of an API in solid dosage form, including its polymorphic shape, solvation state, and degree of crystallinity.The most stable physical form of an API is chosen when bioavailability is not a concern since it is expected to experience minimal changes when scaling up, processing, and storage.2 The production process of a pharmaceutical drug may impact the formation of kinetically stable but thermodynamically metastable forms, as Ostwald's rule makes evident. 3A number of processing steps may be performed on the API in order to create a solid dosage form, such a tablet. Milling, drying, wet/dry granulation, compression, and coating are all part of these processes. In the course of these production processes, the API may come into contact with a wide range of solvents, including granulating fluid, coating solutions, and even water vapour pressure and very high temperatures. Metastable to stable polymorph states, phase transitions (from amorphous to crystalline, anhydrous to hydrate, and back again), and environmental variables all have a role in the potential occurrence of these changes. Processing may create phase shifts, which can sometimes have a major effect on how well the end product works.4

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Phase transformation caused by compression is the subject of this research. A tablet is compressed when an upper and lower punch put axial pressure on a quantity of porous powder inside a die. This load is best described by a stress (sij) that has both normal and shear Hydrostatic pressure is one possible name for this components.5 When a finite stress element is encircled by a fluid, every surface of the element experiences uniformly large normal loads. Here, where -s11 ½ -s22 ½ -s33 and everything else.Hence, sij (is j)=0, and the shear component is unresolved. (Fig. 1a).

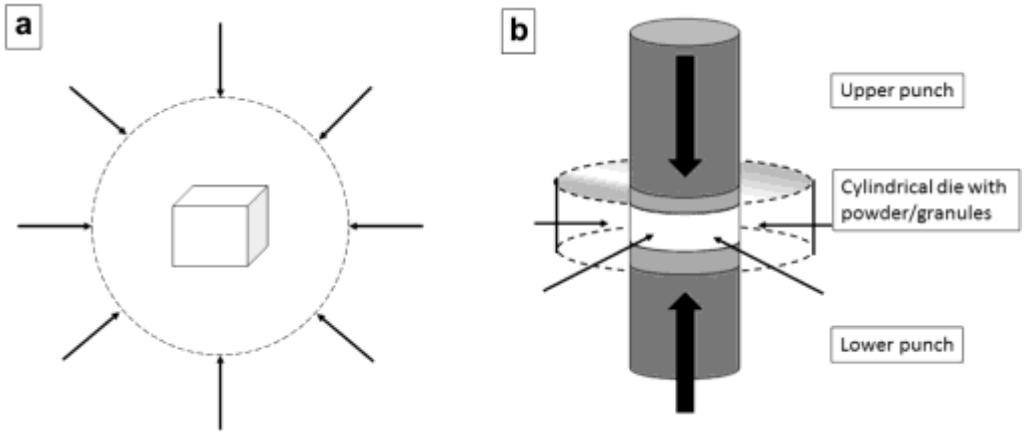

Figure 1. Difference between hydrostatic pressure and tablet compression. (a) a pressure is applied to a fluid in which particle is suspended. Resolved stresses on a finite element within the particles are all normal and equal. (b) a pressure is applied to powders/granules in a cylindrical die. Stress 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 fu tion 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 and deform during consolidation. — s11 —s12 —s13 —s31 —s32 —s33

These shear states may cause phase shift at far lower stresses than just hydrostatically applied states.6 There is a huge difference between the compression force that the top punch produces and the force that is transmitted to the bottom punch. One way to tell this variance is by looking at the force required to release the tablet when compressed.7

The compression pressure used to make tablets typically varies between 40 and 200 MPa and is applied for short durations (about 1 second). A phase shift is not caused by these conditions for many medications. In contrast, compression is known to change a tiny proportion of drugs, yet this group is important. Theophylline, nitrofurantoin, and amlodipine besylate tablets exhibited partial amorphization when subjected to compression pressures commonly used in commercial tablet manufacture.8 On the other hand, when compressed, amorphous medications including celecoxib, indomethacin, and sucrose crystallized.9-11 As a result of the frictional forces acting between the two surfaces, the radial tablet surface, which is in close proximity to the die wall, showed the greatest level of crystallization.10

Furthermore, compression has resulted in other situations
transitions from a crystalline to a non-crystalline state. Caffeine changed from its unstable first form to its more stable second form when subjected to compression at 70–170 MPa with excipients.12 At a pressure of around 800 MPa, the polymorphic transition of fluconazole from form I to form VIII was the subject of the in-depth investigation. Both forms I and VIII were triclinic, although having differing lattice values. Since chlorpro-pamide (CPM) transformations have been studied extensively, it was assumed that compression would have an effect. Form A, which is stable, was transformed from metastable form C during compression.6, 15–17 Conversion from form A to C, or partial reverse transition, at compression pressures relevant to pharmaceuticals has only been noted by a small number of researchers.17, 18

Complex multicomponent pharmaceutical systems (such as tablet dosage forms) have not been well investigated for the parameters that influence compression-induced phase transitions. To achieve this, a two-pronged strategy is needed: (i) adjusting the processing conditions and (ii) systematically testing the effects of different formulation ingredients. It is illuminating to examine the impact of compression conditions in this setting. Compression may speed up physical transformations that are inherently non-hydrostatic or quasi-hydrostatic, meaning they have an induction time or are kinetically delayed under hydrostatic circumstances.19 Accordingly, in hydrostatic circumstances, an API's compression-induced phase change that is seen in a die cavity could be postponed or nonexistent. While compaction at pressures surpassing about 10.5 MPa induced polymorph A 4 C interconversion, Wildfong et al.6 found no phase transition in CPM when exposed to a hydrostatic pressure of 11.7 MPa. According to the authors, shear stress at interparticulate contacts, and not hydrostatic pressure, is responsible for the observed change.

To better understand the processes that cause phase transitions in tablets during processing, an analytical approach is needed that can simultaneously (i) quantify the reactant and product phases and (ii) provide spatial resolution for the phase composition. With this spatial data, we can finally grasp the mechanical nature of the transition. Spectroscopic techniques including X-ray powder diffractometry, infrared spectroscopy, and solid-state nuclear magnetic resonance (NMR) make it easier to identify polymorphic alterations. The major problem with these approaches, however, is that they can only give you the "average" of the data in the sample. Wildfong et al.6 say that shear stress enhances the polymorphic transition; hence, friction may be revealed by

monitoring the phases at the die wall-powder contact. Assuming the phase transition does start (particularly

At the die wall-powder contact, where the transformation is metastable or stable, we may see its propagation toward the tablet core. Doing so is possible if you monitor the phase composition in different areas of the pills. The change in many tablet sections was measured using two-dimensional X-ray diffractometry (2D-XRD), beginning at the radial surface and progressing to the core. This allowed us to achieve our goal. By collecting a substantial amount of each diffraction ring, 2D-XRD not only provides a two-dimensional image, but it also enables fast data collection, enhanced signal intensity, and the prospect of error reduction owing to preferred orientation.20 In the grand scheme of things, we are interested in understanding how the compression of powders into tablets brings about phase changes. Although we focus on a specific polymorphic transition, the ideas may be extended to various compression-induced phase shifts (amorphous/crystalline [and vice versa]; stable/metastable polymorph). Here are our concrete objectives: (i) Determine the impact of hydrostatic pressure and shear stress on tableting by using a hydrostatic pressure bottle that is not affected by die and punch friction. (ii) We are interested in learning how compressed pressure impacts the polymorphic phase transition of the API while producing tablets. We may find the transformation's thickness in proportion to its depth (spatial data) using 2D-XRD. (iii) Figure out how reduction of compression-induced phase transition may be achieved. Four separate methods were employed: (a) a die lined with ceramic, (c) lubrication applied externally or at specified sites, (d) "cavity tablets" to mitigate the effects of compression-induced phase shift, and (a) viscoelastic excipients.

One sulfonylurea that helps with type 2 diabetes is CPM, and this model molecule takes its structure from it. At room temperature, polymorph "C" has a density of 1.317 g/cm3, but the stable polymorph "A" has a density of 1.461 g/cm3. A lot of information on these two polymorphs already exists. The polymorphic transition (C / A) of CPM has been well-documented and the subject of several investigations.6, 15-17

Experimental Section

Materials

The CPM obtained from Sigma-Aldrich Co. (St. Louis, MO) was shown to be pure polymorph A (CPM-A) using powder X-ray diffractometry (PXRD) and differential scanning calorimetry. The formation of CPM polymorph C (CPM-C) was described by Simmons et al. (21), who said that 5 g of CPM-A was thinly layered and placed in glass petri plates. After that, the plates were placed in an oven set at 115 ◦C for a duration of three hours. The phase purity of Form C was confirmed by PXRD. For form C/A stored at ambient conditions, the retransformation kinetics are sufficiently slow, hence experiments and analysis conducted within 24 hours following phase preparation do not show any noticeable transformation. The following ingredients were used in their original forms: magnesia stearate from Fisher Scientific, hydroxypropyl methylcellulose from Methocel® K4M, microcrystalline cellulose from DFE Pharma, and corn starch from National Starch Food Innovation.

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 detector (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).

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 and Spatial 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

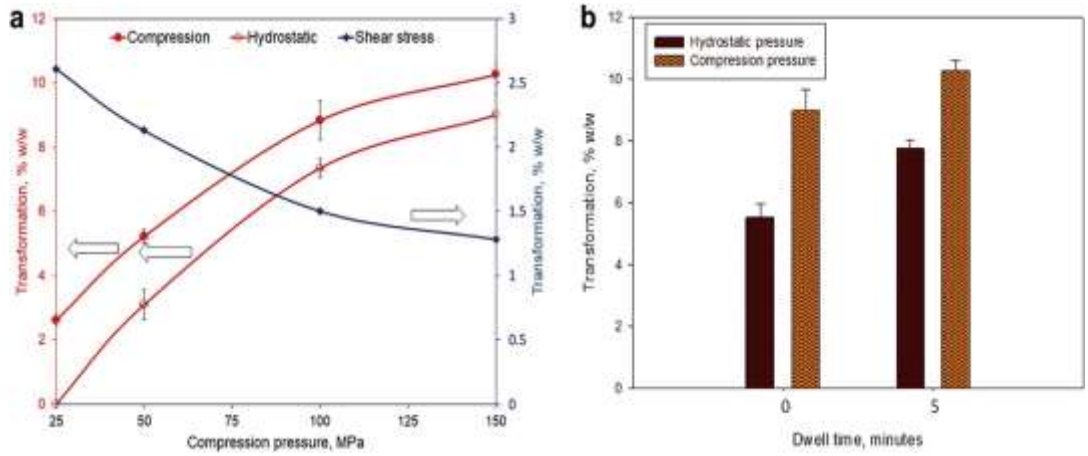

Figure 2. Extent of polymorphic transformation (C⁄A; % w/w) of CPM upon compaction at different compression pressures. (a) Left y-axis: the effect of hydrostatic and compression pressures (n ¼ 3; mean ± SD). Right y-axis: contribution of shear stress in the phase transformation. It is assumed that there 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).

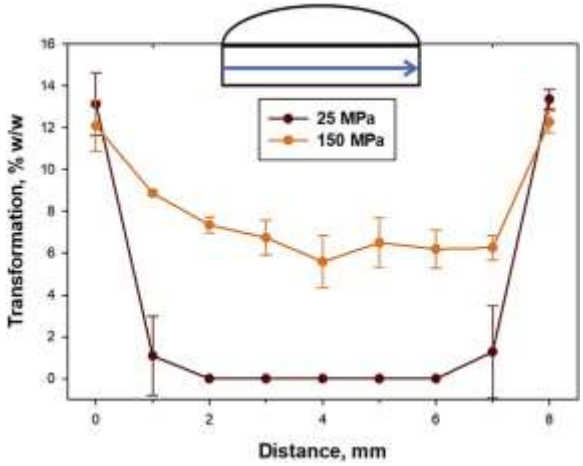

Figure 3. Spatial pattern of polymorphic transformation in split surface of tablets. CPM-C tablets were compressed at either at 25 or 150 MPa using an unlubricated die. Tablets were split and subjected to 2D-XRD, across split surface (inset).

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.

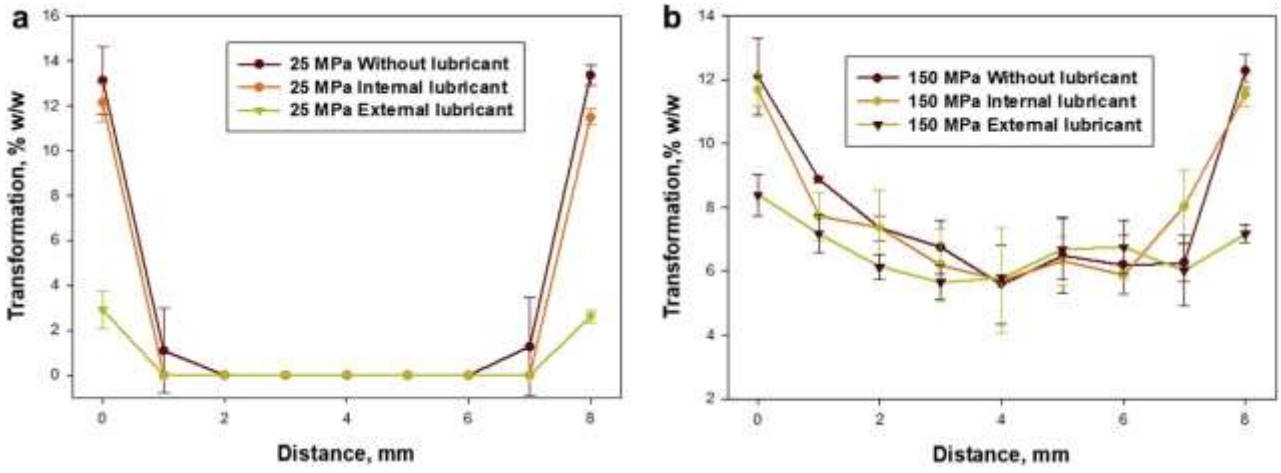

Figure 4. Spatial pattern of polymorphic transformation in split tablets. Tablets were analyzed using 2D-XRD, across split tablet surface. CPM-C tablets were compressed either at (a) 25 MPa or (b) 150 MPa. The compression conditions were (i) no lubricant (control), (ii) internal lubricant (1% w/w), and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

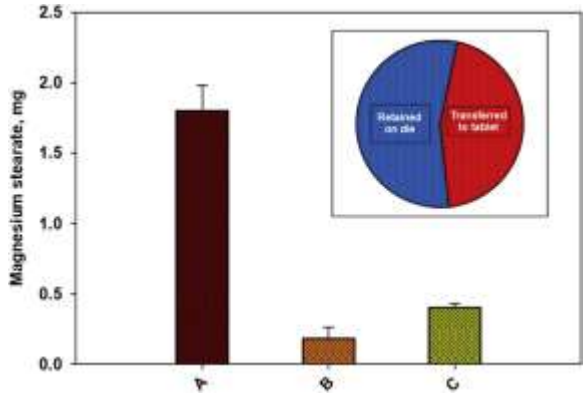

Figure 5. Magnesium stearate (MgSt) content in tablets compressed at 150 MPa with internal (a) or external (b) lubrication. (c) MgSt content in die wall following appli- cation of MgSt slurry. The inset shows the distribution of MgSt following external lubrication. Blue: fraction retained in the die (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 þ MCC	CPM Alone	CPM 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.

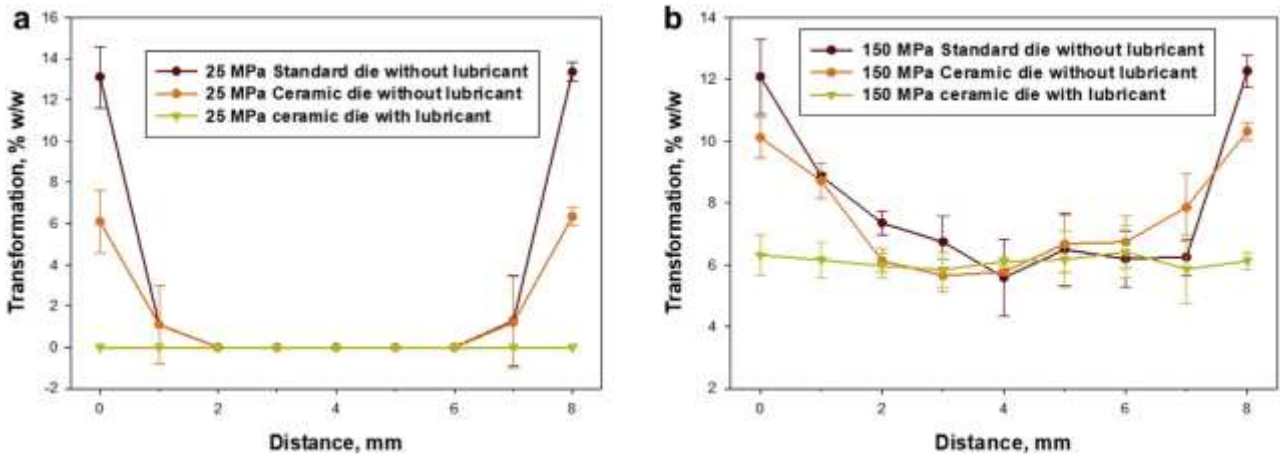

Figure 6. Spatial pattern of polymorphic transformation in split CPM tablets compressed with ceramic-lined die, without or with lubrication. Compression with unlubricated standard die served as the control. Compression pressures were (a) 25 MPa and (b) 150 MPa.

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

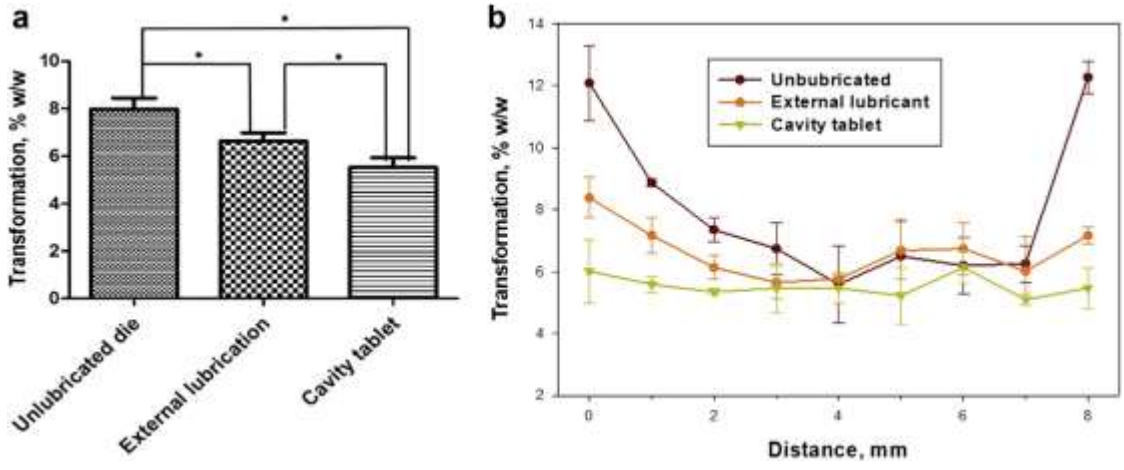

Figure 7. (a) Extent of polymorphic transformation (C⁄A), in tablets compressed at 150 MPa, using unlubricated or externally lubricated die and punches, and in ‘‘cavity tablets.’’ The extent of transformation was found to be statistically significant, using one way ANOVA. * Tukey’s multiple comparison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

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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