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The influence of roller compaction processing variables on the rheological properties of granules

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ABSTRACT

This study is part of an ongoing project to enable the full specification of the Design Space for roller compactor systems and shows how the processing parameters influence the behaviour of the product granulate from a placebo formulation. Granulate was produced using a proprietary roller compactor by varying the compaction pressure and gap width, and the dynamic, bulk and shear properties of the resultant granulates were measured.

The results demonstrate several rheological properties of the granulate, which have been shown to be closely correlated with variance in die filling and tablet strength, and are predictably influenced by the processing parameters.

1. Introduction and background

Pharmaceutical formulations for oral solid dose delivery consist of mixtures of many components, each with a specific role in optimising delivery of the active ingredient(s).

In many instances, the potency of these active ingredients means that the actual quantity required per tablet/capsule is extremely small and to ensure the content uniformity, a granulation process step is often undertaken, especially when some or all of the materials in a formulation have very poor flow properties. This approach combines the active ingredient with one or more of the other components and is frequently carried out as a wet process. The disadvantages of wet granulation are that the resultant wet mass has to be dried and milled to generate a product that can then be tabletted/encapsulated. These downstream steps are time consuming and incur additional costs. Equally, some active materials will be unsuitable for the wet processing route due to chemical and/or thermal degradation.

The option to use a dry granulation process, based around a roller compactor and integral mill/screen, has significant

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benefits not only in terms of processing cost reduction but also for use with active ingredients that cannot be subjected to moisture/solvents and/or heat [1–3]. Roller compactors also occupy much less floor space and have a large throughput. They are, by their nature, a continuous process, which is becoming an increasingly common focus in pharmaceutical manufacturing [4–9].

Dry granulation is not suitable for all types of powdered material but there is little in the literature that indicates what properties of a formulation make it suitable/unsuitable for this method of processing, with most equipment suppliers and pharmaceutical manufacturers relying on historical and ad-hoc trial information to identify suitable candidate formulations. Equally, there is little to indicate which processing parameters produce optimal granulate quality to achieve interruption free processing and high quality products.

However, it is known that the quality of the dry granulate has a significant impact on downstream processes (including mixing and tabletting) which have been shown to be governed by the rheological properties of the feed granules [10–14], and recent regulatory initiatives on PAT and QbD [15–17] have emphasised the need for a greater understanding of all pharmaceutical processes and how input variables, such as variation in powder characteristics or equipment settings, influence process performance and granule quality with respect to the variation in critical quality attributes of the final solid dose product.

The main barrier to determining these relationships has been the insensitivity of the methods that have been historically used to characterise the feedstock/granulate properties. In many studies, the particle size distribution is the primary method used to quantify granule 'quality' [18,19]; however, it is clear from a number of other studies that powders with the same particle size can have vastly different flow behaviour due to the effects of other properties such as surface texture and shape [20–22]. Other studies have evaluated the quality of the ribbon produced [23] and may simply infer the quality of any granules that would have to be generated or did not extend their evaluation to this point.

Where the flow properties of the powders have been considered, several methods are traditionally used in the pharmaceutical industry; Carr's Index [24]; Hausner Ratio [25]; Angle of Repose [26]; Flow Through a Funnel [27]. These techniques are simplistic and generally regarded as insensitive [12,28–30]. Individually, they do not represent the range of conditions that powders experience in either manufacture or application, and this has been acknowledged by the US Pharmacopeia [31]. They also cannot be successfully applied to the widest range of powders; for example, very cohesive powders, such as many active pharmaceuticals, are insensitive to taping and thus produce unexpectedly low Carr's Index values [32]. This is because the vibrational energy supplied during the tests is insufficient to overcome the powder's cohesive forces and thus the consolidation is restricted. Equally, there are many issues with the universality of Angle of Repose and Flow Through a Funnel tests, again mainly with more cohesive samples and predominantly related to the inability of these materials to flow through the apparatus in order to allow a measurement to be made [12].

Recent developments in automated instrumentation have allowed formulation scientists and engineers to assess a wide range of powder properties more rapidly and repeatably. Shear cells evaluate powders under consolidation at the onset of flow – the transition from static to dynamic behaviour – and have been used by several researchers to understand the relationships between the properties of powder feedstocks and the quality of granules with respect to the roller compactor settings [33–35].

As a consequence, the shear properties of the resultant granules are frequently measured and it is assumed that such measurements will provide the necessary information to indicate the relative flow behaviour of the granules and be used to qualify performance in downstream processing.

However, such an assumption has a number of inherent weaknesses. Firstly, the standard shear cell analysis assumes continuum behaviour of the material and as most granules are free flowing – this is what granulation is intended to achieve – the shear test invariably produces results which indicate Flow Functions (FF) significantly higher than 10 [36,37], often in the tens and sometimes in the hundreds. The typical scale that is used to define cohesiveness was defined by Jenike [38] and classifies all powders with an FF above 10 as 'free flowing'; thus it is arguable that any shear cell analysis where an FF above 10 is generated cannot be realistically employed to characterise the powder's flowability. Secondly, the consolidation stress at which shear tests are performed should be commensurate with the stress levels seen by the powder during downstream processing. Often, researchers simply undertake a single shear test with which to characterise flowability. Given that FF invariably changes with pre-consolidation load and that different powders' rates of change will vary, an assumption that a single FF value fully describes a powder's flowability, cannot be justified.

Finally, and perhaps most importantly, it has been shown that the measurement of shear behaviour does not necessarily correlate well with downstream performance and that other powder characteristics – compressibility, permeability, aeration, dynamic flow – can be more relevant to specific powder/process behaviour. To date, no single measurement of a powder property can fully encompass the range of behaviours observed in many unit operations and items of equipment that are used in pharmaceutical manufacturing.

With these considerations in mind, a multivariate analysis of the behaviour of granules produced by roller compaction will provide a more robust understanding of their downstream behaviour and suitability for tabletting.

This study is part of an ongoing project to enable the full specification of the design space for roller compactor systems and will show how the processing parameters influence the behaviour of the product granulate from a placebo formulation (based on lactose, microcrystalline cellulose and magnesium stearate). Granulate was produced using a Mini-Pactor® roller compactor (Gerteis®, Switzerland) where the roller gap, force and speed can be varied together with the screen/sieve size. The powder properties of the feedstock and the granulates were evaluated using an FT4 Powder Rheometer® (Freeman Technology, UK) to measure the dynamic flow, bulk and shear behaviour.

2. Materials and methods

2.1. Roller compaction

A roller compactor generally consists of three major units: a feeding system, which conveys the powder to the compaction area between the rolls; a compaction unit, where powder is compacted between two counter rotating rolls to a ribbon by applying a force; and a size reduction unit, for milling the ribbons to the desired particle size. Fig. 1 shows a schematic of a roller compactor and a photo of the Gerteis Mini-Pactor used in this study.

Several operational parameters can be adjusted/controlled to modify the product granulate; the compaction force, the gap width and the milling size being the main variables. For this study, the variation in the compaction force and the gap width was investigated with respect to the quality of the granulate produced as quantified by the bulk, shear and dynamic flow properties.

2.2. Powder and granule characterisation techniques

An FT4 Powder Rheometer (Freeman Technology), shown in Fig. 2 (far left), was used to evaluate the rheological behaviour of the powders by measuring the flow energy of the samples to quantify the resistance to flow. The Basic Flowability Energy (BFE) results are obtained by means of a patented measurement principle that evaluates the resistance to the motion of a specially shaped twisted blade passing through a precise volume of the sample along a prescribed path. The required torque and force are recorded and converted into a flow energy [29]. The repeatability of all the measurements was enhanced by the use of a conditioning cycle which removes packing history and operator induced variability. Conditioning was undertaken on all samples prior to testing using the range of dynamic, bulk and shear measurements available. Samples were placed into a 50 mm × 160 mL cylindrical vessel and initially conditioned, using the powder rheometer, by passing the specially shaped blade through the powder in a prescribed manner. This creates a stable, uniform and, most importantly, repeatable stress state within the sample. Excess material is removed to generate a 160 mL test sample which allows a very precise value of bulk density – the conditioned bulk density (CBD) – to be determined.

$$Condtioned\ Bulk\ Density = \frac{Sample\ mass}{Sample\ volume}$$

Repeated testing of a single sample (with intermediate reconditioning) can be used to assess the physical stability of a powder (described by the Stability Index – SI) and changes to the blade speed can be used to evaluate how the powder responds to being made to flow at different rates (described by the Flow Rate Index – FRI).

As an extension of dynamic testing, the introduction of a controllable gas stream at the base of the powder bed adds an additional dimension to the understanding of powder properties. This allows performance in fluidised and aerated systems (driers, blenders, filling lines etc.) to be further understood and, as has also been shown to provide a valuable insight for aerosolisation systems such as those used in dry powder inhalers [39–41]. The extent to which a powder can become

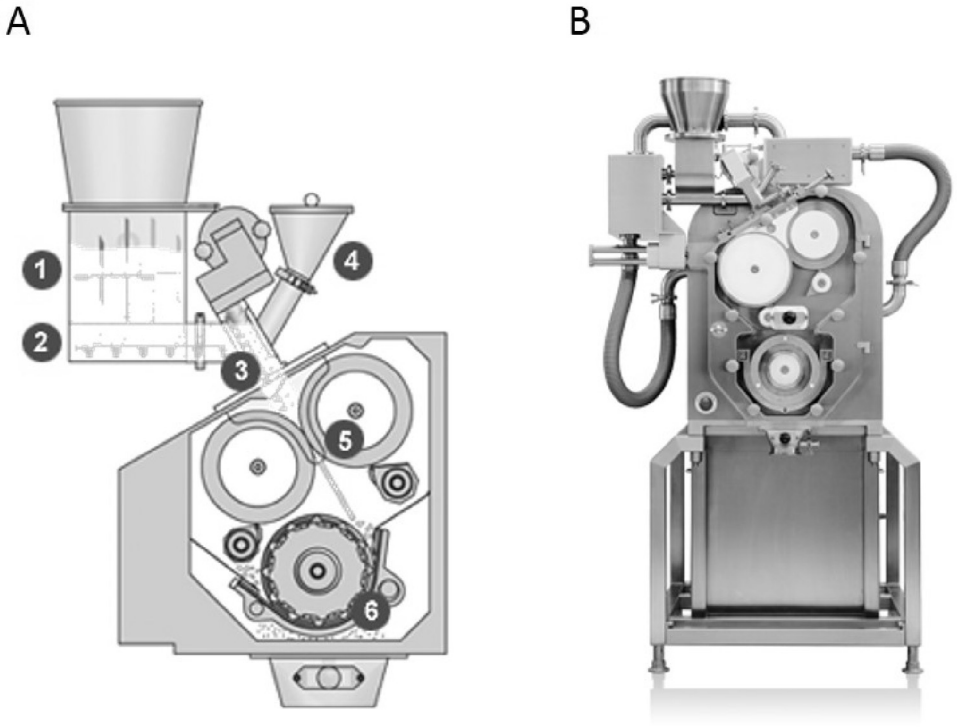

Fig. 1 – Schematic of a roller compactor identifying the: (A) component parts (1. Inlet funnel with agitator; 2. Feed auger; 3. Tamp auger; 4. Small quantity inlet funnel; 5. Press rollers with ribbon; 6. Milling rotor with desired granules) and the (B) Gerteis mini-pactor.

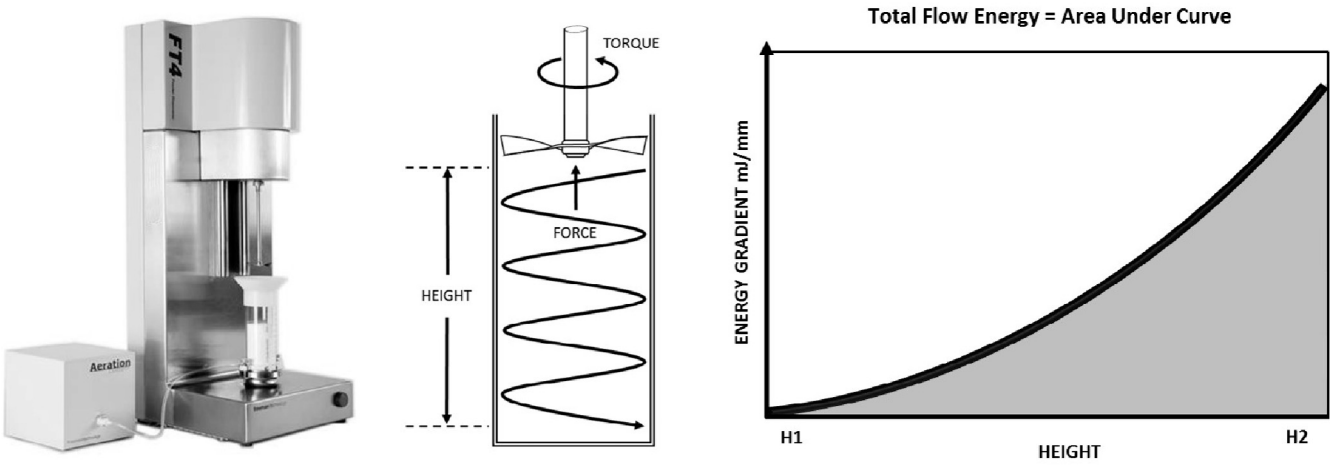

Fig. 2 – Measurement of flow energy using the FT4 powder rheometer.

aerated or even fluidised depends highly on the cohesive forces that exist between the particles; therefore, the test can be used to quantify the absolute inter-particulate cohesion of a material [29]. A typical evaluation would examine the change in a powder's flow properties with increasing quantities of introduced air. The blade traverses through a standard test aliquot (the same as is used in the unaerated standard dynamic testing) such that the aerated and unaerated results can be directly compared. The reported parameters are: Aerated Energy (AE, mJ) which is the Basic Flowability Energy when a specific gas velocity is applied to the sample, and the Aeration Ratio (AR) which is the ratio of the unaerated BFE to the AE for a specific gas velocity.

$$Aeration\ Ratio = \frac{Basic\ Flowability\ Energy}{Aerated\ Energy}$$

Additionally, bulk and shear testing can be undertaken by using additional, interchangeable accessories, shown in Fig. 3, and a smaller, 50 mm × 85 mL test vessel. Derived shear parameters include Flow Function (FF) and Angle of Internal Friction (AIF).

$$Flow\ Function = \frac{Major\ Principal\ Stress}{Unconfined\ Yield\ Strength}$$

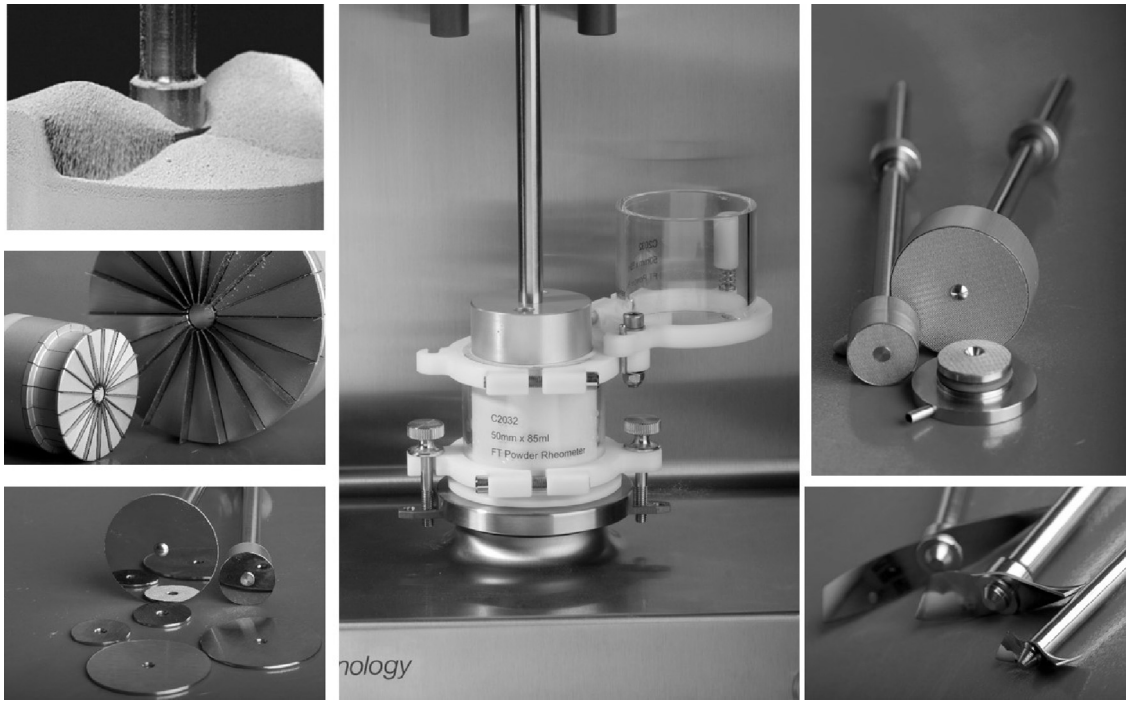

Fig. 3 – Additional accessories and vessels for the FT4 powder rheometer.

$$Angle\ of\ Internal\ Friction = tan^{-1}\frac{Shear\ Stress}{Applied\ Normal\ Stress}$$

2.3. Experimental

The test powder that was used in these experiments was a placebo formulation consisting of 70% FastFlo lactose, 29.5% microcrystalline cellulose 101 and 0.5% magnesium stearate.

In this initial study, two aspects of the control of the roller compactor were adjusted to evaluate the effect on the resultant granulate, namely the compaction force and the roll gap. Compaction force was controlled by modifying roll settings. The roll speed and mill mesh were fixed at 2.5 rpm and 1 mm respectively. Each setting combination was run for approximately 60 s and 200 g of resulting granulate was collected for evaluation. An initial 15 s period was included to allow the process to reach a stable condition.

Phase 1 investigated the effect of roll compaction force on the bulk powder properties, with the roll compaction force increasing from 3 kN/cm to 12 kN/cm in six discrete steps. Phase 2 studied the effect of changing the roll gap from 1.5 mm to 5 mm in six discrete stages. The mill mesh size was maintained for both phases at 1 mm.

It was also possible to combine and compare some of the data from Phases 1 and 2 to compare the effect of the roll gap at two different stresses – 4.5 kN/cm and 9 kN/cm (Phase 2a).

The resultant granulate batches were evaluated by means of the dynamic flow, bulk and shear tests available with the powder rheometer. All tests were repeated twice and errors bars are provided in the results graphs (due to limited sample size, there was insufficient sample to obtain a triplicate run).

The particle size distribution was assessed using standard calibrated sieves (Endecotts, UK). The Fine particle fraction was defined as particles below 106 µm whilst the Coarse particle fraction was defined as particles above 212 µm.

3. Results and discussion

3.1. Phase 1 – effect of compaction force

Phase 1 investigated the effect of roll compaction force on the bulk powder properties, with the roll compaction force increasing from 3 kN/cm to 12 kN/cm, generating six different granulates. Table 1 lists the test conditions employed for each batch of granulate produced.

Clear and repeatable differences were demonstrated between the six batches of granules, with good correlation observed between the roll compaction force and several of the granules' rheological characteristics. The strongest correlations (as designated by high R^2 values) were obtained for the bulk powder properties – permeability, compressibility and the CBD (Fig. 4).

Table 1 – Testing parameters used in the Mini-Pactor in Phase 1.

Batch	I	II	III	IV	V	VI
Force (kN/cm)	3	4.5	6	7.5	9	12
Gap (mm)	3	3	3	3	3	3
Roll speed (rpm)	2.5	2.5	2.5	2.5	2.5	2.5
Screen sieve (mm)	1	1	1	1	1	1

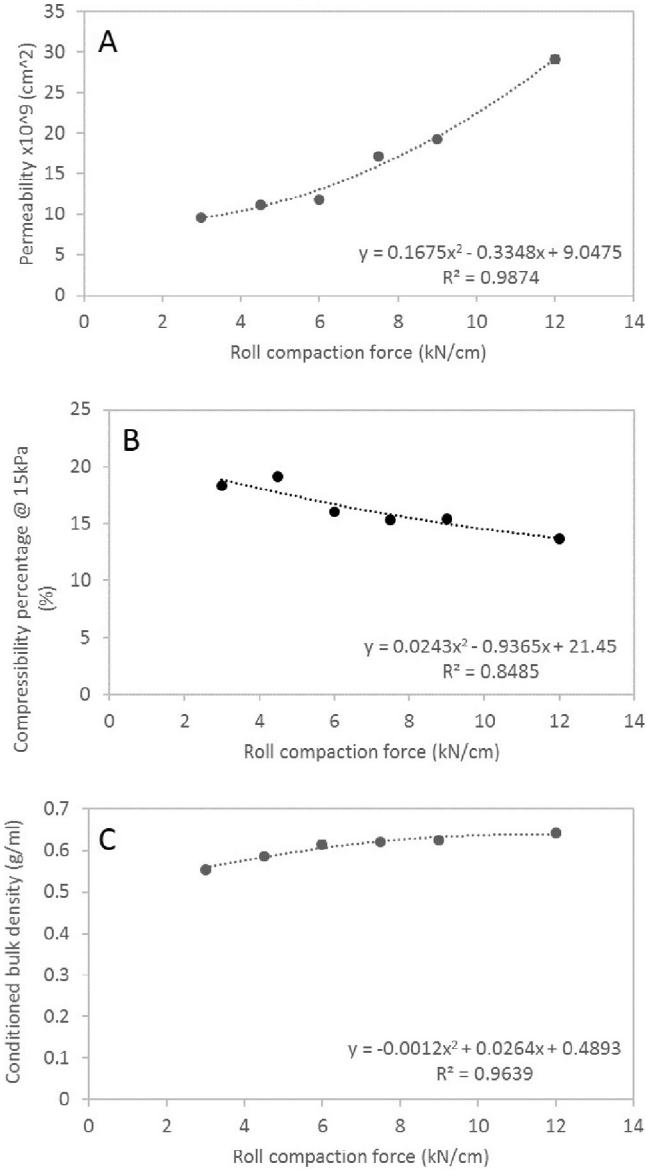

Fig. 4 – Results for granules produced in Phase 1 for: (A) permeability, (B) compressibility and (C) CBD.

These results demonstrate that as the roll compaction force increases, the compressibility decreases and the permeability and the CBD of the resultant granulate increase. This suggests more efficient particle packing for the product granulate formed from higher roll compaction forces and can be clearly related to the proportion of large granules, as indicated by the particle sizes shown in Table 2 and Fig. 5.

As expected, this is not a linear relationship – as the force increases, any air entrained within the powder is expelled and the ribbon density and strength increases. Whilst this leads to stronger ribbon, and hence stronger/larger granules following milling, it can be seen that the coarse particle content asymptotes suggesting that the proportion of larger granules generated during the milling phase is stabilising.

Table 2 – Size analyses of Phase 1 samples.

Batch	Compaction force, kN/cm	Fines % (below 106 μ)	Coarse % (above 212 μ)	Coarse/ Fine
I	3.0	14.36	31.9	2.22
II	4.5	20.5	41.56	2.03
III	6.0	16.12	50.32	3.12
IV	7.5	8.79	56.72	6.45
V	9.0	12.6	59.06	4.69
VI	12.0	9.9	65.6	6.63

Comparing the proportion of coarse fraction with the permeability and compressibility of the powder as a whole – important factors in the downstream tablet manufacturing – it can be seen that these bulk properties are changing faster than the increase in coarse fraction of the granulate (Fig. 6). The permeability is increasing significantly as the coarse fraction stabilises whilst the compressibility is simultaneously decreasing in a uniform manner.

This therefore suggests that relying on particle size analysis alone will not provide the necessary understanding of the relationships between compactor parameters and granule properties.

Good correlation was also observed with a number of the dynamic properties (Fig. 7). As the roll compaction force increases, the AE also increases. Typically, higher AE values are due to higher levels of cohesion or an increase in the particle size/density as larger/heaver particles are harder to lift and separate at low air velocities. The improved particle packing exhibited in the bulk property tests is not indicative of higher levels of cohesion (cohesive powders tend to have inefficient particle packing); as such, the increase in AE value is likely to be due to increased particle size/density. The larger particle size would also explain the more-efficient particle packing exhibited by these powders as larger/denser particles tend to be more free-flowing and therefore able to slide past one-another to form a more tightly packed powder bed. This is, however, dependent on a number of other factors including shape and surface properties. The Flow Rate Index (FRI), a direct measure of the sensitivity of the sample to being made to flow at different rates [29], also shows a strong dependence on the roller compaction force. The more free-flowing the sample, the less sensitive the powder is to changes in flow rate (FRI close to unity), indicating that as the proportion of stronger and larger granules increases, the powder does indeed become more free flowing.

As has been indicated, shear testing is also frequently used to characterise flow behaviour. In this instance, the shear tests were demonstrated to be of limited value, with the shear cell test unable to discriminate reliably between the samples produced using different roll compaction forces. Fig. 8 shows a

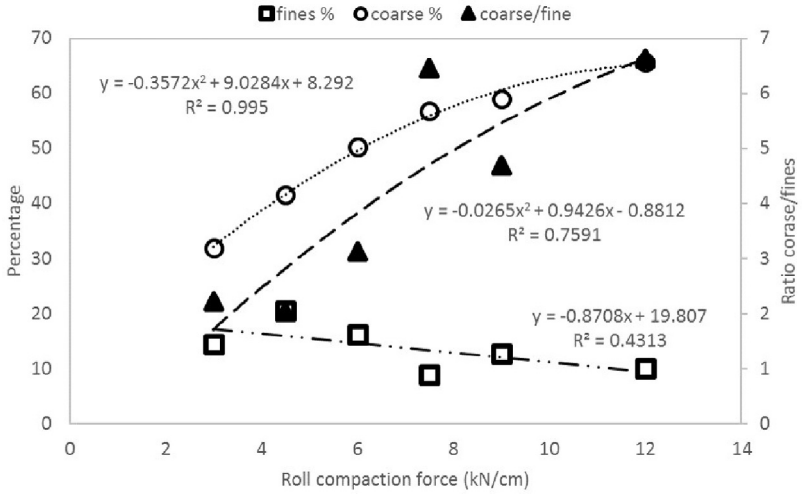

Fig. 5 – Size analysis of the granulate size with respect to roll compaction force.

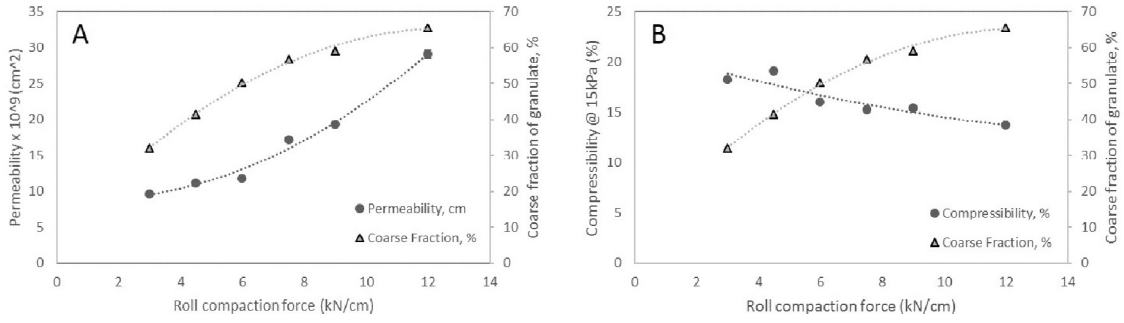

Fig. 6 – Comparison of the (A) permeability and (B) compressibility with the coarse fraction of granules.

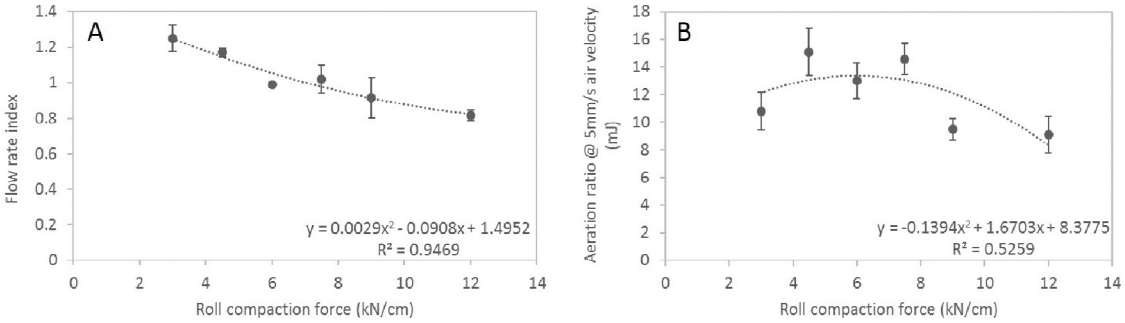

Fig. 7 – (A) Aerated energy and (B) Flow Rate Index for granules produced in Phase 1.

range of parameters derived from shear cell tests, as well as selected measured shear stress values, presented with respect to the roll compaction force.

Whilst it appears that there may be some correlation with the Flow Function, a review of the yield loci that were used to derive the FF values (Fig. 9) shows that there is very little variation in the shear stress values (the actual measured variables) between any of the granulate batches and indeed there is no correlation between the measured shear stress values and the roll compaction force seen in Fig. 8.

Given that the derived parameters are all sourced from an analysis of the yield loci constructed from the measured shear stress values, one might expect that they would show some inter-dependence; however, this is not the case, which demonstrates the limitations of applying a mathematical model to the yield locus.

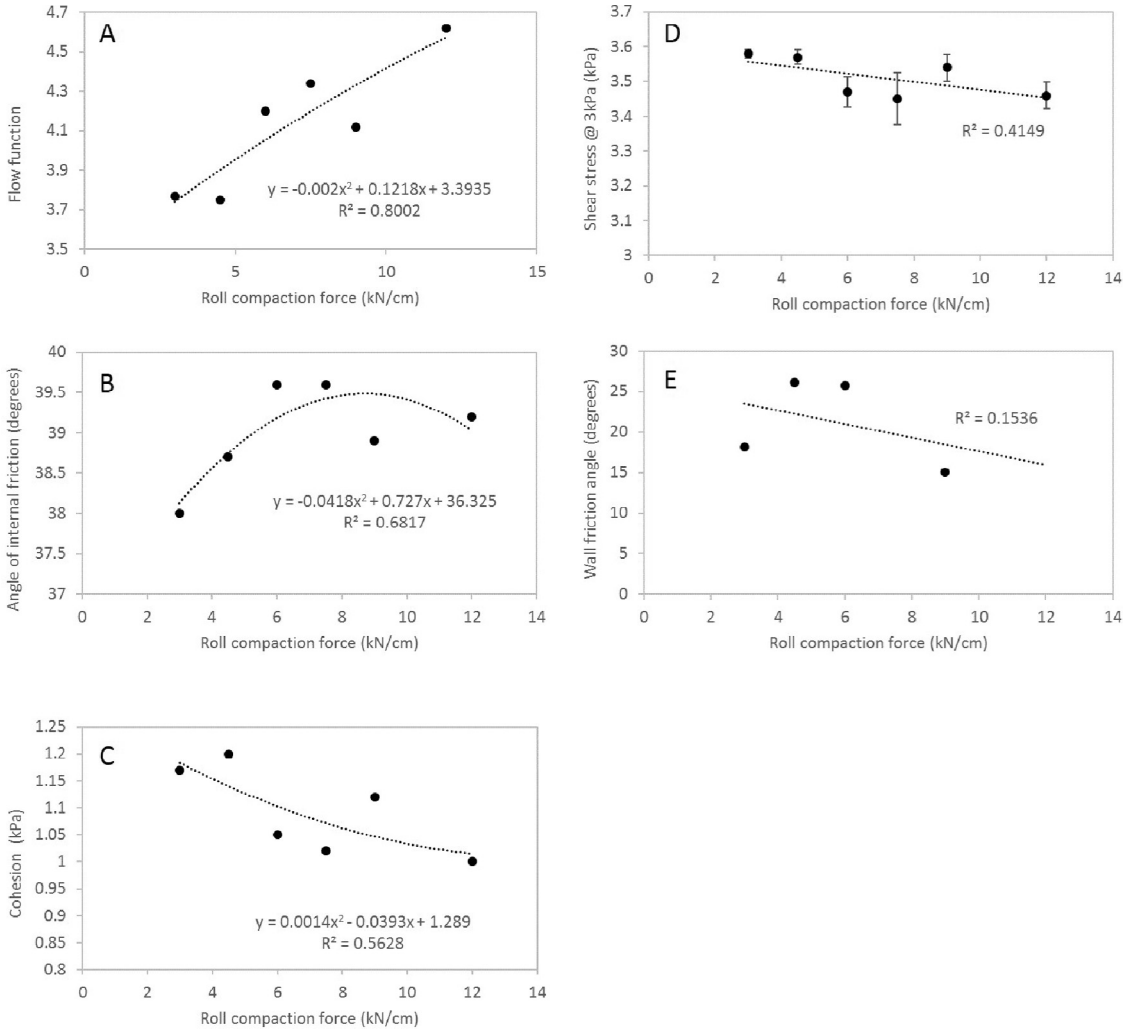

Fig. 8 – Test results for granules produced in Phase 1 including the: (A) flow function, (B) angle of internal friction, (C) cohesion, (D) shear stress at 7 kPa and (E) shear stress at 3 kPa for a 9 kPa Shear test.

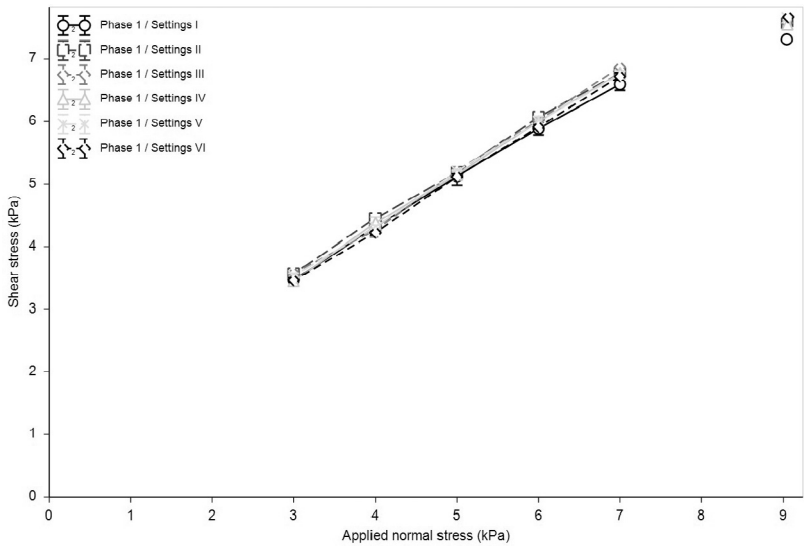

Fig. 9 – Yield loci for granules produced in Phase 1.

Table 3 – Testing parameters used in the Mini-Pactor in Phase 2.

Batch	A	B	C	D	E	F	G	H
Gap (mm)	1.5	2	2.5	3	4	5	5	1.5
Force (kN/cm)	4.5	4.5	4.5	4.5	4.5	4.5	9	9
Roll speed (rpm)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Screen sieve (mm)	1	1	1	1	1	1	1	1

Thus, it is entirely likely, in this instance, that the quality of the FF correlation is not robust and the relationship will be further evaluated for Phase 2 of the study to determine the suitability of shear testing.

3.2. *Phase 2 – effect of roll gap width*

Phase 2 investigated the effect of gap width on the bulk powder properties at two roll compaction forces: 4.5 kN/cm and 9 kN/cm. Batch A through Batch F used a roll compaction force of 4.5 kN/cm, with a gap width increasing from 1.5 mm to 5 mm; Batches G and H used a compaction force of 9 kN/cm and gaps of 5 mm and 1.5 mm respectively.

As the roll gap increases, the constant force applied by the roller has to be transmitted through a thicker ribbon of powder and thus the ribbon will have a lower strength and will likely result in smaller, weaker granules following the milling process.

Table 3 shows the roll compactor parameters used and Table 4 contains the size distribution data for the resultant granulate, which are also presented in Fig. 10.

The results from the rheological testing again suggest correlation with the permeability, compressibility and the CBD (Fig. 11).

The derived shear parameters, Fig. 12, show that any correlation between the FF and the roll gap width is significantly less robust than that with roll compaction force. In this instance, another derived parameter – the change in the angle

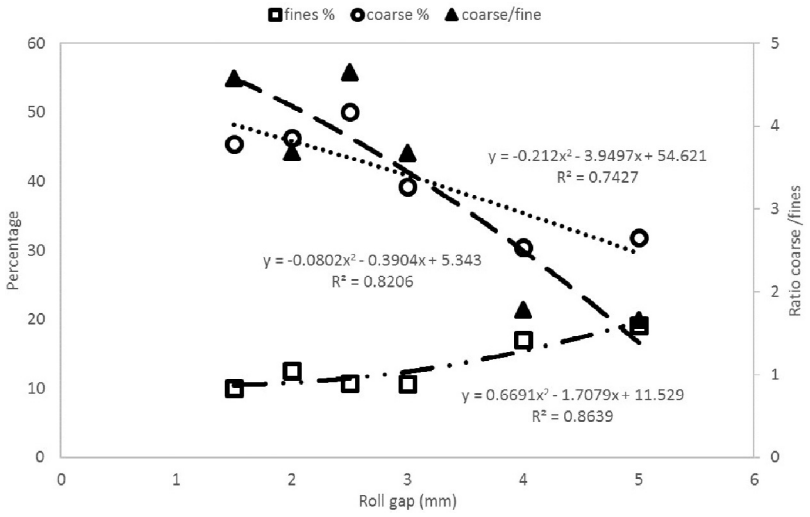

Fig. 10 – Size analysis of the granulate with respect to roll gap.

Table 4 – Size analyses of Phase 2 samples.

Batch	Roll gap, mm	Compaction force, kN	Fines % (below 106 μ)	Coarse % (above 212 μ)	Coarse/ Fine
I	1.5	4.5	9.94	45.45	4.57
II	2.0	4.5	12.57	46.31	3.68
III	2.5	4.5	10.76	50.03	4.65
IV	3.0	4.5	10.69	39.28	3.67
V	4.0	4.5	17.1	30.46	1.78
VI	5.0	4.5	19.19	31.85	1.66
VII	5.0	9.0	11.46	50.48	4.40
VIII	1.5	9.0	2.39	65.5	27.41

of internal friction – may be related to the change in roll gap width.

Despite the reasonable correlation for the AIF, when the actual shear data (rather than this mathematically derived parameter) are compared, there is, again, limited differentiation between the batches, suggesting that there is not necessarily a genuine relationship between roll gap width and shear properties (Table 5).

Overall, the results indicate that as the roll gap width increases, there is less uniformity in the quality of the granules, resulting in changes in the particle packing and hence the bulk properties, which is likely to be due to the greater variation in the consolidation regime between the rollers as the gap width increases.

This results in a lower consistency in the particle size distribution, shape and surface texture which is manifested by the reduction in the particle packing efficiency as demonstrated by the higher compressibility and lower permeability and CBD values.

3.3. *Phase 2a – comparison of 9 kN/cm and 4.5 kN/cm conditions wrt roll gap*

Phase 2 batches G and H used a roll compaction force of 9 kN/cm and gap width of 5 mm and 1.5 mm respectively. For comparative purposes, the equivalent data from Phase 1 – Batch V – were also included in this group as the compaction force, roll speed and screen size were comparable. This sample was produced using a gap width of 3 mm.

The results for batches G and H from Phase 2 and Batch V from Phase 1 were also plotted against the gap width to see if these follow similar trends to those observed at 4.5 kN/cm.

Comparable curves were obtained for the compressibility and CBD values for the 9 kN/cm and 4.5 kN/cm data, confirming the trends observed in Phase 1 (Fig. 13). As expected, lower

Table 5 – Testing parameters used in the Mini-Pactor in Phase 2a.

Batch	I	II	III	IV	V	VI	VII	V (P1)	VIII
Gap (mm)	1.5	2	2.5	3	4	5	5	3	1.5
Force (kN)	4.5	4.5	4.5	4.5	4.5	4.5	9	9	9
Roll speed (rpm)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Screen sieve (mm)	1	1	1	1	1	1	1	1	1

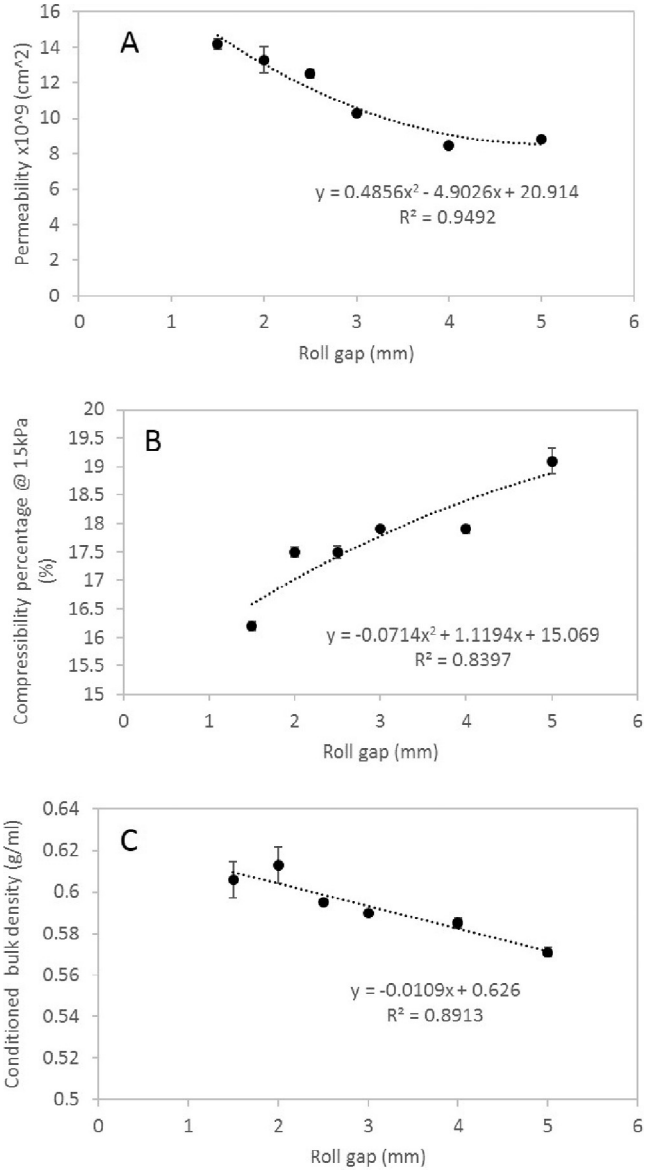

Fig. 11 – Bulk property test results for granules produced in Phase 2 including the: (A) permeability, (B) compressibility and (C) CBD.

compressibility and higher CBD values were generated at the 9 kN/cm compaction force.

The results also indicate a correlation between gap width and permeability; however, the reduction in permeability with respect to roll gap is much more pronounced at the higher compaction force and it can also be seen that the permeability of the granules produced at the highest roll gap is almost independent of the compaction force.

3.4. *Summary*

The results clearly demonstrate how several rheological properties of the product granulate are predictably influenced by the processing parameters – particularly the permeability, compressibility, conditioned bulk density, aeration and dynamic flow

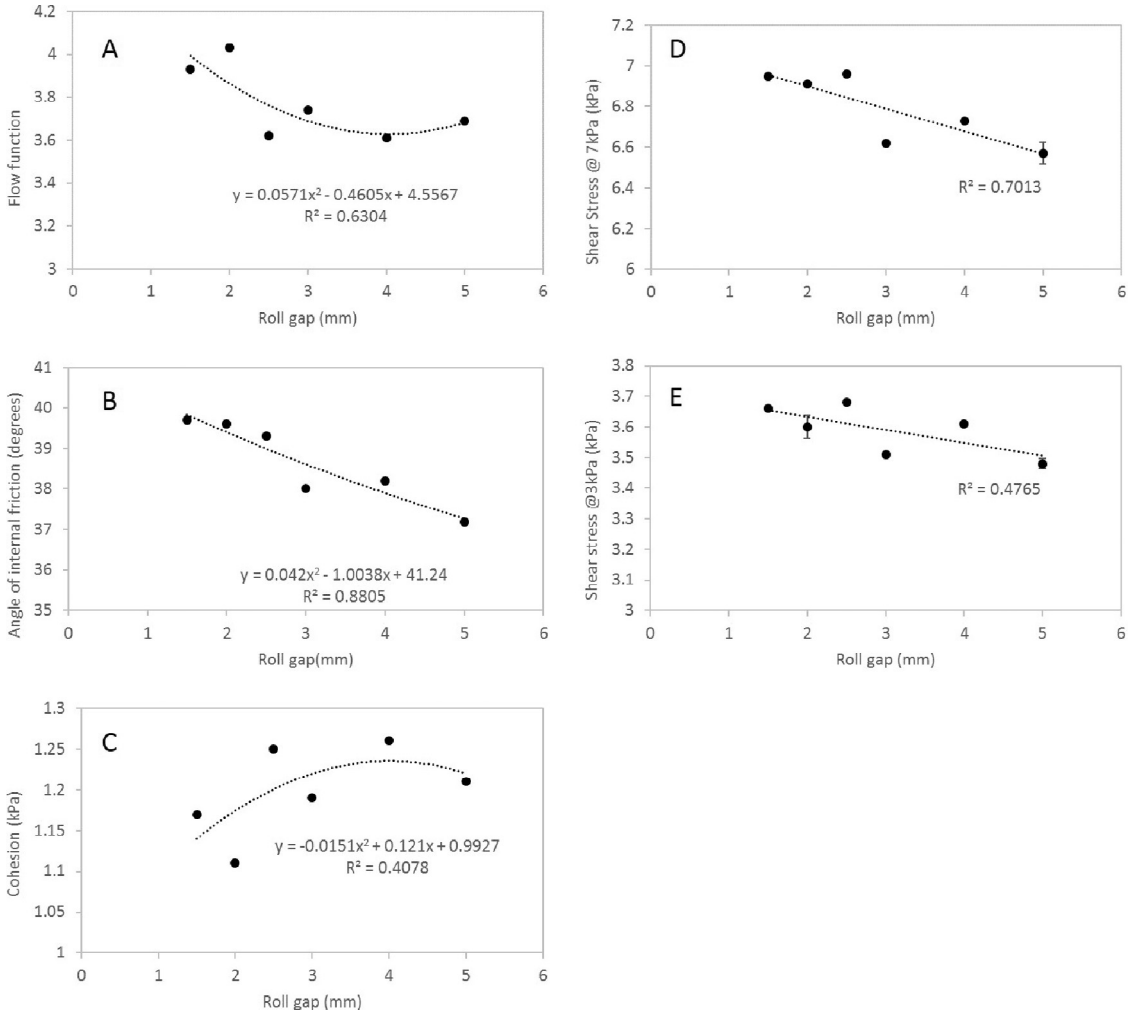

Fig. 12 – Test results for granules produced in Phase 2 including the: (A) flow function, (B) angle of internal friction, (C) cohesion, (D) shear stress at 7 kPa and (E) shear stress at 3 kPa for a 9 kPa Shear test.

properties, which all showed close correlation with several modes of operation of the roller compactor.

There is clear correlation between the roll compaction force and a number of rheological parameters, with the strongest correlation obtained for the bulk properties. Good correlations were also observed for the FRI and AE values, indicating that these measured parameters can be used to predict the flow properties of the final product as a result of changing the roll compaction force. Whilst there were fewer correlations between gap width and the rheological parameters, strong correlations were still evident with the bulk properties. This is not entirely unsurprising as larger roll gaps compromised the uniform distribution of force on the powder to form high quality ribbon (and hence granules). However, the results show that the bulk properties of the granulate are still very strong indicators of the influence of roll gap width.

Overall, the results suggest that a combination of smaller gap width and higher roll compaction force is more likely to result in more uniform/consistent granules which form a more efficiently packed powder bed typically associated with free-flowing powders. These granulate properties have also been shown to be closely correlated with variance in die filling and tablet strength. The bulk properties are not, however, directly proportional to granule size, which demonstrates the limitations of relying on particle size alone as a measure of granule quality.

Another observation was the lack of correspondence between the shear properties of the granulates and the manufacturing parameters. Given that many studies have previously relied on shear behaviour to characterise product granulate, it was clear from this study that, certainly for this particular roller compactor/feedstock combination, due to the limited differentiation between the measured Shear Stress values (rather than mathematically derived values), there is little relationship between the measured and derived shear parameters of granulates and roller compactor settings.

4. Conclusion

With respect to Quality by Design requirements, these results demonstrate that it is possible to control Critical Process Parameters in order to achieve granule properties within a defined

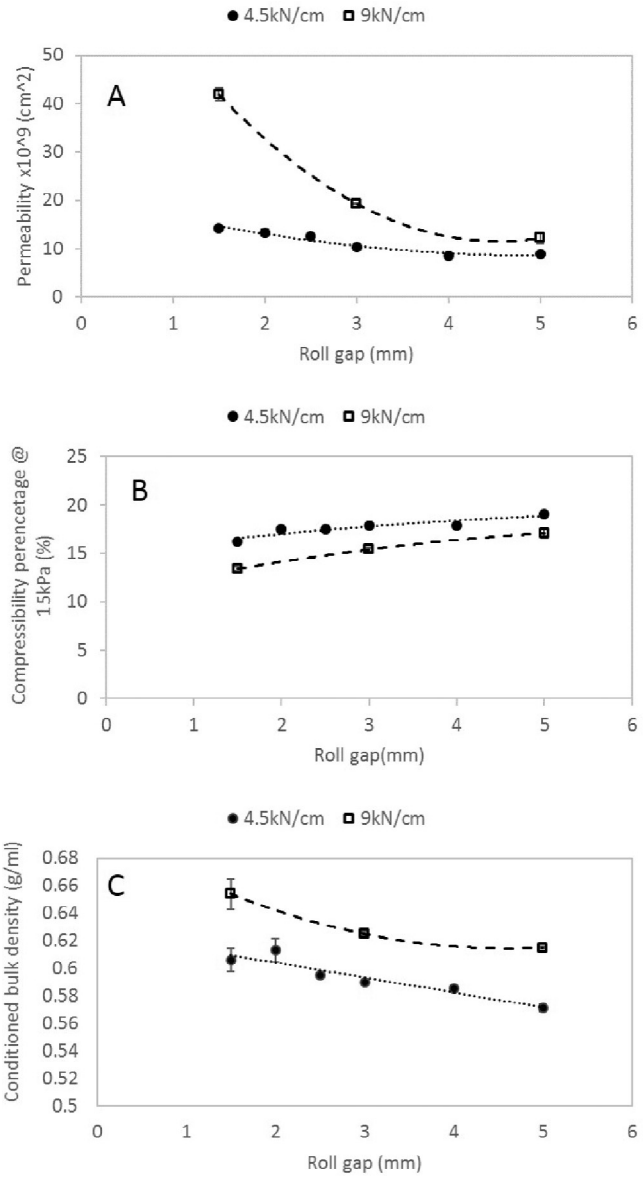

Fig. 13 – Comparison between two different roller compaction forces over a range of gap widths for the: (A) permeability, (B) compressibility and (C) CBD of the granulate.

Design Space – in this case permeability and compressibility – that have been shown to directly influence performance in downstream unit operations and Critical Quality Attributes of the final product.

5. Future work

This study evaluated a single feedstock and a limited number of processing parameters. Further assessments are to be undertaken to expand the number of feedstocks and roller compactor variables, as well as extend the study to include subsequent tabletting performance.

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