The Ubiquity of the Tabletability Flip Phenomenon

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Abstract

The plasticity of materials plays a critical role in adequate powder tabletability, which is required in developing a successful tablet product. Generally, a more plastic material can develop larger bonding areas when other factors are the same, leading to higher tabletability than less plastic materials. However, it was observed that, for a solid form of a compound with poorer tabletability, a mixture with microcrystalline cellulose (MCC) can actually exhibit better tabletability, a phenomenon termed tabletability flip. Hence, there is a chance that a solid form with poor tabletability could have been erroneously eliminated based on the expected tabletability challenges during tablet manufacturing. This study was conducted to investigate the generality of this phenomenon using two polymorph pairs, a salt and free acid pair, a crystalline and amorphous dispersion pair, and a pair of chemically distinct crystals. Results show that tabletability flip occurred in all six systems tested, including five pairs of binary mixtures with MCC and one pair in a realistic generic tablet formulation, suggesting the broad occurrence of the tabletability flip phenomenon, where both compaction pressure and the difference in plasticity between the pair of materials play important roles.

Key words: tabletability flip, bonding area, plasticity, generality, mixture

1. Introduction

Tablet products need to possess sufficient mechanical strength to endure stresses during transportation and handling. Therefore, the tabletability of active pharmaceutical ingredients (APIs) becomes a crucial factor to consider when developing a tablet product (Sun et al., 2009). Generally, more plastic APIs exhibit better tabletability because they can undergo more permanent deformation during compaction, resulting in larger bonding areas between particles (Pratim et al., 2012; Sun, 2011; Wang et al., 2017b). However, a recent study has revealed a "tabletability flip" phenomenon, wherein less plastic materials, despite having poorer tabletability, can exhibit improved tabletability when combined with the same excipient (Paul et al., 2020).

It has been commonly assumed that solid forms with better tabletability also demonstrate improved tabletability when formulated with excipients. However, tabletability flipping can lead to the incorrect exclusion of solid forms during the preformulation stage, based on the anticipated tabletability challenges. It is particularly significant to avoid this error, as the thermodynamically more stable polymorph at room temperature often exhibits inferior tabletability (Burger et al., 2000; Joiris et al., 1998; Khomane et al., 2012, 2013; Singaraju et al., 2020; Sun and Grant, 2001a; Yoshinari, 2003; Young et al., 2019). To date, the tabletability flip phenomenon has been exclusively observed in a limited number of cases involving binary mixtures containing microcrystalline cellulose (MCC) (Paul et al., 2020). However, it remains uncertain whether this phenomenon can occur broadly, particularly in mixtures containing more than two components. Further exploration is necessary to determine the extent and general applicability of the tabletability flip phenomenon across various formulation scenarios.

It is also important to note that the previous study did not control for particle size and tableting speed, both of which are known to have a significant impact on powder tabletability (Persson et al., 2022; Sun and Himmelspach, 2006; Sun and Grant, 2001b; Tye et al., 2005). The lack of control over these variables introduces uncertainty regarding the generality of the tabletability flip phenomenon. These factors should be considered in further investigations to gain a more comprehensive understanding of the applicability of this phenomenon in the development of pharmaceutical tablet formulation.

To this end, we conducted a study involving six different systems, consisting of five pairs of binary mixtures with MCC and one pair in a generic tablet formulation matrix. Here, we carefully controlled particle size and tableting speed. Our investigation yielded results indicating that the tabletability flip phenomenon occurred in all of the systems examined. Thus, the tabletability flip phenomenon is not limited to specific cases but instead has broad applicability in powder compaction.

2. Materials and Methods

2.1 Materials

Anhydrous theophylline form II (THEO-II, CHEM-IMPEX, Wooddale, IL, USA), *p*-Aminobenzoic acid α form (ABAα, Thermo Scientific Chemicals, Waltham, MA, USA), Potassium acesulfame (Acs-K, Hunan Mingrui Pharmaceutical Co., Ltd., Liuyang, China), Acetaminophen (APAP, Novacyl Pharmaceutical Co., Wuxi, China), Copovidone (PVP VA 64, Sigma-Aldrich; St. Louis, MO, USA), Ibuprofen (IBU, BASF; Ludwigshafen, Germany) and L-alanine (ALA; CHEM-IMPEX, Wood dale, IL, USA), Microcrystalline cellulose (MCC; Avicel PH102, FMC Biopolymers; Newark, DE), Spray-dried lactose monohydrate (LM, Foremost; Baraboo, WI, USA), Crospovidone (Kollidon CL; BASF; Ludwigshafen, Germany), Magnesium stearate (MgSt; Covidien; Dublin, Ireland), and Methanol (Sigma-Aldrich; St. Louis, MO, USA) were purchased from respective suppliers and were used as received unless specified.

All these powders and different solid forms generated from them were sieved and only the 44 - 53 μm sieve cuts were used.

2.2 Methods

2.2.1 Preparation of Samples

Anhydrous theophylline form IV (THEO-IV) was prepared by suspending excess THEO-II in methanol under stirring at room temperature for a week, following a procedure described before (Bobrovs et al., 2015). The resulting powder was filtered and dried overnight at 40 ℃. *p*-Aminobenzoic acid β form (ABAβ) was obtained by suspending excess ABAα in distilled water at 4 ℃ under stirring for two weeks, following a procedure described before (Cruz-Cabeza et al., 2019). The resulting powder was filtered and dried overnight at 40 ℃.

Acesulfame free acid (Acs-H) was prepared by the following steps (Paul et al., 2019; Velaga et al., 2010): 1) a solution of Acs-K in distilled water was acidified to pH = 2 with concentrated hydrochloric acid; 2) to the acidified solution, ten volumes of ethyl acetate was added and the mixture was vigorously shaken manually; 3) the resulting ethyl acetate layer, which contained Acs-H, was isolated with a separatory funnel and dried using a rotary evaporator at 40 °C under 85 kPa vacuum. The moist mass was further air dried for a week on a laboratory bench.

A 15% (w/w) amorphous solid dispersion of acetaminophen in Copovidone was prepared using a film evaporation method (Patel et al., 2017). Accurately weighed acetaminophen (15 g) and copovidone (85 g) were dissolved in 1 L methanol. The resulting solution was spread onto a tray, which was formed with alumina foil, and left at room temperature for 30 min to form a viscous film through the evaporation of methanol. The film was subsequently dried in a 70 °C oven for 2 weeks and then pulverized with a food blender after being cooled to room temperature. The resulting powder was further manually ground to the desired particle size using a mortar and pestle.

2.2.2 X-Ray Diffractometry

Powder X-ray diffractometry (XRD) was collected on a powder X-ray diffractometer (PANalytical X'pert pro, Westborough, MA, USA), using Cu Kα radiation (1.54056 Å). Samples were scanned with a step size of 0.02° and 1 s dwell time from 5° to 35° 2θ. The tube voltage and amperage were 45 kV and 40 mA, respectively.

2.2.3 Blend Preparation

Mixing was done using a shaker mixer (Turbula T2F, Glen Mills Inc., Clifton, NJ, USA) at 49 rpm for all powders. Pure model compounds mentioned above were mixed with 1% MgSt for 1.5 min. To prepare binary mixtures, 20% of a model compound was mixed with 80% MCC for 15 min. Then the mixture was further mixed with 1% (w/w) MgSt for 1.5 min. In order to study the tabletability flip phenomenon in more complex systems, a placebo formulation was prepared by first mixing 20% model compound, 49.67% MCC, 24.83% LM, and 5% Crospovidone for 15 min, followed by mixing with 0.5% MgSt for 1.5 min.

2.2.4 Tabletability

A compaction simulator (Styl'One, Medelpharm, Beynost, France) was used to prepare tablets for profiling powder tabletability. Round (8 mm diameter) flat-faced punches were used for all compaction experiments. For each powder, a series of compacts with 195 mg – 205 mg weight were obtained in the pressure range of 20 - 350 MPa with a dwell time of 63 ms, simulating a Korsch XL100 press.

All tablets were allowed to relax for at least 24 h before measuring their diameters, *D*, and thicknesses, *T*, using a digital caliper. Diametrical breaking force was determined using a texture analyzer (TA-XT2i, Texture Technologies Corp., Scarsdale, NY, USA) at a speed of 0.001 mm/s with a 5 g trigger force. Tablet tensile strength was calculated from the maximum breaking force, *F*, and tablet dimensions using equation (1) (Fell and Newton, 1970).

$$\sigma = \frac{2F}{\pi DT} \quad (1)$$

2.2.5 True Density and Tablet Porosity

The true density of the materials under investigation was measured using a helium pycnometer (Quantachrome Instruments, Ultrapycnometer 1000e, Byonton Beach, FL, USA). The sample cell was filled with 1–2 g of a precisely weighed sample, which occupied approximately three-quarters of the cell volume. The experiment was concluded when the variation among five successive measurements was less than 0.005%. The mean of the last five measurements was then recorded as the sample's true density (ρ_t) Table S1 summarizes ρ_t values of various powders used in this work.

The porosity of the tablets was calculated using equation (2),

$$\varepsilon = 1 - \frac{\rho}{\rho_t} \quad (2)$$

where ε is tablet porosity and ρ is tablet envelope density calculated from the weight and tablet diameter and thickness measured using a digital caliper.

2.2.6 In-die Heckel Analysis

In-die tablet porosity ε was calculated from die diameter and tablet thickness (accuracy of 1 µm), tablet weight (determined after ejection), and ρ_t, according to equation (2). Mean yield

pressure, P_y, was obtained from a linear regression of the linear portion of the Heckel plot using equation (3) (Heckel, 1961a, 1961b).

$$-\ln(\varepsilon) = \frac{1}{P_y}P + A \qquad (3)$$

Where P is compaction pressure. P_y from an in-die Heckel analysis, $P_{y,i}$ (the subscribe "i" signifies that the P_y value was determined from "in-die" data) was recently demonstrated to be a reliable method for characterizing material plasticity (Vreeman and Sun, 2021).

3. Results and Discussions

We first investigated two polymorphic systems since polymorphism is commonplace and selecting the most suitable polymorph is an important decision during the development of any APIs (Hilfiker and Raumer, 2019; Li et al., 2020; Lu and Rohani, 2009).

3.1 Theophylline polymorphs

PXRD patterns of both THEO-II and THEO-IV powders matched well with PXRD patterns calculated from corresponding single crystal structures (Ebisuzaki et al., 1997; Khamar et al., 2011) (Figure 1a), confirming their phase identity. THEO-II showed excellent tabletability, reaching a tensile strength of ~4 MPa at 350 MPa compaction pressure, while THEO-IV could not even be made into intact tablets over the pressure range studied (Figure 1b). The substantial difference in tabletability between THEO-II and THEO-IV can be explained by the higher plasticity of THEO-II, based on their different $P_{y,i}$ values (THEO-II = 81.1 $\pm$ 1.5 MPa vs. THEO-IV = 95.4 $\pm$ 3.5 MPa, n = 3). Consequently, THEO-II can form larger bonding areas among particles in a tablet, resulting in better tabletability. In contrast, the less plastic THEO-IV is unable to develop adequate bonding area under compression, resulting in the inability to form intact tablets. When mixed with MCC ($P_{y,i}$ = 54.2 $\pm$ 1.5 MPa) at a 20% drug loading level, both mixtures exhibited good tabletability (Figure 1c). The tensile strength of THEO-IV-MCC is actually higher than that of THEO-II-MCC above 200 MPa, i.e., tabletability flip occurred (Figure 1c).

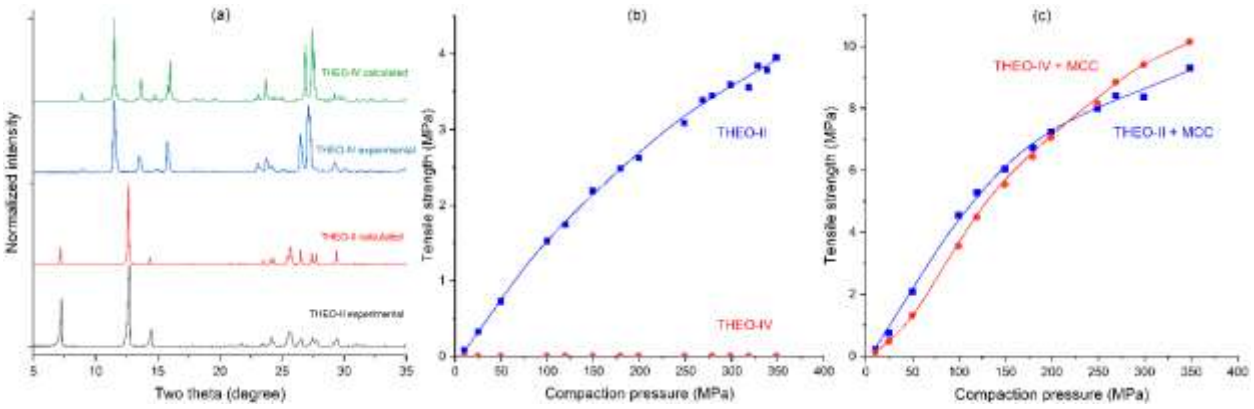

Figure 1. a) Experimental and calculated powder XRD patterns of two THEO polymorphs; b) tabletability plots of the two THEO polymorphs; c) tabletability plots of mixtures of 20% (w/w) THEO polymorph with 80% MCC.

3.2 *P*-aminobenzoic acid polymorphs

The polymorphic forms of two *p*-aminobenzoic acid powders were verified by their experimental PXRD patterns matching calculated ones from crystal structures (Alleaume et al., 1966; Lai and Marsh, 1967) (Figure 2a). The variations in peak intensity between the calculated and experimental PXRD patterns of ABAα are attributed to preferred orientation of crystals. ABAα exhibited a good tabletability, with tensile strength reaching ~1 MPa at 300 MPa compaction pressure, while ABAβ could not form intact tablets across the range of pressure studied (Figure 2b). This stark difference in tabletability is attributed to the significantly better plasticity of ABAα, as indicated by its lower $P_{y,i}$ value (51.5 $\pm$ 1.8 MPa, n = 3) than that of ABAβ (109.0 $\pm$ 6.4 MPa, n = 3). The more plastic ABAα crystals exhibited significant plastic deformation during compression, leading to the formation of a larger bonding area between particles. As a result, the tabletability of ABAα improved. However, when mixed with 80% MCC, the tabletability of ABAα is actually lower than that of ABAβ (Figure 2c), i.e., tabletability flip occurred.

While polymorphs of the same compound can display variations in bonding area, their bonding strengths are not anticipated to differ significantly due to their identical chemical composition. To further explore the broad applicability of the tabletability flip phenomenon, we subsequently examined systems with different chemical compositions.

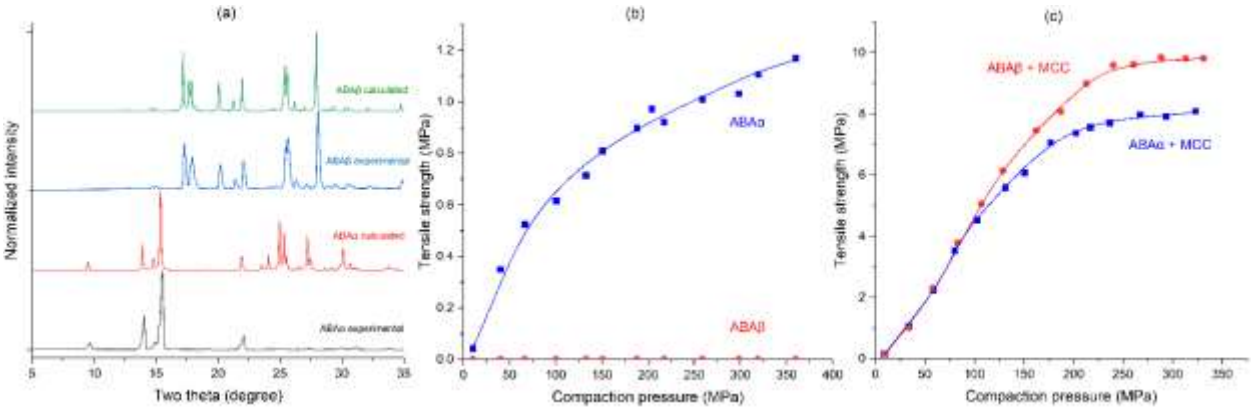

Figure 2. a) Experimental and calculated powder XRD patterns of two ABA polymorphs; b) tabletability plots of two ABA polymorphs; c) tabletability plots of mixtures of 20% (w/w) ABA polymorph with 80% MCC.

3.3 Potassium acesulfame and acesulfame free acid

Salt formation is an effective crystal engineering approach to improve the properties of drugs, such as solubility, dissolution, stability, and mechanical properties (Berry and Steed, 2017; Gwak et al., 2005; Han and Choi, 2007; Hu et al., 2020; Paul et al., 2019; Rahman et al., 2012; Serajuddin, 2007; Sigfridsson et al., 2018; Šupuk et al., 2013; Wang et al., 2017a). Therefore, the selection of salts is a crucial aspect of the development process for ionizable APIs, whether they are acids or bases. To assess the applicability of the tabletability flip phenomenon in salts, we investigated potassium acesulfame (Acs-K) and acesulfame free acid (Acs-H).

Both Acs-K and Acs-H showed experimental PXRD patterns that are in good agreement with PXRD patterns calculated from corresponding crystal structures (Paulus, 1975; Velaga et al., 2010) (Figure 3a), confirming their phase identity. Compared to Acs-K, Acs-H is more plastic as shown by its lower $P_{y,i}$ value (40.0 $\pm$ 1.5 MPa, n = 3) than Acs-K (92.6 $\pm$ 2.3 MPa, n = 3). As expected, Acs-H demonstrated notably superior tabletability than Acs-K. While tablets of Acs-H with tensile strength of ~2.5 MPa could be prepared at 200 MPa pressure, intact tablets of Acs-K could not be obtained at pressures below 140 MPa. Weak tablets (< 0.3 MPa tensile strength) could be formed when compaction pressures were > 200 MPa (Figure 3b), suggesting sufficient amount of bonding area between adjacent Acs-K particles could be formed under these pressures

to form intact tablets, but the bonding area is not large enough to result in high tablet tensile strength.

When two solid forms were mixed with 80% (w/w) MCC, their tabletability profiles are nearly identical up to ~ 100 MPa compaction pressure, but the profile of Acs-K is higher than of Acs-H above 100 MPa (Figure 3c), i.e., tabletability flip occurred. The tabletability flip phenomenon became more pronounced with increasing compaction pressure (Figure 3c).

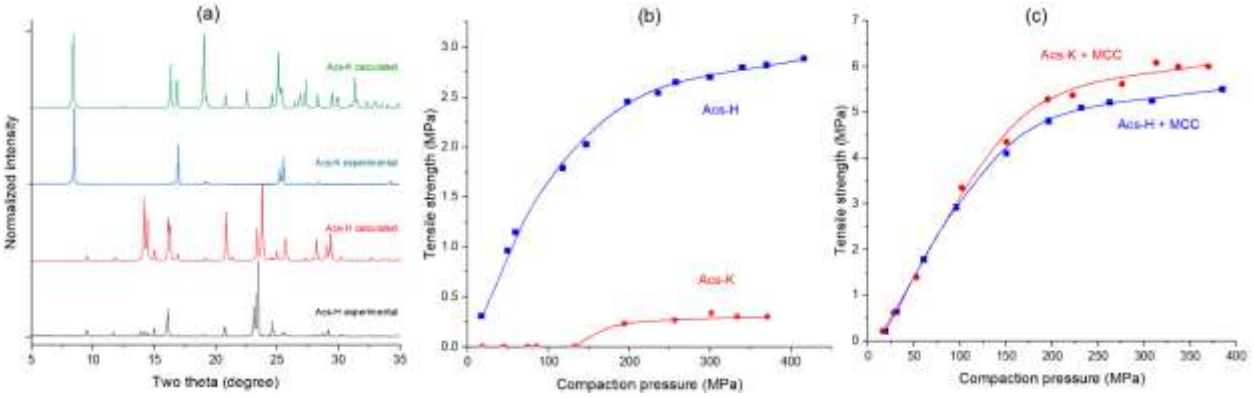

Figure 3. a) Experimental and calculated powder XRD patterns of Acs-K and Acs-H; b) tabletability plots of Acs-K and Acs-H; c) tabletability plots of mixtures of 20% (w/w) Acs-K/Acs-H with 80% MCC.

3.4 Acetaminophen crystals and amorphous solid dispersion

Amorphous solid dispersion (ASD) is being increasingly used in drug development to enhance the dissolution of APIs (Brough and Williams, 2013; Gurunath et al., 2013; Schittny et al., 2020; Van den Mooter, 2012). Since ASDs usually contain a substantial amount of polymer, their chemical compositions are more different from the parent API, relative to that between an API and its salts. Therefore, we investigated both crystalline acetaminophen (APAP) and its ASD in Copovidone to further explore the presence of the tabletability flip phenomenon.

The APAP powder was form II since its experimental PXRD pattern well-matched the pattern calculated from the form II single crystal structure (Stone et al., 2009). Here again, differences in peak intensity are due to the preferred orientation of crystals. The ASD exhibited a broad halo without sharp peaks (Figure 4a), suggesting an absence of a detectable amount of

crystalline APAP. Similar to a previous report (Shi and Sun, 2011), APAP form II was found to exhibit very poor tabletability, where intact tablets could not be obtained over the entire pressure range studied. In contrast, ASD showed a significantly improved tabletability reaching ~0.7 MPa tensile strength at 300 MPa compaction pressure (Figure 4b). The different tabletability profiles can be, once again, attributed to the higher plasticity of the ASD based on its lower $P_{y,i}$ value (80.8 $\pm$ 2.4 MPa, n = 3) than that of ASD (89.5 $\pm$ 2.7 MPa, n = 3).

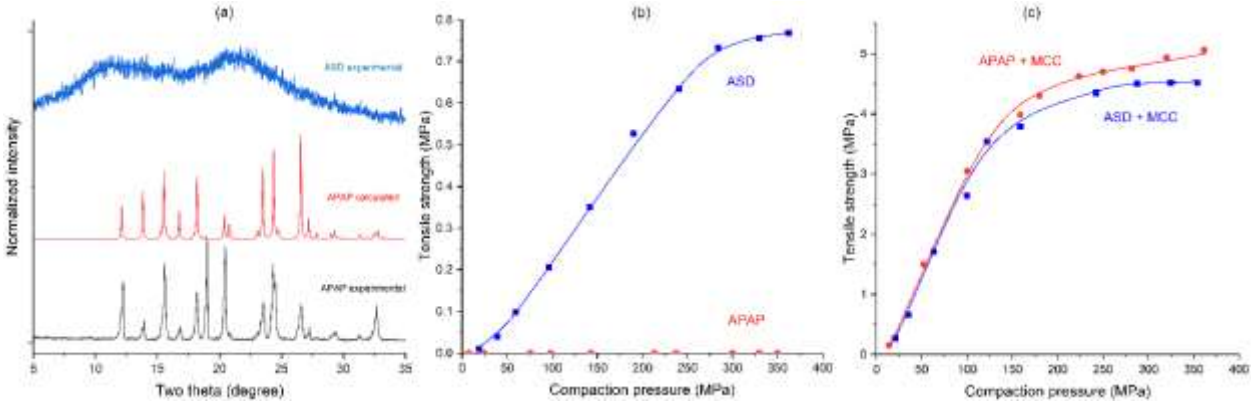

Figure 4. a) Experimental powder XRD patterns of APAP and ASD, and calculated powder XRD pattern of APAP; b) tabletability plots of APAP and ASD; c) tabletability plots of mixtures of 20% (w/w) APAP/ASD with 80% MCC.

When the two solid forms were mixed with 80% (w/w) MCC, the tabletability profiles of the two mixtures are comparable up to 150 MPa compaction pressure, while the APAP mixture is slightly better at higher pressures. Thus, tabletability flip was again observed and the difference in tablet tensile strength is greater at higher compaction pressures (Figure 4c).

3.5 Ibuprofen and L-alanine

Having confirmed the presence of tabletability flip in chemically related systems with increasing difference in composition, we proceeded to further test the generality of this phenomenon by utilizing completely different model compounds, i.e., ibuprofen (IBU) and L-alanine (ALA). In this pair, IBU is more plastic based on its lower $P_{y,i}$ value (22.1 $\pm$ 2.5 MPa, n = 3) than that of ALA (231.0 $\pm$ 2.8 MPa, n = 3). Consistent with the trend observed in earlier systems, the tabletability of IBU is significantly better than ALA. While intact and strong tablets

could be prepared for IBU, reaching ~1.6 MPa tensile strength at 250 MPa, only weak tablets of ALA could be obtained at pressures below 250 MPa. No intact ALA tablet could be formed at higher pressures (Figure 5a). This phenomenon is known as "overcompression", where a higher pressure causes more extensive elastic recovery of tablet, which leads to rupture of interparticulate bonds and tablet lamination or capping.

When mixed with 80% MCC, the tablet tensile strength of ALA mixture is significantly higher than that of the IBU mixture throughout the entire pressure range examined (Figure 5b), i.e., pronounced tabletability flip occurred. As compaction pressure increased, the absolute difference in tensile strength of tablets between two mixtures also increased (Figure 5b).

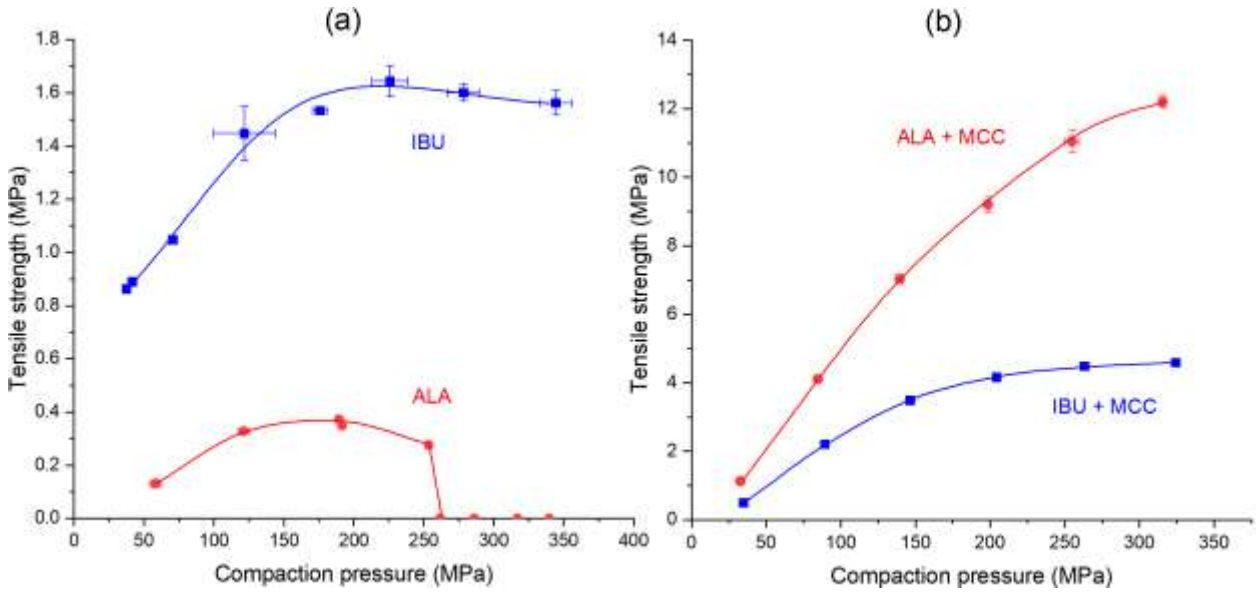

Figure 5. Tabletability plots of a) IBU and ALA; b) mixtures of 20% (w/w) IBU/ALA with 80% MCC.

An examination of the data for the five systems suggests that the difference in plasticity between two materials affects the extent of the tabletability flip (Table S2). For instance, IBU/ALA system had the greatest difference in $P_{y,i}$ values and also the most notable tabletability flip (Figure 5b). The THEO polymorphs and APAP/ASD systems had relatively smaller differences in $P_{y,i}$ values, and only minor tabletability flip was observed (Figure 1c, 4c). It should be pointed out that, despite having a large difference in $P_{y,i}$ values, the Acs-K/Acs-H system did not exhibit a

prominent tabletability flip phenomenon (Figure 3c). Thus, factors besides mechanical properties and compaction pressure may also affect tabletability flipping.

3.6 Generic tablet formulations

Having established the tabletability flip phenomenon in all five binary systems investigated, we sought to determine whether it occurs in complex systems involving more than two components. Such systems are more relevant to tablet product development.

We tested this using two model APIs, THEO-IV and IBU, in a generic formulation. The two APIs exhibited significantly different plasticity based on their $P_{y,i}$ values (THEO-IV = 95.4 ± 3.5 MPa vs. IBU = 22.1 ± 2.5 MPa, n = 3). The generic formulation consisting of a realistic drug loading of 20% API, 49.67% MCC as a binder, 24.83% LM as a filler, 5% Crospovidone as a disintegrant, and 0.5% MgSt as a lubricant.

When compressing the APIs, the more plastic IBU exhibited much better tabletability than THEO-IV owing to the formation of larger bonding areas in the IBU tablets (Figure 6a). However, a clear tabletability flip phenomenon was observed upon formulating with the placebo formulation matrix (Figure 6b). Furthermore, it was observed that higher compaction pressures led to greater difference in the tabletability profile, i.e., greater extent of flipping (Figure 6b). Thus, the tabletability flip phenomenon also occurs in complex mixtures relevant to real tablet formulations.

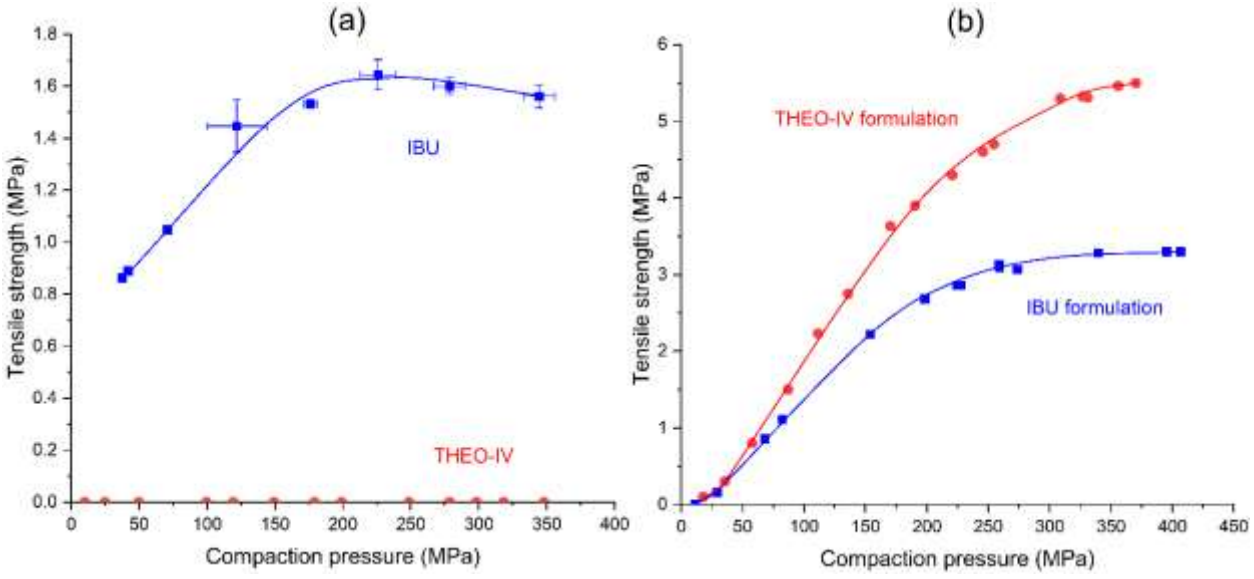

Figure 6. Tabletability profiles of a) IBU and THEO-IV; b) generic formulations containing 20% (w/w) IBU/THEO-IV.

The tabletability flip phenomenon only occurred to a relatively small extent in the cases of Acs-H/Acs-K (Figure 3) and APAP/ASD (Figure 4). However, it remains significant because they both show that the formulation of a poorly compressible API solid form can still exhibit very good tabletability. For the same reason, the tabletability of THEO-IV at < 200 MPa pressures should still be appreciated, even if it is slightly lower than that of THEO-II (Figure 2).

4. Conclusions

The tabletability flip phenomenon was observed in all six systems investigated, including five binary mixtures with MCC and one with a placebo formulation. The model compounds utilized in the binary mixtures encompass a range of increasingly diverse chemical compositions, including polymorphs, salts, and chemically unrelated compounds. Thus, the tabletability flip phenomenon broadly occurs. Given this finding, solid forms with poor tabletability should not be excluded from the list of candidates for tablet development in anticipation of potential problems with tablet manufacturing, as their formulations may actually exhibit better tabletability.

Our results showed that the tabletability flip phenomenon tends to occur at higher pressures. Additionally, tabletability flip phenomenon is likely to be more prominent when the two API powders have larger difference in plasticity. These observations suggest the existence of a complex mechanism underlying this phenomenon. Conducting a more systematic investigation to gain a mechanistic understanding of this phenomenon would greatly contribute to making informed choices regarding the selection of an optimal solid form for formulation development.

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