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Segregation of Formulated Powders in Direct Compression Process and Evaluations by Small Bench-Scale Testers

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Powder segregation can cause severe issues in processes of pharmaceutical drugs for control of content uniformity if the powder is likely to be free or easy flowing. Assessing segregation intensity of formulated powders in a process is challenging at the formulation stage because of the limited availability of samples. An advanced segregation evaluation using small bench-scale testers can be useful for formulation decisions and suggestions of operation conditions in the process, which has not been practically investigated before. In this study, eight formulations (two co-processed excipients blended with one active pharmaceutical ingredient at different ratios) were used for the segregation study on two types of bench-scale testers (air-induced and surface rolling segregation tester), and a pilot simulation process rig as a comparative study. The results show that segregation measured on the bench-scale testers can give a good indication of the segregation intensity of a blend if the segregation intensity is not more than 20%. The comparison also shows that both the bench-scale testers have a good correlation to the process rig, respectively, which means either segregation tester can be used independently for the evaluation. A linear regression model was explored for prediction of segregation in the process.

Keywords: Segregations in process; Formulated powders; Bench-scale testers; Harshness factors; Linear regression model; Direct compression process,

1 Introduction

Powder segregation in pharmaceutical manufacturing can cause serious problems in terms of control of content uniformity (Alyami, et al., 2017), which has been recognised for many years (Harnby, 2000). For powder-formed medicines such as tablets or capsules, segregation in powders leads to a change in the level of active pharmaceutical ingredients (APIs), which is crucial to the quality of any medicines that require APIs to meet the standards enforced (Deveswaran, et al., 2009, Robert, et al., 2022). In a process, powders with significant differences in particle size, shape or solid densities can segregate when the powders are free or easy flowing, which causes failure in the content uniformity control (Velez, et al., 2022, Spahn, et al., 2022). It has been extensively studied from batch processes to continuous blending mode with a wide range of co-processed drug substances (Jaspers, et al., 2022, Erdemir, et al., 2023). However, powder segregation in a process is complicated due to varied material properties, mixing performance, equipment designs and operation methods in processes (Engisch, et al., 2016). Previous studies particularly focused on the material properties and the blending methods (Jakubowska, et al., 2021, Velez, et al., 2022), but with less attention to the

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segregation in process under different mechanisms (Engisch, et al., 2016) and operation conditions. It is hard to evaluate the powder segregation in a process directly (Barik, et al., 2023), but it is important to conduct an assessment before the formulated powder enters the clinical trials, so an adjustment to the formulation can be applied. Evaluation of formulated powders using small bench-scale testers could fulfil the purposes, but comparison between bench-scale testers and a process has not been investigated before. In this study, powder segregation in a direct compression process is investigated as a typical example for evaluation of segregation intensity in a process using small bench-scale testers.

2 Powder segregation in a direct compression process

Moving from a traditional batch process to a continuous process was recommended to avoid issues such as segregation in transitions, as regulated by the Food and Drug Administration (FDA USA, 2004). Since that time, the aim has not changed, which is to promote efficient, agile, flexible pharmaceutical manufacturing to produce high-quality drugs. However, until now, the pharmaceutical sector is still struggling in the transition to meet the target, although the batch process has been tried to avoid it practically. It still suffers from either a difficult flow or high segregation of powders in processes (Myerson, et al., 2014, Nakamura, et al., 2019).

A typical direct compaction tablet manufacturing process is shown in Fig. 1 (Singh, et al., 2016), which shows a combination of milling, blending, tablet press processes with an integrated control system. In the process, one of the challenges is to make a reliable powder flow without losing any control of content uniformity (Engisch, et al., 2016). To avoid the flow issues in the process, powders need to be less cohesive (Vanarase, et al., 2023), however, the powders can segregate if cohesiveness of the powder is not enough (Deng, et al., 2021a). For easy/free-flowing powders, the powders can segregate in terms of particle size, shape, and density, while the powders are in movement, such as discharging from the blender through a dropping chute (as indicated in Fig. 1), and feeding into tabletting dies (Schulze, 2008). The intensity of powder segregation in the process can accumulate throughout multiple stages, and the segregation can be passed to the products at the end of production (Oka, et al., 2022). Most of the segregation happens at the feeding chute, as shown in Fig. 1.

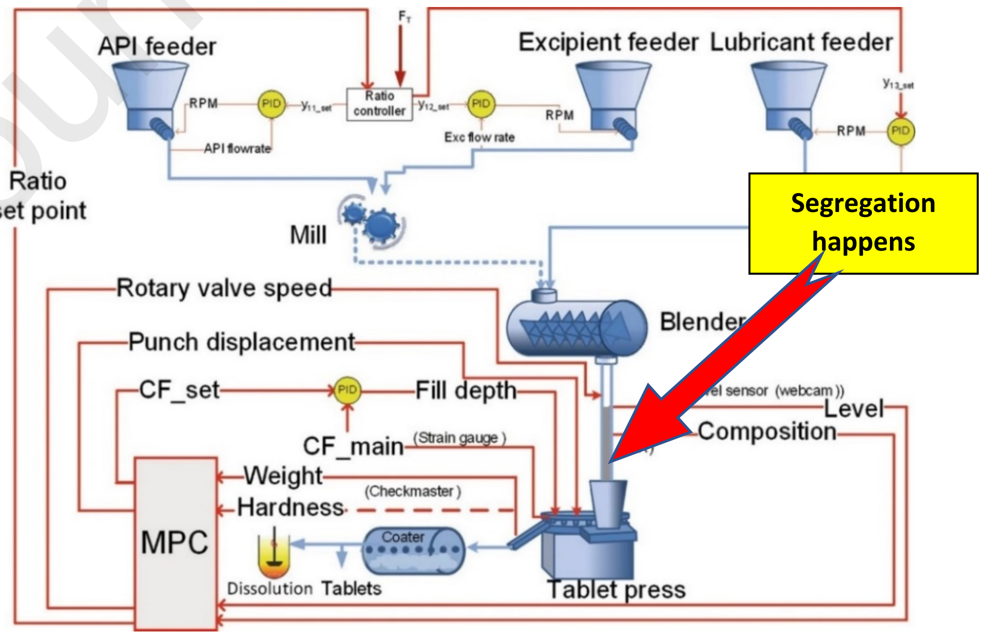


Figure 1: Flowsheet of direct compaction tablet manufacturing process (Singh, et al., 2016).

2.1 Segregation mechanisms in the direct compression process

Particulate solids can segregate into different groups in terms of size, shape, or true density due to several mechanisms, including five primary mechanisms as: trajectory, sifting, air current, fluidization, and surface rolling (de Silva, et al., 2000, Hogg, 2009, Jian, et al., 2019). Based on particle size, these mechanisms can be classified as: surface rolling segregation including trajectory and sifting, air-induced segregation including fluidization and air current, and agglomeration segregation such as electrostatic (Tang, et al., 2004). Pharmaceutical powders can have more issues because the powders contain more than one ingredient and the ingredients have different physical properties (Jaspers, et al., 2021). As an example of a pharmaceutical process shown in Fig. 1, from the blender to the tablet press, three major types of segregation mechanisms can occur, out of which two mechanisms are common: air-induced segregation (entrainment of air) and surface rolling segregation (sifting segregation). Segregation caused by electrostatic charges (known as agglomeration segregation) can also play a significant role. If any of the ingredients in a formulation is highly chargeable, segregation due to electrostatic charge can be significant. Different segregation mechanisms may have different contributions to the total segregation intensity of the powders.

Air-induced segregation of powders is a separation of particles caused by the aerodynamic influence (Jaklič, et al., 2015). This type of segregation can be caused by, either air fluidisation or air elutriation. In an air stream, fine particles may migrate easily to a different location compared to coarse particles. Also, different-sized particles have different responses to the counterflow of air, and the air drag effects are different. As a result, fines can be removed easily from original mixture and redeposited, more likely on the top of the powder bed. Therefore, this type of segregation has more effects on fines, because of the small mass of the particles and the high influences of the air drag force.

Surface rolling segregation is particle reclassification during particle movement on an inclined surface of powder bed, where big particles can gain a high moving velocity and stop at the far end of the bottom (Drahun, et al., 1983). This type of segregation is mainly influenced by the size difference, the shape and the density difference, also the frictions between the particles (Mateo-Ortiz, et al., 2014). Fine particles are smaller and cohesive, which are likely to percolate in the voids and stop quickly, but the coarse particles can move further. So, the intensity of rolling segregation is subject to the mobility of coarse particles.

Powder segregation in a process can be complex and can suffer from multiple mechanisms. In case of the process in Fig. 1, three types of segregation can be identified, and the total segregation in the process could be a combination of these types of segregations acted.

2.2 Influential factors on the powder segregation

The factors influencing powder segregation in a process can be variations in material properties, equipment design and operational methods, *etc*. (Jakubowska, et al., 2021). The powders, including APIs and excipients can be significantly different in terms of size, shape, and true density. If any of the ingredients are non-cohesive, the intensity of powder segregation can increase considerably.

Beside the material properties, design of equipment can be a significant influential factor for powder segregation in a process such as drop height and geometry. The feeding system of a direct compression process in pharmaceutical industry can have different types of design. For example, as shown in Fig. 1, the feeding system can consist of a blender, a rotary feeder, a dropping chute, a sampler and a connection dropping chute to a feeding hopper of tabletting press machine. In this case, blended powders can segregate in a few stages, including inside the dropping chute, in the sampler fitted in the chute, the connection chute, in the tablet press feeding hopper and in the tabletting die, which is not shown in the figure. In terms of the segregation risks in the process described here, the risk level of the segregation and the mechanisms are classified as likely to be appeared from low to high, as shown in Table 1, including air-induced, surface rolling and electrostatic segregations (Tang, et al., 2004).

Table 1: Segregation risks of powders in a direct compression process

Stages in Process and Equipment	Air induced segregation	Surface rolling segregation	Electrostatic segregation
API / Excipients blender	Low	Low	High
Rotary Valve Feeder	N/A	N/A	High
Dropping Chute	High	High	High
Sampler & Diverter	N/A	High	Low
Connection Dropping Chute	High	High	High
Tablet press feeding hopper	High	High	High
Tabletting dies filling	High	High	Low

Operation methods also have a significant impact on powder segregation at any stage of a process whether it is a continuous process or a batch process (Karttunen, et al., 2019). For example, as shown in Table 1, the powder segregation in tablet press can be influenced by the feeding frequency and the feeding rate of the blended materials from the feeder.

2.3 Segregation indices used in this study

Segregation index (*SI*) is defined as a statistical number of standard deviations, variances, or variation coefficients of compositions in a mixture, which quantifies the variations of the species of interest from the homogeneously blended to segregated powder. Many segregation indices have been introduced previously (Dai, et al., 2020). One of the most common indices is the Lacey index (Lacey, 1954), which is defined based on the variance of number fraction of the target particles. The limitation of Lacey index is determining the uniformity of the particle sizes in the mixture without consideration of time sequence or space dimensions. For pharmaceutical blends in the material handling process, it is important to monitor the proportionate variation from the intended content of a component (API) in time sequence or space dimensions. For this purpose, a new SI was introduced using a variation ratio of the cumulative volumetric concentration of fine particles at a certain particle size, as shown in Eq. (1) (Deng, et al., 2021b).

$$SI_{s(i)} = \left(\frac{C_i - C_{o(i)}}{C_{o(i)}}\right) \times 100\% \qquad (1)$$

where C_i is an accumulated volumetric concentration of fines after segregation at the size i and $C_{o(i)}$ an accumulated volumetric concentration of fines in the original material at the size i before the segregation. The size i is the upper limit of the accumulated concentration.

The *SI* can be calculated up to any particle size interested. Commonly, the *SI* in Eq. (1) at the particle size of D_{50} for various locations can be expressed as Eq. (2).

$$SI_{D50(i)} = \frac{\Delta C_{D50}(segregated\,between\,locations)}{C_{D50}(virgin)} \times 100\% \qquad (2)$$

where ΔC_{D50} is the difference between the concentrations of fines at the size of D_{50} between two locations after segregation, and C_{D50} is the concentration of fines at the size of D_{50} for the virgin material. The *SI* can also be calculated in a single size fraction using the concentrations in the size fraction before and after segregation, as shown in Eq. (3).

$$SI_{s(i)} = \frac{\Delta C_i(Segregated\,between\,locations\,in\,a\,size\,fraction)}{c_i(virgin\,in\,the\,size\,fraction)} \times 100\% \qquad (3)$$

where ΔC_i is the difference of the volumetric concentrations of the particle in the size fraction i between two locations after segregation. C_i is the concentration at D_{50} of the virgin material.

2.4 Segregation harshness factors

The contribution from different segregation mechanisms in a process is hard to evaluate. The difficulty is that segregation in a process can be influenced by many mechanisms, for example, the equipment design may lead to different levels of air-induced or surface rolling segregation. Also, operation conditions can change the levels of powder segregation in the process. On the other side, the segregation intensity of a powder blend based on material properties can be assessed easily using a standard bench-scale tester if the formulated powder is available even with a small quantity of the APIs that is enough for making the samples.

Generally, it is impossible to take a direct measurement of the proposed process for all formulations interested. If the contribution from each of the segregation mechanisms can be evaluated using a bench-scale tester, harshness of the segregation in a process could be represented as a function of contributions of each or a combination of different segregation mechanisms with a harshness factor (F_h) as in Eq. (4). The contribution of the segregation mechanism for a powder can be tested on a corresponding bench-scale tester.

$$SI_{p(i)} = f(F_h \cdot SI_{s(i)}) \qquad (4)$$

where $SI_{p(i)}$ is the segregation intensity of a powder in a process, F_h is the harshness factor of a segregation mechanism in the process, and $SI_{s(i)}$ is the segregation intensity of the powder based on the segregation mechanism. To explore the segregation harshness in a process shown in Eq. (4), eight formulation blends based on one API and two excipients were used in this study on a dedicated designed pilot-scale process rig and then compared to two types of bench-scale testers for air-induced or surface rolling segregation.

3 Materials and methods

3.1 Materials and formulations

One API and two Co-Processed Excipients (CPEs) were used to form eight formulations at different mixing ratios, as shown in Table 2. The API/CPEs were supplied by various suppliers, as shown in Table 2, with the material codes used in the analysis and corresponding names with their formulations. Because of availability and safety, acetaminophen dense is selected for this study as a typical API material which is a widely used nonprescription analgesic and antipyretic medication for mild-to-moderate pain and fever. A CPE used to be a combination of two or more excipients obtained by physical co-processing that does not lead to the formation of covalent bonds (Bhatia, et al., 2022). Because of the functionalities that are not achievable through sample blending, nowadays CPEs are widely used in many pharmaceutical products to avoid complicated blending process (Mamatha, et al., 2017, Zhao, et al., 2022). A mixture of an API and a CPE will be more representative for practical applications and simple for the study. In this study, CPEs used are the Ludipress® and the Prosolv® EasyTab SP. Ludipress® Polymer is a mixture of Lactose monohydrate (93%), Kollidon® 30 and Kollidon® CL supplied as white, free-flowing granules. PROSOLV® EASYtab SP is a lubricant-coated high functionality excipient composite, which is comprised of four individual components: a binder/a filler, a glidant, a super disintegrant, and a lubricant as Microcrystalline Cellulose (96%), Colloidal Silicon Dioxide, Sodium Starch Glycolate, and Sodium Stearyl Fumarate.

Table 2: A list of the formulations studied and suppliers of the materials

Code	Materials & Compositions	Grade	Supplier
AD	Acetaminophen Dense	API	Mallinckrodt Pharma
EasyTab	Prosolv® EasyTab SP	CPE	JRS Pharma
Ludipress	Ludipress® LCE	CPE	BASF Pharma

AD40P	40% AD + 60% EasyTab	Formulation	-
AD20P	20% AD + 80% EasyTab	Formulation	-
AD10P	10% AD + 90% EasyTab	Formulation	-
AD05P	05% AD + 95% EasyTab	Formulation	-
AD40L	40% AD + 60% Ludipress	Formulation	-
AD20L	20% AD + 80% Ludipress	Formulation	-
AD10L	10% AD + 90% Ludipress	Formulation	-
AD05L	05% AD + 95% Ludipress	Formulation	-

3.2 Material characteristics

Characteristics of the materials and the formulations studied are given in Table 3, which include particle sizes at D_{10}, D_{50} and D_{90} (volume % measured on a Malvern MasterSizer 3000) and other physical properties, including size span, and angle of repose (AoR) measured using a heap on the flat surface created by a fixed funnel according to ASTM C1444-00. Particle size span is defined in Eq. (5) to demonstrate the particle size range that can significantly influence the powder flow.

$$S_{span} = (D_{90} - D_{10})/D_{50} \qquad (5)$$

where, D_{50} represents the particle size where the percentage of powder is less or equal to 50% in volume. D_{10} and D_{90} are the sizes where 10% and 90% of the powder are below the size, respectively.

3.3 Experimental methods

3.3.1 Bench-scale segregation testers

Air-induced segregation of the formulated blends was studied on a fluidization segregation tester (ASTM D6941) built at the Wolfson Centre, as shown in Fig. 2(a). The air-induced segregation tester consists of a feeding hopper to allow the powder sample to be fed from the top, a vertical sectional column made from acrylic, and an air supply chamber at the base fitted with a permeable membrane. The column has 3 sections, each section is 31 mm in height and 24 mm in diameter, plus a top and a bottom section. A controlled airflow (about 5

L/min to 10 L/min depending on test materials) is introduced from the air chamber at the base of the column to the powder in the test column at a fluidization condition (just above the minimum fluidized air velocity) for one minute. The air was stopped gradually to allow particles to settle. The hopper and the upper section were cleaned of any spouted fines. The test sections were emptied into sample containers (approximately 7 g in each section). The experiments were undertaken under ambient conditions at temperature of 20°C and 40-60% Relative Humidity (RH). In this study, 5 sample sections were used, which are named Top, Top Centre, Centre, Bottom Centre and Bottom section, as shown in Fig. 2(a).

Table 3: Material physical properties of the ingredients and the formulations

Code	***Particle Size*** **(μm)**			**Size Span** ***(D_{90}-D_{10})/D_{50}***	**AoR (˚)**
	D_{10}	D_{50}	D_{90}		
AD	5.9 ±0.3	38.0 ±2.0	177.0 ±2.0	4.50	53.1 ±0.8
EasyTab	38.0 ±1.0	122.0 ±3.0	246.0 ±9.0	1.70	37.4 ±0.9
Ludipress	43.0 ±0.8	161.0 ±6.0	491.0 ±30.0	2.78	36.2 ±0.3
AD40P	12.5 ±0.2	79.0 ±0.9	198.0 ±2.0	2.35	51.3 ±1.0
AD20P	21.5 ±0.4	98.6 ±0.3	226.4 ±0.8	2.08	49.3 ±0.5
AD10P	26.4 ±0.2	106.0 ±1.0	232.0 ±8.0	1.94	42.3 ±0.5
AD05P	31.0 ±0.4	111.0 ±1.0	229.0 ±3.0	1.78	38.8 ±0.3
AD40L	12.6 ±0.6	85.0 ±5.0	294.0 ±10.0	3.32	48.8 ±0.8
AD20L	21.0 ±0.3	119.0 ±3.0	411.0 ±15.0	3.28	44.2 ±0.2
AD10L	26.2 ±0.6	129.0 ±5.0	420.0 ±20.0	3.05	37.1 ±0.6
AD05L	36.7 ±0.3	160.0 ±3.0	490.0 ±9.0	2.83	35.6 ±0.3

Surface rolling segregation tests were undertaken on a surface rolling segregation tester (Bridle, et al., 2004), as shown in Fig. 2(b), which can quantify segregation intensity in a heap formation where particles segregate due to surface rolling (including percolation) mechanism. The segregation tester consists of a cubic mixer and an adjustable inclined trough. In this study, the cubic mixer was not in use because some of the blends were cohesive and not suitable for the cubic mixer. In the experiments, the samples were blended in a tumble blender, as described in Section 3.3.3. The sample was discharged using a screw feeder at about 15 g/s feed rate with a drop height of about 10 cm above the first compartment (the same height as the cubic mixer outlet). The trough was placed at an angle equivalent to the angle of repose (AoR) for the powder to create a smooth and consistent heap of powder. The sample formed a slope of a heap with segregated patterns. Six equally sized compartments by sliding gates were discharged individually, and the sample was collected for further analysis. The section is named from top to bottom of the trough, as shown in Fig. 2(b). The trough is about 380 mm long, and the cross-section is 55 mm wide by 55 mm high. A sample of approximately 0.5l bulk material was used for the test. All test samples were subdivided using a mechanical riffler splitter, so appropriate samples (about 10 grams) could be obtained for size analysis to minimise random errors. Duplicate segregation tests were repeated.

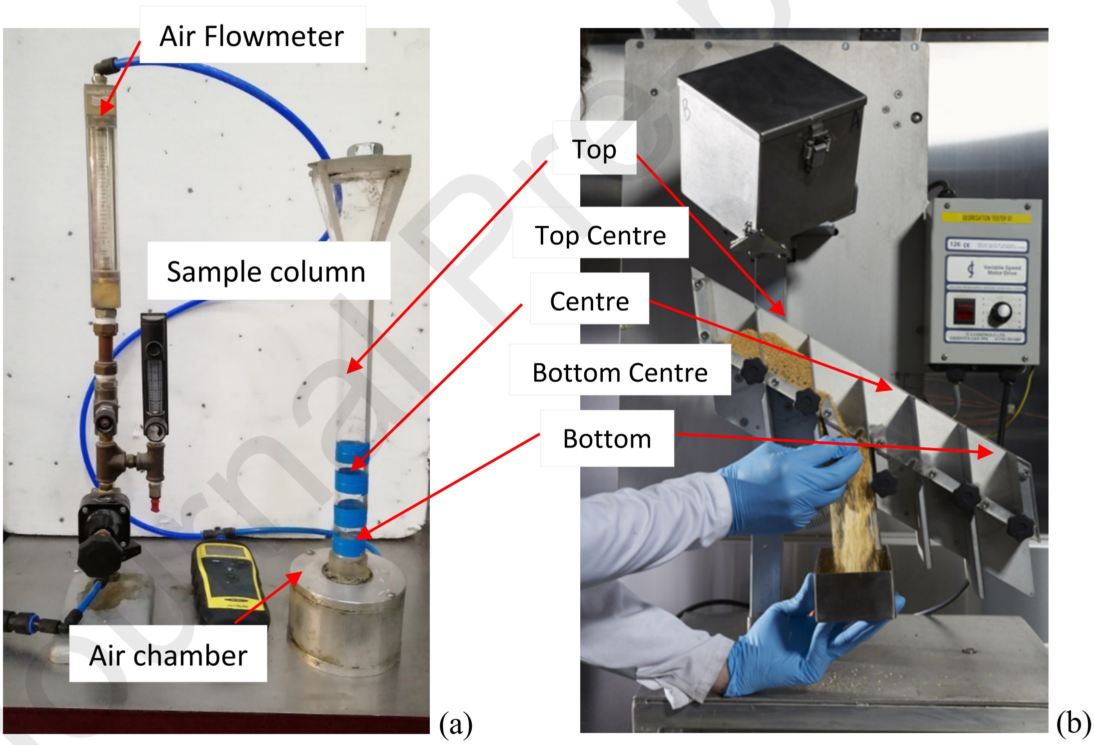
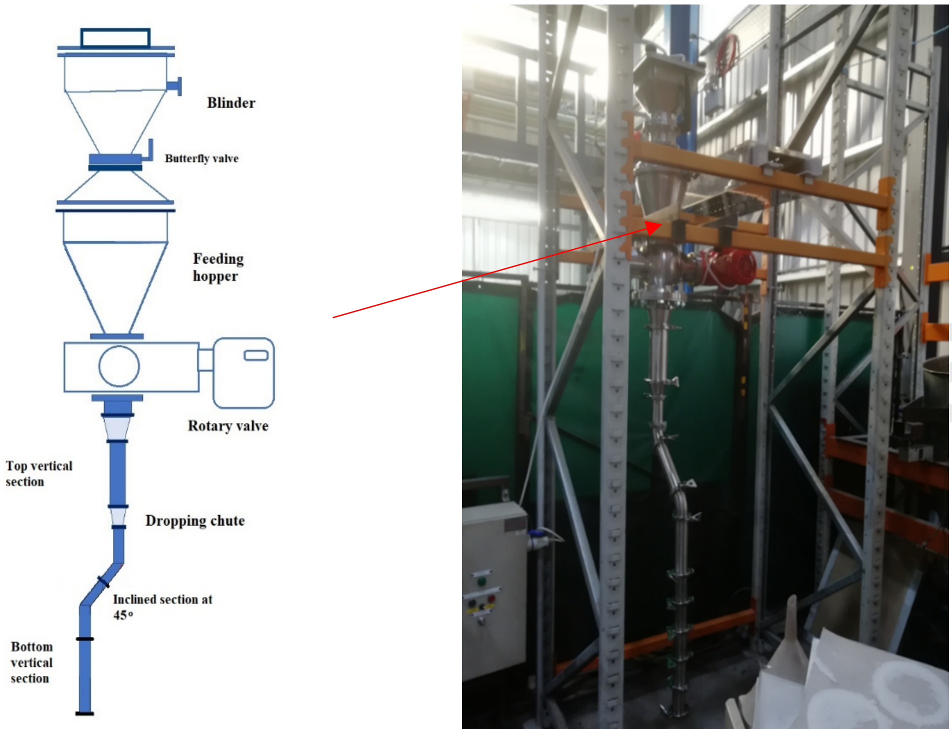


Figure 2: (a) Air-induced segregation tester, (b) Surface rolling segregation tester.

3.3.2 Pilot simulation rig at the Wolfson Centre

To study powder segregation in direct compression process of pharmaceutical formulations, with Roche's support an industrial scale simulation facility was constructed at the Wolfson Centre for segregation assessment in process. A sketch of the rig (not in scale) without the sampling section is shown in Fig. 3(a), and a photo of the pilot simulation rig with the sampling section is shown in Fig. 3(b).



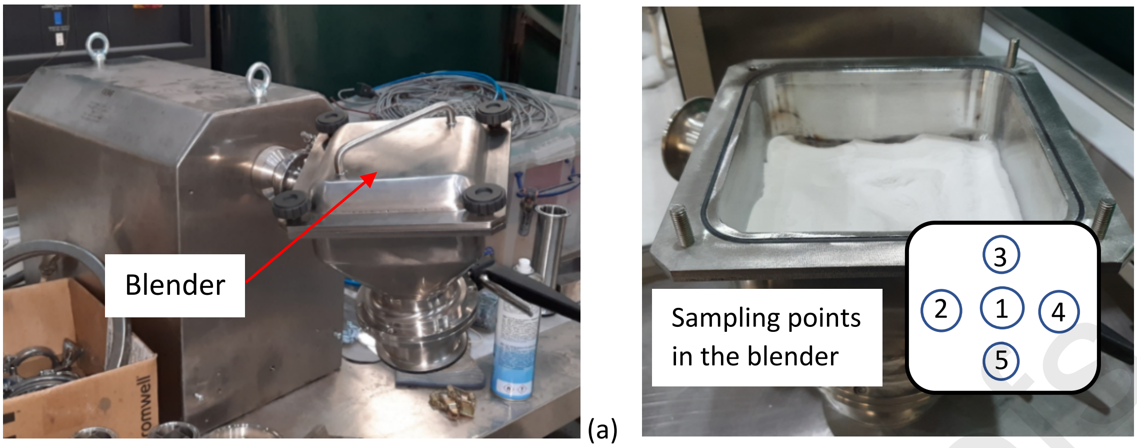
(a) (b)

Figure 3: (a) Sketch of a simulation pilot rig at the Wolfson Centre, and (b) a photo.

The pilot simulation rig was designed according to a practical design in industry, including a blender, a feeding hopper, a rotary valve, and a dropping chute replicating a sampling device used in practice. The rig simulates a feeding section for direct compression process of multiple blended batches. The drop height of the chute is about 1.06m with an inclined section of about 0.27m in length and 45^{o} degree located in the middle of the chute. The pipe diameter is 50mm. Five sampling points at the top and the bottom of the 4 samplers (0.5m in total) are used for the segregation check, which is named as Top, Top Centre, Centre, Bottom Centre, and Bottom, as indicated in Fig. 3(b).

3.3.3 Sample blending

A tumble blender was used for blending the samples, as shown in Fig. 4(a), which was closely based on a common design used in pharmaceutical manufacturing and had a total working capacity of about 2 litres. However, for sample mixing, every time, only about 0.5-litre sample was mixed in one sample preparation. In the blending process, sample powders were mixed at a rotational speed of 50 rpm for about 23 minutes for all blending processes. For validation of homogeneity, samples were taken from five different sampling points in the blender for measurements of Particle Size Distributions (PSDs), as shown in Fig. 4(b). The averaged result of the PSDs was used as the data for virgin samples in the calculation of the *SI*.



(a) (b)

Figure 4: Photo of the tumble blender (a) and 5 sampling points for analysis (b).

3.3.4 Particle size analysis

Particle size distributions (PSDs) were measured using the laser diffraction method (Malvern Mastersizer 3000). About 7-10 g sample taken from the segregation tests was introduced into a dry dispersion unit and formed five repeated measurements. For the measurement settings, the air dispersion pressure was 2.5 bars with a vibration feed rate of 40% at a gate gap of 1.5 mm for all the tests. The particle volume distribution was calculated using the 'general-purpose model' in the Mastersizer software. PSD of each sample was measured with all the repeats, and the average with standard deviation was reported and used for data analysis. With this method, volumetric concentrations of the PSDs were given, and particle sizes at D_{10}, D_{50} and D_{90} were also found.

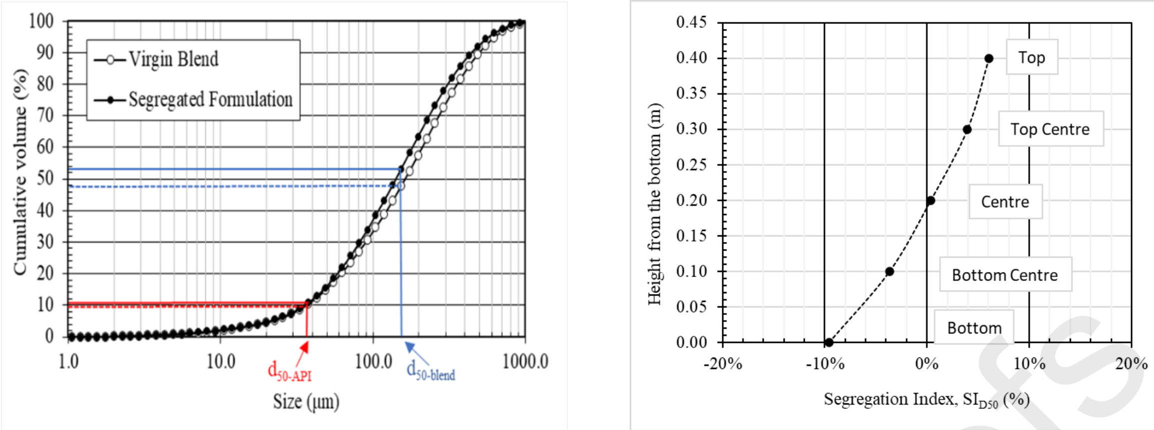
3.3.5 Averaged and Maximum SI

In this study, the *SI* is calculated based on the median size of a virgin blend (D_{50}) and a segregated sample of the blend. The procedure is exemplified in Fig. 5(a) for the formulation with 5% AD and 95% Ludipress, which has the D_{50} of 160 µm. The dotted blue line indicates the volumetric concentration of the virgin at the D_{50}, which is about 47.7%. In contrast, the plain blue line corresponds to the volumetric concentration of the segregated material at the D_{50} is about 53.1%. Thus, the SI_{D50} for this sample is about 11.3%, calculated using Eq. (1).

The SI_{D50} have been calculated for the segregated materials in the five regions (Top, Top Centre, Centre, Bottom Centre, and Bottom) of the pilot rig and bench-scale testers. An average, and a maximum SI can be calculated according to Eq. (6) and (7) using the *SI* values in the different regions, as shown in Fig. 5(b) for the process rig. In this example, the values for the average and the maximum *SI* are 4.7% and 15.6%, respectively.

$$SI_{avg} = \frac{1}{n}\sum_{i=1}^{n}|SI_i| \; (n = 5 \; as \; 5 \; positions) \qquad (6)$$

$$SI_{max} = |Max(SI_i) - Min(SI_i)| \qquad (7)$$



(a) (b)

Figure 5: (a) The method of the *SI* calculated at the D_{50} of the blend, (b) The *SI* calculated at the D_{50} for the EasyTab only at the five sampling points.

4 Results and discussion

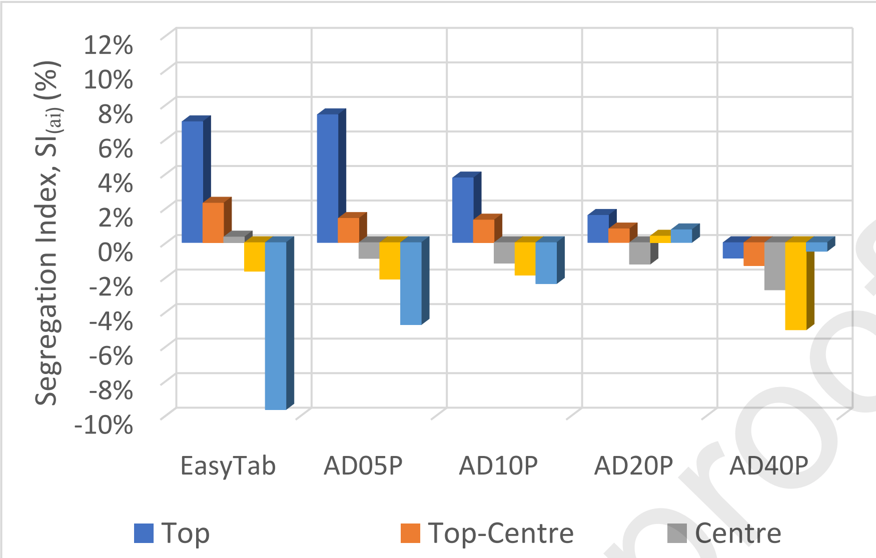
For this study, two CPEs and eight formulations formed with one API (Acetaminophen Dense) and the CPEs were used for segregation study on bench-scale tests and a pilot simulation process test rig. The results on the bench-scale testers and the pilot simulation rig are compared for correlation determination.

4.1 Segregation tests on the bench-scale testers

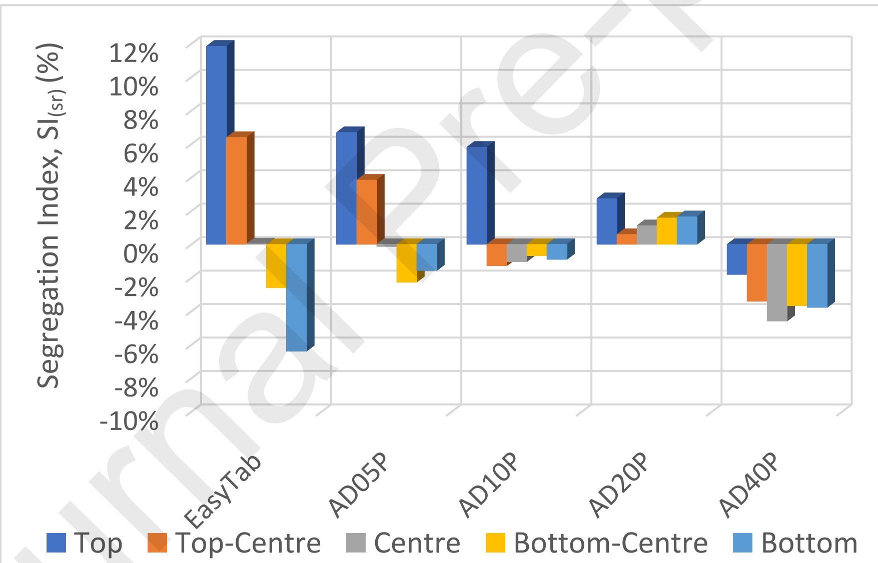
The results of the *SI* at the sample positions of Top, Top Centre, Centre, Bottom Centre, and Bottom (see Fig. 2) for the air-induced and surface rolling segregation tests are shown in Fig. 6 and 7, for the formulations formed with Prosolv® EasyTab and Ludipress®, respectively. The *SI* for the CPE only is also included in the results.

From the results, it is hard to differentiate the air-induced segregation tester and surface rolling segregation tester, although the segregation mechanisms for the testers are different. The results in Fig. 6 show the same trend of the segregation in terms of sample locations, where the fines are enriched in the top section and deficient in the bottom section, if the powder or the formulation is less cohesive in nature. With an increased API content, the materials tend to become more cohesive, resulting in less segregation. However, further increased API content does not prevent the segregation completely, but it tends to lose some fine contents in all the sections. This is because, sometimes, that could be significant due to other segregation mechanisms, such as electrostatic charge, which has not been evaluated here.

The results in Fig. 7 are for the Ludipress and the formulations, which show a similar tendency as the formulations of the EasyTab, but a much stronger effect of the segregation. For the Ludipress and the formulations, the levels of segregation for the two testers are also similar, but air-induced segregation is slightly higher than the surface rolling segregation. Compared the CPEs, the Ludipress has a wider particle size range and less cohesiveness. The material properties for the CPEs also strongly influence the material properties of the formulations. As shown in Table3, the Ludipress contains quite significantly large particles with a D_{90} of 491 μm, compare to the EasyTab which has a D_{90} of 246 μm. However, they have a similar angle of repose (37.4° for EasyTab and 36.2° for Ludipress).



(a)



(b)

Figure 6: Segregation Index at the 5 sampling points for the EasyTab and the formulations on: (a) the air-induced segregation tester and (b) the surface rolling segregation tester.

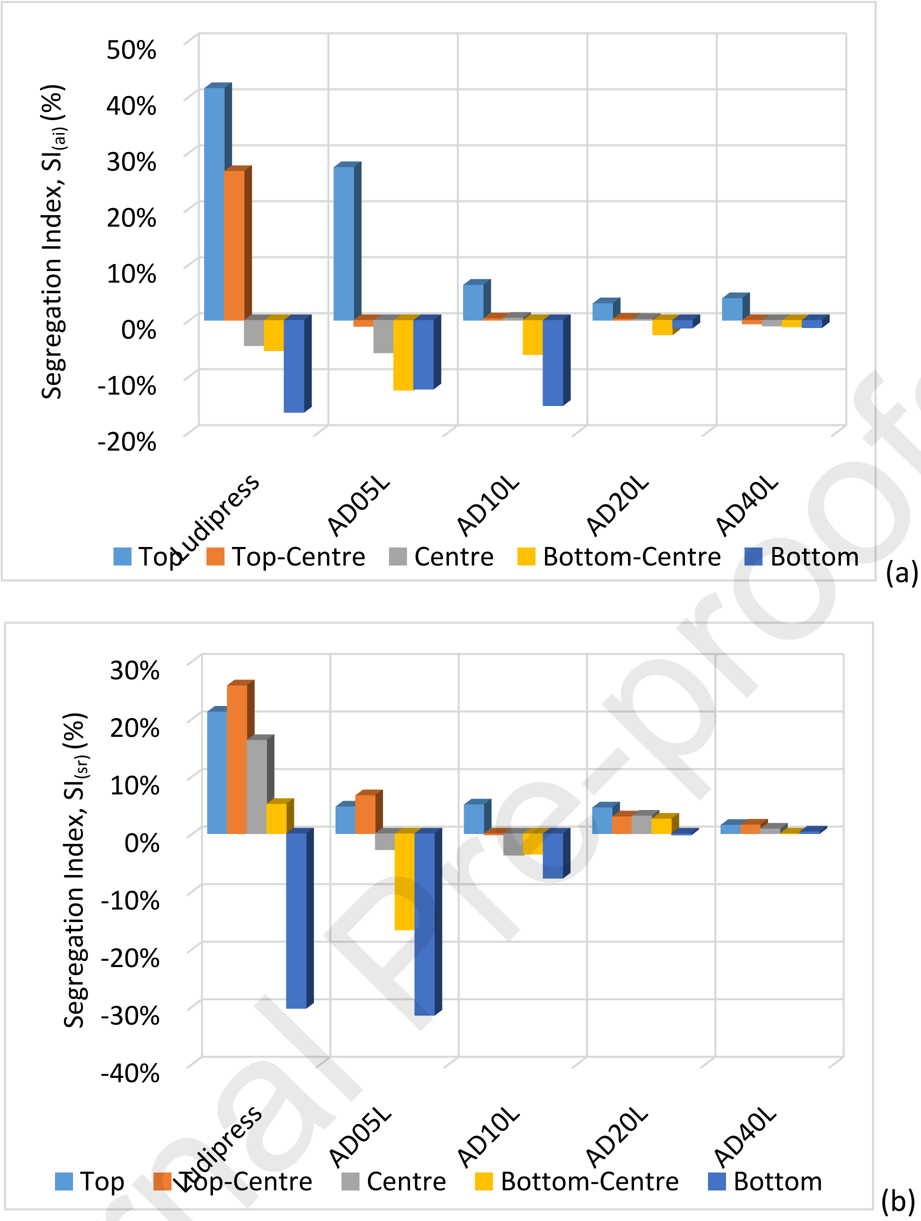


Figure 7: Segregation Index at the 5 sampling points for the Ludipress and the formulations on: (a) the air-induced segregation tester, and (b) the surface rolling segregation tester.

4.2 Segregation tests on the pilot simulation rig

The CPEs and the formulations have been tested on the pilot simulation process rig. Taking the samples at the five location points (shown in Fig. 3(b)), the PSD of the samples was measured, and *SI* at the sampling points was calculated according to the virgin sample prepared. The results of the segregations for the pilot simulation rig are shown in Fig. 8 in terms of the CPE used in the formulations.

The results show a clear decreasing trend of the segregation in the process rig, when the content of API is increased, and the powder becomes more cohesive. Compared to what has been seen on the bench-scale testers, the segregations are much similar, but the behaviour of the Ludipress formulations is different (Fig. 8(b)). For the Ludipress and the formulations, in the process, it loses fine particles in the top section rather than accumulating the fines (as the *SI* is a negative number, which means the percentage of fines is reduced). This could be due to a stronger effect of electrostatic charge for Ludipress where the fines which contains more charge are easily coated onto the metal surface of the equipment, and the fines removed from the blends are remained on the equipment surface. It is noticed that from Table 3 the API (Acetaminophen Dense) is much finer than the CPEs. If the CPE contains more charges, the charges can easily be passed to the API material and then influence the segregation of the formulations.

Also, the Ludipress has a large size range compared to the EasyTab, so more segregation found in the formulations of Ludipress but not as much as that found in bench-scale testers.

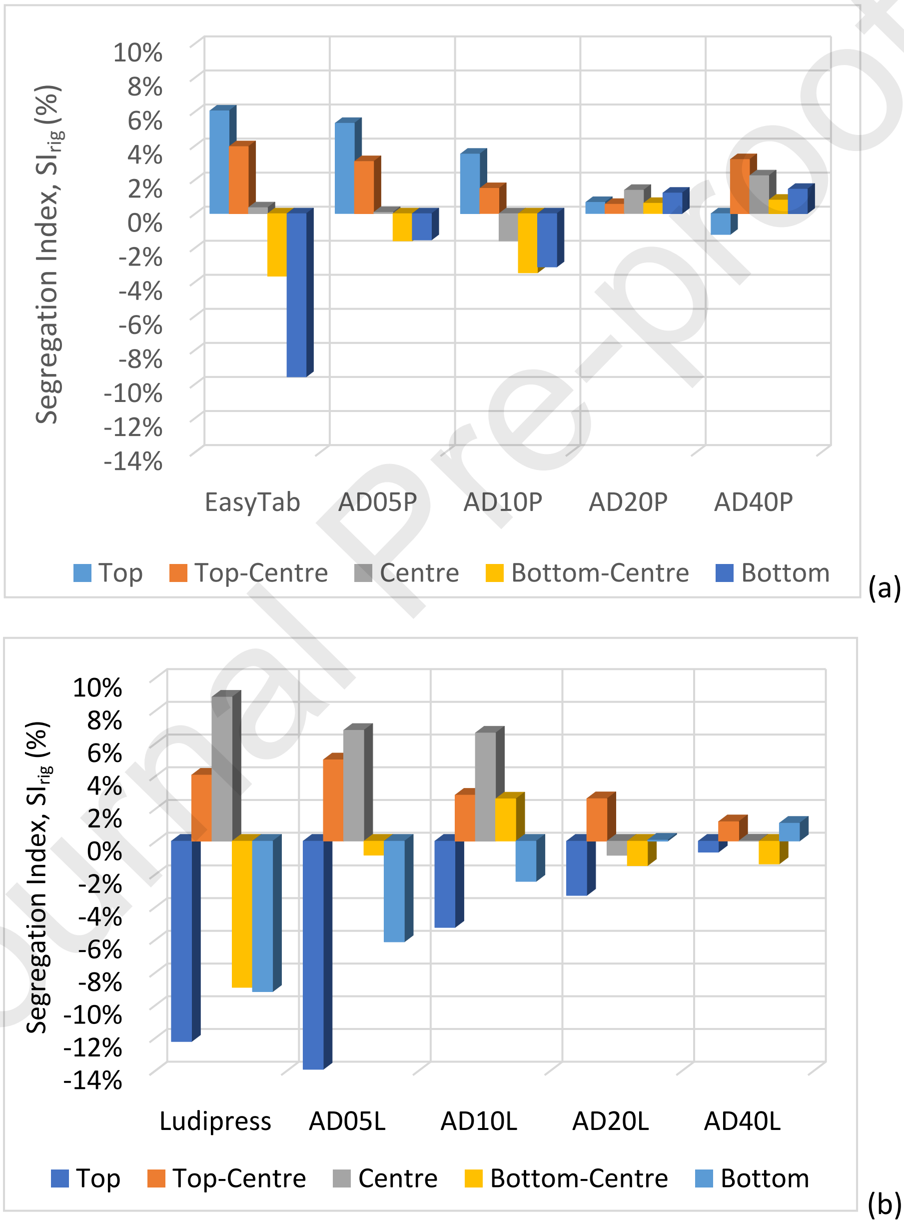
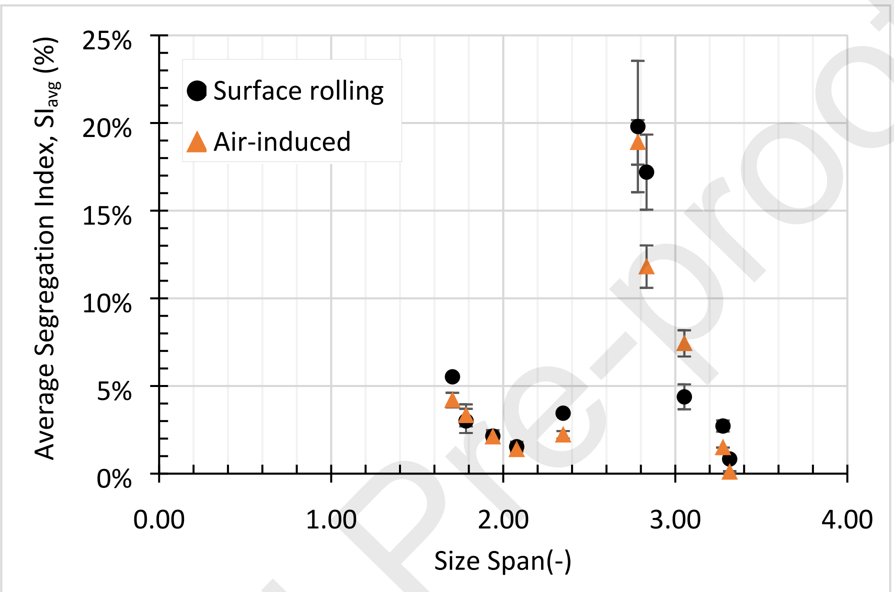


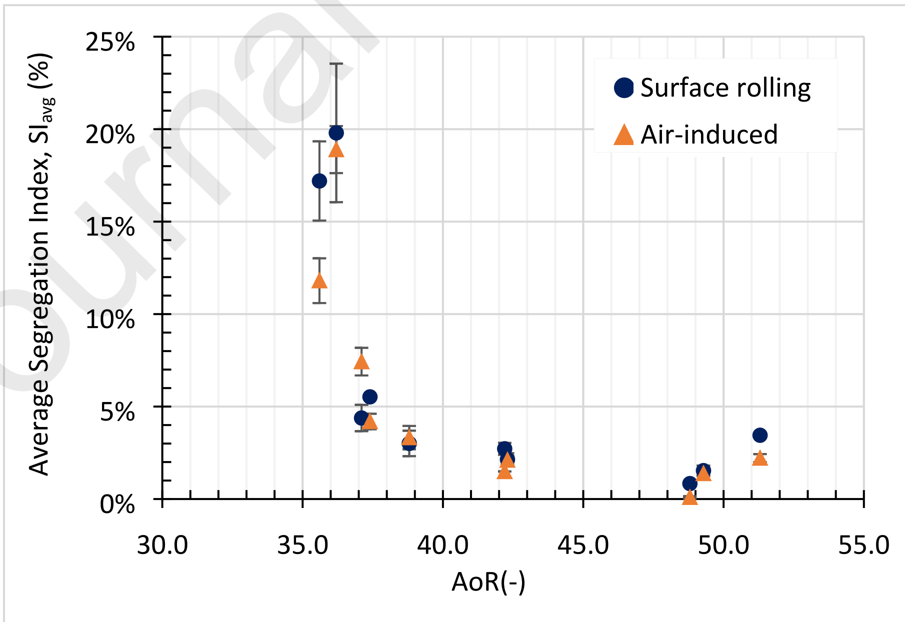
Figure 8: Segregation Index, SI_{D50} at the five sampling points on the pilot rig for (a) the EasyTab and the formulations, and (b) the Ludipress and the formulations.

4.3 Influences of size span and angle of repose

The SI_{avg} of the CPEs and formulations on the bench-scale testers are calculated using Eq. 6, which are compared with the particle size span (using Eq. 5) and the angle of repose measured. The results in Fig. 9(a) show the influences of particle size span clearly, but it is hard to correlate them. Normally, a higher size span gives a higher risk of particle segregation, but it really depends on the cohesiveness of the powders. The angle of repose for a powder can represent the cohesiveness of the powder. The results in Fig. 9(b) show a sharp drop of the segregation when the angle of repose reaches about 37-38 degrees, which is slightly bigger than the value obtained in the previous work (about 33-34 degrees) (Deng, et al., 2021b).



(a)



(b)

Figure 9: The averaged SI_{avg} measured on the bench-scale testers versus (a) size span of particles, (b) the angle of repose for all formulations and CPEs.

4.4 Comparison between the bench-scale testers and the process rig

The segregation indices SI_{avg} and the SI_{max} of the CPEs and formulations on the bench-scale testers and on the pilot simulation rig using Eq. 6 and 7 are shown in Table 4. The standard deviation of the SI for each bench-scale tester point can be found in Fig. 10.

Table 4: Segregation index measured for the CPEs and the formulations studied

Materials	Surface Rolling Seg.		Air Induced Seg.		In the Pilot Rig	
	SI_{avg}	SI_{max}	SI_{avg}	SI_{max}	SI_{avg}	SI_{max}
EasyTab	5.5%	18.2%	4.2%	16.7%	4.7%	15.6%
AD05P	3.0%	9.0%	3.3%	12.5%	2.3%	6.9%
AD10P	2.1%	8.0%	2.1%	6.1%	2.6%	7.0%
AD20P	1.5%	2.2%	1.4%	3.6%	0.9%	0.8%
AD40P	3.4%	2.8%	2.2%	5.0%	1.8%	4.4%
Ludipress	19.8%	57.9%	18.9%	57.9%	8.7%	21.1%
AD05L	17.2%	38.2%	11.8%	41.4%	6.5%	20.7%
AD10L	4.4%	12.8%	7.4%	23.1%	4.0%	11.9%
AD20L	2.7%	5.1%	1.5%	6.0%	2.1%	5.9%
AD40L	0.8%	2.0%	0.1%	5.3%	1.5%	4.1%

The comparison of the SI measured on the testers and the process rig used in this study is shown in Fig. 10. A good agreement is observed between the bench-scale testers and the process rig for the SI_{avg} lower than 5% and the SI_{max} less than 20%. Also, it is almost a linear relationship between the small bench-scale testers and the process rig. For the measurements using the bench-scale testers, the SIs measured are only subject to the materials properties without the influence of the test equipment. However, in the process rig, the segregation intensity of a powder is limited to a constant level due to limited kinetic energy applied to the powder. It is thought that with the solids flow rate used the drop height is not enough to produce aerodynamic effect on the powders, so the segregation intensity is limited even if the material is more segregable. This phenomenon is clearly shown for the maximum segregation index shown in Fig. 10(b), where the SI_{max} in the pilot rig is limited to about 20% for the powders, while the SI_{max} is higher than 20% as measured in the bench-scale testers.

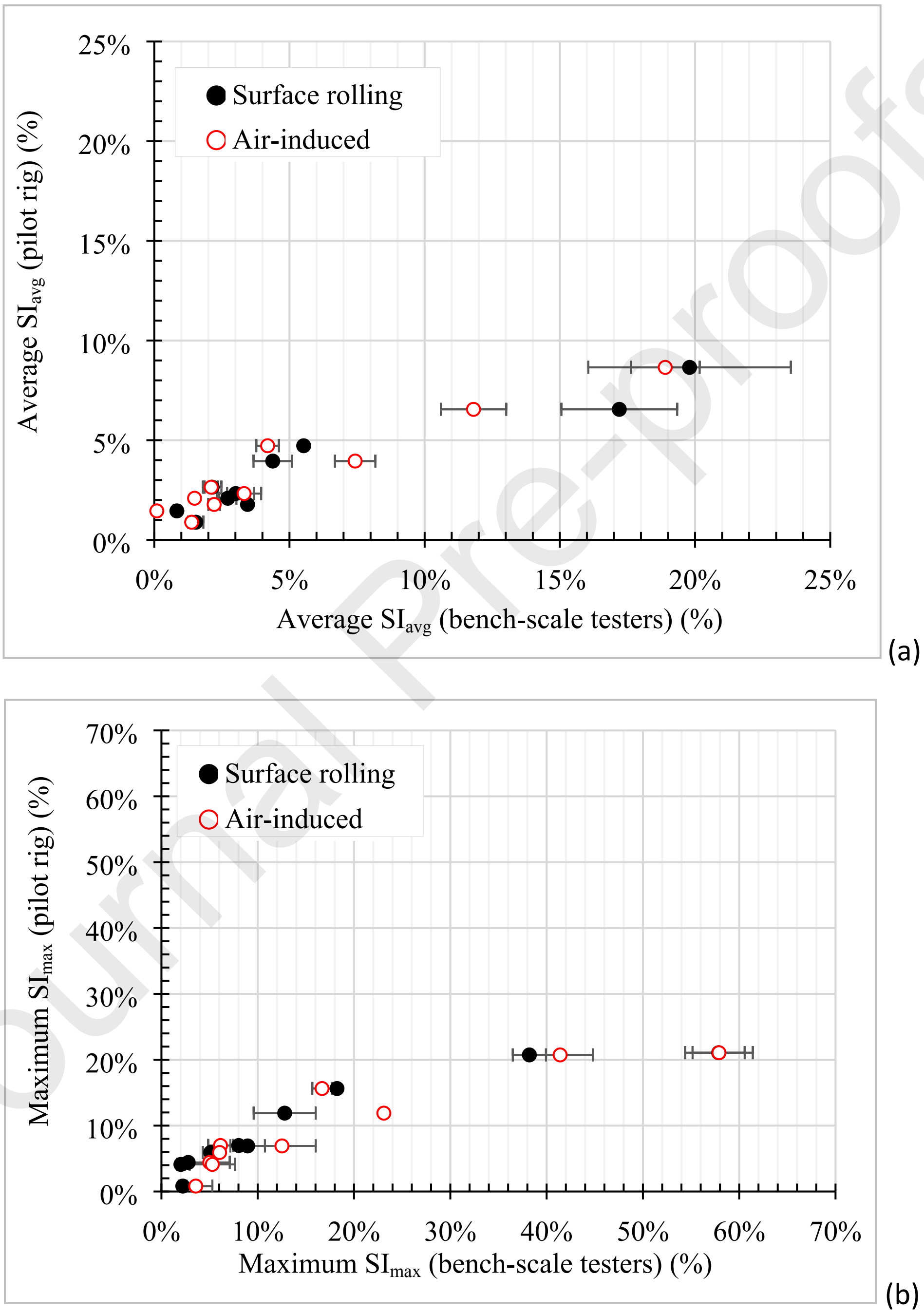


Figure 10: (a) The SI_{avg} and (b) the SI_{max} measured on the bench-scale testers versus the SI_{avg} and the SI_{max} on the pilot process rig, for all formulations and CPEs.

By taking the range of the SI_{max} <20% in Fig. 10(b), a linear correlation of the SI_{max} is recognised between the bench-scale testers and the process rig (see Fig. 11), although a lot of scatters of the data to the fitted line are shown. It shows the bench-scale testers give a slightly higher measured segregation compared to the process rig overall by the gradient of the fitted lines. This can be because the segregation of powders in a process may suffer from different types of segregation or a combination of different mechanisms. Nevertheless, the results in Fig. 11 indicate that powder segregation in a process can be evaluated by a small bench-scale tester, whatever the segregation mechanism is. However, there could be a combination of different mechanisms.

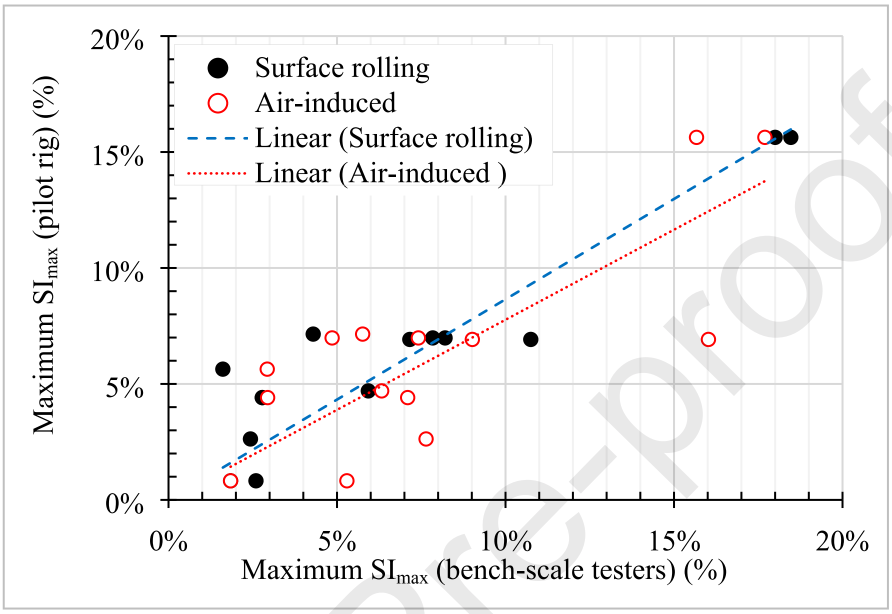


Figure 11: Comparison of the SI_{max} between the process rig and the bench-scale tester for the formulations where the SI_{max} is less than 20%.

Taking the data in Table 4, the correlation coefficients of the *SIs* between the bench-scale testers and the pilot simulation rig are obtained and shown in Table 5. It shows that the correlations between the bench-scale testers and the pilot simulation rig are strong, and always over 90%. The results in Fig. 10 (a) show that both the bench-scale testers give almost identical correlations to the process, although the powder in a process can suffer from multiple types of segregation. Thus, the bench-scale testers can be used for the segregation assessment of a process individually.

Table 5: Correlation coefficients of the SIs between the testers and the process rig

	Average SI			***Maximum SI***		
	Rolling	*Air-induced*	*Pilot rig*	*Rolling*	*Air-induced*	*Pilot rig*
Rolling	1			1		
Air-induced	0.9309	1		0.9771	1	

Pilot rig	0.9145	0.9420	1	0.9050	0.9001	1

4.5 Linear regression model for segregation mechanisms

The results in Fig. 11 highlighted that there is a possibility to develop a predictive model for a process using harshness factors in Eq. (4) based on the segregation mechanisms. Taking the assumption as a linear regression, the Eq. (4) can be expressed as:

$$SI_p = F_{h(0)} + F_{h(sr)} \cdot SI_{s(sr)} + F_{h(ai)} \cdot SI_{s(ai)} \tag{6}$$

where SI_p is a segregation level in a process, $F_{h(0)}$ is the constant harsh level of segregation in the process, $F_{h(sr)}$ is the harshness factor for the surface rolling segregation, and $F_{h(ai)}$ is the harshness factor for the air-induced segregation. Using the method of least squares for multiple regression for the data shown in Table 4, the harshness factors in Eq. (6) can be obtained as 0.0133 ($F_{h(0)}$), 0.1369 ($F_{h(sr)}$) and 0.2537 ($F_{h(ai)}$) respectively for the averaged SI. The Eq. (6) can be expressed as:

$$SI_p = 0.0133 + 0.1369 \cdot SI_{s(sr)} + 0.2537 \cdot SI_{s(ai)} \tag{7}$$

The statistical analysis of this model is shown in Table 6:

Table 6: Statistic analysis of the segregation harshness model in the process

Regression Statistics

Multiple R	R Square	Adjusted R Square	Standard Error	Observations
0.9882	0.9765	0.8654	0.0068	10

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	0.01742	0.0174	373.36	5.3403E-08
Residual	9	0.00042	4.667E-05		
Total	10	0.01784			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0	N/A	N/A	N/A	N/A	N/A
Prediction of Rig	1	0.0518	19.322	1.23E-08	0.8829	1.1171

Using the model of Eq. (7), the predictions of the SI_p based on the measured *SI* for surface rolling and air-induced segregation are compared to the measurements for the averaged *SI* of the process rig. The line fit plot of the predictions is shown in Fig. 12 compared to the measurements, which shows that the model can give a good prediction if multiple linear regression is used. The correlation coefficient (R^2) between the predictions and the measurements is 0.977. The standard error of the predictions is about 5.2%. The predicted SI_p values based on the measured *SI* on the bench-scale testers are directly compared and shown in Fig. 13.

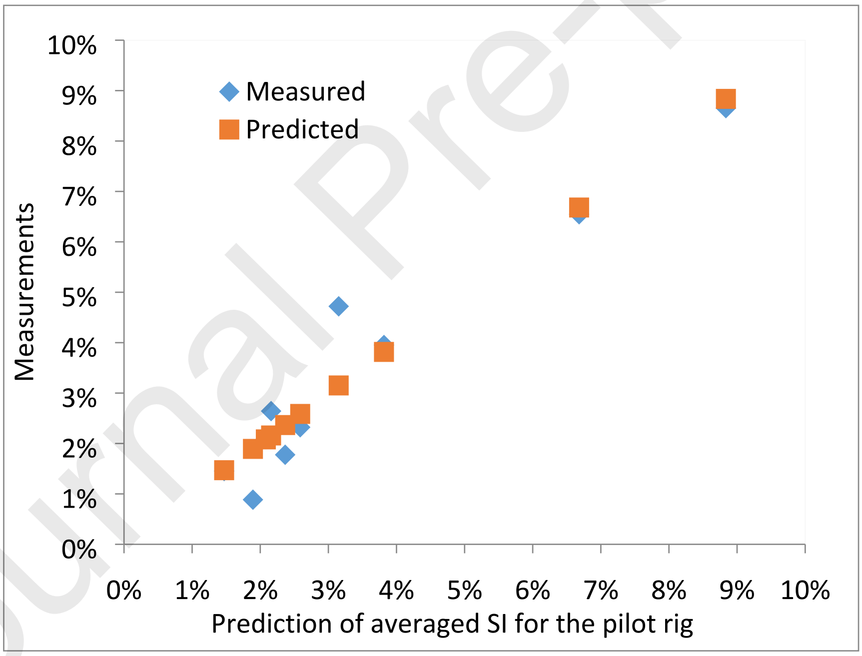


Figure 12: Line fit plot for the averaged SI_p between the measurements on the process rig and the prediction from the model of Eq. (7) for the formulations tested.

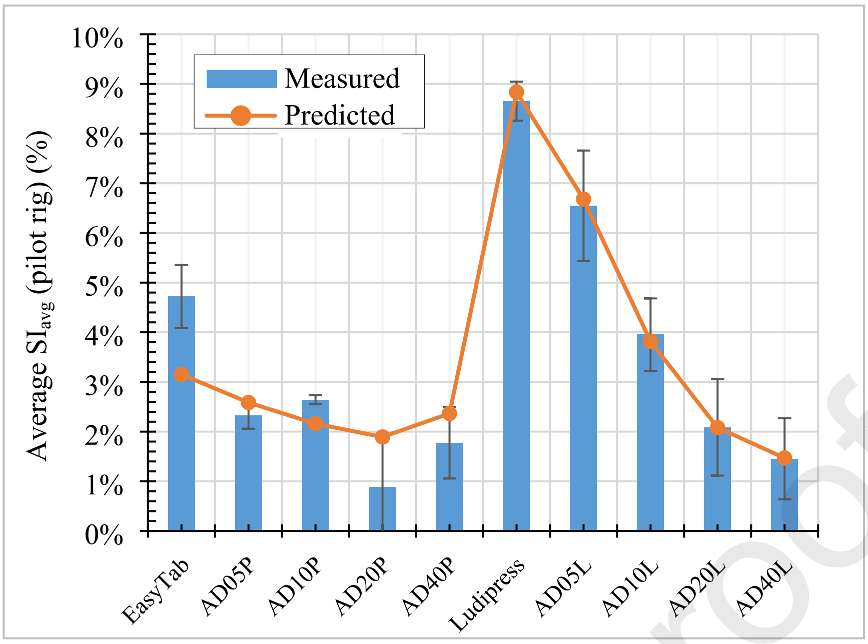


Figure 13: Comparison of the averaged SI_p between the measurements on the process rig and the prediction from the model of Eq. (7) for the formulations tested.

The model shows some significant errors in the predictions of the EasyTab only and the blends with a high ratio of API. Particularly for EasyTab and the AD20P formulation, the errors of predictions are about 33% and 52% respectively. For the Ludipress and the blends, the predictions are very good to match the experimental results. It reveals that the concept of harshness factors and the model may work subject to the material and the process. In this study, the linear regression model works well with Ludipress and blended formulations, but the model shows more significant errors for the predictions of EasyTab and blends. Also, it is noticed that the coefficients for the mechanism factors are about 0.14 and 0.25, which means the mechanism factors may not be so important as the material properties.

5 Conclusions

Segregations of eight formulated pharmaceutical powders were studied using two types of small bench-scale testers (air-induced and surface rolling segregation) and a pilot simulation process rig for a direct compress process.

The results show that the segregation intensity measured by segregation index on the bench-scale testers is linearly correlated to that in the process if the maximum segregation index (SI_{max}) for the powders is less than 20%. The correlation coefficients of the segregation intensity between the bench-scale testers and the process are all higher than 0.9. Therefore, it can be concluded that either of the small bench-scale testers can be used for the evaluation of powder segregation in a process.

Also, it shows that the segregation in the process does have a limit for the powders with high segregation intensity on the small bench-scale testers (SI_{max}>20%). This is believed that the powder with high segregation intensity on the small bench-scale testers cannot gain enough kinetic energy in the process, so the segregation of the powder is limited to a constant level of segregation intensity in the process even if the powder has a high segregation intensity on the small bench-scale testers. The bench-scale testers measure the segregation intensity of a powder only based on material properties.

For the powders, a consistent linear relationship was obtained between the bench-scale testers and the process equipment regardless of the segregation mechanisms. Based on the segregation harshness factors, a linear regression model was developed to predict the segregation in a process. The model shows good predictions, but some large errors for the EasyTab and the AD20P formulation. Correlation analysis shows that the segregation mechanisms do not play an important role in the segregation of a process, although the powders can suffer from multiple types of segregations in the process, such as air-induced and surface rolling segregation. This study indicated that any of the small bench-scale testers could provide an advanced segregation evaluation for formulated powders in processes.

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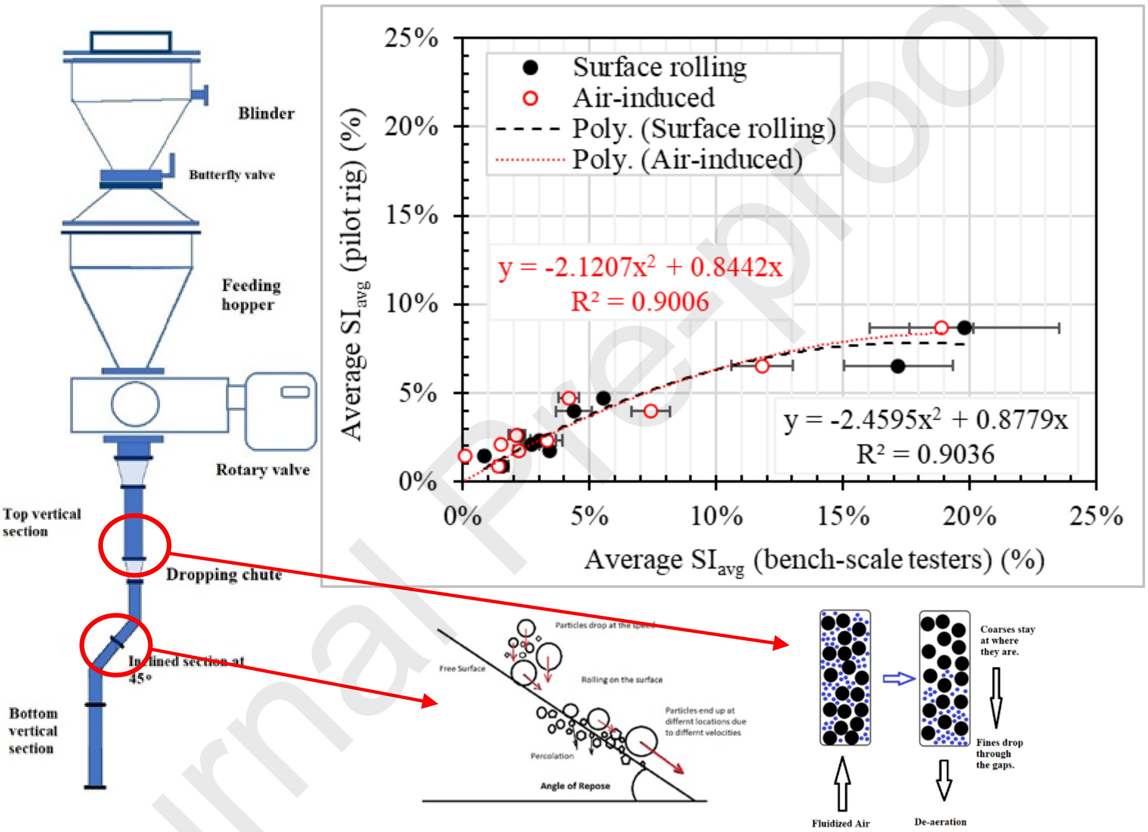
Highlights:

- Segregation of formulated powders in a direct compression process,
- Assess powder segregation in a process using bench-scale testers,
- Validation of segregation index measured from bench-scale testers with process rig,
- Segregation on bench-scale tester is highly correlated to the segregation in process,
- A prediction model was established based on segregation harshness factors,
- Measured segregation index on bench-scale testers linearly correlated to process rig,



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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:

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