Stress transmission coefficient is a reliable and robust parameter for quantifying powder plasticity

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1 Introduction

Many processes in pharmaceutical manufacturing are highly influenced by material plasticity. For example, high plasticity can render the milling process inefficient at reducing particle size due to a lower propensity of fragmentation [1]. Plastic deformation also promotes interparticulate bonding area formation during tablet manufacturing, which is necessary to achieve adequate tableting strength [2]. Thus, plasticity is an essential material property for designing high-quality pharmaceutical tablet products. As such, modulating the plasticity of active pharmaceutical ingredients (API) through crystal and particle engineering is important in product development [2–10].

Currently, methods to quantify powder plasticity in facilitating tablet compression invariably require the value of the compact porosity (ε). In one approach, pressure (P) – ε data are analyzed using a suitable mathematical model, such as the Heckel [11,12], Kawakita [13], Kuentz and Leuenberger (KL) [14], and Walker [15] equations. In the macroindentation approach, the hardness of compressed tablets (H) is measured, and H at zero porosity (H_0) is obtained by extrapolating H – ε data using an exponential relationship [16]. Established plasticity parameters include $P_{y,o}$ from the out-of-die Heckel analysis, $1/C$ from the KL analysis, and H_0 from the macroindentation experiments.

Accurate determination of ε is essential for accurately determining the plasticity of a powder using these approaches, as small errors in ε can lead to significant errors in plasticity parameters because of the sensitivity of these analyses to ε [17]. Thus, the accurate determination of powder plasticity using any of these methods requires accurate measurements of both compact density (ρ) and the true density of the material (ρ_t), which are used to calculate ε according to Equation 1.

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

Unfortunately, the accurate out-of-die ρ is not always possible to obtain due to several issues with accurately determining tablet volume, including 1) complex tablet geometry [18], 2) inability to form an intact tablet due to capping, lamination [19], punch sticking [20,21], 3) internal tablet defects [22], and 4) tablet flashing [23]. Additionally, even for materials free from these issues, the out-of-die approach for determining ρ requires a significant amount of material. Typically at least 5–10 g are required to prepare an appropriate set of tablets for data collection to assure accurate determination of the plasticity parameter. Additionally, it takes a few hours even for a skilled researcher to collect each set of data. Therefore, adopting the out-of-die approach to guide efficient formulation design and development is not appealing in the early drug development stages.

These issues associated with ρ measurements can be avoided with an analysis of in-die data obtained during compression with a modern compaction simulator, i.e., ρ as a function of force. Subsequently, $P - \varepsilon$ data throughout a compression cycle can be derived from ρ and force, if the cross-sectional area of the punch and ρ_t are known. We have shown that the mean yield pressure obtained from the in-die Heckel analysis, $P_{y,i}$, is a reliable measure of material plasticity [24]. Hence, it is suitable for quantifying powder plasticity early in drug development. However, an accurate in-die Heckel analysis still requires an accurate ρ_t. Methods for determining ρ_t include 1) calculation from the solved crystal structure [25], 2) helium pycnometry [26], and 3) fitting out-of-die $\rho - P$ data using the Sun approach [27]. However, none of these methods is broadly applicable for obtaining an accurate ρ_t for all pharmaceutical powders. Since pharmaceutical solids are not always perfectly crystalline, calculated ρ_t values from crystal structures tend to be over-estimated. Due to crystal thermal expansion, errors are larger when the crystal structures are solved

from data collected at sub-ambient temperatures, which is a common practice to reduce thermally induced disorders for a better structure model. Helium pycnometry cannot yield accurate ρ_t of powders that contain sealed pores or volatile components, e.g., water [17,28]. The Sun analysis allows for the determination of ρ_t for water-containing materials [28], but suffers from the same issues that impact the out-of-die ρ measurements mentioned above. Since there are no methods that can be used to measure an accurate ρ_t for all pharmaceutical powders at the present, the in-die Heckel analysis still cannot yield accurate plasticity parameters for all powders.

The stress transmission between applied axial stress (σ_a) and radial stress (σ_r), can be viewed as a measure of the ability of the compressed material to flow under pressure [29]. The inverse correlation observed between crystal hardness and stress transmission indicates a potential correlation between stress transmission and powder plasticity [30,31]. It was also observed that materials exhibiting a good conversion of axial pressure to radial pressure tend to form better tablets, [29,32] due to a larger degree of plastic deformation [33]. Thus, it is reasonable to expect a correlation between the stress transmission coefficient (STC), i.e., the slope of σ_r versus σ_a after a solid plug has been formed during compression, and powder plasticity. Importantly, the STC can be experimentally determined without using ρ_t and ρ information. However, aside from these indirect pieces of evidence that associate stress transmission and plasticity, such a correlation has not been firmly established. Here, using a large set of powders exhibiting a wide range of mechanical properties, we show that the STC is indeed a reliable measure of powder plasticity suitable for adoption in an early stage of drug development.

2 Materials and Methods

2.1 Materials

Microcrystalline cellulose (MCC; Avicel PH102, FMC Biopolymer, Philadelphia, PA), lactose monohydrate (LM; #316 Fastflo® NF, Foremost Farms, Clayton, WI), mannitol 200SD (Mann; Pearlitol® 200SD, Roquette America Inc., Keokuk, IA), dicalcium phosphate anhydrate (DCPA; Anhydrous Emcompress®, JRS Pharma, Patterson, NY), dicalcium phosphate dihydrate (DCPD; Emcompress®, JRS Pharma, Patterson, NY), ibuprofen (IBN; Sigma Aldrich, St. Louis, MO), celecoxib (CEL; Aarti Drugs Pvt Ltd., Mumbai, India), hydroxypropyl cellulose (HPC; Klucel EF-PHARM, Ashland, Wilmington DE), and magnesium stearate (MgSt; non-bovine, HyQual™, Mallinckrodt, St. Louis, MO) were used as received.

2.2 Mixing and tableting

LM, Mann, and DCPA were studied both individually and as mixtures in 25% increments with MCC. An additional mixture of 90% DCPA with 10% MCC and two mixtures of 20% IBN or CEL with 80% MCC were also prepared. All mixtures were blended for 10 min at 49 rpm in a blender (Turbula, Glen Mills, Clifton, NJ). Pure MCC and HPC were compressed without further treatment. All other powders were mixed with 1% (w/w) MgSt in the blender for 2 min at 49 rpm. The MgSt was used as an internal lubricant to reduce frictional forces between the tablet and die wall during compression.

Tablets were prepared using a compaction simulator (Styl'One Evolution; MedelPharm, Beynost, France) with a round instrumented die (11.28 mm in diameter) using a symmetrical, force-controlled, single compression cycle at 2% speed, composed of a 2 s compression (1 s rise and a 1 s fall without holding at the maximum force) followed by 3 s relaxation and a 2 s ejection step. The calibration of the instrumented die was verified before data collection using a stack of

rubber discs per the instructions in the instrument manual. Round, flat-faced punches were used to compress tablets.

The middle of the tablet was set at 6 mm below the surface of the instrumented die, and the minimum thickness of the tablets was set to 3.2 mm for all materials to ensure consistent STC measurements. Due to the 200 MPa limit for σ_r that can be measured by the instrumented die without risking damage to the die, the target σ_a was around 200 MPa by using an appropriate amount of each material.

2.3 STC analysis fitting and data analysis

Mean σ_a and σ_r values for each cycle exported from the compaction simulator were plotted. To avoid data corresponding to the compression phase before a solid plug is formed, the terminal linear region (typically >100 MPa in σ_a) of the loading curve was used for linear regression using the curve_fit function in SciPy's optimize package. The slope of the fitted line is taken as the STC. For the plot of STC versus other plasticity parameters ($P_{y,i}$, $P_{y,o}$, $1/C$, and H_0), fitting was performed using SciPy's orthogonal distance regression (ODR) package (SciPy version 1.6.2, Python version 3.8.2) using ordinary least squares (job=2), unless otherwise specified.

3 Results and Discussion

3.1 Correlation between STC and established plasticity parameters

The STC values of the powders studied in this work varied over a wide range, 0.506 – 0.959, with that of HPC (0.959) being the highest. The nearly 100% transmission of stress from the punches to the die wall suggests highly efficient stress transmission by HPC. This qualitatively correlates with the high plasticity of HPC [16,24,34]. In contrast, the STC of DCPA was only 0.506, suggesting its inefficiency in transmitting stress from the axial to the radial direction, which

is consistent with the low plasticity of DCPA [16,35]. Overall, STC strongly correlates with all plasticity parameters explored in this work, including $P_{y,i}$ (R^2=0.956), $P_{y,o}$ (R^2=0.886), $1/C$ (R^2=0.988), and H_0 (R^2=0.916). All four plasticity parameters ranged over two orders of magnitude, and a power-law relationship adequately describes all these correlations (Figure 1). Numerical values of all parameters used in Figure 1 are summarized in Table 1.

The good correlations between STC and other plasticity parameters suggest that STC can be used to quantify material plasticity with similar authority as these traditional plasticity parameters. A key advantage of the STC is that it can be obtained to measure material plasticity without using tablet density and true density.

3.2 Robustness of STC measurements

Radial stress transmission has been previously characterized for a number of APIs [37–39], excipients [39–42], and mixtures [43]. However, a comparison of results in the previous studies must be made with caution because accurate die wall stress measurements require appropriate calibration, and they may be affected by compaction conditions [44], which differed among the various studies. Appropriate calibration of the instrumented die entails simulating a hydrostatic environment using hydraulic fluids or a pseudo-hydrostatic environment using natural or synthetic rubbers [44]. Die wall stress calibration constants may differ when rubbers with different mechanical properties are used. In this study, the calibration of the instrumented die was performed using rubber discs over a range of thicknesses according to the manufacturer's specifications. Although this calibration can theoretically minimize or eliminate the effects of tablet thicknesses and compression depths on measured σ_r [44,45], the measured STC decreases slightly with increasing tablet thickness for rubber (Figure 2). This is attributed to the fact that the

136 calibration was performed under a static stress condition, but the STC was measured dynamically.
137 Hence, we have not given any physical meaning to the slight deviation (<5%) of STC values of
138 rubber from unity across the thickness range examined in this work.
139
140 During dynamic powder compression, frictional force between the powder bed and the die
141 wall dampens the stress transmission, which reduces measured STC. Hence, thinner tablets are
142 more efficient in transmitting stress, corresponding to a higher STC. This is generally observed for
143 all four materials (Figure 2). To minimize this effect, tablet thickness was fixed at a user-set
144 thickness of 3.2 mm (Figure 2**a**), which corresponds to the actual minimum tablet thickness of ~4
145 mm after correcting for machine deformation (Figure 2**b**). Reproducibility was further improved
146 by fixing the middle point of the tablet at the middle of the strain gauges, which is located 6 mm
147 below the surface of the die. This fixation of tablet thickness and compression location resulted in
148 highly reproducible STC measurements for all materials studied (Figure 3 and Table 1).
149 It should be noted that the variation in STC caused by different tablet thicknesses over a
150 wide range, e.g., 2 – 4 mm, is much smaller than the differences among rubber, HPC, MCC, and
151 DPCA (Figure 2). Therefore, STC can be used to rank order materials accurately according to their
152 plasticity even when the user-set minimum tablet thickness is allowed to slightly vary.
153
154 **3.3 Applications of STC**
155 Given the strong correlation between STC and a number of established plasticity
156 parameters examined in this work using materials exhibiting plasticity over at least two orders of
157 magnitude, STC can be used as an excellent alternative parameter for characterizing the plasticity
158 of pharmaceutical powders. The independence of STC from true density or tablet density, the high

reproducibility, and the *in situ* data collection by a computer collectively make it a reliable and objective parameter. Hence, STC data among laboratories can be compared with confidence, provided the calibration of the instrumented die is properly performed.

Potential applications of STC include 1) rapid characterization of plasticity of different solid forms of an API, e.g., cocrystals, salts, and hydrates, to inform the solid form selection; 2) better understanding of the effects of particle size, crystal habit, blend composition, and excipient grade on powder plasticity; 3) evaluation of different compaction conditions, e.g., tableting speed, on the extent of plastic deformation of a formulation to guide scale-up of a tablet manufacturing process.

4 Conclusion

The STC is strongly correlated with four traditional plasticity parameters, $P_{y,i}$, $P_{y,o}$, $1/C$, and H_0, indicating that it can be used as a reliable powder plasticity parameter. The independence of the STC from tablet porosity renders it immune to unavoidable errors with tablet and true density encountered by other existing methods for quantifying powder plasticity. Thus, the STC is a highly expedited and material-sparing method for characterizing material plasticity, making it an excellent alternative to traditional methods of evaluating powder plasticity for adoption in the early stages of drug development.

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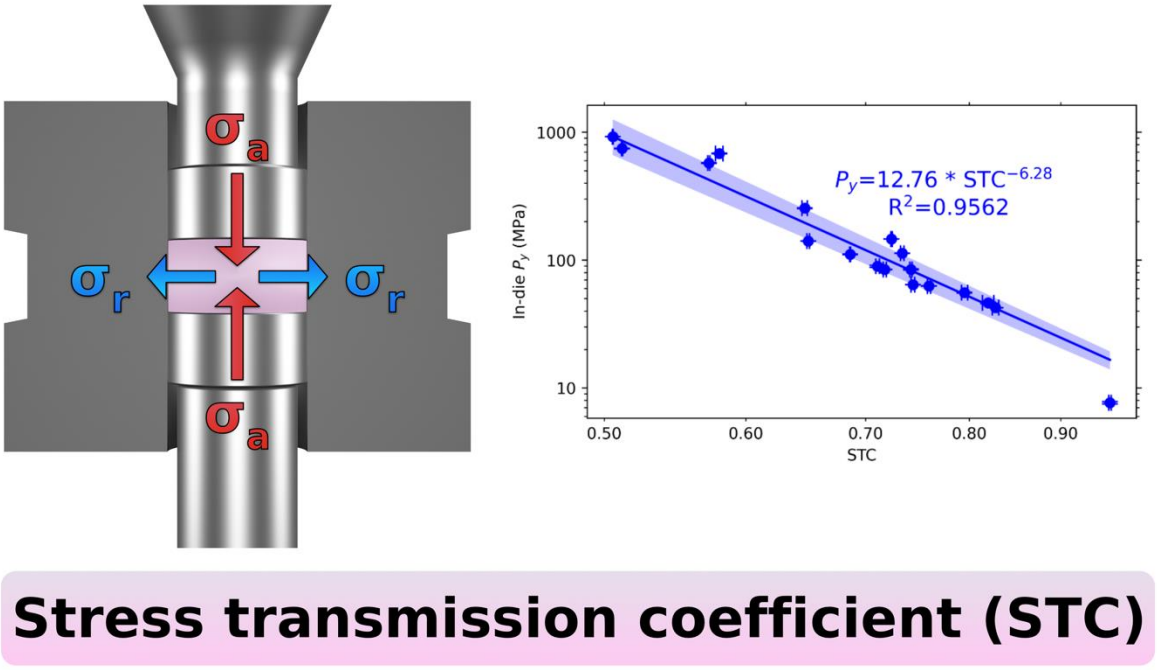
Figure Legends

Figure 1: (**a**) $P_{y,i}$, (**b**) $P_{y,o}$, (**c**) $1/C$, and (**d**) H_0 versus STC for a variety of pharmaceutical powders. The shaded regions correspond to ±1 standard error on the fitted lines. All markers have error bars in both x and y directions, but some are hidden by the symbols.

Figure 2: Effects of (**a**) user-set minimum tablet thickness and (**b**) machine-deformation corrected minimum tablet thickness on the STC of rubber, HPC, MCC, and DCPD.

Figure 3: σ_r versus σ_a curves for (a) MCC, (b) LM mixtures with MCC, (c) Mann mixtures with MCC, (d) DCPA mixtures with MCC, and (e) DCPD, IBN and CEL mixtures with MCC, and HPC. The black dotted line indicates perfect hydrostaticity. The dashed line is the average of 3 linear regressions from 3 separate compressions. The solid line indicates the region in which linear regression was applied.

Graphical abstract



Abstract

Powder plasticity parameters derived by existing methods are sensitive to errors in porosity measurements resulting from inaccurate measurements of compact density, true density, or both. Using a number of materials exhibiting plasticity over a range of more than two orders of magnitude, the post-powder densification stress transmission coefficient (STC) strongly correlates with all four existing in-die and out-of-die plasticity parameters. Since the STC determination requires only axial and radial stress measurements, it is free from errors in the determination of tablet porosity suffered by other existing methods. Additionally, STC is immune from user error, because data can be collected by a computer using a compaction simulator with an instrumented die. Overall, the STC is an excellent alternative to traditional powder plasticity parameters for guiding the tablet formulation design in early stages of drug development.

Table 1: STC, $P_{y,i}$, $P_{y,o}$, H_0, and *1/C* plasticity parameters used in Figure 1. Values in parenthesis indicate either the standard deviation of three measurements for STC and $P_{y,i}$ or the standard error of regression for out-of-die measurements.

Material	STC	$P_{y,i}$ (MPa)	$P_{y,o}$ (MPa)	H_0 (MPa)	*1/C* (MPa)
MCC	0.795 (0.003)	55.7 (0.4)[2]	79.4 (1.1)[2]	124.8 (4.4)[1]	97.5 (10.7)[2]
25% LM	0.744 (0.002)	64.3 (0.04)[2]	88.5 (1.89)[1]	-	121.8 (11.2)[1]
50% LM	0.717 (0.001)	84.4 (0.3)[2]	107.5 (2.75)[1]	-	176.8 (12.3)[1]
75% LM	0.686 (0.0004)	110.8 (0.5)[2]	138.9 (2.95)[1]	-	312.1 (14.5)[1]
100% LM	0.650 (0.001)	141.0 (0.4)[2]	172.4 (3.16)[1]	393.1 (36.1)[1]	504.4 (19.2)[1]
25% Mann	0.760 (0.002)	62.7 (0.1)[2]	90.9 (1.7)[1]	-	127.8 (8.1)[1]
50% Mann	0.742 (0.001)	84.5 (0.6)[2]	116.3 (2.12)[1]	-	199.1(10.3)[1]
75% Mann	0.734 (0.002)	113.3 (0.4)[2]	161.3 (4.09)[1]	250 (9.4)[1]	368.5 (16.3)[1]
100% Mann	0.724 (0.001)	146.2 (0.1)[2]	181.8 (4.13)[1]	263.0 (12.1)[1]	455.2 (12.4)[1]
25% DCPA	0.711 (0.002)	89.3 (1.6)[2]	143.5 (2.5)[2]	-	252.6 (13.1)[2]
50% DCPA	0.647 (0.002)	254.5 (1.0)[2]	397.3 (12.4)[2]	665.4 (49.4)[1]	796.9 (62.2)[2]
75% DCPA	0.572 (0.001)	573.5 (2.2)[2]	730.7 (24.8)[2]	2374 (346)[1]	1921.8 (103.1)[2]
90% DCPA	0.512 (0.0003)	745.5 (2.8)[2]	972.7 (32)[2]	4501 (865)[1]	3686.8 (113.5)[2]
100% DCPA	0.506 (0.0003)	921.3 (0.2)[2]	1243.7 (35.7)[2]	6790 (1494)[1]	4203.8 (77.1)[2]
100% DCPD	0.580 (0.003)	681.4 (3.7)[2]	925.2 (60)[2]	2715 (295)[1]	3573.7 (349.0)[2]
20% IBN	0.828 (0.003)	42.4 (0.1)[2]	76.9 (2.23)[1]	87.1 (2.85)[1]	95.3 (8.3)[1]
20% CEL	0.820 (0.006)	46.3 (0.7)[2]	81.9 (4.26)[1]	1043 (3.01)[1]	102.0 (7.8)[1]
HPC	0.959 (0.002)	7.7 (0.2)[2]	16.1 (0.7)[2]	-	34.7 (2.7)[2]

[1][36], [2][24]

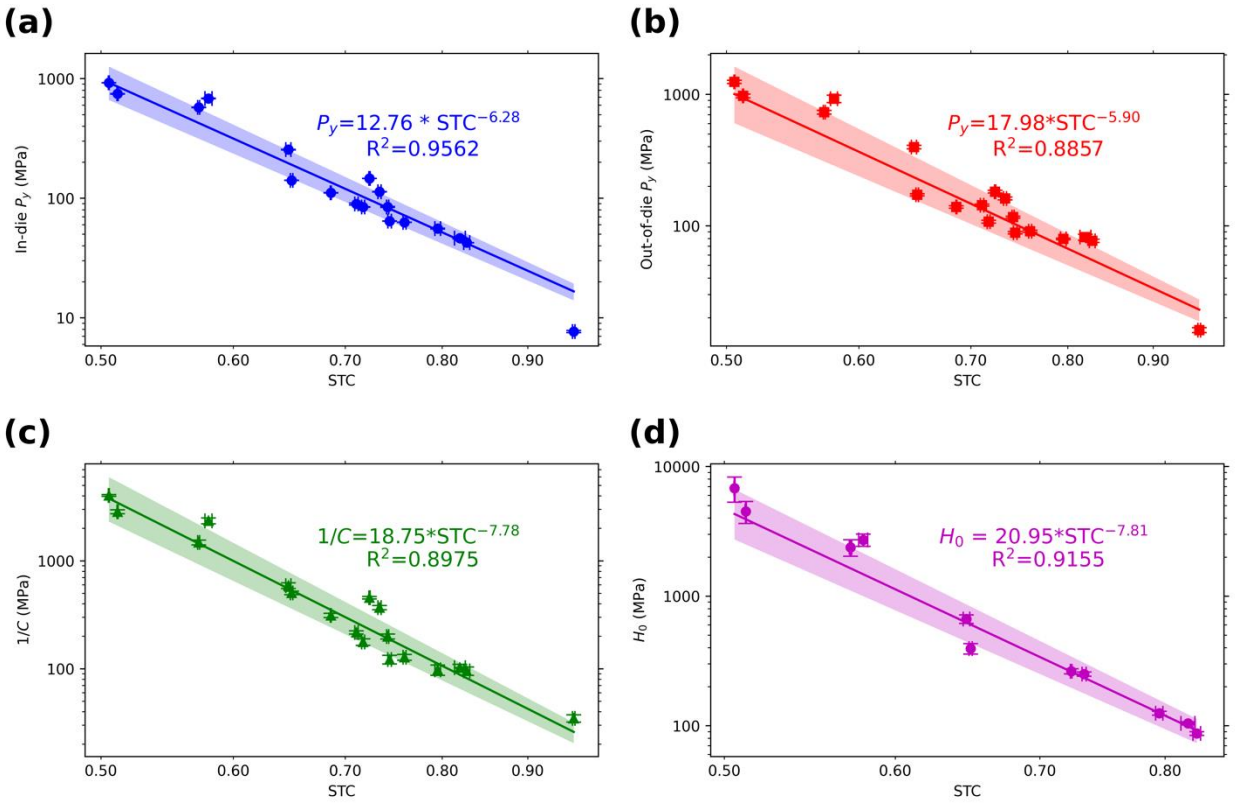


Figure 1: (**a**) $P_{y,i}$, (**b**) $P_{y,o}$, (**c**) $1/C$, and (**d**) H_0 versus STC for a variety of pharmaceutical powders. The shaded regions correspond to ±1 standard error on the fitted lines. All markers have error bars in both x and y directions, but some are hidden by the symbols.

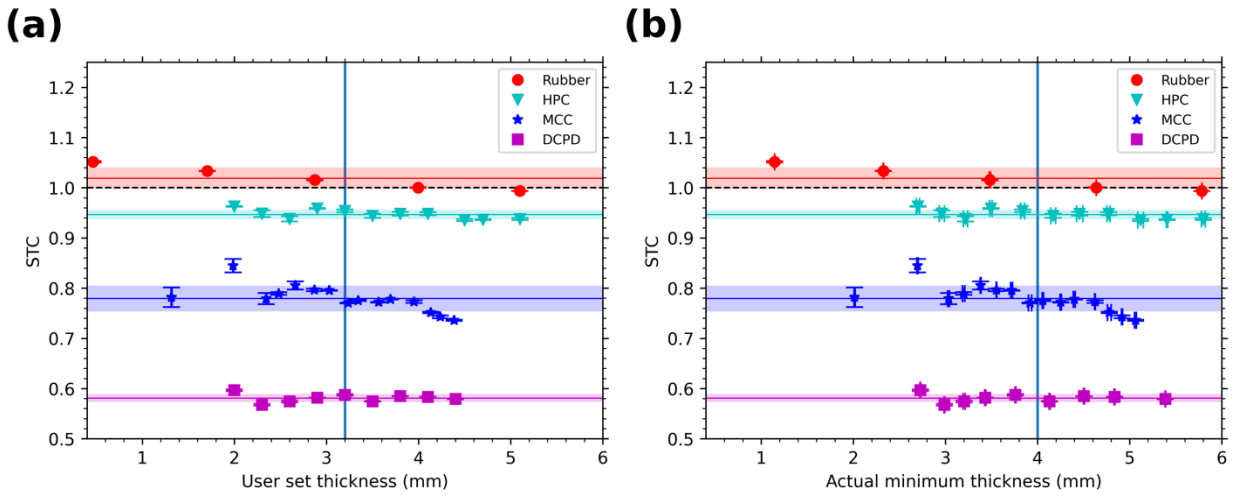


Figure 2: Effects of (**a**) user-set minimum tablet thickness and (**b**) machine-deformation corrected minimum tablet thickness on the STC of rubber, HPC, MCC, and DCPD.

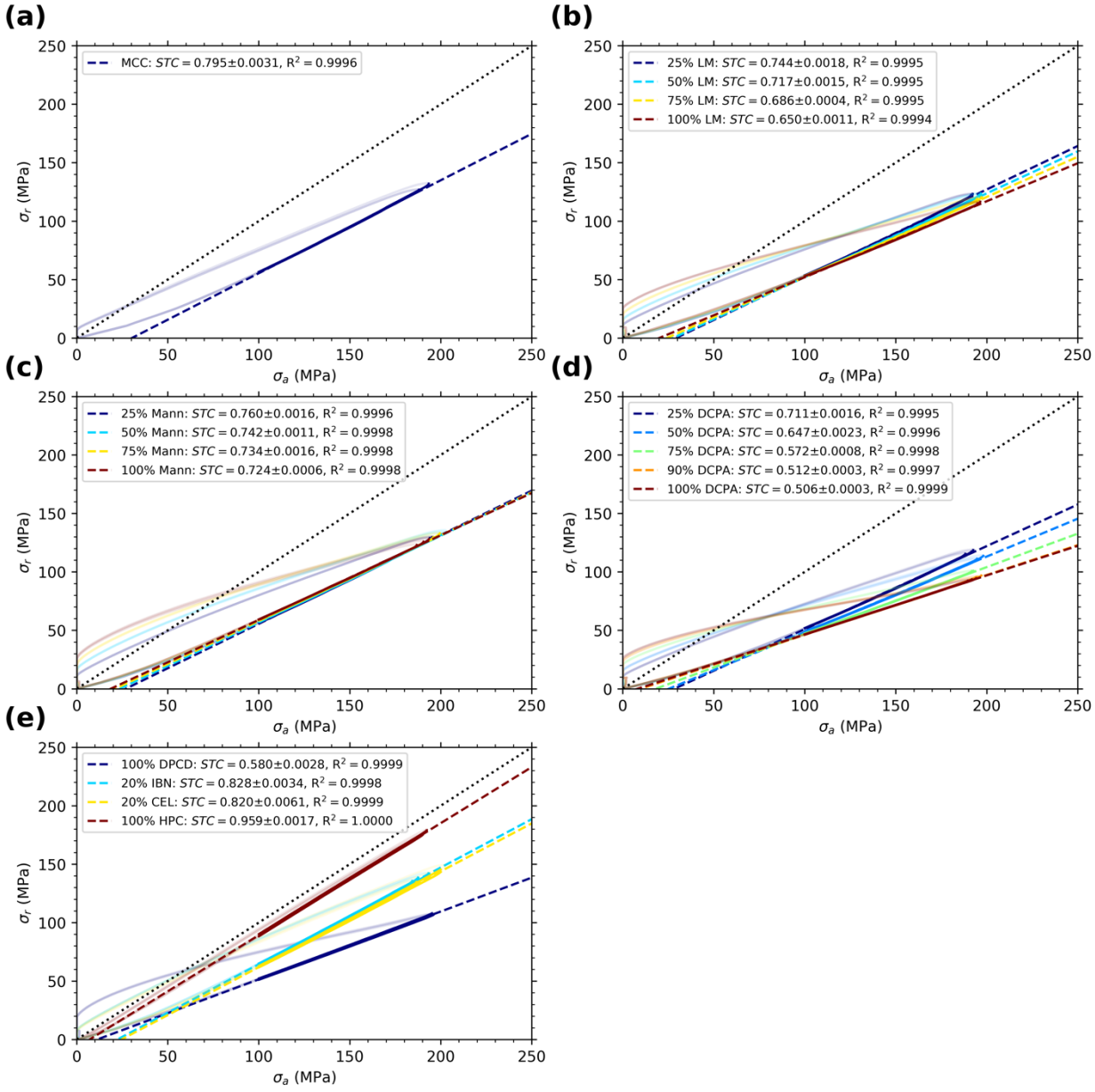


Figure 3: σ_r versus σ_a curves for (a) MCC, (b) LM mixtures with MCC, (c) Mann mixtures with MCC, (d) DCPA mixtures with MCC, and (e) DCPD, IBN and CEL mixtures with MCC, and HPC. The black dotted line indicates perfect hydrostaticity. The dashed line is the average of 3 linear regressions from 3 separate compressions. The solid line indicates the region in which linear regression was applied.

Highlights

- Stress transmission coefficient (STC) affects transmission of stress to die wall
- STC is quantified using a compaction simulator with an instrumented die
- STC correlates well with the plasticity of a large set of powders
- STC is free from errors in traditional methods for quantifying plasticity

Credit Author Statement

Gerrit Vreeman: Methodology, Formal analysis, Investigation, Writing- Original draft preparation.

Changquan Calvin Sun: Supervision, Conceptualization, Writing- Reviewing and Editing, Resources, Funding acquisition

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:
