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RESEARCH PAPER

# A critical Examination of the Phenomenon of Bonding Area - Bonding Strength Interplay in Powder Tableting

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## ABSTRACT

***Purpose*** Although the bonding area (BA) and bonding strength (BS) interplay is used to explain complex tableting behaviors, it has never been experimentally proven. The purpose of this study is to unambiguously establish the distinct contributions of each by decoupling the contributions from BA and BS.

***Methods*** To modulate BA, a Soluplus® powder was compressed into tablets at different temperatures and then broken following equilibration at 25°C. To modulate BS, tablets were equilibrated at different temperatures. To simultaneously modulate BA and BS, both powder compression and tablet breaking test were carried out at different temperatures.

***Results*** Lower tablet tensile strength is observed when the powder is compressed at a lower temperature but broken at 25°C. This is consistent with the increased resistance to polymer deformation at lower temperatures. When equilibrated at different temperatures, the tensile strength of tablets prepared under identical conditions increases with decreasing storage temperature, indicating that BS is higher at a lower temperature. When powder compression and tablet breaking are carried out at the same temperature, the profile with a maximum tensile strength at 4°C is observed due to the BA-BS interplay.

***Conclusion*** By systematically varying temperature during tablet compression and breaking, we have experimentally demonstrated the phenomenon of BA-BS interplay in tableting.

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**KEY WORDS** bonding area · bonding strength · compaction · powder · tableting

## ABBREVIATIONS

| | |
|---|---|
| BA | Bonding area |
| BABS | Bonding area bonding strength |
| BS | Bonding strength |

## INTRODUCTION

Compact formation by compression is a process critical to many industries, including energy (coal, petroleum, and nuclear), foods, automobiles, metallurgy, pharmaceuticals, and ceramics (1–5). Although many compression equations have been proposed to describe the density-pressure relationship (5–8), few attempts have been made in quantitatively describing the relationship between tablet tensile strength and compaction pressure, which is known as tabletability (9,10). While tensile strength-pressure data can be fitted with equations, e.g., Leuenberger's equation (9), the ability to predict tabletability based on material mechanical properties and particulate properties is the ultimate goal. The difficulty in reliably predicting tabletability arises from the challenges in quantifying the area of contact between particles in a compact (11) and summarizing the intermolecular forces over these areas to arrive at a final strength value. Further complications are caused by the heterogeneity in the particle size and shape, surface structures at atomic level, and the orientation of contact planes in the compact (12).

The qualitative bonding area (BA) – bonding strength (BS) model has been a useful tool in providing an explanation of complex powder tableting behavior (13). Specifically, the BABS model simplifies the problem by treating tensile strength as an outcome of the BA between adjacent particles and BS, i.e., the strength of the interaction over a unit area.

This allows the BA-BS interplay to be qualitatively described. Thus for example, with everything else being equal, a harder material develops a smaller BA, because particles deform less easily under pressure. However, a harder material will usually have higher interaction strength over the BA that is formed. In contrast, a softer material will undergo deformation more readily but the resulting BS tends to be smaller (14). As such, a change in the material mechanical property, hardness, tends to cause opposite effects in the BA and BS. This interplay between BA and BS, in turn, often leads to complex tableting behavior, depending on compaction pressure, temperature, compositions, and particulate properties (15–18). Therefore, an effective examination of the BA-BS interplay is critical for a mechanistic understanding of different tableting behaviors among powders and for identifying the cause of poor tabletability (19).

Although the BABS model is conceptually sound, its direct demonstration is difficult due to the challenge in completely separating the contributions from BA and BS. BA is influenced by particle size, particle surface roughness, and morphology. For two different powders, it is impossible for these particulate properties to be identical even when they are prepared by the same process, such as crystallization or milling. This problem can be partially addressed by comparing tableting properties of a crystalline anhydrate-hydrate pair because anhydrate-hydrate phase change can be achieved through a vapor mediated process without eliciting changes in particulate properties (20,21). Amorphous solids containing different amounts of moisture can also be used to address this problem in an analogous manner (15). Although the different mechanical properties between the hydrate and anhydrate (or amorphous solids with different water contents) are expected to simultaneously impact BA and BS, the contributions from BS may be compared by extrapolating tensile strength to zero porosity. When porosity is zero, difference in BA between tablets of the two powders with essentially identical particle shape and size distribution is minimal. That is, the tablet mechanical strength at zero porosity is proportional to BS. On the other hand, BA can be assessed indirectly by comparing tablet porosity of the two materials under the same compaction conditions. A tablet with lower porosity is expected to have a larger BA. In this way, different tableting behaviors of powders can be explained by applying the BABS model, i.e., they are good systems to show applications of the BABS model in interpreting different tableting behaviors.

In these systems, the coupling between effects on tensile strength by BA and BS still makes it difficult to directly demonstrate contributions from BA and BS, which is required to study the BA-BS interplay. The goal of decoupling the contributions from BA and BS can be met by using a material with the ability to have the BA and BS individually modulated by external stimuli, such as temperature and pressure. To this end, organic glasses are promising as long as their glass transition temperature, $T_g$, is not too far away from temperatures suitable for carrying out powder compression and tablet strength experiments. Using such materials, the BA can be altered by changing the temperature at which the powder is equilibrated and compressed. For example, the higher plasticity of the same glass at a higher temperature will favor the development of larger BA. We can also control BS by equilibrating tablets at different temperatures after they are formed. BS is expected to be lower when the tablet is equilibrated at a higher temperature. Moreover, compaction pressure impacts BA but not BS for a given material under constant environmental conditions.

## MATERIALS AND METHODS

### Material

We selected Soluplus®, a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (BASF, Ludwigshafen, Germany), as a model material. Dry Soluplus has a $T_g$ ~70°C. $T_g$ is ~45°C, ~36°C, and < 23°C when equilibrated at 52, 67, and 75% relative humidity (RH), respectively. In the vicinity of $T_g$, it is possible to change particle plasticity while keeping particle size, shape, and surface properties unchanged. Soluplus powder was obtained by milling dried films, cast from a polymer solution in methanol, under cryogenic temperature (liquid nitrogen bath) and sieving through 75 μm mesh. The as-received Soluplus is comprised of relatively large granules and tablet tensile strength is relatively weak. The cryo-milled Soluplus exhibits much higher tabletability and, therefore, is more suitable in this study. The powder was equilibrated at 67% RH at 25°C (cupric chloride saturated salt solution (22)) before further use or handling.

### Methods

Powder compression was carried out on a universal material testing machine (Model 1485, Zwick, Ulm, Germany) at a speed of 10 mm/min using round (8 mm diameter) flat-faced tooling. Two custom-made rigid PVC blocks were used to align the punches and die to allow successful compression. Tablet dimensions were measured using a digital caliper and tablet density was calculated from tablet weight and volume just before tablet breaking force determination. The tablet diametrical breaking force was determined using a texture analyzer (Texture Technologies Corp., Scarsdale, NY/ Stable Micro Systems, Godalming, Surrey, UK), at a speed of 0.01 mm/s with a 5 g trigger force. A total of five tablets were tested under each condition.

Soluplus tablets were also characterized with a micro computed tomography (μ-CT, Model: XT-H 225, Nikon Metrology Inc. NV). A scan setting of 45 kV and 80 μA was used with

a voxel size of 2.7 μm. The image acquisition time was 50 min. Acquired images were reconstructed using CT Pro 3D software on the instrument and a total of five 2D slices of tablet structure at different heights were generated using Volume graphics 2.2 and percentage of area occupied by pores was determined using Image-J 1.49 (Bundle with Java 1.8.0) for estimating tablet porosity. In this experiment, as-received Soluplus were used because its larger particle size (~300 μm) makes the demonstration of the effect of temperature on tablet porosity, which is directly related to bonding area, by micro-CT more clearly.

### *Modulating BA by Compressing Powders at Different Temperatures*

Capped 1.5 mL plastic vials that contain Soluplus powder, wrapped with paraffin film and aluminum foil, were equilibrated at 25, 4, and −20°C for at least 48 h. The water content in Soluplus was stable during storage as suggested by TGA shortly before powder compression. Each powder was compressed at three compaction pressures, 50, 100, and 400 MPa. Tooling pre-equilibrated to a target temperature was assembled in the block, and powder was filled at the desired temperature (in either a refrigerator or a freezer). The temperature inside the refrigerator or freezer was monitored continuously, which varied less than 2°C during die filling. The whole assembly was then quickly moved to the materials testing machine for compression at 25°C. The chilled tooling and holding block served as temperature buffer that minimizes gross deviation of the powder bed temperature from the target temperature during the course of compression, which lasted < 1 min at 25°C. The tablets compressed from the 4 and −20°C powders were quickly wrapped in paraffin film after ejection and allowed to equilibrate to 25°C in sealed vials (to avoid condensation of water vapor on tablets) before exposing to 67% RH. Under these conditions, differences in mechanical strength of tablets equilibrated at 25°C are due to differences in BA. Since particles at lower temperature are harder, smaller BA is developed during compression. However, the relative difference in BA also depends on compaction pressure. When pressure is sufficiently high, extensive deformation of even harder particles may be expected. Therefore, the relative difference in BA of powder differing in plasticity is small (negligible when porosity of all tablets is close to zero). As a result, difference in BA is less sensitive to difference in particle plasticity at a higher pressure.

### *Modulating BS by Changing Tablet Equilibration Temperature*

We prepared a set of tablets at 400 MPa at 25°C. Tablets, sealed in individual 1.5 mL plastic vials, were equilibrated under specified temperatures (−20°C, 4 C, and 25°C) for at least 24 h before breaking force determination. Tablet breaking experiments were performed at 25°C and 4°C . Due to equipment limitations, tablets equilibrated at −20°C were broken at a 4°C environment immediately after they were taken out of the freezer. The total time of exposure to the 4°C environments was less than 1 min for all tablets to limit the influence of tablet "warming" during the course of breaking test.

BA remains essentially unchanged in a tablet during equilibration at a different temperature, but BS changes significantly with equilibration temperatures in this experiment. Therefore, differences in breaking strength are due to differences in BS not to BA. The use of a relatively high compaction pressure, 400 MPa, is intended to maximize the BA in tablets so that a change in BS can be detected more easily.

### *Modulating BA and BS Coupled Effects*

Powders were equilibrated and compressed at −20, 4, and 25°C. Tablets were also stored and broken at the same temperature as compression, with the exception of −20°C tablets that were quickly broken at 4°C. In this design, BA is expected to be lower at a lower temperature because the glassy material is harder (23). The higher material hardness also means that BS is higher when the tablets are equilibrated and broken at a lower temperature. The net effect of lowered temperature on tablet tensile strength depends on the interplay between the negative effect on BA and positive effect on BS. In addition, we also varied compaction pressure, 50, 100, & 400 MPa, to allow further examination of the effect of BA.

## RESULTS AND DISCUSSION

Soluplus sorbs 8% water at 67% RH and 25°C, in both a static RH chamber and a dynamic moisture sorption balance. With this water content, $T_g$ of Soluplus is 36°C.

Figure 1a shows the results of powder equilibrated and compressed at different temperatures, but the tablets were broken at 25°C. A powder that is equilibrated and compressed at a lower temperature exhibits lower tabletability. Since tablets are equilibrated at 25°C, BS is the same for the same material. The difference in tabletability is attributed to the different BA. At a lower temperature, particles are harder and are expected to be more resistant to plastic deformation (17,23–25). As a result, the area of contact is reduced.

Figure 1b shows that the tensile strength of otherwise identical tablets (compressed at 25°C and 400 MPa) decreases with increasing equilibration temperature. Since the contact areas in these tablets are the same, the difference in tablet mechanical strength is due to the differences in energy required to separate the particles, i.e., different BS. This is consistent with the expectation that the glassy material is harder at a lower temperature below $T_g$.

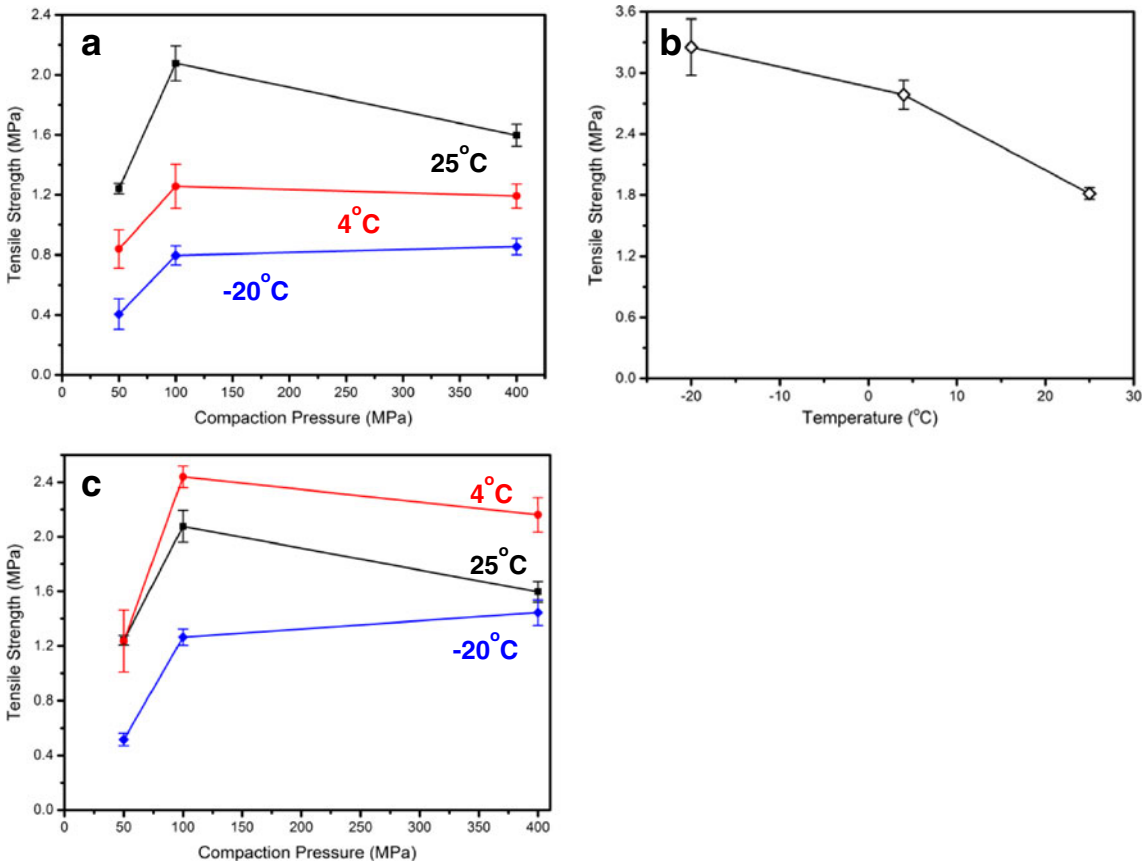


**Fig. 1** Tableting data ($n = 5$): (**a**) powder equilibrated at different temperatures but broken after temperature equilibration at 25°C; (**b**) tablets (compressed at 25°C and 400 MPa) equilibrated at different temperatures; (**c**) the powder and tablets equilibrated at respective temperatures.

When tablets are formed and broken at the same temperature, both BA and BS are impacted by a change in temperature. Figure 1c shows that tabletability follows the order of 4°C > 25°C > −20°C. This may be explained by considering the interplay between BA and BS. At a lower temperature, smaller BA is developed (Fig. 1a) but larger BS is also expected (Fig. 1b). Comparing to tablets that are warmed to 25°C before breaking, tensile strength of tablets formed and broken at 4°C and −20°C is higher. This again confirms the expectation that BS is higher at a lower temperature. However, at −20°C, the negative effect of lower BA on tensile strength overshadows the positive contribution due to higher BS. Therefore, lower tablet tensile strength is observed (Fig. 1c). The highest tabletability at 4°C suggests that the BABS interplay at 4°C is optimum among the three temperatures.

At the same compaction pressure, tablet density of Soluplus stored at a lower temperature is lower. This means that there is a larger volume of pores in the tablet (Fig. 2a). Similar results were also observed for several pharmaceutical excipients and mixtures (24). This is consistent with the fact that powder consolidation by compaction is less effective for less plastic (harder) materials (23).

Thermal expansion is associated with a decrease in density. When the same tablets are equilibrated at a higher temperature, tablet density at 25°C is slightly (about 2%) lower than those observed at 4 and −20°C (Fig. 2b), hinting possible thermal expansion when approaching its $T_g$. When both powder compression and tablet storage are carried out under the same temperature, lower temperature corresponds to lower tablet density (Fig. 2c). This means that the effect of the extent of plastic deformation on powder consolidation and tablet density dominates that of thermal expansion.

At 4 and 25°C, tablet density is slightly lower at 400 MPa than that at 100 MPa (Fig. 2c). This is not observed when compression was carried out at −20°C. We attribute this to the phenomenon of flashing, which occurs when plastic material escapes into the gap between punches and die under a high compaction pressure. One striking example of this phenomenon is the die compression of magnesium stearate, where much of the material can escape through the gap if given a sufficient amount of time (26). Therefore, measured tablet thickness is associated with a positive error, which leads to lower tablet density. This effect is negligible for Soluplus at −20°C, which is much less plastic than at the two higher temperatures. Figure 2d shows the effect of equilibration temperature on the density of tablets compressed at −20°C. Tablet density is noticeably higher at −20°C storage temperature than at 25°C, which is due to the effect of tablet thermal

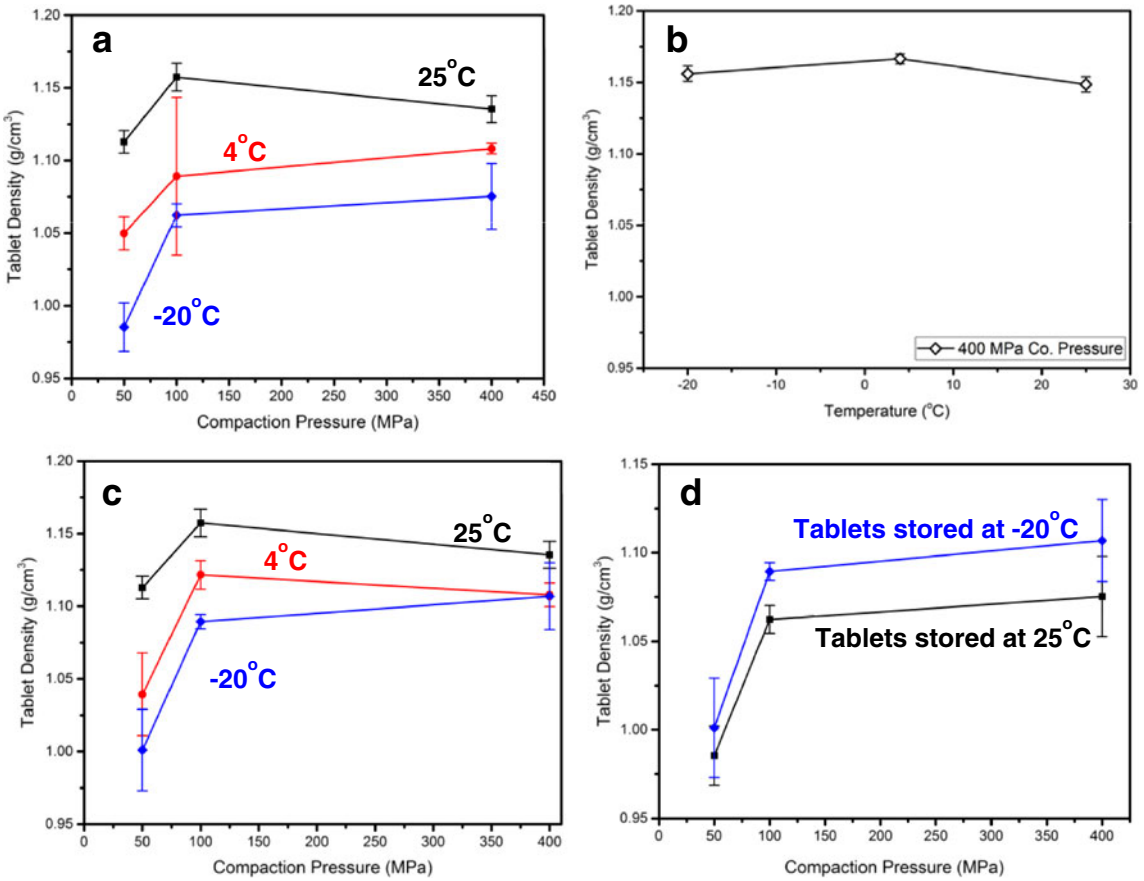


**Fig. 2** Dependence of tablet density on pressure and equilibration temperature: (**a**) tablets compressed at different temperatures and stored at 25°C; (**b**) tablets (compressed at 25°C and 400 MPa) equilibrated at different temperatures; (**c**) powder equilibration, compression, and tablet equilibration carried out at constant temperatures; (**d**) density of tablets (compressed from a powder equilibrated at −20°C) stored at 25°C and −20°C.

expansion. However, this thermal expansion effect is insignificant when tablet storage temperatures of 4 and 25°C are compared, similar to what is shown in Fig. 2b.

Figure 3 shows the impact of BA, BS, as well as the BABS interplay on tablet tensile strength. Tablet tensile strength is the lowest when powder equilibrated at −20°C is compressed and tablets are equilibrated at 25°C before being broken. Here, both BA and BS are low because Soluplus particles undergo less extensive plastic deformation at a lower temperature (less BA), and BS is lower at a higher temperature. On the other hand, tablets compressed at 25°C but stored at −20°C are the strongest because both BA and BS are the highest in this series. The BS effect is shown by line *a* in Fig. 3, where powder is compressed into tablets at 25°C and tablets are equilibrated at different temperatures. In this case, BA is comparable in these tablets but BS is higher at a lower storage temperature below $T_g$. Therefore, tablet tensile strength decreases with increasing tablet equilibration temperature. The BA effect is shown by line *b* in Fig. 3, where tablets compressed at different temperatures are stored at 25°C. When a powder is compressed at a lower temperature, the tensile strength is lower because BS is comparable in these tablets at 25°C but BA is smaller when powder storage temperature is farther below its $T_g$. The detrimental effect of lower storage temperature on BA, inferred from tablet tensile

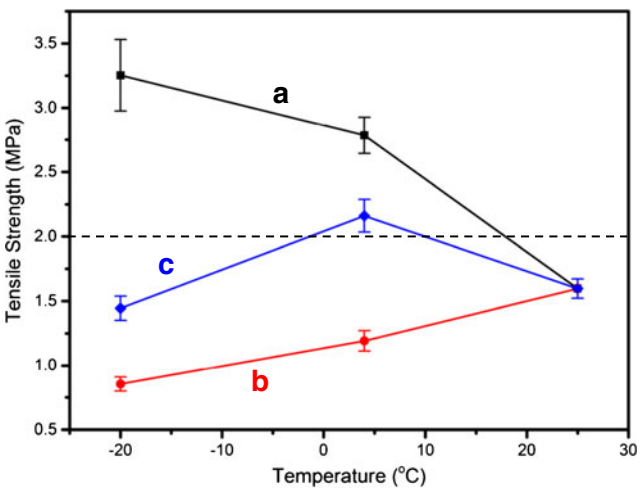


**Fig. 3** Tensile strength of tablets compressed at 400 MPa and under different combinations of powder temperature and tablet equilibration temperature. (**a**) Tablets were compressed at 25°C but equilibrated at different temperatures; (**b**) Powders were equilibrated at different temperatures before compression while tablets were equilibrated at 25°C before breaking; (**c**) tablet storage temperature is the same as powder equilibration temperature.

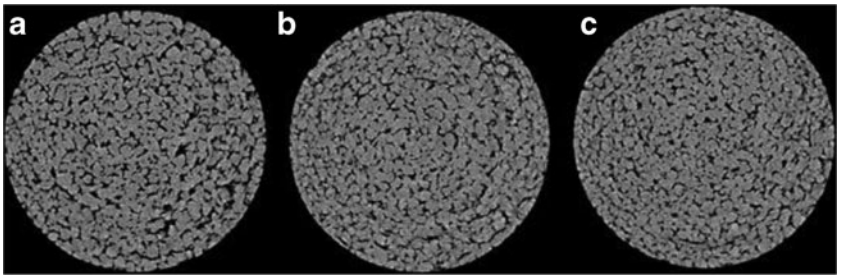


**Fig. 4** Micro-CT images of Soluplus tablets compressed at 100 MPa and different temperatures, (**a**) −20°C (15.7 ± 0.6 calculated porosity), (**b**) 4°C (12.4 ± 0.4 calculated porosity), (**c**) 25°C (11.6 ± 0.7 calculated porosity). Density of tablet appears higher at a higher temperature.

strength data discussed above, is supported by the different tablet structures (porosity) revealed by micro-CT (Fig. 4). Under the same compression condition, a lower temperature corresponds to a more porous tablet, which necessarily leads to smaller BA, due to lower degree of particle deformation. At 100 MPa compaction pressure, percentage tablet porosity calculated from the micro-CT images is 15.7 ± 0.6, 12.4 ± 0.4, and 11.6 ± 0.7 for temperatures of −20, 4, and 25°C, respectively. We expect that the trend of lower tablet porosity at higher temperature obtained here using the large as-receive Soluplus can be extrapolated to the fine processed Soluplus in the tableting studies. In fact, this is in excellent agreement with the trend of increasing tablet density with increasing temperature (Fig. 2c). The BA-BS interplay is shown by line *c* in Fig. 3, where powder compression and tablet breaking are carried out at the same temperature. As discussed earlier, lower temperature can lead to both smaller BA and higher BS, which has a negative and positive effect on tensile strength, respectively. The net effect on tensile strength depends on which factor dominates the interplay. Tablet tensile strengths at 25 and −20°C are comparable. Had only these two temperatures been studied, one would have observed no significant effect on tableting performance by temperature because of the cancellation of two opposing effects. However, the effect of temperature is clearly shown when the third temperature, 4°C, is also included.

## CONCLUSIONS

The concept of BA-BS interplay, although useful for explaining complex tableting behaviors of powders, has not been experimentally demonstrated. Through systematic control of temperature during powder compression and tablet breaking of an amorphous polymer, we have unambiguously demonstrated the contributions of BA and BS to tablet tensile strength as well as the role of BA-BS interplay on tabletability. An identification of the origin of poor powder tabletability, either BA, BS, or both, can facilitate the effective formulation design to address tabletability problem of a powder.

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