Size-induced segregation during die filling

A. Zakhvatayeva, C. Hare, C.Y. Wu*

Department of Chemical and Process Engineering, University of Surrey, Guildford GU2 7XH, UK

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ABSTRACT

The present study investigated particle size-induced segregation during die filling of binary pharmaceutical blends, consisting of fine and coarse particles in various fractions. Coarse fraction was made of milled and sieved acetylsalicylic acid, whereas the fine fraction was mannitol. The die filling process was carried out in gravity filling and suction filling. The segregation was assessed through determination of the coarse component concentration using UV–Visible spectrophotometry. The obtained values of concentration, determined for ten units of identical volume inside the die, were used to calculate the segregation index (SI), which was an indicator of uniformity of the powder blend deposited into the die. It was found that high segregation tendency was generally observed during gravity filling at a low velocity, due to the effect of air drag, and during gravity filling at a high velocity, as it was carried out through three consecutive filling steps. The lowest segregation tendency was generally observed during suction filling at a low velocity. The horizontal segregation was mostly observed in the top layers of the die, due to mainly two mechanisms: coarse particles cascading down the heap formed by the powder in the final steps of die filling, which produces higher coarse concentration at the near side of the die, observed at low coarse concentration; or coarse particle cascading down the top surface of the flowing powder stream into the die, which increases the coarse concentration at the far end of the die.

1. Introduction

Tablets are the most common pharmaceutical solid dosage form, accounting for approximately 70% of all clinically used dosage forms (Kaur, 2012). Tableting is also widely used in the manufacturing of metallurgical and ceramic components, as well as food products and detergents (Coube et al., 2005; European Commission, 2011). Die filling is a critical manufacturing step and involves the delivery of powders into a mould (die) of given shape and size, followed by compression of the blend into a tablet.

One of the most important parameters in quality control of medicinal tablets is their content uniformity (European Pharmacopoeia, 2008), which is assessed on a certain number of dosage units. The content of active pharmaceutical ingredient (API) in the tested units is required to be within certain limits of concentration. This value, however, does not provide any indication about the distribution of API particles within a single tablet, which in turn is affected by the distribution of the API within the powder blend deposited into the die during die filling. It is desirable to have a uniform distribution of API and excipient particles in the die, as a non-uniform component distribution might lead to such tableting issues as lamination and sticking (Furukawa et al., 2016).

The investigation of powder flow behaviour during die filling has been commonly performed using a model system, consisting of a stationary die and a moving shoe feeder (Schneider et al., 2007; Wu et al., 2003; Wu and Cocks, 2004; Wu et al., 2012). Such a system allows the actual die filling process to be mimicked and the influence of die geometry, powder properties and filling velocity on the die filling behaviour to be investigated. The process of powder delivery into the die can generally occur in the presence of air, where powders are deposited into the die under the influence of the gravitational force. This type of filling is known as gravity filling (Wu et al., 2003; Wu and Cocks, 2004). The filling can however be aided by a vertically displacing piston, positioned inside the die, that creates a pressure gradient in the die when the piston moves downwards, drawing (sucking) the powder into the die. This kind of filling is known as suction filling (Wu and Guo, 2012; Mills and Sinka, 2013).

The presence of air has a significant impact on die filling. As demonstrated by Guo et al. (2009), the sensitivity of powder particles to air can be expressed using a dimensionless parameter:

$$\xi = A_r \Phi_\rho \qquad (1)$$

where Φ_ρ is the ratio of particle density, ρ_s, to the air density, ρ_a, and A_r is the Archimedes number, calculated as:

$$A_r = \frac{\rho_a(\rho_s - \rho_a)gd_p^3}{\eta^2}$$

(2)

where d_p is the particle diameter, η is the air viscosity and g is the gravitational acceleration. Depending on the combination of particle density and size, two regimes can arise during die filling in air. The flow of smaller and/or lighter particles is significantly affected by the presence of air (air-sensitive regime), whereas for larger and heavier particles the effect of air is negligible (air-inert regime). To quantify the powder flow sensitivity to the presence of air, an air sensitivity index was introduced (Yu et al., 2009):

$$\zeta = 1 - \ln \xi/\ln \xi_c$$

(3)

where ξ_c describes a critical value of the dimensionless parameter, which corresponds to the transition from the air-sensitive to the air-inert regime. The particles are considered air-inert when $\zeta \leq 0$, and air-sensitive when $0 < \zeta < 1$. When a blend of air-sensitive and air-inert particles is deposited into a die in the presence of air, a layer of air-sensitive particles is observed on the top of the powder bed under the influence of air drag, indicating that segregation occurs with a lower concentration of air-sensitive particles in the bottom and a higher concentration at the top.

Gravity filling has been extensively investigated over the last two decades (Guo et al., 2009, 2011; Schneider et al., 2007; Wu et al., 2003, 2012; Wu and Cocks, 2004; Zahrah et al., 2001). However, relatively few studies on suction filling have been reported. Mills and Sinka (2013) investigated the die filling behaviour of microcrystalline cellulose of various grades, using gravity and suction die filling systems. They found that the critical velocity (Wu et al., 2003; Wu and Cocks, 2004; Wu et al., 2012) was significantly improved during suction filling, particularly for fine powders. The authors observed that the concept of critical velocity might not be suitable for fitting the suction fill data, since powder filling behaviour differs in gravity and in suction conditions. In suction, the die filling performance is more reliant upon powder properties, such as particle size an density (Mills and Sinka, 2013).

The lack of an appropriate term to describe the concept of critical filling velocity in suction was addressed recently (Zakhvatayeva et al., 2019). For a given suction filling system, an optimal ratio of suction to filling velocity could be identified that is influenced by the geometry of the system (fill shoe length and die width). It was observed that above this ratio, the filled mass of both free-flowing and cohesive powders would face a gradual decrease. Below this optimal suction to filling ratio, the behaviour of the free-flowing and cohesive materials differed. Therefore, for a given suction filling system a single velocity value is not enough, but it should be replaced with a ratio of filling (shoe) velocity to the suction (piston) velocity.

Suction filling was numerically modelled by Wu and Guo (2012). The numerical results agreed with previous experimental investigations of suction filling (Jackson et al., 2007), showing a significant ability of suction to improve the mass flow rate, and therefore the efficiency of the die filling process. However, most of these studies mainly focused on monodisperse, single-component systems, and did not address the issue of size-induced segregation inside the die. The tendency to segregation increases with the increase of particle size difference (Xie et al., 2008; Ketterhagen et al., 2007). Particle size was found to influence cohesive forces between particles in terms of electrostatic, van der Waals and hydrophilic interactions (Davies, 2001).

To some extent, die filling is similar to the powder discharge from a hopper, and the phenomenon of size-induced segregation in hopper flow has been extensively analysed. According to Standish (1985), the concentration of fines during the hopper discharge is high at the beginning and then decreases towards the end due to the percolation of fines through the voids in the bed of coarse particles. Interestingly, it was found (Arteaga and Tüzün, 1990) that segregation was reduced when there was a sufficiently high concentration of fines in the mixture.

A model was proposed, according to which the segregation could be prevented by covering the surface area of all the coarse particles with fines.

Extensive studies of segregation during die filling have been carried out numerically. Guo et al. (2011) conducted a numerical analysis of size-induced segregation, using a coupled DEM-CFD method, to investigate the segregation behaviour of binary blends with different particle sizes. The simulated mixtures consisted of spherical fine particles of 90 μm and spherical coarse particles of 360 μm. Mass fraction of fine particles was set to 10%. The experimental die filling system was represented by either a stationary or a moving feeding shoe, and a stationary vertical die. The tests were carried out both in air and vacuum. It was generally observed that the presence of air significantly influenced the particle segregation. Along the width of the die the concentration of fines was the lowest in the centre in vacuum filling, and the highest in the presence of air. Fine particles are more sensitive to the presence of air, which restricts their flow in the regions close to the die walls. In the presence of air the powder stream is therefore enriched in fine particles in the centre and in coarse particles closer to the die walls. Along the die height, more fines were present at the bottom in vacuum filling, due to the percolation of fines through the empty spaces between coarse particles. This percolation was reduced in the presence of air.

In the case of the moving shoe, the free-flowing coarse particles tend to cascade over the top of the fines, thus resulting in the stream of coarse particles flowing to the far end of the die (with respect to the shoe direction). This type of flow, described by Wu et al. as "nose flow" (Wu and Cocks, 2004; Mills and Sinka, 2013), prevails at low filling velocities and is the most efficient in filling the die completely. As the shoe moves over the die, the nose flow is replaced by bulk flow (Wu and Cocks, 2004; Mills and Sinka, 2013), where particles start detaching from the bottom of the powder bed. This way, the powder in the shoe and the powder deposited into the die shear against each other, facilitating the percolation of fines through the bed of coarse particles and thus causing more fines to be deposited in the upper layers of the die.

Computational studies on die filling were performed using a tablet press feed frame equipped with rotating paddles (Mateo-Ortiz et al., 2014). The size-induced segregation was investigated numerically using a coupled discrete element method (DEM) and computational fluid dynamics (CFD). It was observed that at low paddle speed the difference in average particle size along the die height increases, whereas it decreases as the paddle speed increases. Due to segregation, there are smaller particles in the bottom half of dies. At low paddle speeds the particles are moving relatively slowly and the gravity force prevails over the force exerted by the rotating paddles. The particles have more time to rearrange and to percolate, rather than to move horizontally. As the paddle speed increases the percolation is reduced because particle are prevented from moving vertically towards the die bottom. The results again highlight the contribution of gravity in promoting the vertical segregation in the absence of any additional die filling mechanisms (such as paddle or suction feeding).

The influence of die velocity and particle size on the segregation of binary blends was also assessed numerically (DEM) by Furukawa et al. (2016). The authors observed that small particles tend to flow toward the bottom corner of the die in the moving direction of the shoe. The uppermost region of the die, however, presented little vertical segregation. The lower half of the die presented vertical segregation due to the particles percolation. The percolation phenomenon was increased by a decrease of the smaller particle size.

Despite detailed numerical investigations of segregation during die filling (Furukawa et al., 2016; Guo et al., 2011a, 2011b; Mateo-Ortiz et al., 2014), the issue is not fully understood. The present study aims to experimentally explore size-induced segregation of binary blends with various fine-to-coarse ratios during die filling. Moreover, this study also aims to explore the influence of gravity and suction filling on the size-induced segregation of pharmaceutical mixtures.

2. Materials and methods

2.1. Materials

Binary blends were prepared using mannitol (Pearlitol® 100SD; Roquette Pharma, France) and Acetylsalicylic acid, referred to as ASA ($\geq 99.0\%$, Sigma-Aldrich, USA). Reagents used to prepare analytical solutions for ASA concentration estimation included salicylic acid (ACS reagent, $\geq 99.0\%$, Sigma-Aldrich, USA), iron (III) chloride (reagent grade, 97%, Sigma-Aldrich, USA), potassium chloride (ACS reagent, 99.0–100.5%, Sigma-Aldrich, USA) and sodium hydroxide pellets (Fisher Chemical, UK).

2.2. Sample preparation

ASA was milled using a cutting mill (SM100, Retsch, Germany) at 1500 rpm, with a square hole sieve of 2.0 mm, and sieved using a sieve tower (AS200, Retsch, Germany) with sieves of 350 μm and 425 μm. The fraction between 350 μm and 425 μm was retained and used in the investigation. Mannitol was sieved as well, and the fraction between 107 μm and 125 μm was used.

Three binary blends, containing 10%, 25% and 45% of ASA (w/w), were prepared by mixing mannitol and ASA at 20 rpm for 10 min in a Turbula mixer (Willy A. Bachofen AG, Switzerland). Three random samples were taken from each blend and their ASA concentration was assessed according to the analytical procedure described in §2.4.

2.3. Particle size analysis

The analysis of particle size was carried out with a QICPIC particle size analyser equipped with the GRADIS dry powder disperser (Sympatec, Inc., Clausthal-Zellerfeld, Germany). Particle size used was defined in terms of equivalent projection circle (EQPC), which is the diameter of a circle that has the same area as the projected area of the particle (Sympatec GmbH). Each sample, collected from different points in the milled and sieved material, was analysed three times. The size parameter d_{50} was evaluated, i.e. the value of EQPC that splits the cumulative distribution with 50% of particles above and 50% below this particle size.

2.4. Determination of ASA concentration

The concentration of ASA in blend samples was determined by means of UV–Visible spectrophotometry. The ASA in the powder sample is hydrolysed to salicylate ion in a basic medium. The solution is then acidified and made to react with Fe^{3+}, forming a coloured violet complex (Weiss et al., 1983), with maximum absorption at 530 nm.

Salicylic acid (SA) was dissolved in approximately 5.0 mL of NaOH 1.0 M. The solution was transferred into a 100 mL volumetric flask and filled with deionized water (stock solution). The stock solution was used to prepare 5 standard solutions with concentrations from 0.10 mM to 0.60 mM by acidifying aliquots of the stock solution with FeCl$_3$ 0.02 M (buffered to pH 1.6 with HCl/KCl). The absorbance of each solution was measured and recorded at 530 nm, using FeCl$_3$ solution as a blank. The resulting absorbances were used for a standard concentration curve.

Each analysed blend sample was transferred into a class A 100 mL volumetric flask. The powder was dissolved in approximately 5 mL of NaOH 1.0 M. The flask was then filled up to 100 mL with deionized water. A precisely known volume of the prepared solution (150–300 μL) was transferred in a 10 mL volumetric flask and brought up to volume with acidified FeCl$_3$ solution. Each sample was analysed in triplicate. The determination of ASA concentration was carried out using Evolution 201 UV–Visible spectrophotometer (Thermo Fisher Scientific, USA) and polystyrene cuvettes. The absorbance was measured at 530 nm at a temperature of 23 °C, aiming to keep the peak absorbance
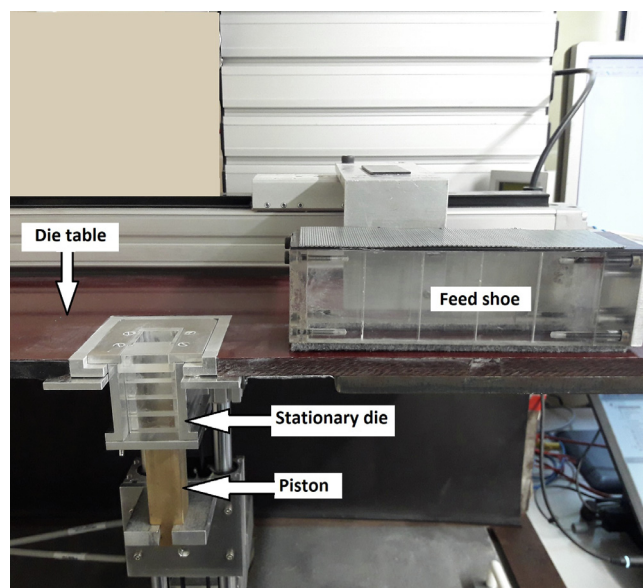

Fig. 1. Model die filling system.

between 0.1 and 1.0. The corresponding concentration was calculated using the standard curve, obtained with SA solutions.

2.5. Die filling

Die filling was carried out using a linear die filling system (Fig. 1). The system consists of a pneumatically driven cuboidal feed shoe, which is moved at a certain velocity over a stationary die fitted on a die table (Fig. 1). The shoe measures 150 mm (length) × 30 mm (depth) × 55 mm (height). The shoe is equipped with a perforated steel lid that prevents powder from being expelled out of the shoe as it is accelerated to a target velocity. The velocity of the shoe, known as filling velocity, can be specified using a controller.

The stationary die is made of an aluminium casing, which contains five vertical sampling units (Fig. 2). Each unit is made of aluminium, with a transparent PMMA frontal wall, and measures internally 20 mm (length) × 20 mm (depth) × 10 mm (height). After the die has been filled with powder, the sampling units can be pulled out of the aluminium casing one by one starting from the top, in order to pour the contained powder into a dedicated sample separator (Figs. 2 and 3). The separator is a rectangular aluminium container, consisting of two parallel cavities of 10 mm (width) by 10 mm (height). As the sample is poured into the separator, it is divided in two equal amounts, corresponding to the far and near half of the sampling unit (Fig. 2).
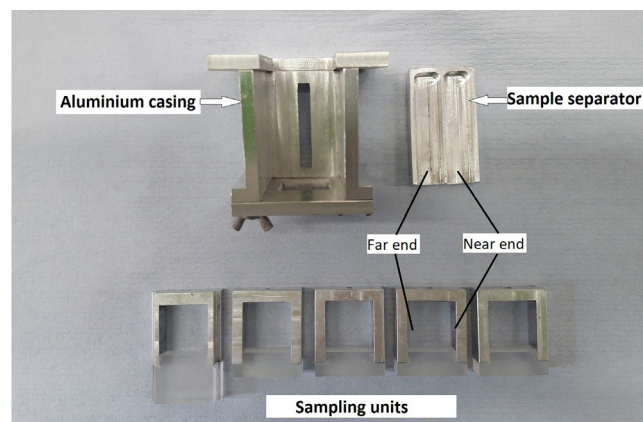

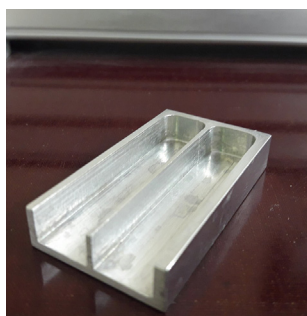**Fig. 2.** The sampling die with sampling units and the sample separator.
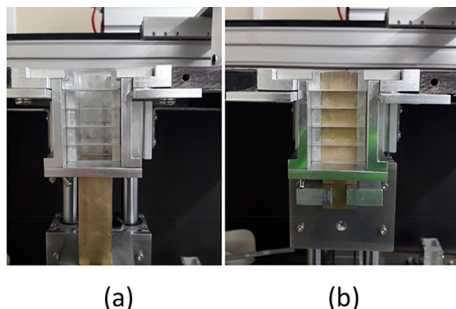
Fig. 3. The sample separator.

(a)   (b)

Fig. 4. Initial set up with the die and the piston in (a) gravity and (b) suction filling.

Table 1
Process conditions considered.

Filling velocity	Suction velocity
70 mm/s	0 mm/s (gravity)
	26 mm/s (suction)
260 mm/s	0 mm/s (gravity)
	100 mm/s (suction)

velocity were determined by precisely measuring the time the shoe/piston required to cover a known distance between two reference points: i) for the piston, the distance was between the starting point (aligned with the die table) and the bottom position (50.0 mm below the die table); ii) for the shoe it was between the starting position and the right side of the die (immediately before the leading edge of the shoe starts covering the die opening).

2.6. Sampling and determination of segregation index

After each filling step, the concentration of the filled die is separated into 10 samples. Each sampling unit (Fig. 2), starting from the top, is pulled out of the die and its content is emptied into the sample separator (Fig. 3). The left half of the sample separator contains the powder blend from the far end of the die, and the right half contains the sample from the near end. The step is repeated for each sampling unit, until the bottom is reached, for a total of 5 units. Therefore, a total of 10 samples is collected from each die filling experiment. Each sample is weighed (Entris® Analytical Balance, Sartorius) and transferred into a 100 mL volumetric flask. The determination of ASA concentration is carried out according to the procedure described in §2.4.

The obtained concentrations can therefore be used to examine vertical (top-bottom) and horizontal (near end – far end) segregation at various filling conditions. The die filling results are therefore expressed in terms of average ASA concentration (expressed as mass fraction of ASA to the blend mass), determined for a given sampled volume of the die, as a function of die depth. The die depth is a dimensionless parameter, given by the ratio of the sampling unit distance from the die table (centre of the unit) to the total filling depth (50 mm).

In order to compare the segregation tendency among the three blends, containing different amounts of ASA, it is necessary to develop a concentration-independent indicator. For this purpose, the following segregation index (SI) was introduced:

$$SI = \sum_{i}^{n} \frac{|c_i - c_t|}{c_t}$$

(5)

where c_i is the concentration of the analysed sample, detected by the analytical procedure described in §2.4., c_t is the starting concentration of the blend, determined after blending prior to die filling by the same procedure, and n is the number of sampling units. Therefore, by applying the following equation to each of the 10 samples (5 die levels and 2 halves for each level) produced from each die filling analysis, SI_a for a given suction/filling velocity combination can be estimated. Each die filling analysis is repeated three times (conducted in triplicate), therefore, an overall SI can be obtained as an average of three SI_a that characterises the degree of segregation within the die for each investigated filling condition.

2.7. Data analysis

The data of ASA concentration were analysed in IBM SPSS Statistics Version 25.0 (Armonk, NY, IBM Corp.) using Welch's One-Way Analysis of Variance (ANOVA) with Tukey's HSD (equal variances) or Games-Howell (unequal variances) post-hoc tests.
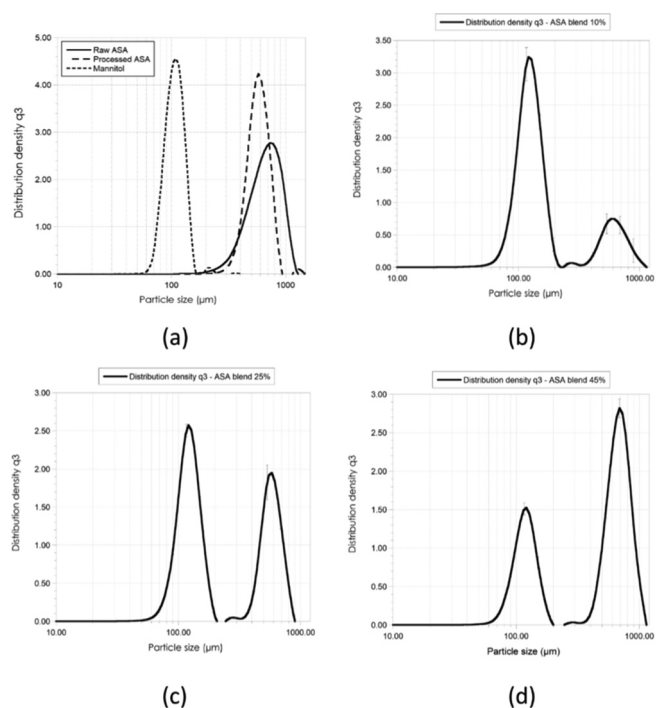
The die is equipped with a brass piston (Fig. 1), connected to an electromechanical toothed belt axis (Festo Ltd., UK), which can move at a linear velocity of 3 m/s and a maximum acceleration of 30 m/s^2. The die filling experiments are carried out under gravity and suction conditions. In gravity filling the piston is positioned at the bottom of the die, 50 mm below the surface of the die table (Fig. 4a). In suction filling, the piston's top surface is initially aligned with the die table (Fig. 4b), and as soon as the leading edge of the shoe covers the die, the piston is pulled downwards at a specified velocity (suction velocity) until it reaches the terminal position 50 mm below the die table.

In suction filling, die filling occurs as a result of two simultaneous displacements, of the shoe and of the piston. In order for the piston displacement to start precisely when the leading edge of the shoe covers the die opening, and to reach the terminal position when the trailing edge of the shoe uncovers the die opening, the shoe and the piston velocity have to satisfy the following equation (Zakhvatayeva et al., 2019):

$$v_s = \frac{L_s - L_d}{H/v_p}$$

(4)

where v_s is the filling velocity, L_s is the shoe length (150 mm), L_d is the die width (20 mm), H is the filling depth (50 mm) and v_p is the piston (or suction) velocity.

The powder is introduced into the shoe manually using a scoop. The amount to be introduced is weighed accurately using a Kern PCB1002 laboratory balance with a sensitivity of 0.01 g (KernandSohn GmbH, Germany).

The die filling experiments were performed at two different filling velocities: 70 mm/s and 260 mm/s. Table 1 shows all the possible combination of suction and filling velocity for each analysed blend. For each velocity combination, the die filling was repeated three times, for each blend concentration. The dynamics of the die filling process were visually evaluated using a high-speed camera at 1000 fps (Phantom VEO, Vision Research Inc., USA).

The calibration of the piston and shoe velocity, as well as the assessment of synchronisation between the shoe and the piston displacement, were assessed using the high speed camera. Piston and shoe

Fig. 5. Particle size distribution data. (a) Comparison of particle size distributions of raw ASA and processed (milled and sieved) ASA. (b) Blend 1 (10%). (c) Blend 2 (25%). (d) Blend 3(45%).

3. Results and discussion

3.1. Blend particle size and concentration analysis

The comparison of the frequency distribution of the raw and processed ASA, as well as the peak of sieved mannitol, are shown in Fig. 5a. The peak of the distribution of the as-received ASA is at around 660 μm, whereas for the processed ASA it is at 580 μm. The distribution width of the processed ASA is narrower than that of the as-received ASA. This particle size, measured by the optical method (§2.3) differs from the size of the sieve, used for the ASA separation (§2.2). This is caused by the fact that the optical method estimates the EQPC, which is the diameter of a circle that has the same area as the projected area of the particle. The sieving method estimates the sieve diameter, which is defined as the width of the minimum square aperture through which the particle will pass (Sympatec GmbH); therefore the two values differ, especially for irregular elongated particles.

The particle size distribution of the three ASA-mannitol blends are shown in Fig. 5b–d. The Fig. 5b shows the distribution density of the blend containing 10% of ASA. Two peaks can be observed, one slightly above 100 μm and the other at approximately 600 μm. Analogous bimodal distributions can be observed for the blends with 25% ASA (Fig. 5c) and 45% ASA (Fig. 5d). The peak at 100 μm can be attributed to the fine mannitol, whereas the second peak is clearly associated with ASA. Importantly, no overlapping is observed between the two. It can also be observed that the peak intensity of ASA increases as its concentration increases. The concentration of the three blends was determined after blending. The obtained values are presented in Table 2. It is clear that the measured concentration is very close to the corresponding specification.

3.2. Die filling with 10% ASA

The average ASA concentration determined at various combinations of filling and suction velocities is presented in Fig. 6. The vertical distribution of ASA concentration at low velocity gravity filling is

Table 2
Real concentration of ASA in the prepared blends (average and standard deviation).

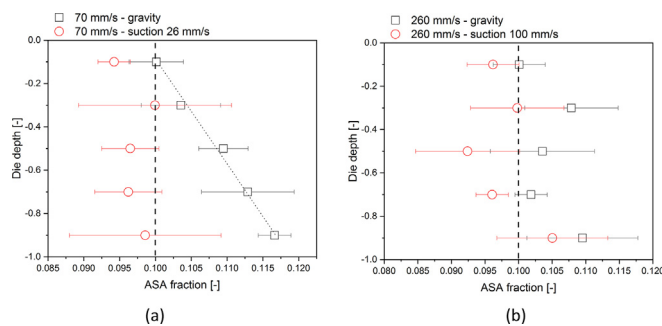| Name	Concentration of acetylsalicylic acid [%]	Expressed as mass fraction [−]
Blend 1 (10%)	9.4 ± 0.3	0.094 ± 0.003
Blend 2 (25%)	24.3 ± 0.2	0.243 ± 0.002
Blend 3 (45%)	44.3 ± 0.6	0.443 ± 0.006

Fig. 6. Vertical segregation of the 10% ASA blend at (a) low and (b) high filling velocity.

presented in Fig. 6a (square marker), where the average concentration of ASA increases with magnitude of die depth. The vertical distribution of ASA concentration at low velocity suction filling (round marker) does not vary significantly. The ASA concentrations at high velocity gravity (square marker) and suction (round marker) filling are shown in Fig. 6b, where no clear trend can be identified. The average vertical concentration is variable under both gravity and suction condition.

The results of ANOVA applied to the four testing conditions are shown in Table 3. According to the data, the vertical ASA concentration increases significantly from top to bottom at low velocity gravity filling, as indicated by Fig. 6a (square marker) while it does not change significantly at low velocity suction filling (Fig. 6a, round marker). At high velocity in both gravity and suction filling ASA is not distributed equally. The post hoc test applied to the high velocity gravity filling (Fig. 6b, square marker) shows that at the ASA concentration at die depth 0.1 differs significantly form die depths 0.3 and 0.5, but it is not different from die depths 0.7 and 0.9, whereas at high velocity suction filling the only statistically significant difference is between the die depths 0.5 and 0.9.

At low velocity gravity filling the flow of powder into the die is influenced by the presence of air that flows out of the die, thus resisting the powder flow into the die (Guo et al., 2009). Therefore, the values of air sensitivity of the ASA and mannitol need to be considered. The

Table 3
Results of Welch's ANOVA of ASA vertical content in the three blends at various process conditions.

Name	Test	Result
Blend 1	Gravity at 70 mm/s	$F_{(4,40)} = 17.395$, $p = .000$
	Suction at 70 mm/s	$F_{(4,40)} = 0.727$, $p = .579$
	Gravity at 260 mm/s	$F_{(4,40)} = 3.858$, $p = .010$
	Suction at 260 mm/s	$F_{(4,40)} = 4.606$, $p = .004$
Blend 2	Gravity at 70 mm/s	$F_{(4,40)} = 7.354$, $p < .000$
	Suction at 70 mm/s	$F_{(4,40)} = 3.328$, $p = .019$
	Gravity at 260 mm/s	$F_{(4,40)} = 4.773$, $p = .003$
	Suction at 260 mm/s	$F_{(4,40)} = 1.530$, $p = .212$
Blend 3	Gravity at 70 mm/s	$F_{(4,40)} = 3.398$, $p = .017$
	Suction at 70 mm/s	$F_{(4,40)} = 1.663$, $p = .178$
	Gravity at 260 mm/s	$F_{(4,40)} = 3.949$, $p = .009$
	Suction at 260 mm/s	$F_{(4,40)} = 2.168$, $p = .090$

Table 4
Air-sensitivity index of ASA and mannitol.

Powder	ρ_s (kg/m³)	d_{50} (μm)	ρ_a (kg/m³)	ϕ_p (−)	g (m/s²)	η (N$_s$/m²)	A$_r$ (−)	ξ (−)	ζ (−)
ASA	1402.0	565	1.205	1163	9.81	1.78×10^{-5}	9394.5	1.09×10^7	-8.33×10^{-3}
Mannitol	1479.6	106	1.205	1228			65.5	8.04×10^4	0.297

sensitivity of ASA and mannitol to air in die filling is calculated according to Eqs (1)–(3) (Guo et al., 2009; Yu et al., 2009), and shown in Table 4: ASA is air-inert ($\zeta = -8.33 \times 10^{-3}$) and mannitol is air-sensitive ($\zeta = 0.297$). The air flowing out of the die therefore slows down the deposition of the air-sensitive mannitol, whereas the coarse air-inert ASA is not restricted and its concentration increases towards the bottom of the die. As suction is introduced at the same filling velocity (Fig. 6a, round marker), the air influence is eliminated, and the vertical segregation is therefore reduced.

The high velocity gravity filling represents an exceptional condition, i.e. the filling occurs at 260 mm/s. This velocity is too high for the die to be filled completely in one filling step, hence three consecutive filling steps are necessary. This in turns creates three consecutive nose-bulk filling sequences (Wu and Cocks, 2004; Mills and Sinka, 2013). This can be seen by observing the die filling profile images in Fig. 7a. The images 1–4 show the first filling step, that fills approximately 2 bottom sampling units, that correspond to the die depth of 0.7–1.0 (Fig. 7, image 4). The second filling step (images 5–8) fills slightly less than 2 units (die depth −0.4 to 0.7). Finally, the third filling step (images 9–12) fills the remaining space. The ASA concentration variation, observed in Fig. 6b, follows the die filling sequence: in the first filling step, the ASA concentration is higher at the die depth of 0.9 than 0.7 (however not statistically significant), due to flow of mannitol being slowed down by air. The second filling step partially fills the die depth 0.3 and 0.5, however, this does not result in a significantly different concentration of ASA at die depths 0.3 and 0.5. Finally, the third step fills the two top units, resulting in a slightly higher, statistically significant concentration of ASA at die depth 0.3 compared to 0,1, which contains less ASA (and therefore more fine mannitol), due to the combined effect of air resistance and fines percolation through the powder bed due to shearing (Wu and Cocks, 2004). Therefore, the kind of segregation observed in high velocity gravity filling is similar to that occurring in low velocity gravity filling (Fig. 6a).

At high velocity filling in the presence of suction, the die is filled in one step (Fig. 7b). The ASA concentration appears to be significantly different between the die depths of 0.5 and 0.9, however, the concentration at the die depth of 0.5 is not statistically different from that of the die depth 0.1, 0.3 and 0.7. The same is true for the die depth
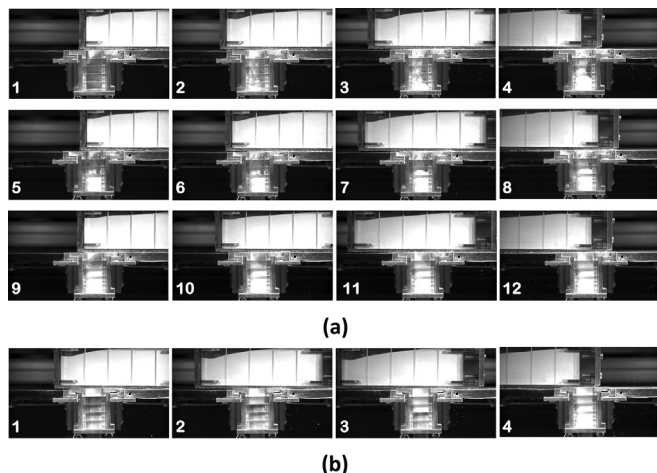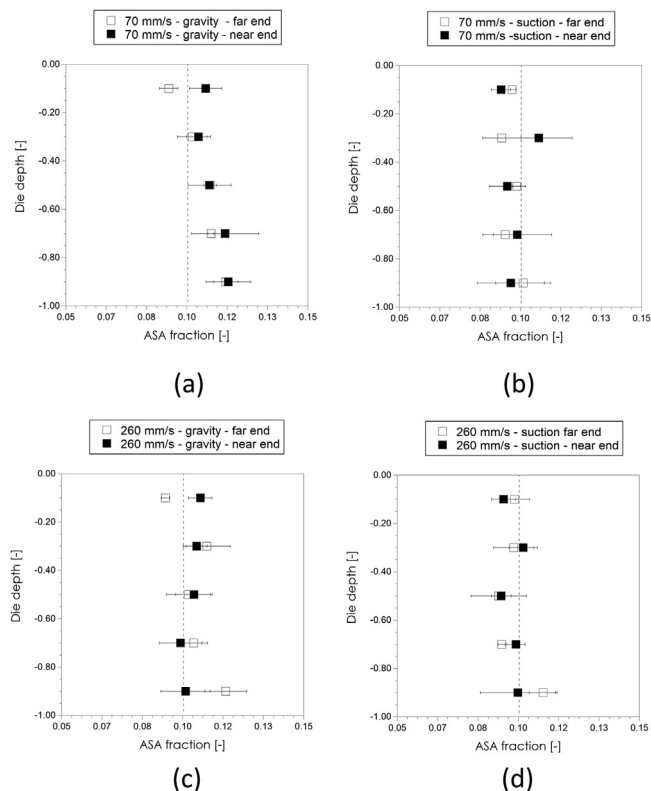
Fig. 8. Horizontal segregation of 10% ASA blend at various filling and suction velocities. (a) Low filling velocity under gravity. (b) Low filling velocity under suction. (c) High filling velocity under gravity. (d) High filling velocity under suction.

0.90. As the powder filling into the die occurs as a single continuous plug and there is no pre-existing air in the die before the filling starts, the observed variation of concentration is believed to be caused by inherent inhomogeneity of the blend inside the feed shoe.

The data of ASA concentration in far and near ends at each die depth are shown in Fig. 8. At low velocity gravity filling (Fig. 8a), the ASA concentration at the top is significantly higher in the near end of the die (Games-Howell post hoc test, Mean difference = −0.1524, p (0.002) < α (0.05)). The ASA concentration of the near and far end in the remaining four levels appears to be essentially identical. The values of ASA concentration at low velocity suction filling are presented in Fig. 8b. No clear trend between the far and the near end is observed.

At high velocity gravity filling (Fig. 8c) the ASA concentration at the top is higher in the near end of the die (Mean difference = -0.0144, p (0.001) < α (0.05)), as in the case of low velocity gravity filling. The differences between the two die ends in the remaining levels are not significant. At high velocity suction filling (Fig. 8d) no significant concentration variation between the two ends of the die is observed.

The horizontal segregation has been observed only in gravity conditions, at both low and high filling velocities. As shown in Fig. 7a, three consecutive filling steps are necessary to fill the die at the high filling velocity. The gravity filling at low filling velocity occurs in a similar way (not shown), however only one filling step is sufficient to fill the die completely. Therefore, as can be seen from the images 11–12
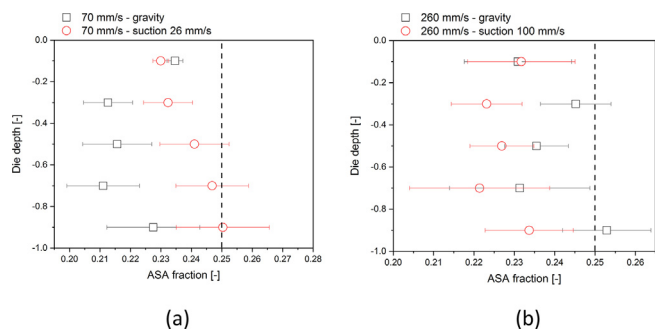
Fig. 7. Flow profile of 10% ASA blend at (a) high filling velocity in gravity and (b) high filling velocity in suction.

Fig. 9. Vertical segregation of the 25% ASA blend at (a) low and (b) high filling velocity.

(Fig. 7a), in the final stages of gravity filling the powder forms a heap, which allows coarse and free-flowing ASA particle to roll on its surface. This in turns causes ASA accumulation close to the near side of the die. As the heap is formed during the bulk flow phase at the end of the filling step, the ASA concentration variation is particularly evident in the upper layer.

3.3. Die filling with 25% ASA

The vertical distribution of ASA concentration is presented in Fig. 9. The concentration of ASA at low velocity gravity filling (Fig. 9a, square marker) is significantly higher in the upper layer (Table 3), whereas the rest of the die has a uniform concentration of ASA. At low velocity suction filling (Fig. 9a, round marker) the concentration of ASA apparently increases towards the bottom, however only the bottom layer is significantly different form the rest of the die concentration. At high velocity gravity filling (Fig. 9b, square marker) the concentration of ASA is variable across the die, with the highest concentration observed at the die depth 0.3 and 0.9, with the concentration at 0.9 being statistically different from the rest. Finally, at high velocity suction filling (Fig. 9b, round marker), no segregation is observed (Table 3).

The ASA concentration at low velocity gravity filling (Fig. 9a, square marker) is more uniform, except for the upper layer, which is likely to be an outlier, caused by the blend segregation in the feed shoe. Similar local blend non uniformity in the feed shoe could also be responsible for the slightly increasing ASA concentration in presence of suction, where only the bottom layer is significantly different from the rest (Fig. 9b, round marker). The ASA concentration variation at high velocity gravity filling (Fig. 9b, square marker) is influenced by the three-step filling procedure, as discussed before for the 10% ASA blend. For the 25% blend the bottom layer is significantly more concentrated than the rest. For high filling velocity during suction filling (Fig. 9b, round marker), no segregation can be observed, which is an indication of the good uniformity of the blend in the feed shoe, that is preserved during the fast suction filling.

ASA concentration in the near and far end at each die depth is shown in Fig. 10. At low velocity in gravity filling the concentration of ASA is higher in the far end (Fig. 10a). At low velocity suction filling (Fig. 10b) the ASA concentration is significantly higher in the far end of the upper layer (Mean difference = 0.0373, p(0.000) < α (0.05)). As the filling velocity increases, in gravity condition (Fig. 10c) the ASA concentration is distributed equally between the far and the near end of the die. Similarly, no significant difference in ASA concentration between the two ends of the die can be observed at high velocity suction filling (Fig. 10d).

It is worth noting that the ASA concentration distribution at low velocity gravity filling shows an inversion if compared to the 10% ASA blend (Fig. 8a). This could be due to a higher concentration of ASA (25% against 10%), since a higher concentration of coarse and very free-flowing ASA particles could facilitate their mobility inside the feed
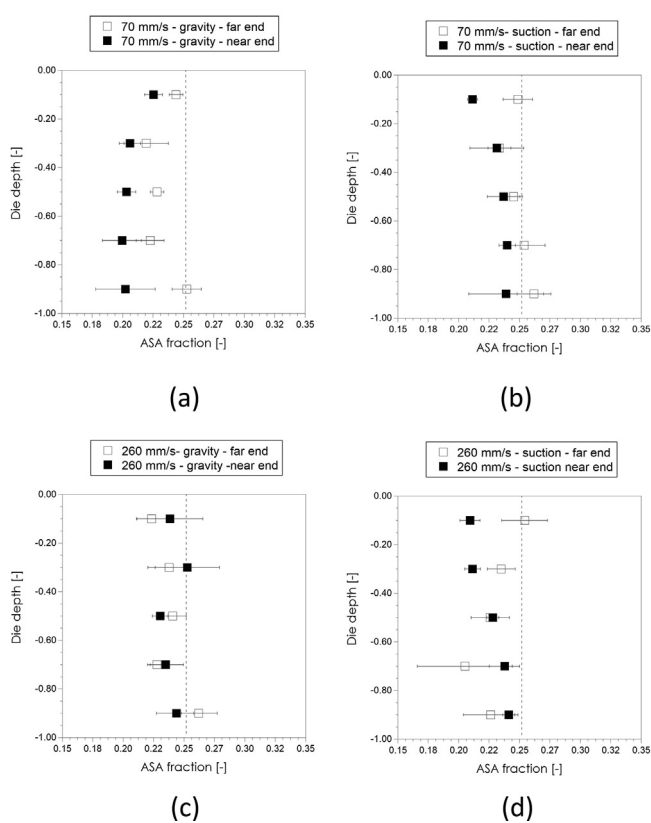

Fig. 10. Horizontal segregation of 25% ASA blend at various filling and suction velocities. (a) Low filling velocity under gravity. (b) Low filling velocity under suction. (c) High filling velocity under gravity. (d) High filling velocity under suction.

shoe, allowing them to flow over the fine mannitol particles and over other ASA particles. This would facilitate the formation of a coarse particles-rich stream flowing to the far end of the die, as also demonstrated by Guo et al. (2011). This, however, does not explain why there is no observed fine concentration increase in the top layer, as the powder bed shearing against the powder in the die should facilitate the sifting of mannitol through the powder and promote its deposition in the top layers. This could be caused by ASA particles efficiently flowing even when the die is almost full, thus forcing the fine mannitol particles to occupy the remaining near side of the die, that is the last to be filled (Fig. 7a, image 12).

A large particle size reduces the efficiency of suction filling, as demonstrated by Mills and Sinka (2013). The higher ASA concentration, which makes the blend more porous, also reduces its sensitivity to suction effects, especially at low suction velocity, as in the case of low velocity suction filling (Fig. 10b). This results in the top layer being less affected by the suction applied by the piston withdrawal, therefore making it similar to the gravity filling. Therefore, there is a higher ASA presence in the far end of the upper layer, due to the same effect presumed for the gravity filling (Fig. 10a).

No statistically significant differences were observed at the high velocity gravity filling, although there appears to be a slightly higher concentration of ASA in the far end of the bottom layer (Fig. 10c). Lower tendency to segregation could be caused by a higher feed shoe velocity, that interferes with the formation of the coarse particles-rich surface stream flowing into the far end of the die. At high velocity suction filling (Fig. 10d), no significant segregation is observed, except for the upper layer, where the ASA concentration is higher in the far end. This can be explained once again in terms of lower sensitivity of the upper layers of the more porous blend to the suction influence, which causes a higher ASA presence in the far end due to the gravity
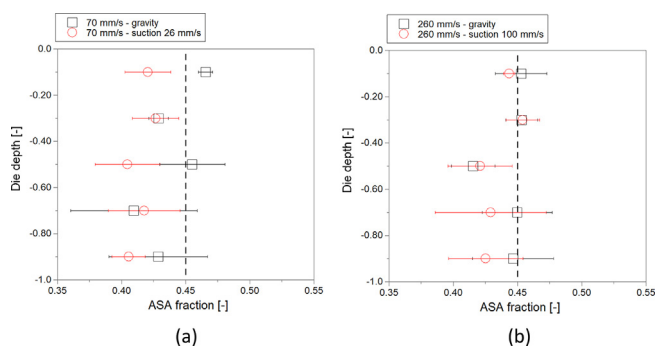
Fig. 11. Vertical segregation of the 45% ASA blend at (a) low and (b) high filling velocity.

filling-like conditions in the upper layer.

3.4. Die filling with 45% ASA

The vertical distribution of ASA concentration is shown in Fig. 11. The ASA concentration at low velocity gravity filling (Fig. 11a, square marker) is mostly uniform across the die, with a slightly lower concentration right above the bottom layer (die depth 0.70). The concentration of ASA in the presence of suction is uniform and no statistically significant differences are observed (Fig. 11a, round marker). As the filling velocity increases (gravity condition), the ASA concentration is still uniform (Fig. 11b, square marker), with a slightly lower value in the centre (die depth 0.50). As suction is applied (Fig. 11b, red), the concentration of ASA becomes uniform across the whole die. It appears that overall a very high ASA concentration prevents vertical segregation in all conditions, except for minor deviation in gravity filling at both low and high filling velocities, which are mostly likely due to ASA concentration fluctuations in the feed shoe.

The horizontal distribution of ASA is shown in Fig. 12. At low velocity gravity filling (Fig. 12a) the ASA concentration in the far and near end of each level varies, but not significantly, except for the centre of the die (die depth 0.50), where the ASA concentration is higher in the far end. In the presence of suction (Fig. 12b) the ASA concentration is not significantly different between the two halves in the top of the die, whereas some separation is observed in the centre (die depth 0.50) and in the bottom. As the filling velocity increases, in gravity condition (Fig. 12c) the ASA concentrations in the two upper layers appear to differ between the far and the near end, with higher ASA concentration in the far end. Finally, in the presence of suction (Fig. 12d), ASA concentration differs between the far and the near ends of the top two layers, as in the case of gravity filling, and in the bottom layer.

Similarly, as observed for the vertical segregation, a high ASA concentration reduces the extent of horizontal segregation. This is especially evident at low filling velocities (Fig. 11a, b), where only limited volumes of the die present higher ASA concentration in the far end. As the filling velocity increases, the coarse particles-rich powder stream that reaches the bottom of the die, made up of a high amount of free-flowing ASA, spreads uniformly across the die. The second filling step, that also introduces a stream of coarse particles, finds a bed of previously deposited powder. This most likely prevents the ASA particles from spreading across the die, thus causing its accumulation in the far end, where it was originally headed. This causes a uniform horizontal ASA distribution in the bottom and a far-near separation in the top (Fig. 12c). As the high concentration of ASA reduces its sensitivity to the suction filling, the effect of the suction is less significant in the upper layers (Fig. 12d), which explains the similarity with the gravity filling condition shown in Fig. 12c.
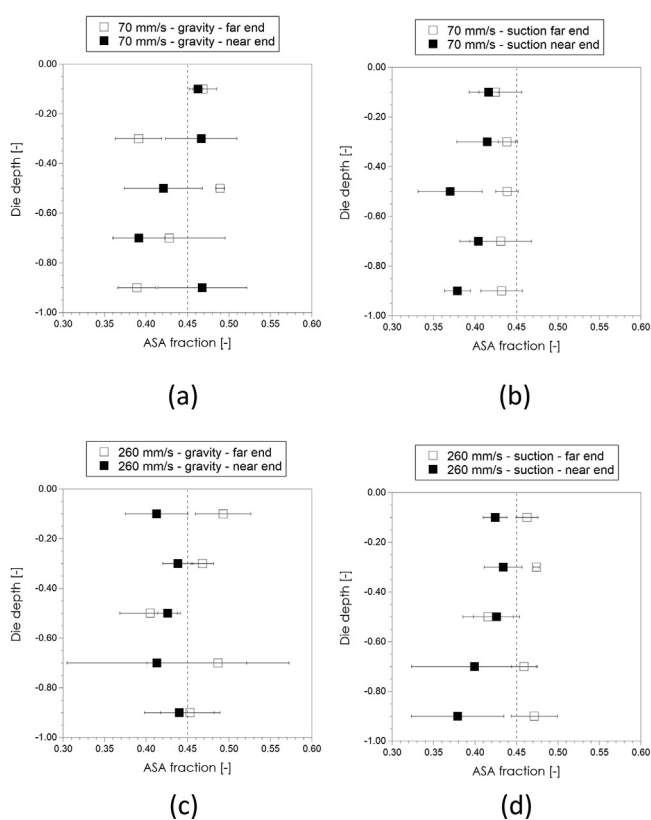

Fig. 12. Horizontal segregation of 45% ASA blend at various filling and suction velocities. (a) Low filling velocity under gravity. (b) Low filling velocity under suction. (c) High filling velocity under gravity. (d) High filling velocity under suction.
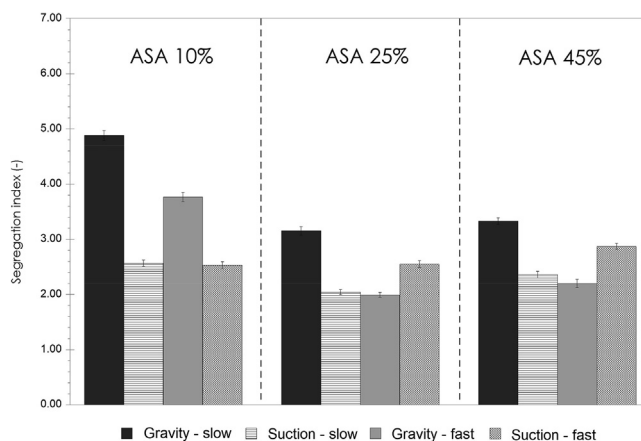

Fig. 13. Segregation index values of the three ASA blends in various process conditions.

3.5. Segregation index

The comparison of Segregation Index (SI) values, calculated for each blend at every filling condition according to the Eq. (5), is shown in Fig. 13. For the 10% ASA blend the highest SI is observed at low velocity gravity filling. The second highest SI is observed at high velocity gravity filling. The lowest SI values are obtained in both low and high velocity suction filling. For the 25% ASA blend the highest SI is again observed at low velocity gravity filling, though this is noticeably lower than for 10% ASA. The second highest, quite surprisingly, is shown by the high velocity suction filling, whereas the SI of the low velocity suction filling and high velocity gravity filling are quite similar. Finally,

for the 45% blend, the highest SI is again exhibited by the low velocity gravity filling, the second highest is the high velocity suction filling, and the SI values of the low velocity suction and high velocity gravity filling are quite similar.

For all the analysed blends, the most significant segregation was observed for the low velocity gravity filling, which can be explained in terms of the different air-sensitivity of the two components. The segregation in gravity filling appears to be generally reduced by increasing the filling velocity, which, however, is due to the fact that the high velocity gravity filling is a sequence of three gravity filling steps, which reduces the influence of air drag as the die filling depth is gradually decreased at after each filling step. This effectively reduces the distance that the powder has to travel inside the die before reaching the surface of the previously deposited powder, and it also results in the mixing of the incoming powder stream with the powder already present in the die, thus reducing the extent of segregation (Wu and Cocks, 2004). Using a longer fill shoe would allow for the die to be filled in one step at this filling velocity, however, the segregation behaviour might be affected. In the presence of suction, SI appears to be less influenced by the filling velocity for the 10% ASA, however a slight increase at high velocity suction filling can be observed for the two concentration s of 25% and 45%. This might be caused by a decreased sensitivity of the powder bed to the suction effects as the coarse fraction increases. At the same time, higher shoe velocities might promote coarse particle mobility and therefore increase the overall SI.

As for the effect of concentration in gravity filling, the highest degree of segregation is observed for the 10% blend. Generally, low active pharmaceutical ingredient (API) concentrations are associated with a higher risk of segregation (Kukkar et al., 2008; Tovey, 2018), therefore, as the API concentration increases, the risk of segregation decreases. In suction filling, however, the influence of the concentration on the segregation is limited, even though small reductions in SI are observed for 25% (low velocity suction filling), whereas for 45% there appears to be an increase of SI in high velocity suction filling, most likely due to the same combination of phenomena, described above (reduced influence of suction and increased particle mobility).

4. Conclusions

The extent of size-induced segregation in die filling was evaluated for three blends of ASA and mannitol, containing 10%, 25% and 45% of ASA. The die filling was carried out at low and high filling velocity, in gravity filling or suction filling conditions. As for the vertical segregation of ASA within the die, in gravity filling conditions there was generally a trend for an increase in ASA concentration towards the bottom of the die. This was associated with ASA being air-inert, which allowed it to be less hindered by the counterflowing air (Guo et al., 2011b, 2011a). Improvement of ASA vertical distribution uniformity in comparison to gravity filling was generally observed during suction filling (within the same concentration).

As for the horizontal segregation, at 10% ASA concentration there was a slight prevalence of ASA in the near end in the gravity filling condition. Flow profile images, obtained with a high speed camera, evidenced the formation of a powder heap, which allowed the scarcely present coarse ASA particles to roll over the heap side towards the near end of the die, thus resulting in a higher ASA concentration in the near end of the upper layer of the die.

At higher ASA concentrations the observed horizontal segregation was due to a higher ASA concentration in the far end of the die. An increasing ASA concentration produced a more free-flowing, porous powder bed, which allowed the formation of a coarse particle-rich powder stream, directed towards the far end of the die. This effect was also observed in the top layers in the presence of suction, as a more porous bed was less susceptible to the effects of suction, effectively creating gravity filling-like conditions in the top layers of the die.

This study demonstrates that the presence of suction not only

increases the die filling efficiency (Schneider et al., 2007; Mills and Sinka, 2013; Jackson et al., 2007), but it also generally reduces the tendency of segregation when compared to the gravity filling of the same blend concentration. As for the horizontal segregation, it was observed that it either originates from coarse particles flowing over free surfaces inside the die or from inside the feed shoe, producing higher coarse powder concentration in the near or far end of the die, respectively. It was also observed that for a given combination of die width and depth, the suction effect of the withdrawing piston might be less significant in the top layer deposition, particularly for blends containing a large fraction of coarse particles.

Further experimental investigations could be performed at such high suction velocities that are similar to the suction velocities typically employed in tableting production, and on the particle density-induced segregation.

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.

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