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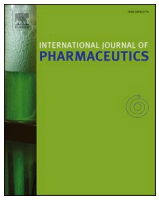

Impact of dry coating lactose as a brittle excipient on multi-component blend processability

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ABSTRACT

Previous work demonstrated the benefits of dry coating fine-grade microcrystalline cellulose (MCC) for enabling direct compression (DC), a favored tablet manufacturing method, due to enhanced flowability while retaining good compactability of placebo and binary blends of cohesive APIs. Here, fine brittle excipients, Pharmatose 450 (P450, 19 μm) and Pharmatose 350 (P350, 29 μm), having both poor flowability and compactability are dry coated with silica A200 or R972P to assess DC capability of multi-component cohesive API (coarse acetaminophen, 22 μm, and ibuprofen50, 47 μm) blends. Dry coated P450 and P350 not only attained excellent flowability and high bulk density but also heightened tensile strength hence processability, which contrasts with reported reduction for dry coated ductile MCC. Although hydrophobic R972P imparted better flowability, hydrophilic A200 better enhanced tensile strength, hence selected for dry coating P450 in multi-component blends that included fine Avicel PH-105. For coarse acetaminophen blends, substantial bulk density and flowability increase without any detrimental effect on tensile strength were observed; a lesser amount of dry coated P450 was better. Increased flowability, bulk density, and tensile strength, hence enhanced processability by reaching DC capability, were observed for 60 wt% ibuprofen50, using only 18 wt% of the dry coated P450, i.e. 0.18 wt% silica in the blend.

1. Introduction

Tablets have long been preferred as a solid dosage form for drug delivery due to their stability, cost-effectiveness, ease of administration, and excellent patient compliance (Awad et al., 2022; Sam and Fokkens, 1997; Sheth et al., 1980). Among various tablet manufacturing methods, direct blending and direct compression (DB-DC) route is preferred owing to its fewer processing steps, easier validation, and improved drug stability (Bolhuis and Anthony Armstrong, 2006). However, adoption of DB-DC option requires the APIs as well as blend to have good bulk density, flowability, and tabletability (Han et al., 2011; Huang et al., 2015a; Huang et al., 2015b; Huang et al., 2017; Jallo et al., 2012; Jivraj et al., 2000; Shi et al., 2011). Unfortunately, not all active pharmaceutical ingredients (APIs) exhibit suitable tableting characteristics on their own for direct compression (G Mirani et al., 2011; Sastry et al., 2000), necessitating the use of excipients to facilitate DB-DC tableting. That has led to added emphasis on the use of higher functionality excipients that enable enhanced formulations (Garg et al., 2013; Gohel and Jogani, 2005; Rojas et al., 2012; Sastry et al., 2000), motivating the development of novel excipients (Gupta et al., 2006).

Co-processed excipients have emerged as a solution to improve tabletability and flowability for direct compression (Garg et al., 2013; Garg et al., 2015; Gohel and Jogani, 2005; Rojas et al., 2012). These powders are composed of two or more parent particulate materials physically assembled at the sub-particle level to modify their characteristics (Gohel and Jogani, 2005). However, existing manufacturing processes for co-processed excipients may present concerns such as the environmental burden due to the need for using solvents and liquids, additional milling or drying steps, low yield rates, or high silica concentration (Carlin, 2008; Maury et al., 2005; Ståhl et al., 2002). Excessive silica content, particularly exceeding 2 wt% in the blend, is not FDA compliant (FDA, 2015) and can have detrimental effects on tablet properties (Chattoraj et al., 2011; Chen et al., 2018b; FDA, 2015; Van Veen et al., 2005; Zhou et al., 2012). Another likely limitation of co-processed excipient mixtures is their fixed ratio of constituents, which may not be optimal for specific APIs and desired tablet doses for the most effective formulation development (Bolhuis and Chowhan, 1996; Gohel and Jogani, 2005).

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Dry coating, which has proven to be an efficient and robust method for improving the required properties of excipients or APIs, such as bulk density, flowability, and tabletability (Chattoraj et al., 2011; Chen et al., 2018a; Chen et al., 2018b; Chen et al., 2020; Chen et al., 2019; Han et al., 2011), may offer an alternative to above-described co-processed excipients. Dry coating involves using a suitable dry high-intensity mixing process to apply mechanical force to coat small guest particles onto the surface of larger host particles (Chen et al., 2008). Numerous studies have reported dry coating of ductile excipients, for example, microcrystalline cellulose (MCC), and demonstrated the success of dry-coated MCC formulations for placebo (Chattoraj et al., 2011; Chen et al., 2018a; Chen et al., 2018b) as well as binary blends (Chen et al., 2018b). Previous reports also demonstrated significant improvements in the flowability of individual MCC powders and further demonstrated improved flowability, bulk density, and tabletability of placebo and binary blends (Chen et al., 2018a; Chen et al., 2018b; Chen et al., 2020; Chen et al., 2019). However, the topic of dry coating effectiveness in multi-component blends or on the blends containing dry coated brittle excipients such as lactose has not been reported.

This research aims to fill this gap by examining the dry coating effect on lactose, one of the most widely used brittle pharmaceutical excipients due to its excellent filler properties and its ability to expedite liquid penetration followed by dissolution that promotes tablet disintegration and dissolution (Gomes et al., 2021; Hebbink and Dickhoff, 2019; Maclean et al., 2021). There are examples of previous work concerning dry coating of lactose by itself, where the flowability and bulk density of individual lactose was found to be improved due to dry coating (Kunnath et al., 2021; Kunnath et al., 2023). However, unlike previous work involving dry coating of MCC as an excipient (Chattoraj et al., 2011; Chen et al., 2018b; Chen et al., 2020), there are no reports concerning the effect of dry coating for lactose as an excipient and the impact of dry coating on its tabletability. Unlike ductile MCC, lactose is a brittle material (Roberts, 2011). It would be clearly important to understand if lactose being brittle, behaves differently from MCC where dry coating resulted in reduced tensile strength (TS), attributed to the lower surface energy of the hydrophilic silica coating as compared to the surface energy of MCC (Chen et al., 2018a; Chen et al., 2018b; Chen et al., 2019; Etzler et al., 2011). In fact, the reported work with MCC avoided using even lower surface energy hydrophobic silica R972P due to the tabletability loss concerns. An interesting recent paper has reported that while dry coating of MCC resulted in a loss of the placebo tablet TS, the blends including dry coated MCC did not have such adverse effects (Chen et al., 2019). Such investigation for the effect of dry coated lactose in blends has not been explored and hence it is considered in the current paper. Further, generally speaking, MCC enhances tabletability through ductile deformation and high bonding strength, while brittle lactose achieves it through fragmentation and a high bonding area (Sun, 2011). The combination of plastic deformation of MCC and lactose fragmentation contributes to their synergistic compatibility (Al-Ibraheemi et al., 2013) hence study of their combination where lactose is dry coated would also be a worthwhile consideration in the current paper, which has motivated examination of multi-component blends.

Consequently, this study investigates the effect of dry coating on lactose particles with various silica types and their amounts on lactose by itself in its multi-component blends containing APIs. As a part of such investigation, the impact of lactose particle size and relative loading in blend formulations on bulk density, flowability, and tabletability are explored. To be consistent with the previous papers where dry coated MCC exhibited good improvement in flowability and bulk density, while keeping low TS loss (Chen et al., 2018a; Chen et al., 2018b), this paper considers lactose of the same size as MCC in previous papers, i.e., 20 μm and 30 μm. Selecting two sizes for lactose allows examination of the influence of silica amount, type, and lactose particle size, on individual lactose flowability and bulk density, as well as tabletability of their placebos. Pharmatose 450, which is the finer of the two lactose types, is selected here for its higher TS although it poses challenges due to its finer size with respect to flowability and bulk density. Coarse Acetaminophen (CAPAP) and Ibuprofen 50 (IBU) will serve as the model APIs in the blend formulation; the rationale behind their selection is presented in the results section. By addressing such objectives, this research aims to contribute valuable insights into the application of dry-coated lactose as a novel co-processed excipient along with uncoated MCC in multi-component tablet formulations.

2. Materials and methods

2.1. Materials

Pharmatose 450 (P450) and Pharmatose 350 (P350), both as received, were generously provided by DFE Pharma Corporation, USA. In the process of dry coating, hydrophilic Aerosil A200 silica (A200) and hydrophobic Aerosil R972P (R972P) silica were utilized, also donated by Evonik Corporation, USA. Magnesium Stearate (MgSt), a lubricant, was obtained from Mallinckrodt Inc., USA. The model drugs selected for this study were Coarse Acetaminophen (CAPAP) and Ibuprofen 50 (IBU), acquired from Changshu Huagang Pharmaceutical CO., Ltd (China) and BASF, USA, respectively. Avicel PH-105 (Av105), a binder, was graciously provided by FMC Biopolymer, USA. Additionally, the disintegrant used in the research, Kollidon CL-F (CLF), was donated by BASF, USA.

2.2. Preparation of dry coated materials

In a 300 ml plastic jar, a mixture of lactose and silica with varying mass ratios was prepared, totaling 50 g of material. Details of formulation for dry coated and uncoated Pharmatose are shown in Table 1. The mixing process was carried out using a high-intensity vibrational mixer called LabRAM, manufactured by Resodyn, USA. LabRAM was selected due to its simplicity, efficiency in material usage, and appropriateness for dry coating experiments. Operating at an approximate frequency of 60 Hz and with a fixed intensity of 75G, LabRAM employs vertical vibration that leads to accelerations 75 times greater than gravitational force. The processing time was set to 5 mins. The LabRAM operating conditions were established based on previous studies involving microcrystalline cellulose (MCC) (Chen et al., 2018b). Through the generation of strong shear forces, LabRAM effectively breaks agglomerates, facilitating the uniform distribution of silica guest particles as small clusters onto the surfaces of the larger host particles (Huang et al., 2015b). Consequently, this process induces nanoscale surface roughness on the host particles and diminishes the cohesive forces between particles.

2.3. Preparation of blends

The blending process was carried out using a V-blender manufactured by Patterson-Kelley, USA. For the preparation of placebo blends, the 4-pint V-blender was filled, and blending was conducted at a speed of 25 rpm for a duration of 1 min. Each run involved 200g of material, adhering to the formulation outlined in Table 2. While the placebo blends consisted of more than two components, the predominant constituent was lactose. Hence, for ease of reference, these blends are referred to as individual lactose blends.

For the preparation of multi-component blends, the 4-pint V-blender was filled with the specified formulation outlined in Table 3, excluding the addition of MgSt. Blending was carried out at a speed of 25 rpm for a duration of 12 min. Each run consisted of 100g of material. Following the initial 12-minute blending period, the blends were supplemented with 1 wt% MgSt. Subsequently, the blender was operated at a speed of 25 rpm for an additional 1 min.

Table 1
Detail of formulation for dry coated and uncoated Pharmatose.

	Lactose	Lactose (%, w/w)	Silica	Silica (%, w/w)	SAC (%)	D50 (μm)	D32 (μm)
P450	Pharmatose 450	100	–	–	–	18.65	6.81
P450A1	Pharmatose 450	99	A200	1	100	19.05	6.92
P450A38	Pharmatose 450	99.62	A200	0.38	38	17.93	6.36
P450R1	Pharmatose 450	99	R972P	1	60	19.09	6.48
P350	Pharmatose 350	99	–	–	–	28.69	10.23
P350A1	Pharmatose 350	99	A200	1	157	28.69	8.96
P350A38	Pharmatose 350	99.45	A200	0.25	38	28.81	9.11
P350R1	Pharmatose 350	99.18	R972P	1	94	29.22	9.24

Table 2
Detail of formulation for single component blends. Uncoated Pharmatose is mixed with a 1 wt% addition of MgSt 1 min V-blender mixing at 25 RPM. Following the dry coating process, Dry coated Pharmatose is blended with 1 wt% MgSt.

	Lactose	Lactose (%, w/w)	MgSt (%, w/w)
P450M	P450	99	1
P450A1M	P450A1	99	1
P450A38M	P450A38	99	1
P450R1M	P450R1	99	1
P350M	P350	99	1
P350A1M	P350A1	99	1
P350A38M	P350A38	99	1
P350R1M	P350R1	99	1

Table 3
Detail of formulation for multi-component blends.

	API (w/w)	Lactose (w/w)	Av105 (w/w)	CLF (w/w)	MgSt (w/w)
cAPAP + 72UC	10 % cAPAP	72 % P450	12 %	5 %	1 %
cAPAP + 72DC	10 % cAPAP	72 % P450A1	12 %	5 %	1 %
cAPAP + 42UC (or 42 %450 + 42 % Av105)	10 % cAPAP	42 % P450	42 %	5 %	1 %
cAPAP + 42DC (or 42 %450A1 + 42 %Av105)	10 % cAPAP	42 % P450A1	42 %	5 %	1 %
IBU + 18UC (or 18 %450 + 18 % Av105)	60 % IBU	18 % P450	18 %	3 %	1 %
IBU + 18DC (or 18 %450A1 + 18 %Av105)	60 % IBU	18 % P450A1	18 %	3 %	1 %

2.4. Particle sizing via laser diffraction

The particle sizes of powders, both d50 and d3, 2, were determined using a Sympatec Helos/Rodos laser diffraction particle size analyzer obtained from Sympatec Inc., NJ. To ensure reliable and consistent results, a dispersion pressure of 1.0 bar was chosen based on previous studies (Chen et al., 2018b). This pressure setting was selected to accurately measure the primary particle sizes without inducing undesired attrition or measuring agglomerate sizes. Each measurement was conducted in triplicate to ensure precision and maintain consistency across the data. The calculated d3, 2 value obtained from this analyzer was utilized to determine the surface area coverage (the calculation will be discussed in the following section).

2.5. Surface area coverage calculation

Surface area coverage (SAC) represents the theoretical percentage of the host particle's surface area that is covered by guest particles (Huang et al., 2017). The SAC is influenced by various factors, including the quantity and type of silica used, as well as the surface area of the host particle. The calculation of SAC can be performed using the following equation, where D represents the diameter of the host particle, d denotes the particle size of the guest particle, ρ_d and ρ_D correspond to the material densities of the guest and host particles, respectively, and G wt% indicates the weight percentage of the guest particle relative to the host particle.

$$SAC = Gwt\% * \frac{D\rho_D}{d\rho_d} * 100\% \quad (1)$$

2.6. Powder characterization by FT4 powder rheometer

The bulk density and flow function coefficient (FFC) of the multi-component blends were determined using the Freeman Technology FT4 powder tester from Freeman Technologies Ltd., Worcestershire, UK. To measure the FFC, a standard FT4 program called "shear_3kPa" was utilized, which applied a consolidation pressure of 3 kPa during shear tests. The FFC represents the ratio of consolidation stress to the unconfined yield stress, providing insights into the bulk flowability of the blends. The interpretation of FFC values is as follows: FFC < 1 indicates non-flowing behavior, $1 <$ FFC < 2 suggests very cohesive, $2 <$ FFC < 4 implies cohesive, $4 <$ FFC < 10 signifies easy flowability, and FFC > 10 indicates free-flowing characteristics (Kunnath et al., 2018). The measurement of bulk density was conducted using another standard FT4 program, specifically the "1C split 1 T" procedure. Further details and information regarding the measurement and data analysis of bulk density and FFC can be found in previous studies (Freeman, 2007; Huang et al., 2015b; Kunnath et al., 2018).

2.7. Tableting performance

Tablets were prepared using a Carver platen press (Carver, Inc., USA) with two different compaction forces: 1.5 and 2.0 metric tons (corresponding to 114 MPa and 152 MPa, respectively). A flat-faced round punch was utilized to compress 500 mg of the individual lactose blends and cAPAP multi-component blends within a stainless-steel die with an inner diameter of 0.5 in., resulting in the formation of tablets. Prior to and after each compression, alcohol wipes were employed to clean both the die and punch thoroughly. One day after tablet preparation, the breaking force of the tablets was measured using a Texture analyzer (Texture Technologies Corp., USA) through the diametrical compression test.

To produce tablets of multi-component blends containing IBU, a compaction simulator (Styl'One, MedelPharm, Beynost, France) was employed. The "DEFAULT CYCLE - 2 Compressions" cycle was utilized, with the pre-compression step deselected. Force sensors in the form of strain gauges were utilized to measure the forces exerted on the upper and lower punches. The upper compression force was adjusted to 5, 10, 15, and 20 kN, corresponding to compression pressures of 60 MPa, 121 MPa, 181 MPa, and 241 MPa, respectively. All compaction experiments

were conducted using round, flat-faced punches with a diameter of 11.28 mm. One day after tablet preparation, the diametrical breaking force of the tablets was measured using an Automated Tablet Tester EasyCheck (ERWEKA GmbH., Germany).

To calculate the TS for each formulation and compaction force, Eq. (2) was applied (Fell and Newton, 1970), where σ is TS, F is tablet breaking force, D_t is tablet diameter, and t is tablet thickness.

$$\sigma = \frac{2F}{\pi D_t t} \tag{2}$$

2.8. Scanning Electron microscopy

For qualitative analysis of particle morphology and coating efficiency of dry coated powders, a Field Emission Scanning Electron Microscope (SEM) model EM JSM-7900F from JEOL USA was employed. Samples were extracted from the prepared powders and sputter-coated using a carbon coating technique (Q150T 16017, Quorum Technologies Ltd, Laughton, East Sussex, England) to enhance conductivity during SEM imaging. This coating process ensures improved imaging quality and reliable analysis of the samples under examination.

2.9. Guest-host compatibility performance

The guest–host compatibility testing may be done based on the interactive mixture model [58,89], used for computing the spreading coefficient ($\lambda^{2/1}$) for the guest (particle 2) over the host surface (particle 1) and vice versa using the dispersive and polar surface energy values of the guest and host powders. The spreading coefficient is determined using Eq. (3) and assumes an even and discrete distribution of guests,

$$\lambda^{2/1} = 4[\left(\frac{\gamma_1^d \times \gamma_2^d}{\gamma_1^d + \gamma_2^d}\right) + \left(\frac{\gamma_1^P \times \gamma_2^P}{\gamma_1^P + \gamma_2^P}\right) - (\frac{\gamma_2}{2})] \tag{3}$$

wherein γ_1^d and γ_2^d represent the dispersive surface energy of particle 1 and particle 2, respectively. The polar surface energy of particle 1 and

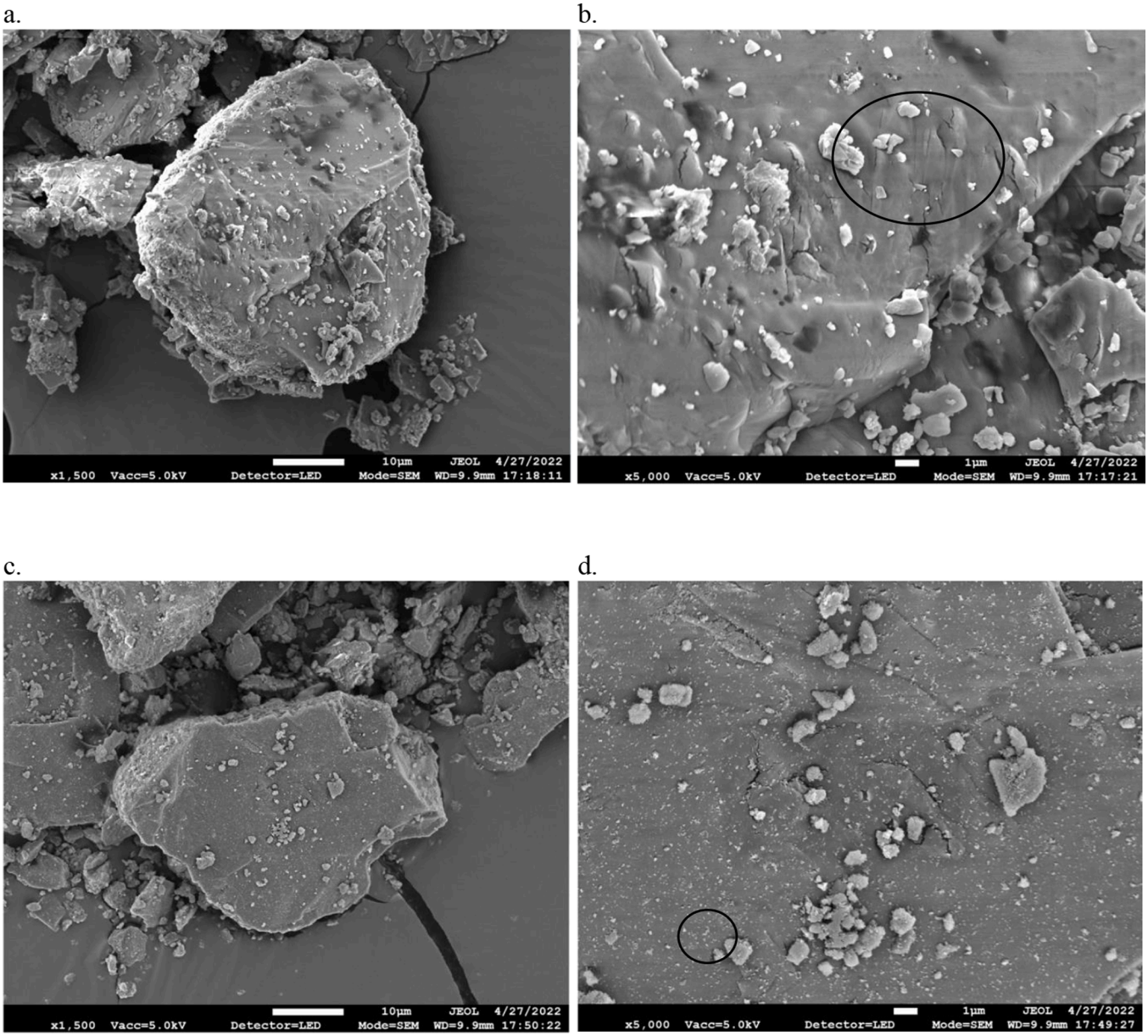

Fig. 1. SEM images of as received Pharmatose 450 at two different magnifications (a and b) and dry coated Pharmatose 450 with 1 wt% Aerosil 200 (c and d), 1 wt% Aerosil R972P (e and f), and 0.38 wt% Aerosil 200 (g and h) under different magnifications. Images of 0.38 wt% Aerosil 200 are provided at slightly higher magnifications for better visualization of sparser silica coating.

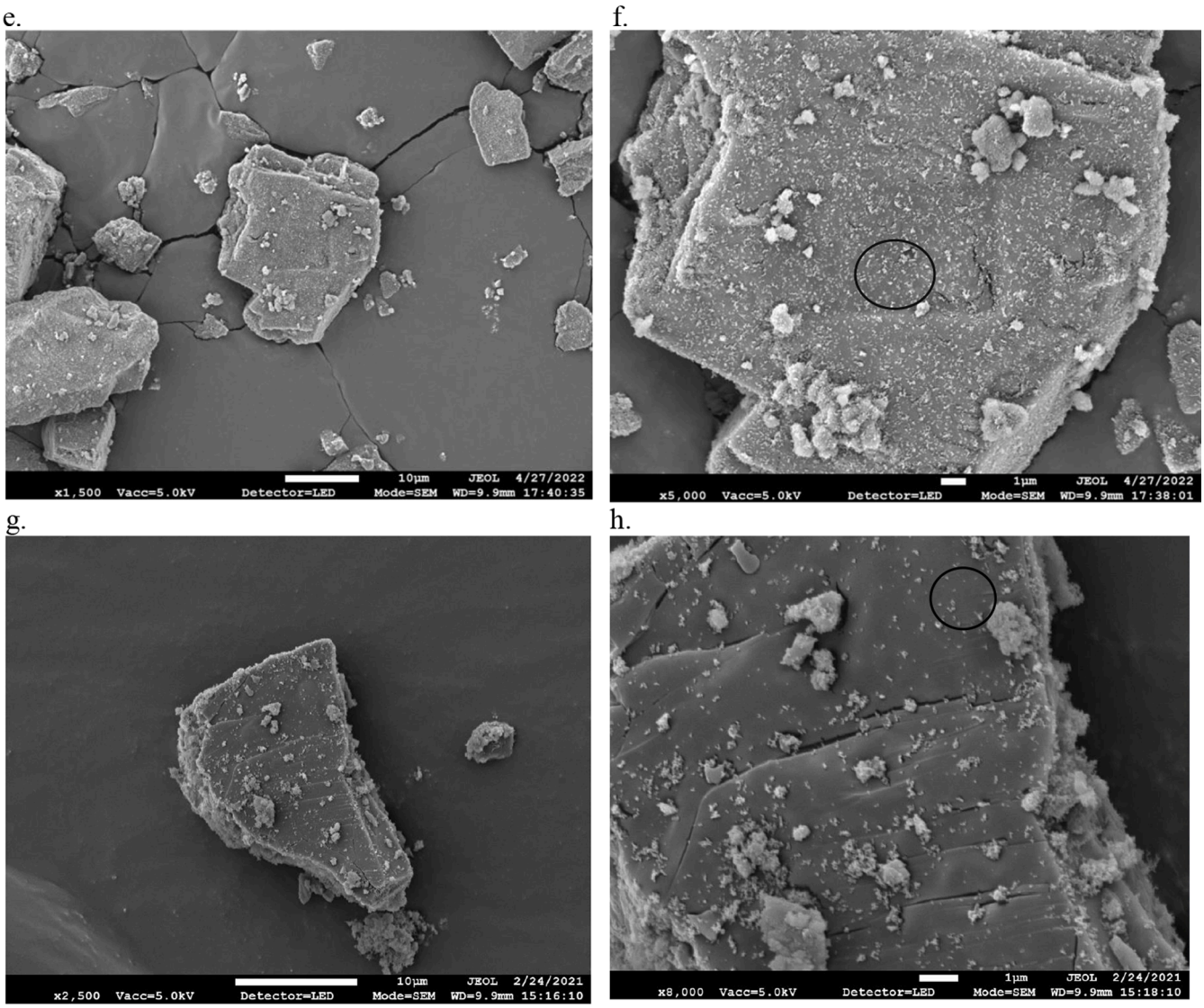

Fig. 1. (*continued*).

particle 2 are denoted as γ_1^P and γ_2^P. Additionally, γ_2 or γ_1 signifies the total surface energy of particle 2 or 1. Jallo et al. [77] suggested a simplified method of determining the guest–host compatibility for the special case involving two disparately sized powders. It was proposed that if the absolute difference, termed λ, between $\lambda^{2/1}$ and $\lambda^{1/2}$ exceeds 5, preferably > 10, a high level of compatibility between host and guest particles is anticipated [58,69,75]. The absolute difference, λ, based on using Eq. (3) could be easily simplified through algebraic manipulations, and is presented in Eq. (4). The difference expressed in Eq. (4) of surface energy between host particle and guest particle is a key parameter to determine guest–host compatibility.

$$\lambda = \left|\lambda^{2/1} - \lambda^{1/2}\right| = 2|\gamma_2 - \gamma_1| \tag{4}$$

3. Results

3.1. Individual excipients

3.1.1. SEM images of individual lactose without and with dry coating

In Fig. 1, SEM images are presented comparing uncoated P450 particles with dry-coated P450 particles using different wt% of A200 and R972P, illustrating the effectiveness of silica coating. The formation details are provided in Table 1. The uncoated P450 particles display a flat surface but are accompanied by irregular small lactose debris (as circled in Fig. 1b). Conversely, the dry-coated P450 particles with a 1 wt % Aerosil 200 show a uniform dispersion of nano-sized silica particles on their surface (as circled in Fig. 1d), although the original debris is still observable. In contrast, the dry-coated Pharmatose 450 particles with a 0.38 wt% Aerosil 200 composition exhibit sparsely distributed nano-sized silica particles (as circled in Fig. 1h). The compatibility model results presented in Table 4 reveal a compatibility score of 2.28 for P450 and A200, indicating a relatively low compatibility level between host and guest particles. This might explain the uneven silica distribution and the tendency to form agglomerates. The lesser silica coverage in the

Table 4
Surface energy based compatibility testing for host–guest pairs.

Host-Guest Pairs	Absolute Difference (Eq. (4))
P350 + A200	7.28
P350 + R972	18.12
P450 + A200	2.28
P450 + R972	23.12
cAPAP + A200	15.9
cAPAP + R972	9.5
IBU + A200	19.62
IBU + R972	5.78

latter case suggests insufficient SAC and potentially higher cohesion forces compared to the 1 wt% coating (Chen et al., 2008). In contrast, the dry-coated P450 particles with a 1 wt% R972P composition demonstrate superior and uniform dispersion of nano-sized silica particles on their surface (as circled in Fig. 1f). This observation also aligns with the guest–host compatibility testing for P450 and R972 (absolute difference of 23.12, as shown in Table 4), indicating a high level of compatibility between this pair of host and guest particles. Silica R972P is observed to completely cover the surface of Pharmatose 450, indicating enhanced coating efficacy as has been reported previously (Kunnath et al., 2021).

3.1.2. *Bulk density and flowability of individual lactose with MgSt added*

As mentioned before, for the adoption of the DB-DC option, it is imperative that the blend exhibits favorable attributes such as good bulk density, flowability, and tabletability (Han et al., 2011; Huang et al., 2015a; Huang et al., 2015b; Huang et al., 2017; Jallo et al., 2012; Jivraj et al., 2000; Shi et al., 2011). Consequently, our investigation begins by assessing individual lactose samples with and without dry coating to identify the best option amongst silicas and their amounts. Given the inherent high ejection force associated with lactose, 1 % MgSt was introduced into uncoated and dry-coated individual lactose samples, followed by a 1-minute V-blender mixing at 25 RPM. However, introducing a lubricant has the potential to enhance both flowability and bulk density, presumably by filling surface voids and generating more spherical and smoother particles (Morin and Briens, 2013; Pingali et al., 2009). In order to assess the dry coating effectiveness in presence of the possible confounding effects from the added MgSt, the results of the bulk density and flowability (FFC) with and without MgSt addition were examined. As demonstrated in Fig. 2, the addition of MgSt has a minimal impact on lactose bulk density and exerts only minor effects on lactose flowability. This is likely due to the relatively good coating of silica and the surface of Pharmatose being mostly flat, featuring minimal surface cavities, hence the addition of a lubricant causing marginal improvements. Consequently, the subsequent assessments of individual lactose samples flow and bulk density enhancements are not presented prior to incorporation of MgSt addition.

The bulk density and flowability characteristics of both dry-coated and uncoated lactose samples are presented in Fig. 3 as a phased map, intended to indicate combined improvement through movement of the values from lower-left quadrant to upper-right quadrant. The plots demonstrate significant enhancements in these two key properties for

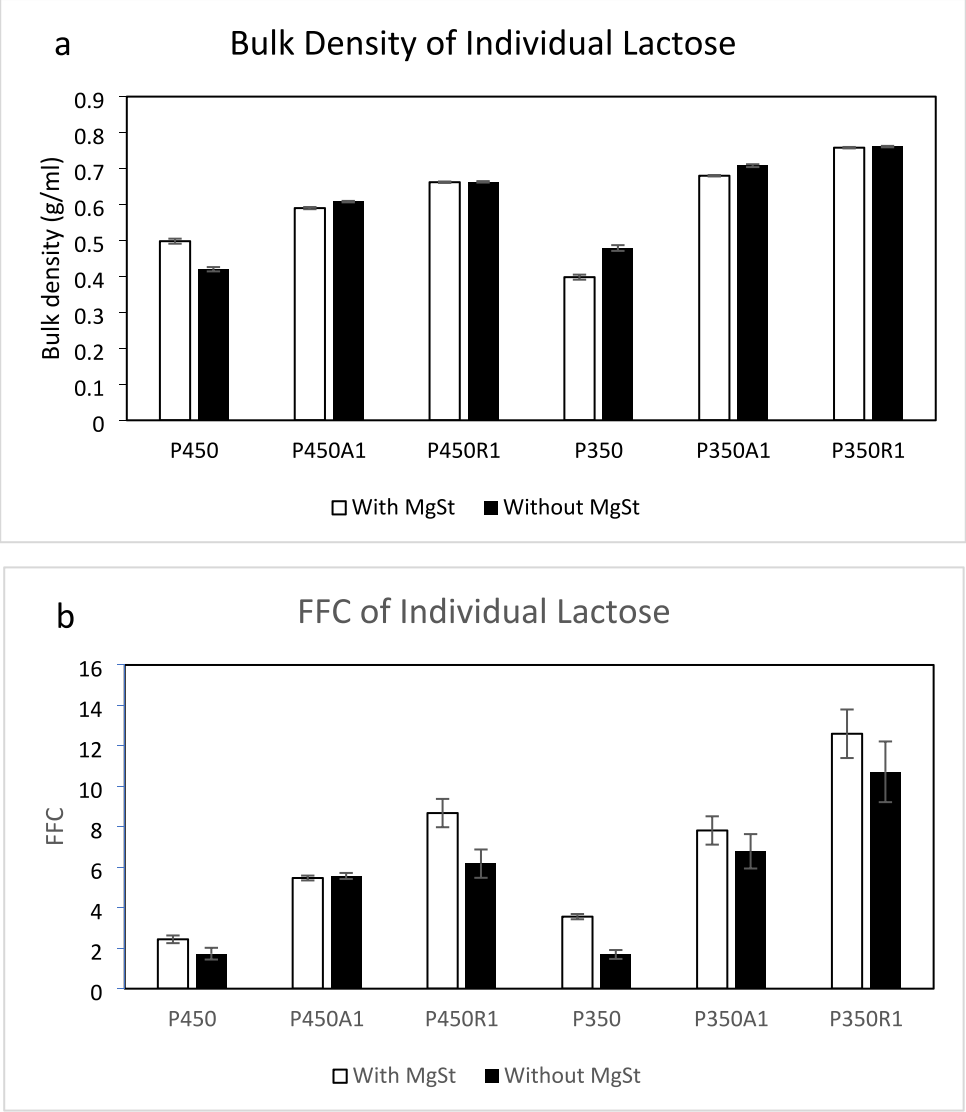

Fig. 2. FFC and bulk density of dry coated and uncoated Lactose. The "P" followed by a number (e.g., P450) denotes the type of lactose, while the letter following the number A1 and R1 represents the type and amount of silica used in the formulation. "With MgSt" and "Without MgSt" represent with and without 1 wt% addition of MgSt for 1 min V-blender mixing at 25 RPM, respectively.

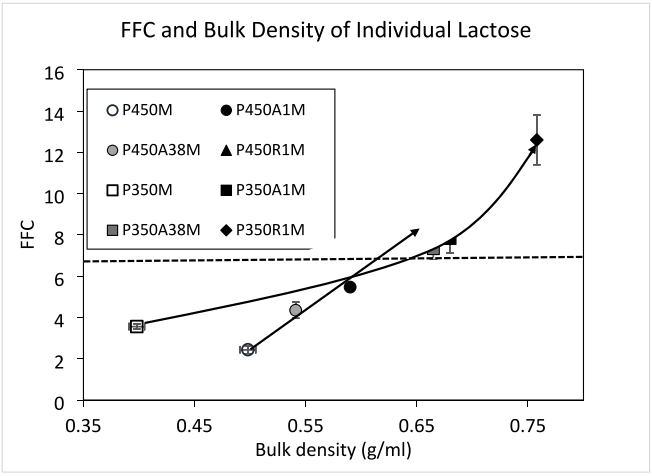

Fig. 3. Effect of silica amount and excipient particle size on FFC and bulk density. The "P" followed by a number (e.g., P450) denotes the type of lactose, while the letter following the number (e.g., "A1," "A38," "R1″) represents the type and amount of silica used (1 % and 0.38 %) for dry coating. The "M" at the end indicates the addition of 1 wt% Magnesium Stearate in each corresponding case. The horizontal line is a suggested value of FFC above which the powder has adequate flowability for enabling direct compression tableting.

P450 and P350 after different levels of silica coating. Dry-coated lactose particles exhibit a consistent coating of silica particles on their surfaces, as depicted in Fig. 1, resulting in a nanoscale surface roughness (Huang et al., 2015b). This coating effectively reduces cohesion among particles, as shown mechanistically through the multi-asperity model by Chen (Chen et al., 2008). Reduced cohesion facilitates improved packing within the powder bed and forming weaker structures that are more prone to collapse (Abdullah and Geldart, 1999). Consequently, this reduction in cohesion contributes to higher bulk density and correspondingly improved flowability compared to uncoated powders, consistent with prior research findings (Jallo et al., 2011; Jallo et al., 2012). According to previous studies (Chen et al., 2008; Yang et al., 2005), the SAC of dry-coated lactose, as indicated in Table 1, plays a pivotal role in influencing flowability and bulk density. Theoretically, higher SAC values, preferably up to 100 %, based on established models, correspond to lower adhesion forces, thus resulting in higher FFC and bulk density (Chen et al., 2008; Kunnath et al., 2023; Yang et al., 2005). Within the dataset presented in Fig. 3, it is evident that both P350A1M and P450A1M exhibit superior performance in terms of FFC and bulk density compared to P350A38M and P450A38M, respectively, as SAC increases from 38 % to higher values. Furthermore, for both the finer-size dry-coated P450 and the larger-size dry-coated P350, such as P450A1M and P350A1M, they attained significant enhancements in FFC and bulk density. This can be attributed to having silica SAC well above 50 % which assures the highest possible property enhancements (Chen et al., 2008). In cases with identical SAC (P450A38M and P350A38M), P350, owing to higher compatibility (as shown in Table 4), its larger size and higher individual particle weight, find it easier to overcome adhesion forces between particles, hence exhibiting superior performance (Kunnath et al., 2021; Kunnath et al., 2023). The reader is referred to these references for further discussion on the role of granular Bond number, which is the ratio of the cohesive forces to particle weight and hence affords a relative measure of powder cohesion. Additionally, comparing two types of silica coating, for instance, P450A1M and P450R1M, R972 exhibits greater improvement than A200, possibly due to its lower dispersive surface energy (Chen et al., 2018b). Remarkably, even P450R1M, not to mention all dry coated cases of P350, already surpasses the FFC of Avicel pH 102 (shown in horizontal dashed line in Fig. 3) indicating capability for direct compression tableting which for lactose would not be possible for such finer sizes without dry coating (Chen et al., 2018a; Chen et al., 2018b). It should be noted that higher silica amounts were neither necessary, nor recommended to minimize potential adverse effects on TS (Chen et al., 2018b). Overall, in terms of bulk density and flowability, dry coated lactose as a brittle excipient exhibits similar behavior as ductile MCC (Chen et al., 2018b).

3.1.3. *Tensile strength of individual lactose*

TS is a crucial parameter that quantifies the amount of pressure required to fracture a tablet, making it one of the most vital metrics for assessing the quality and integrity of tablets. In Fig. 4, the TS characteristics of both dry-coated and uncoated lactose samples, with variations involving P450 and P350 and different levels of silica coating where MgSt was added to aid tableting, are presented. Most surprisingly, the dry coating process yields a significant enhancement in the TS of lactose. For instance, after dry coating, P450A38M exhibits a two-fold increase in TS compared to P450M at a compression pressure of 152 MPa. This stands in contrast to previous findings wherein individual MCC experienced a reduction in TS following the dry coating process (Chen et al., 2018a; Chen et al., 2018b). In stark contrast, dry coated lactose demonstrates an appreciable increase in TS. This disparity may be a result of their different consolidation mechanisms during compaction and highlights major differences between the brittle and ductile materials. Materials such as MCC, exhibit ductile deformation, and the low surface energy silica that is residing on the surface can reduce the bonding strength (Chen et al., 2018b; El Gindy and Samaha, 1982). In contrast, lactose is consolidated by fragmentation (Roberts, 2011). The new surface area generated by fragmentation indicates that the bonding strength is less likely to be impacted by silica on the surface. Moreover, reduced cohesion between particles improves the packing of the powder bed during pre-consolidation stage (Abdullah and Geldart, 1999), leading to an increase in tablet bonding area, and hence, tablet TS. In the investigation of SAC effect on TS, it's evident that higher SAC achieved through silica coating typically results in reduced TS. For instance, dry-coated P450A1M and P450A38M exhibit superior TS compared to uncoated P450M, and P450A1M having 100 % SAC displays lower TS than P450A38M with 38 % SAC. However, it's noteworthy that even with increased SAC, the TS of dry-coated samples consistently surpasses that of uncoated lactose. Considering another factor, particle size, it's observed that smaller-sized lactose particles (P450M) demonstrate comparable TS to larger-sized lactose particles (P350M), aligning with previous research findings (Eriksson and Alderborn, 1995; Sebhatu and Alderborn, 1999). For dry coated lactose particles, this is not the case and surprisingly, finer dry coated lactose particles exhibit higher TS than their larger dry coated counterparts, especially under higher compression pressures. That indicates a major departure from conventional understanding of the behavior of brittle excipients where it is believed that particle size has a limited impact on TS during the tableting process (Sun, 2011). Clearly, after dry coating, a brittle material like lactose for which silica coating effectively mitigates particle cohesion, may have facilitated enhanced particle rearrangement and improved packing during compaction. This, in turn, results in a larger bonding area and, consequently, higher TS, and thus achieving the potential benefits of its finer size which was not previously investigated in the literature for dry coated lactose or brittle excipients. Another influential factor affecting TS is the surface energy of the silica used. Specifically, R972P, characterized by a lower dispersive component of surface energy compared to A200 (Chen et al., 2018b), leads to P450R1M and P350R1M exhibiting lower TS than P450A1M and P350A1M, respectively. This observation underscores that the choice of silica type also plays a crucial role in determining the TS of dry-coated lactose.

As shown in these results, the dry coating involving silica serves to significantly augment the TS of lactose particles. While factors such as higher SAC, larger particle size, and lower silica surface energy play roles in achieving improved bulk density and flowability, they can also lead to a decrease in TS. Taking into account the comprehensive performance metrics, it is observed that P450A1M strikes the most optimal

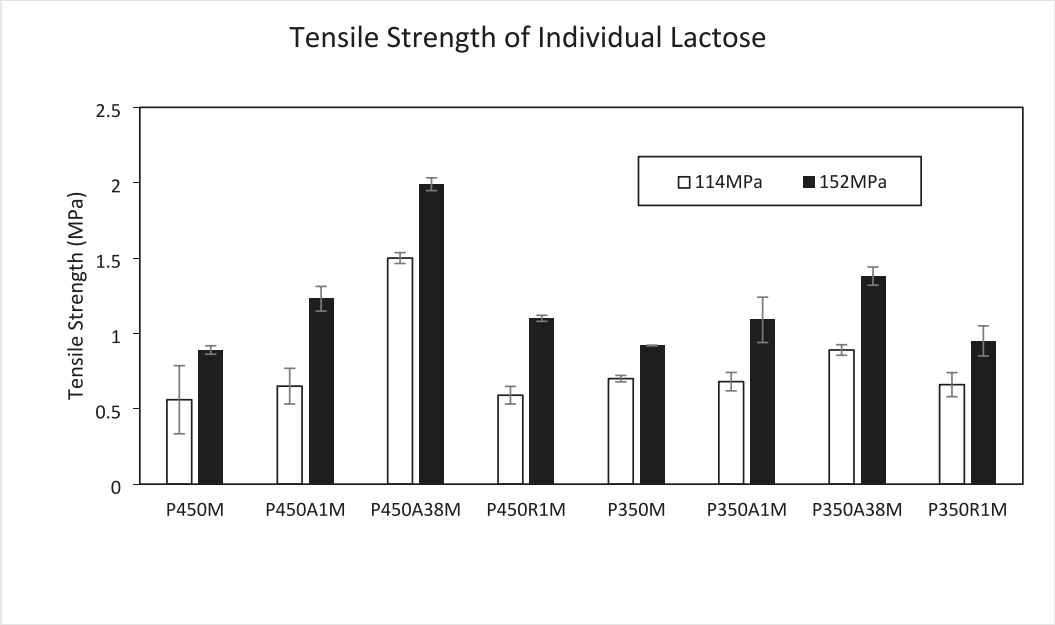

Fig. 4. Effect of silica amount and excipient particle size on tensile strength. The "P" followed by a number (e.g., P450) denotes the type of lactose, while the letter following the number (e.g., "A1," "A38," "R1″) represents the type and amount of silica used in the formulation. The "M" at the end indicates the presence of 1 wt% Magnesium Stearate in each formulation.

balance, maintaining high TS while simultaneously ensuring good bulk density and flowability, which were presented in the previous section.

3.2. Multi-component blends

3.2.1. Multi-component blends with cAPAP

Based on the results for the cases of dry coating of individual lactose powders, P450 with a 1 wt% A200 coating was selected for preparing blends with an API due to its well-balanced improvements in acceptable FFC, good bulk density, and higher TS than coated P350. The blends included dry coated P450, prepared using LabRAM running at 75G for 5 min, blended with all other blend ingredients (details are shown in Table 3) except for MgSt in a V-blender running for 12 min, followed by the addition of MgSt, mixed for 1 additional minute as described in method section. The choice of cAPAP as a poorly flowing and poorly compactable API is expected to test the effectiveness of dry-coated brittle excipient in multi-component blends (Chen et al., 2019; Huang et al., 2017; Kunnath et al., 2021). Av105, as a binder, is included in the formulation due to low TS of lactose itself.

Bulk density and flowability of multi-component blends with 10 wt% cAPAP loading are presented in Fig. 5. As shown in Table 3, two different wt % of P450, 72 wt% and 42 wt%, were considered. Note that all the main ingredients are fine-sized, as shown in Table 5. The vertical and horizontal dashed lines in Fig. 5a represent the bulk density and FFC of cAPAP. The bulk density and flowability of both 72 wt% and 42 wt% P450 without dry coating of lactose are poor. Remarkably, they are greatly improved with the use of dry coated lactose. The improvement may be attributed not only to the enhanced properties of the dry-coated material itself (Huang et al., 2017; Kunnath et al., 2018), but also to the potentially synergistic transfer of silica during blend mixing (Chen et al., 2019) due to a relatively high compatibility level between cAPAP and A200; i.e., compatibility score of 15.9; in contrast to a low level of 2.28 between P450 and A200. While the dry coated blend flowability is comparable, cAPAP + 72DC exhibited the best bulk density, as it contained higher amounts of dry-coated Pharmatose 450 (72 %). Interestingly, cAPAP + 42DC demonstrated slightly higher FFC compared to cAPAP + 72DC, despite having less dry-coated 450 (42 %) and overall lesser silica (0.42 %) in the blend, indicating that the excess transfer of silica from lactose might not contribute to further improvement of the blend's flowability.

In the above results, although shear testing based flow function coefficient (FFC) was used as the main and only indicator of flowability, there are other measures such as the angle of repose (AoR), AeroFlow (avalanche tester), or Hausner ratio. However, since the main objective of this paper is to examine if dry coating can make cohesive excipients and their blends better flowable, using FFC is more appropriate compared with other measures such as the AoR, AeroFlow (avalanche tester), or Hausner ratio, see for example (Thalberg et al., 2004), specifically, Table 3 in that paper. Nonetheless, the AoR values were measured for a few selected examples as shown in Table S1, *supplementary material*. As shown, the AoR and FFC show generally similar trends in Table S1 where a blend with higher FFC also has lower angle of repose. As known already, the discernibility of the AoR method is not as good as that for FFC for cohesive powders having varying levels of cohesiveness, and hence AoR outcomes cannot clearly differentiate blends having FFC values ranging from 4.84 to 6.85, although the AoR is a better parameter for better flowing powders (Thalberg et al., 2004).

These blends were used to prepare tablets at two different compaction forces. The outcomes for all cases, at the compaction pressure of 114 MPa and 152 MPa are presented in Fig. 5b. As seen, TS remained almost the same for the uncoated and dry coated lactose cases. It is intriguing that, unlike improved TS for lactose individual tablet, dry-coated Pharmatose did not cause significant improvement or decline in the blend tablet TS. Nonetheless, adequate tablet TS of 1.7 MPA (Pitt and Heasley, 2013) or above was attained for both dry coated lactose formulations at the compression force of 152 MPa. In a direct comparison between the TS of 42 % loaded Pharmatose, with Av105 at 42 %, and 72 % loaded Pharmatose, with Av105 at 12 %, a notable difference emerges. The TS of the 42 % Pharmatose blend is significantly higher than that of the 72 % Pharmatose blend. That clearly demonstrates that in multi-component blends consisting of high amounts of lactose and MCC, the dominant factor influencing TS is MCC, which has intrinsically higher TS than lactose being a brittle excipient (Batuyios, 1966; Chen et al., 2020; Rojas and Kumar, 2011). Thus, the potentially negative or positive impact due to dry coated lactose is overshadowed by the strong bonding ability of MCC.

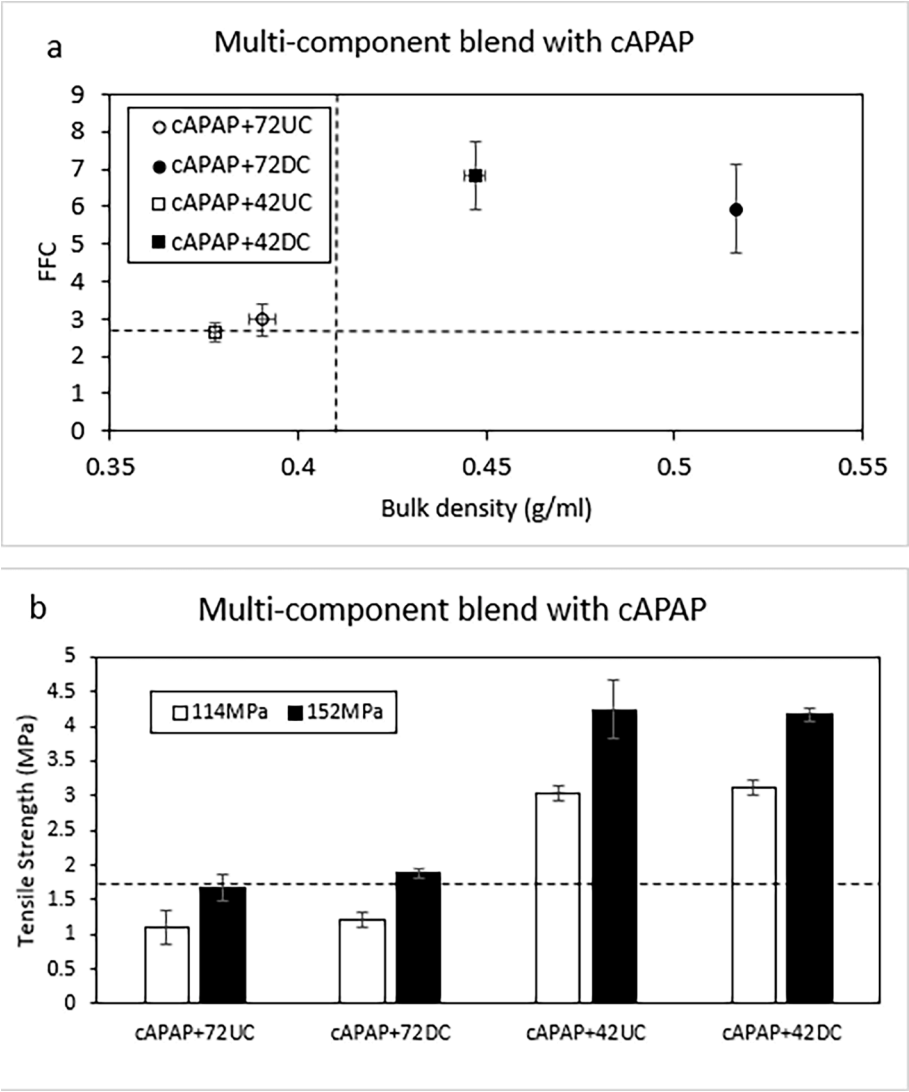

Fig. 5. (a) FFC, bulk density and, (b) tensile strength of cAPAP multi-component blends. The "cAPAP" represents the API used in formulation; number represents the weight percentages of Pharmatose 450; UC and DC represent uncoated Pharmatose 450 and dry coated Avicel Pharmatose 450, respectively. The horizontal and vertical lines in Fig. 5a represent FFC and bulk density of cAPAP, respectively. The horizontal line in Fig. 5b represents desirable minimum tablet tensile strength of 1.7 MPa (Pitt and Heasley, 2013).

Table 5
Properties of ingredients in multi-component blends.

Materials	Bulk Density (g/ml)	FFC	D50 (μm)
cAPAP	0.411	2.66	21.72
IBU	0.438	4.29	47.23
P450	0.420	1.73	19.29
P350	0.479	1.69	28.99
Av105	0.356	2.35	18.90
CLF	–	–	40.09
MgSt	–	–	5.80

In summary, at low drug loadings, the incorporation of dry coated lactose brings about a substantial enhancement in the bulk density and flowability of the blend. In a multi-component blend that includes MCC, a higher amount of dry coated lactose is associated with higher bulk density, whereas its lower amount results in improved flowability. When it comes to TS, the inclusion of dry coated lactose does not yield any detrimental effects when the formulation contains MCC.

3.2.2. *Multi-component blends with IBU*

In order to explore the impact of dry-coated lactose at a higher drug loading, IBU, which exhibits better compactability as compared to cAPAP, is selected as another model API (Chen et al., 2019). IBU loading was set at 60 wt% along with the amount of lactose P450 and Av105 set to 18 % each, see Table 3.

The results for the flowability and bulk density are presented in Fig. 6a, which includes the vertical and horizontal dashed lines representing the bulk density and flowability of the IBU by itself, respectively. Angle of repose and FFC show similar trends in Table S1 as blend with higher FFC has lower angle of repose. As expected, the bulk density and flowability of the uncoated blend are about the same or slightly worse than IBU itself due to the use of fine excipients in the blend, i.e., low bulk density and flowability of P450 and Av105 (see Table 5). In contrast, dry coated Pharmatose in the blend significantly enhances these two blend properties. The blend attains free flowing property, along with a bulk density reaching 0.495 g/ml, see Fig. 6a. It is indeed remarkable that a mere 18 % dry coated P450 in the formulation can significantly enhance the blend's flowability from a cohesive category to one characterized by free-flowing behavior. This finding suggests that an excessive amount of dry coated lactose is not necessary for improving the fine powder blend

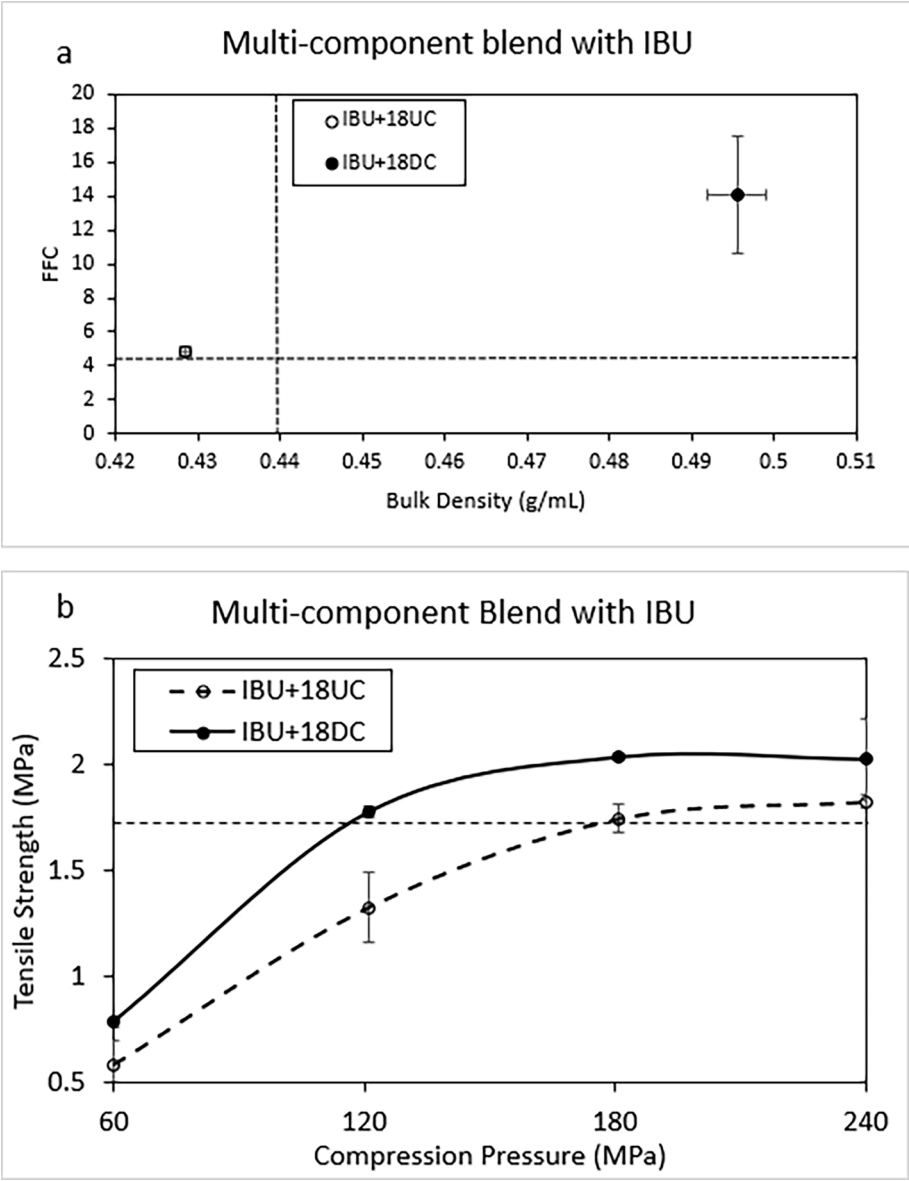

Fig. 6. (a) FFC, bulk density and, (b) tensile strength of IBU multi-component blends. The "IBU" represents the API used in formulation; number represents the weight percentages of Pharmatose 450; UC and DC represent uncoated Pharmatose 450 and dry coated Avicel Pharmatose 450, respectively. The horizontal and vertical lines in Fig. 6a represent FFC and bulk density of IBU, respectively. The horizontal line in Fig. 6b represents desirable minimum tablet tensile strength of 1.7 MPa (Pitt and Heasley, 2013).

flowability. Next, IBU blends were used to prepare tablets at four different compaction forces, and their TSs were tested. The results are plotted in Fig. 6b, where the solid markers and corresponding solid connecting line indicate the tablets containing dry coated lactose in the blend. The horizontal dashed line in Fig. 6b denotes the minimum desirable tablet TS of 1.7 MPa (Pitt and Heasley, 2013). A significant improvement in TS is evident for the tablets made from the blends containing dry coated P450; its TS exceeds 1.7 MPa at all three higher compression pressures. In fact, dry coated P450 led to higher TS at 121 MPa compaction than what was attained for uncoated P450 at 181 MPa. The observed increase in TS of IBU blend with dry coated P450 is likely attributed to the transfer of silica and the presence of dry-coated materials, resulting in reduced cohesion of IBU and facilitating particle rearrangement prior to and during compression (Capece et al., 2015; Capece et al., 2014), likely leading to a greater particle contact area, hence, higher TS. The SEM images of IBU in the multi-component blend in Fig. 7 show silica on the surface, clearly visible in a higher magnification image in Fig. 7d. In contrast, for the blend with uncoated lactose, the IBU particle shown in the SEM image of Fig. 7b, no silica is seen. Circles in Fig. 7b and 7d depict the difference between the surfaces of IBU particle within blends without and with dry coated lactose where presence of silica in Fig. 7d is evident. Fig. 7e is provided to show the typical morphology/shape of an as-received IBU particle, which when compared with Fig. 1a, demonstrates that the IBU particles are easily distinguished in both the blends examples shown in Fig. 7. The compatibility model results in Table 4 reveal a high compatibility score of 19.62 for IBU and A200, indicating a high compatibility level between API host and guest particles, when compared with a low score of 2.28 between P450 and A200. These results from Table 4 and Fig. 7 strongly support the assumption of silica transfer. However, the increase in tablet TS observed for IBU after dry coating is relatively higher than what was observed for cAPAP blends at low drug loading. This suggests that an excess amount of dry-coated lactose, which was used for the cAPAP blends, may be counter to attaining higher TS. This finding contradicts the observed trend with dry-coated MCC in binary blends, where a higher amount of dry-coated MCC led to increased tensile strength but

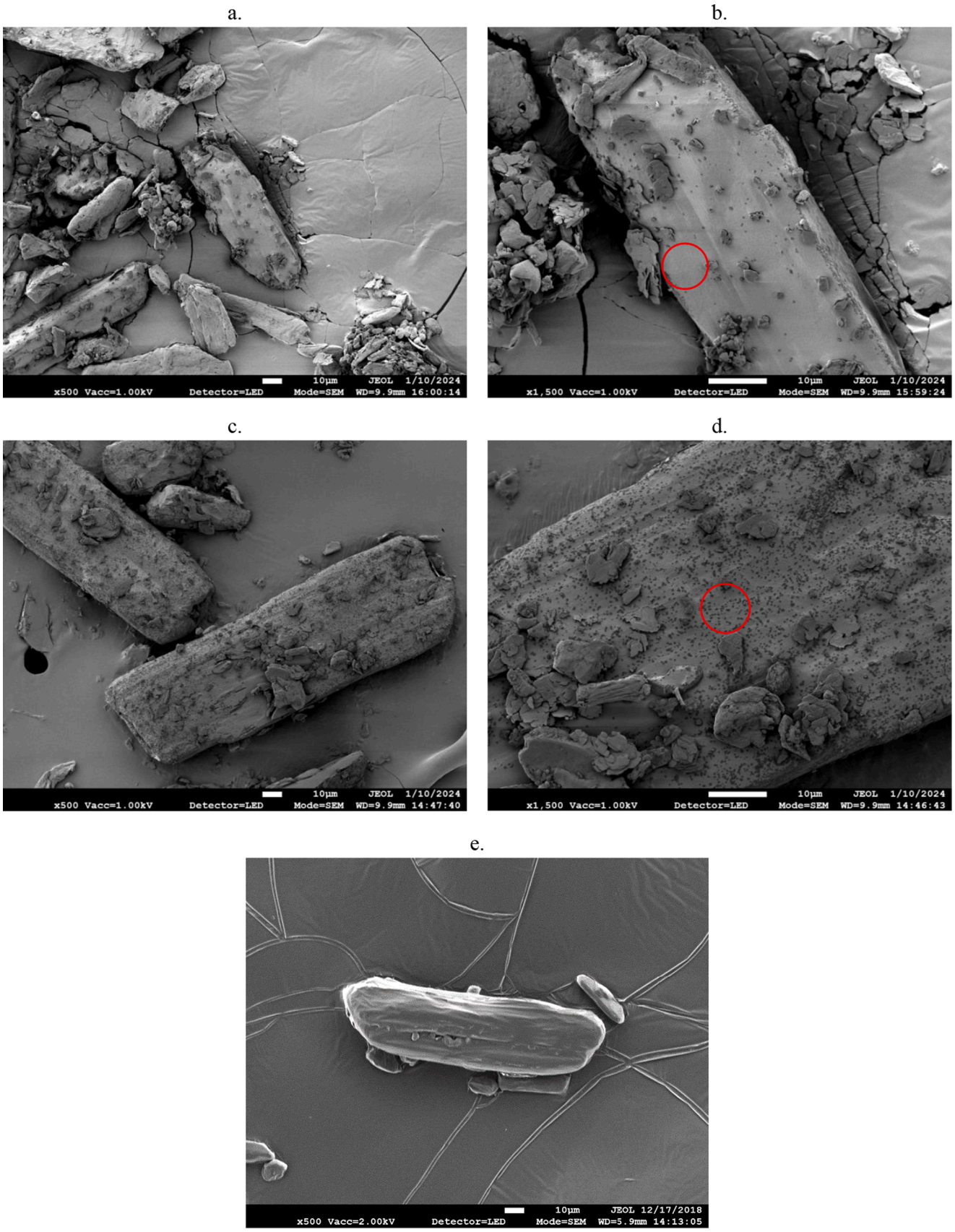

Fig. 7. SEM images of IBU in multi-component blend with uncoated P450 (a and b), with dry coated P450 (c and d), and IBU itself (e) under slightly different magnification. Circles in Fig. 7b and 7d depict the difference between the surfaces of IBU particle within blends without and with dry coated lactose where presence of silica in Fig. 7d is evident.

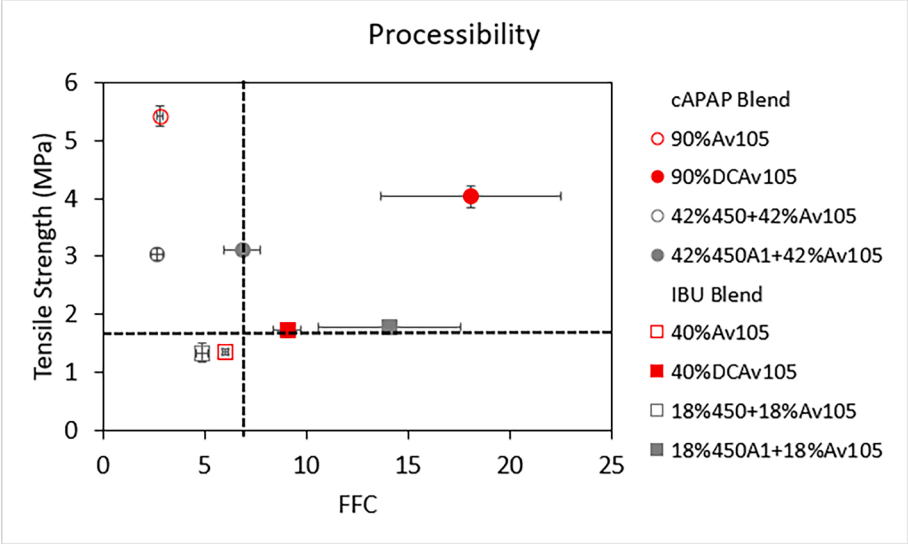

Fig. 8. Processibility of multi-component blends. Horizontal and vertical lines denote direct compression capability which is indicated by the proximity to the top-right quadrant. For cAPAP formulations, 90 % Av105 and 90 % DCAv105 denote a 10 % cAPAP blend, with 90 % Av105 and 90 % Av105 dry-coated with a 1 wt% A200 coating, respectively, from the Chen paper (Chen et al., 2019). Likewise, for IBU formulations, compositions 40 % Av105 and 40 % DCAv105 represent a 60 % IBU blend, with 40 % Av105 and Av105 dry-coated with a 1 wt% A200 coating, respectively, also from the Chen paper (Chen et al., 2019). All other formulations denoted by non-red markers are as outlined in Table 3. Except for the 18 % 450 + 18 % Av105 and 18 % 450A1 + 18 % Av105 cases, which were compressed at 121 MPa, all others were compressed at 114 MPa. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

may have been due to reduced portions of the API (Chen et al., 2019). Overall, the reduced tensile strength for the placebo MCC tablet from previous work (Chen et al., 2018b) and improved tensile strength for the placebo lactose tablet from the previous section, indicate that an excess of dry-coated lactose in the multi-component blend, resulting in an excess amount of silica transfer, can decrease the tabletability of MCC. That can limit the overall improvement in tensile strength of the multi-component blend, even though the tabletability of lactose is enhanced by dry coating. As a conclusion, in a multi-component blend, a partially dry-coated excipient may perform better than having major or all excipients dry-coated.

In summary, the use of dry-coated lactose at just 18 %, implying a mere 0.18 wt% of silica in the entire blend, yielded significant improvements in bulk density, flowability, and TS for the 60 % IBU multicomponent blend, indicating the advantages of dry coated brittle excipients in enhancing processability of solid dosage formulations.

3.2.3. Processability enhancement with dry coated lactose

The enhancements in two key attributes, flowability and tablet TS may be better visualized for cAPAP as well as IBU blends in a property map shown in Fig. 8, which includes horizontal and vertical lines denoting DC capability in the top-right quadrant. In this figure, the TS values are plotted against FFC of cAPAP and IBU formulations investigated in this paper along with the previously reported results (all red colored points are from (Chen et al., 2019)) for comparable cases where the dry coated excipient was Avicel PH-105 instead of P450 for the present work. For cAPAP blends at low drug loading, the current results demonstrate enhanced FFC due to 42 wt% dry coated lactose. In comparison, previous results for the blend containing 90 wt% dry coated Avicel PH-105 are better but require larger amount of dry coated material while both are DC capable. More interestingly, for larger drug loaded IBU blends, P450 dry coated blends have slightly better TS and much better FFC, and nearly attained DC capability, again with much lesser dry coated ingredient, i.e., 18 wt% P450 versus 40 wt% Avicel PH-105. This comparison suggests that dry coated excipients are useful in attaining DC capability and a formulator may have options regarding which ingredient to select for dry coating.

4. Conclusion

As expected, dry coated lactose exhibited significant enhancements in flowability for both the powder sizes, moving from almost very cohesive to easy flow and better with either silica. Particle size, silica type, and coating amount emerged as key factors influencing the properties of dry-coated lactose. As a major novelty, in contrast to the reported results for MCC, dry coating of lactose led to increased tablet TS, more so for the finer grade (P450) with A200 silica coating. These outcomes demonstrate that fine lactose can attain good flowability, bulk density, and compaction after dry coating with small amount of silica, hydrophilic being a better overall choice. Multi-component blends featuring dry-coated P450 exhibited improved properties without requiring a large portion of lactose to be dry coated. For low drug loaded cAPAP blends, substantial bulk density and flowability increase without any detrimental effect on TS were observed; a lesser amount of dry coated P450 was better. For 60 wt% ibuprofen50, using only 18 wt% of the dry coated P450, i.e. 0.18 wt% silica in the blend, led to increased flowability, bulk density as well as TS, attaining enhanced processability by reaching DC capability. Notably, the silica amounts necessary for such enhancements, for example, a 16 % increase in bulk density, 30 % in TS, and one or more flow category improvements in FFC, were no more than 0.18 wt% of the multi-component blends, indicating that in general dry coating of less than 50 wt% of the blend ingredient is sufficient for attaining desirable processability. Such outcomes corroborate previously reported results attributed to mixing-induced synergy of silica transfer from a minority dry coated blend component (Kim et al., 2021; Kim et al., 2023).

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CRediT authorship contribution statement

Zhixing Lin: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bian Cabello:** Validation, Investigation. **Rajesh N. Davé:** Writing – review & editing, Visualization, Supervision, Resources, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

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