Expert Opinion

Pneumatic dry granulation: potential to improve roller compaction technology in drug manufacture

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Introduction: Solid dosage form manufacture still remains the most common in the production of pharmaceutical products. Established granulation processes can benefit from novel technical improvements, which can in turn enhance the behavior and properties of the process intermediates, that is, granules. These improvements in the manufacturing process can ultimately shorten development times, provide processing solutions for challenging materials and improve quality of drug delivery systems.
Areas covered: The aim of this review is to give the reader an overview of the latest trends in research with regard to roller compaction technology. Pneumatic dry granulation is also discussed as a new development with the potential to improve and extend the use of dry granulation processes, which can result in a substantial contribution to drug delivery system development and drug product manufacture.
Expert opinion: Dry granulation techniques, and more specifically roller compaction, can provide many advantages over the more established wet granulation techniques. There are still problems with roller compaction such as high amounts of fines and poor flow of granulate. Technical innovations that improve existing processes will have a considerable impact on development times and contribute to improved material processability and behavior of the end product. Pneumatic dry granulation has the potential to provide such alternatives.

Keywords: compactibility, flowability, granules, pneumatic dry granulation, powders, recompactibility, reducing fines, roller compaction, solid dosage forms

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1. Introduction

Granulation is a common unit operation in the manufacture of solid dosage forms to improve the properties of powders. According to Kristensen and Schaefer [1], the purpose of wet or dry granulation in pharmaceutical dosage form manufacture is to:

1) Improve powder flow properties for dosage filling and compression processes
2) Eliminate wet granulation-induced degradation and improve product stability
3) Prevent segregation
4) Reduce bulk volume thereby minimizing storage volume and improving transport efficiencies
5) Reduce potential environmental and safety hazards [1].

Several granulation techniques exist. The most common ones are wet granulation using either high-shear mixing or fluid-bed processing. However, dry granulation

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Article highlights.

- Roller compaction has gained popularity lately in drug manufacture.
- Roller compaction also offers advantages over wet granulation regarding moisture, solvent or heat sensitivity of the drug substance.
- There are still potential problems with roller compaction such as adequate powder flow and material compactibility.
- Pneumatic dry granulation (PDG) is a technical extension to dry granulation and provides good flowability at low ribbon densities.
- PDG enables the use of high drug loads of 70 – 100% and extends the application of dry granulation considerably.

This box summarizes key points contained in the article.

has recently increased in popularity [2]. Technical innovations that improve existing processes can have considerable impact on development times and contribute to improved material processability and behavior of the end product.

1.1 Dry granulation through RC is gaining popularity

The most common dry granulation technique is roller compaction (RC) that is combined with the consequent gentle milling of the flakes. Although the RC process has been in use for many years, it has lately become increasingly popular, and its use in pharmaceutical solid dosage from processing has grown considerably [3,4]. Whilst having all the benefits a granulation process can provide, including the improvement of material flow behavior and content uniformity, RC also offers advantages over wet granulation regarding moisture, solvent or heat sensitivity of the drug substance. According to Miller and Sheskey [4], the increasing scale of manufacturing of pharmaceutical products worldwide, the need for high processing rates, increased levels of good manufacturing practices, together with a desire to reduce manufacturing complexity means that RC is an increasingly attractive option for the manufacture of oral solid dosage forms. These authors continue by stating that this has been accomplished by instrumenting roller compactors to automate and control the mechanical process. Furthermore, RC technology plays a very important role in providing competitive cost control because of its high throughput at a minimum of operator presence and floor space, and last but not least, RC-based dry granulation scale up efforts are minimized. Key RC benefits observed have been compiled in **Table 1**.

RC is a continuous dry granulation process with the aim of manufacturing free flowing granulate, increasing the bulk density and ensuring the uniformity of particulate formulations by preventing the segregation of the constituents of the powder. In RC, a powder blend is compacted between two counter-rotating rolls. In the narrow region of the gap between the rolls, the powder is subjected to pressure, leading to the formation of a compact, which is called a ribbon or flake. This ribbon is then reduced in size using dry milling to achieve the desired granule size. The main purpose is to obtain granulate with acceptable flow properties and sufficient secondary compactibility for the subsequent processing steps, typically tableting or encapsulation. The theory of compaction and RC is not covered in this review but provided elsewhere [3,5]. Successful use of RC has been demonstrated in the development and production of conventional immediate release solid dosage forms [6-9] as well as for controlled release drug delivery systems [10].

1.2 Increased activity in research of RC

In the past decades, research with regard to RC has concentrated on how different types of commonly used excipients behave during the RC process and how variability in the material properties (such as particle size, polymorphic form or moisture content) affect the processing and resulting end products. Examples exist of single excipients, simple binary mixtures with actives or two excipients, and model formulations including the effect of lubrication during RC [11-15].

In the spirit of the process analytical technology (PAT) and other regulatory initiatives (such as Quality-by-Design) [16,17], there has been an increased interest in understanding the process and material behavior during RC using sophisticated analytical tools, such as near-infrared spectroscopy [18]. Gupta *et al.* have written a series of papers investigating real-time control of the RC process during the past few years [19-22]. However, already in the late 1990s there were examples of the successful application of PAT to RC using acoustic emission spectroscopy. For example, Salonen *et al.* measured acoustic relaxation emissions from microcrystalline cellulose and maize starch during the dry granulation process [23]. Because, for a given formulation, the solid fraction is the most important parameter regarding ribbon properties, for example, compact strength, the simplest means of in-process control of granulate properties is achieved by controlling the so-called 'at gap' density during RC by determining both the volume of compacted powder made per unit of time between the rolls (from gap, roll speed and roll width) and the corresponding amount of granulate prepared by continuously measuring the weight of granulate [24,25].

In recent years, there has been increasing interest in understanding the RC process through modeling of fundamental process parameters. The one-dimensional model of Johanson published in 1960s is useful in predictive purposes [26,27]. Johanson divides the regions of compaction into two parts: the feed region, where a slip boundary condition is applied to the roller surface, and the nip region, where a no-slip boundary condition is utilized. The Johanson model allows prediction of the pressure profile as a function of roller angle, with the peak pressure at the minimum separation distance. This model has been applied, for example, by Bindhumadhavan *et al.* [5]. Reynolds *et al.* recently demonstrated the practical potential of modeling in process design and scale-up,

Table 1. Advantages of roller compaction.

Simplifies processing
Uses less raw materials
Eliminates aqueous and solvent granulation
Eliminates heat and/or water-induced degradation products
Improves powder flow
Improves process cycle time
Uses minimal energy
Prevents particle segregation
Requires less man-hours
Process with a large throughput
Low batch related personnel costs
Reduced floor space
Facilitates continuous manufacturing
Improves drug dosage weight control
Improves content uniformity
Reproduces consistent particle density
Does not require explosion-proof room or equipment
Produces good tablet and capsule disintegration
Technology with the most straightforward scale up factor

Modified from [3], Handbook of Pharmaceutical Granulation Technology.

and the use of predicted peak pressure to present RC of different formulations in a scale-independent manner [28]. Hsu *et al.* derived a dynamic model for RC process based on Johanson's rolling theory, which is used to predict the stress and density profiles during the compaction, and the material balance equation, which describes the roll gap change. The proposed model considers the relationship between the input parameters (roll pressure, roll speed and feed speed) and output parameters (ribbon density and thickness), and makes design, optimization and control of the process possible using the model-based approach [29,30]. Zinchuk *et al.* developed a method for simulation of the RC process using a laboratory scale compaction simulator [31]. The simulation was evaluated using microcrystalline cellulose as model material where ribbon solid fraction and tensile strength were the key ribbon properties. Recently, Peter *et al.* predicted RC forces for achieving a given ribbon solid fraction from an easy to understand slab model, and 'in die' pressure density measurements of the powder mix of interest using 'normal' single stroke tablet presses [32]. Soh *et al.* utilized multivariate modeling, namely principal component analysis (PCA) and partial least squares, to model the effects of raw material properties and RC operating parameters [33]. Other examples of modeling and simulation range from finite element-based modeling [34] to neural network modeling approaches [35] and include a wide range of useful examples [32,36].

1.3 Challenges with RC

As mentioned above, RC is designed to improve the flow properties, increase the bulk density and ensure the uniformity of particulate formulations by preventing segregation. It offers advantages compared to wet granulation for processing physically or chemically moisture-sensitive materials because granulation liquid is not needed. Another advantage is that it does not require a drying stage and is, therefore, suitable for use with compounds that either have a low melting point or degrade rapidly on heating, thus, making it a cost-effective manufacturing option [1-3].

The key factor in roll compaction is that the binding of particles results solely from the compaction forces requiring a certain degree of compactibility of the powder blend. Some active ingredients can be compressed directly, whilst others require the addition of excipients, which are selected based on their compaction properties. Consequently, in RC, the material to be compacted often consists of a mixture of (poorly compactible) drug substance and (compactible) excipients in order to obtain a ribbon with sufficient mechanical strength so as to result in a sufficiently coarse flowable granulate. Commonly used excipients for this process are microcrystalline cellulose, dicalcium phosphate, lactose monohydrate and mannitol [1,2].

RC may be inappropriate for substances which strongly adhere to metal surfaces or that are non-compactible. The robustness of RC can also be affected by the variability in drug substance physical and mechanical properties; however, less so than in direct compression. In general, depending on the compression and flow properties of the drug substance, the drug load can vary from 2 to 50% in RC [2]. Kleinebudde has listed possible problem areas with regard to processing using RC [2]. The main issues are: i) high amount of fines/leakage of uncompacted material ii) loss in compactibility, iii) homogeneity of the ribbon and iv) extensive sticking of material to the rolls.

2. Pneumatic dry granulation

Until recently, there has been little emphasis on the possibilities of technical improvements or extensions to the RC process. Miller and Sheskey discuss the importance of the design features of the RC process including roll configurations, feed screw design and so on [3]. In principle, all roller compactors consist of the same basic elements and have similar configurations. Commercially available roll compactors may have rolls mounted in a horizontal, vertical or even inclined position. Powder feed to the compaction area between the rolls is achieved by one or more augers, seldom by gravity. Manufacturers obviously make disputed claims about the relative merits of these different types of configurations. In 1997, Miller [37] described a new machine design improvement in which vacuum deaeration is claimed to remove air entrainment from the powder just prior to the nip angle during RC. Although it is questionable that vacuum is maintained within the powder to be conveyed during usual processing times, because fine particles may cause quick clogging of filter systems, benefits have been observed regarding a more uniform feed to the rollers, especially when compacting low density raw materials [3]. Similar improvements in powder feed could be achieved by activating the so-called torque

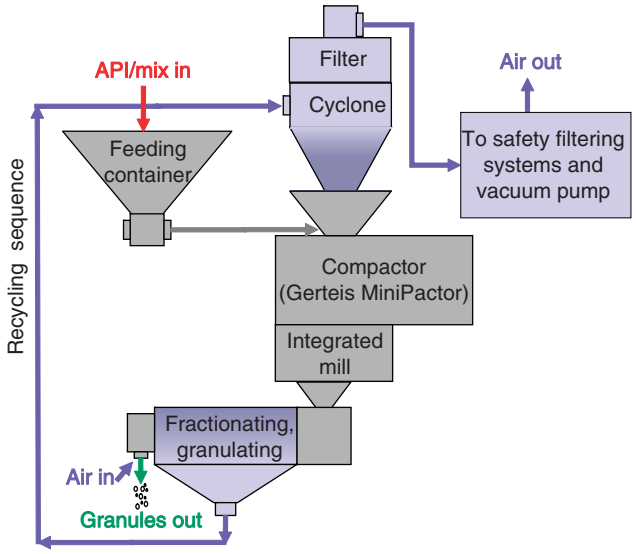

Figure 1. Schematic of a pneumatic dry granulator with a gas flow-based fractionating/granulating device.

control option [38], which results in a controlled degree of predensification before the powder is conveyed into the compaction area between the rolls. These experiments clearly demonstrated the importance of increasing the bulk density of the powder just prior to compaction. According to Sheskey and Miller, a key factor limiting compaction throughput and quality is air entrapment in powder materials [3]. During compression, air-occupying voids between particles are compressed and squeezed. The gas then escapes from the powder causing powder fluidization and a non-uniform filling of the compaction area between the rolls just before powder draw-in [37].

In addition, the way in which the compaction area and especially the nip area are sealed to avoid leakage of uncompacted and compacted powder from the compaction area plays an important role with respect to the quality of the ribbon. Static sealing systems always cause a low density and thus reduced ribbon strength at the edges, whilst sealing the nip area with so-called rim rolls in general results in a nearly flat density or a uniform density distribution and thus strength distribution. Depending on the interaction of the powder with the roll and rim surface, the density at the edges of rim roll ribbons might be larger than at the center of the ribbon [39]. Because this effect depends on the gap size, the extent of these differences in density can clearly be reduced towards a flat distribution by increasing the gap for a given roller compactor set up. In this way, flat density distributions can be achieved; these being optimal with respect to the recompactibility of the dry granulate.

In spite of these technical improvements, the ultimate aim of the dry granulation process manufacture of granules having the desired size, flowability, packing, durability and recompaction properties, that is, the ability to form strong compacts on tableting cannot always be achieved, especially when high ribbon densities using high roller forces are required to obtain a flowable granulate. In general, such an operation results in poor recompaction properties. Recently, pneumatic dry granulation (PDG) has been introduced, which is based on classical RC and considerably extends the application of dry granulation, because flowability is achieved at low ribbon density thus improving recompactibility of the resulting dry granulate [40]. PDG is a method in which the granulated material from a RC process is pneumatically fractionated using controlled conditions of circulating gas in a rotating perforated cylindrical drum. The purpose of this paper is to give an insight into the PDG technology and to discuss some of the potential benefits of this granulation technology using an experimental example.

2.1 Process description

Figure 1 schematically shows the various components of the equipment train. Granules are made from a powder by applying a force between two rolls so as to produce a compacted ribbon as in conventional RC. The ribbon is then granulated using a suitable milling system. The resulting mixture of different sized granules is separated by a fractionating device in such a way that fine particles and/or small granules are separated from the coarser ones by entrainment in a gas stream.

The gas stream may be provided by any suitable means, for example, a vacuum pump. The gas stream, for example, air or nitrogen, is directed through the fractionating chamber. The gas stream separates fine particles and small granules from the larger ones. Basically, the gas flows in a direction opposite to the movement of the roller compacted granulate. The separated fine particles and/or small granules entrained in the gas stream are transferred from the fractionating chamber to a separating device, for example, a cyclone, in which they are separated from the carrier gas. The material may then be returned to the system for immediate re-processing (i.e., they are re-circulated for compaction) or they may be placed into a container for later re-processing. For suitable protection of the system and environment, the gas inlet of the vacuum pump is provided with a filtering system to remove any particles from the gas stream before they pass through the pump. **Figure 2** demonstrates a fully functional unit in operation.

One of the main advantages of PDG is the possibility of using very low compaction forces to make ribbons with a low density or solid fraction. Generally, the solid fraction (relative density) increases as the material is processed from powder to tablet form [41] and is thus an indicator of the degree to which the powder has been compressed. Some materials or formulations can only tolerate a certain degree of compaction, and once that is exceeded they will not recompact. Thus, a lower solid fraction gives more available compaction from the recompaction stage. This degree of densification directly affects the mechanical properties of materials. For instance,

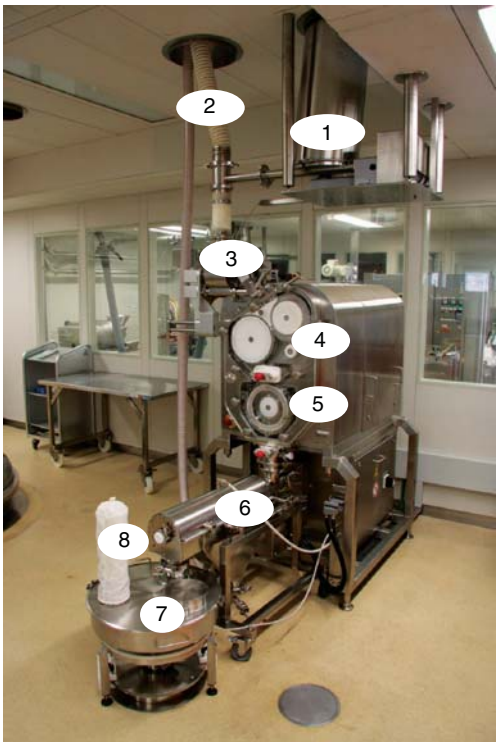

Figure 2. An example of a fully operational pneumatic dry granulation system. 1: blend to be granulated and 2: recycled powder fed into 3: feed hopper of 4: roller compactor (Minipactor, Gerteis) with 5: integrated mill 6: fractionator, granulator 7: PD-granules container with 8: air inlet.

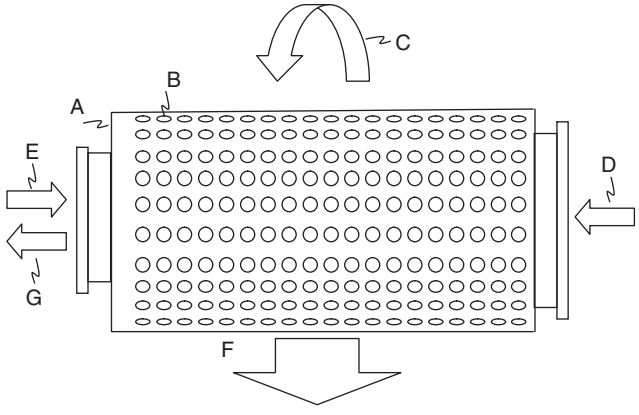

Figure 3. PDG fractionation/granulation cylinder (A) with perforations (B). The cylinder rotates (C) as the granules and fine particles enter the cylinder (D) and the carrier gas (E) enters the cylinder from the opposite direction. Rejected particles (F) are guided to be reprocessed whereas accepted granules are collected (G).
PDG: Pneumatic dry granulation.

tensile strength, modulus of elasticity and indentation hardness of compacted powders all depend on the solid fraction of the material [42,43]. Recently, density distributions of ribbons have been studied with modern tools such as micro-indentation and X-ray microtomography [44,45].

The main difference compared to conventional RC is that due to an optimally controlled RC process (optimal powder feed, user selectable constant compaction force and gap, and gentle milling) and a very gentle pneumatic separation of fine from coarse particles, together with an additional granulation effect within the fractionator, far lower compaction forces (at a given gap and roll speed) are required to obtain a flowable granulate, thus preserving maximum binding capacity of the granules.

For instance, it has been demonstrated that at 1 kN/cm and a gap of 4 mm excellent granules with very good flowability were obtained, whereas with conventional RC such low pressures are not large enough to produce free flowing material because of an excessive amount of fines. Typically, the PDG process is operated so as to make ribbons at a solid fraction ranging from ~ 0.4 to 0.6. In general, this corresponds to roll compaction forces between ~ 2 and 6 kN/cm, for example, at a gap of ~ 4 mm. The exact roller compactor settings (force, gap and roll speed) to achieve the desired solid fraction depend on the compressibility properties of the powder to be granulated.

2.2 The fractionation of granules

The fractionating device as shown in **Figure 3** consists of a perforated rotating cylinder in which the compacted mass is moved into the gas stream. There are many options as to how to guide the movement of the compacted mass. For instance, it can be by gravitation or it may be facilitated mechanically, for example, by baffles or spirals guiding the movement of the compacted mass. The residence time of the material in the device can be adjusted to optimize the efficiency of fractionation and granulation. The device comprises a perforated cylinder through which the gas stream flows into and out of the device. Fine particles and/or small granules may fall through these perforations and be entrained in the gas stream. The size of the perforations in the rotating drum may be substantially larger than the size of the fine particles which are to be removed from the roller compacted granulate. For example, the apertures may have a minimum diameter of around 250 – 750 microns, or larger. This helps prevent the apertures from clogging even when relatively large volumes of fine particles are being fractionated from the roller compacted granulate. In this respect, the classification differs substantially from an air or vibrational sieving system, of which the mesh size must be equivalent to the size of the largest particle to be removed from the powder. Instead, the fractionating device relies on the gas stream's ability to entrain fine particles from the moving granules.

Due to the fact that the gas flow-based fractionating device recycles the majority of the fine particles until adequately

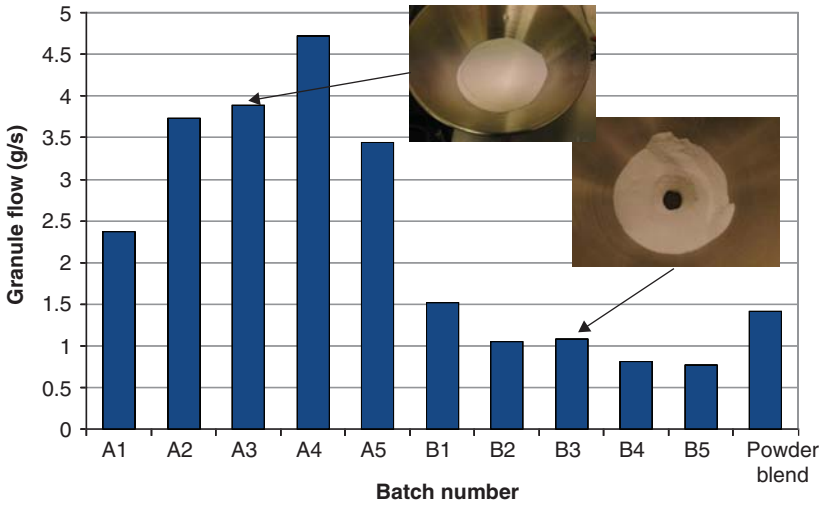

Figure 4. Powder flow data (g/s) of PDG batches (A1–A5), RC batches (B1–B5) and the powder blend. Photographs from batches A3 and B3 are shown to demonstrate the arching/ratholing behavior of RC batches during power flow measurement. All RC batches also needed feeding assistance in order to perform the flow analysis.
PDG: Pneumatic dry granulation; RC: Roller compaction.

sized particles are ready to be collected by the fractionating unit, considerably less fines exist in the granulate resulting in good flow properties. Because of the efficiency of the pneumatic recycling system, the loss in material during PDG is limited to material present in the so-called dead spaces of the equipment. Because this is a constant, which depends slightly on the powder properties, generally the yield for production batches of, for example, 100 kg is 99% or greater.

Furthermore, because PDG is performed in a closed loop system with at least two filter units in series, the leakage of dust is reduced to a minimum. Together with, for example, a Gerteis roller compactor having a standard Operator Exposure Banding level of 3 $\mu g/m^3$, PDG will be suitable for substances requiring high containment manufacturing conditions. Research has shown that the PDG process results in soft granules with a porous structure, which is favorable for the downstream processing, namely, tablet compression (unpublished data).

2.3 Metformin as an example formulation

PDG and conventional RC were compared using a model high-dose metformin formulation. The PDG technology was compared to conventional RC using a Hosokawa Bepex Pharmapaktor and a model formulation consisting of metformin hydrochloride (80% w/w) and microcrystalline cellulose (10% w/w) and maize starch (10% w/w). Five 500 g batches were produced using both technologies at five different roll forces ranging from 2 to 14 kN/cm (2, 5, 8, 11, 14). Below, the PDG batches are marked A1–A5, the roller compacted batches B1–B5 and the untreated powder blend is indicated as PB.

All granules were assessed for particle size (by laser diffraction; Sympatec HELOS, Sympatec Gmbh, Clausthal, Germany), powder flow (FS3D, Intelligent Pharmaceutics Ltd, Helsinki, Finland), tablet compression behavior (EK0. Korsch, Germany) and physical end product characteristics (tablet hardness, disintegration). The results for powder flow in **Figure 4** indicate that the PDG granules show significantly better flow properties than conventional RC granules. This can be explained by the efficient fractionation, which resulted in a shift towards larger particle sizes of granules as shown in the particle size distributions in **Figures 5A–C** and the surface images shown in **Figure 5C**. As expected, the granule size distributions show that RC samples consisted of a substantial amount of fines compared to PDG granules. **Figure 5C** demonstrates that the amount of fines and large particles for the highest RC force (B5) and lowest PDG force are very similar, whereas when comparing **Figure 5A** and **B** we can clearly see that the amount of fines for the PDG granules is very low already for the 5 kN/cm force and upwards. PDG and RC granules showed fairly similar crushing strengths and disintegration times at nearly equal compression forces (not shown). However, compression profiles showed differences for PDG and RC granules (**Figure 6A,B**). For instance, as indicated for batches A1 and B1 with similar tablet densities, the PDG granules had slightly higher crushing strength. In general, as expected due to the difference in the amount of fines, the weight variations (relative standard deviation (RSD)%) were smaller for PDG granules indicating more consistent die filling during tableting. A summary of the results is shown in **Figure 7**. The PCA correlation plot shows how each batch relates to each other in terms of all the measured responses. The plot shows clear clustering/differentiation of the PDG and RC batches. The location of a batch close to

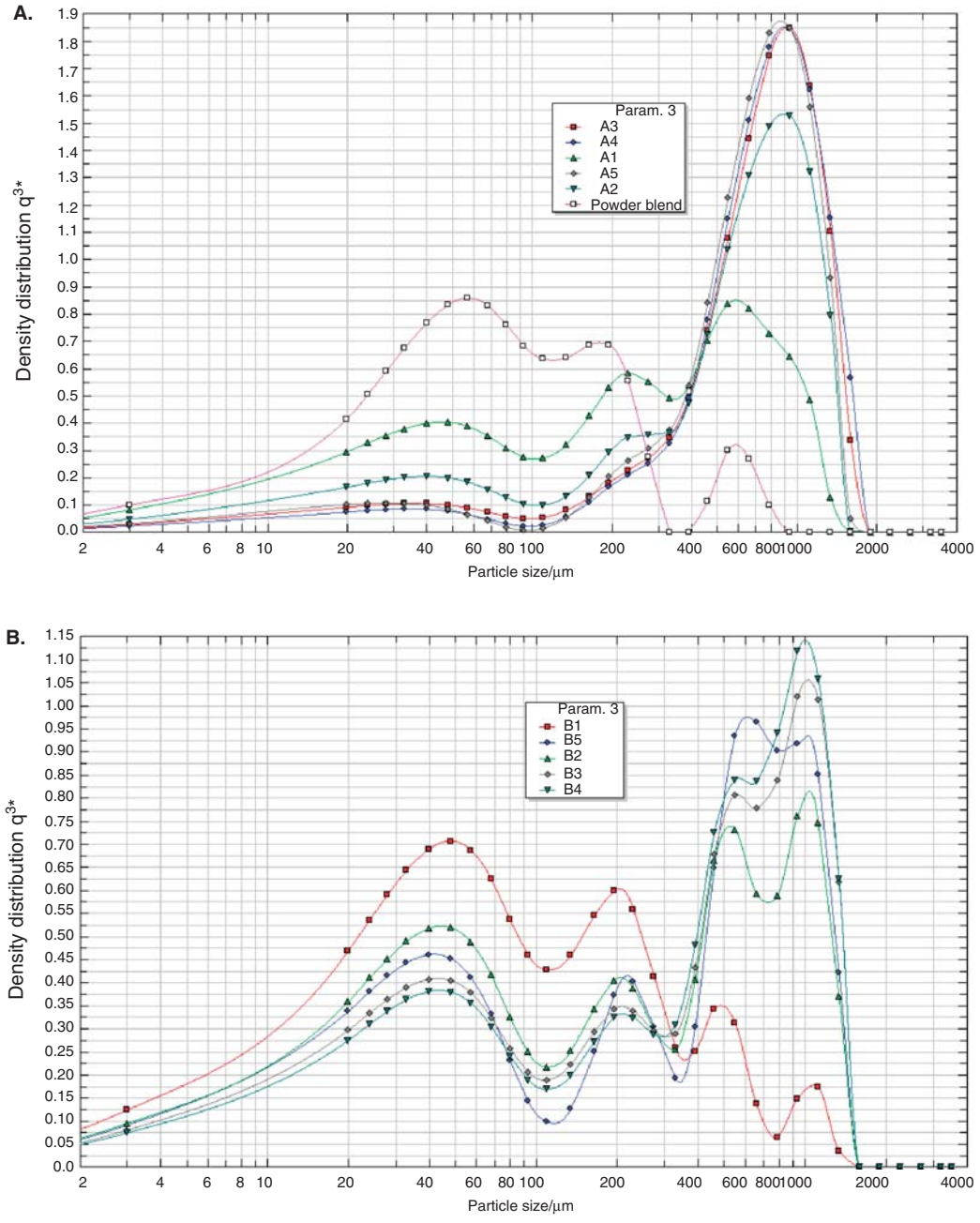

Figure 5. A) Particle size data of PDG batches A1–A5 (processed with 2, 5, 8, 11 and 14 kN/cm roll pressures, respectively) and the unprocessed powder blend. **B)** Particle size data of RC batches B1–B5 (processed with 2, 5, 8, 11 and 14 kN/cm roll pressures, respectively). **C)** Surface images of PDG and RC granule batches and the powder blend.
PDG: Pneumatic dry granulation; RC: Roller compaction.

a response marked with a black triangle (e.g., tablet hardness) in the graph means that the batch has a high value of that given parameter as compared to a batch that is further away. From the plot, it can be seen that larger particle size and increased flow are descriptive for the PDG batches as they are projected closer to the flowability (Flow) and the particle size (ps) descriptors (mean sizes d10, d90, d50). Also, there is increased weight variation and hardness variability of tablets for RC batches as the B1–B5 are closer to these properties on the PCA plot. The plot also indicates higher tableting compression force variabilities (RSD) at larger granulation forces for both techniques. In conclusion, the PDG technology produced granules with improved downstream processability (especially powder flowability and particle size distribution) compared to conventional RC at all roll forces used.

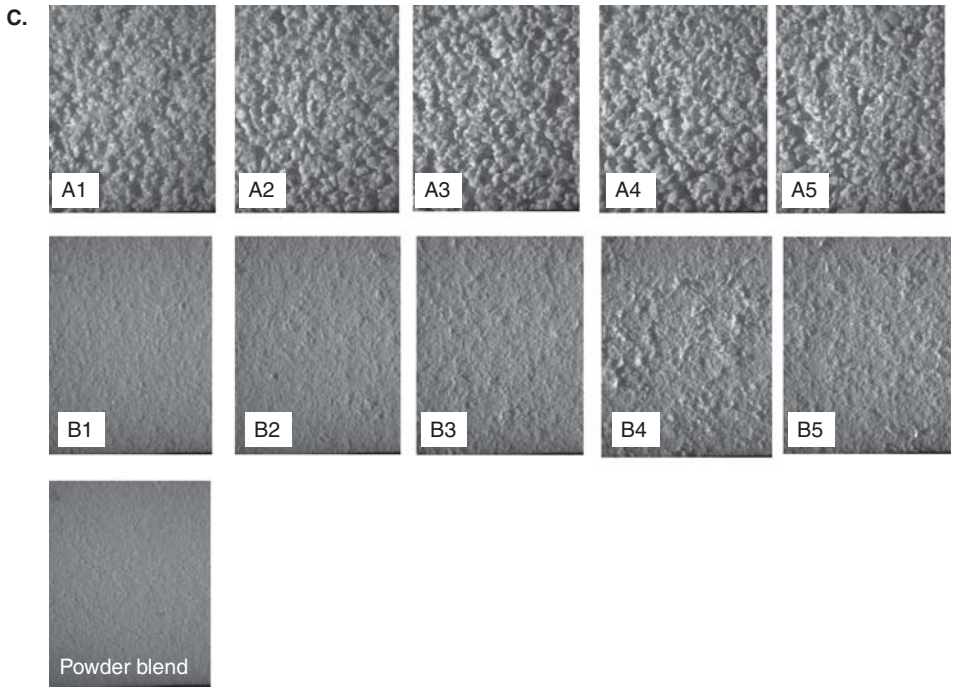

Figure 5. (continued). A) Particle size data of PDG batches A1–A5 (processed with 2, 5, 8, 11 and 14 kN/cm roll pressures, respectively) and the unprocessed powder blend. **B)** Particle size data of RC batches B1–B5 (processed with 2, 5, 8, 11 and 14 kN/cm roll pressures, respectively). **C)** Surface images of PDG and RC granule batches and the powder blend.
PDG: Pneumatic dry granulation; RC: Roller compaction.

3. Conclusions

The use of dry granulation, that is, RC, has increased recently in the development and manufacturing of pharmaceutical dosage forms. There are still potential problems with RC such as adequate powder flow and material compactibility. Technical process improvements can solve these problems and provide solutions to these issues. In this context, PDG might have potential to give answers to the problems.

4. Expert opinion

Dry granulation techniques, and more specifically RC, can provide many advantages over the more established wet granulation techniques. As has been mentioned above, RC is designed to improve the flow properties, increase the bulk density and ensure the uniformity of formulations by preventing the segregation. It clearly offers advantages compared to wet granulation for processing physically or chemically moisture-sensitive materials because a liquid binder is not required. Moreover, because there is no need for a drying phase, RC technology is suitable for compounds with low melting points or substances, which degrade rapidly on heating. In principle, RC is a continuous process, which can be operated in a batch or semi-batch mode, whereas other granulation methods are usually operated in batch mode and are not easily adapted to allow continuous processing, although there are recent advances in the area of continuous wet granulation processes. Because RC is a continuous process, scale up problems, if any, are reduced to a minimum. Furthermore, in dry granulation using roller compactors, the throughput is relatively large compared to other methods. A recent systematic approach to formulation and process development has been proposed for excipient selection and critical process parameter identification by Teng *et al.* [46].

As stated above, there are still problems with RC. In particular, achieving flowable granulates at drug loads > 50%, especially with a poorly compactible drug substance, can be difficult because of the large amount of fines in the final powder mix. In addition to these fines from the process, flowability will also be decreased due to the so-called uncompacted fines, which result from inefficient mechanical sealing of the compaction area between the rolls, allowing uncompacted powder to bypass this area without being compacted. Powder blends requiring a large solid fraction (and thus a large roll force) to achieve the desired flowability in general will lose too much of their compactibility, resulting in weak tablets. Reduced tabletability and insensitivity of compaction properties have been recently studied by Sun and co-workers [47,48].

The problem of uncompacted fines may be solved by improving the equipment design and construction, but

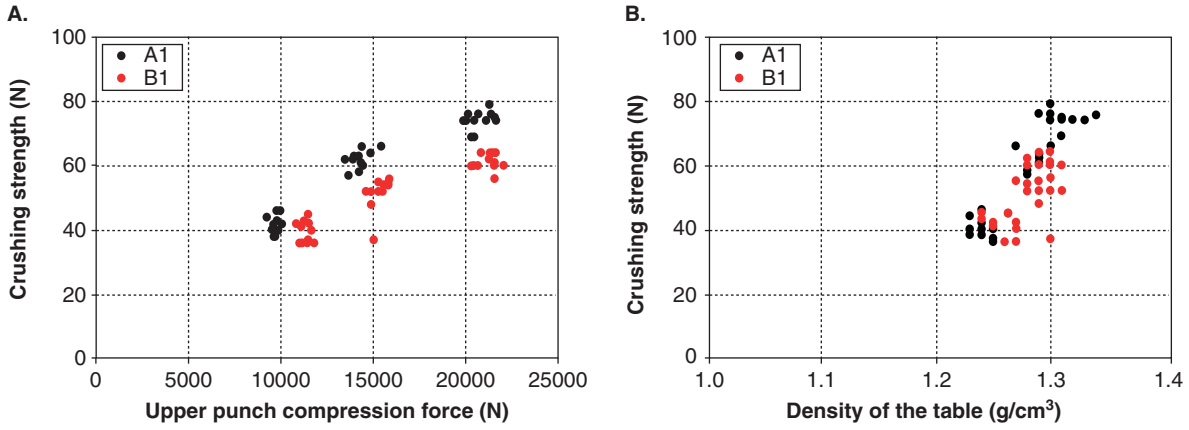

Figure 6. A) Force hardness profiles for batches A1 (PDG) and B1 (RC) **B)** Crushing strength vs density of the individual tablets for batches A1 (PDG) and B1 (RC).
PDG: Pneumatic dry granulation; RC: Roller compaction.

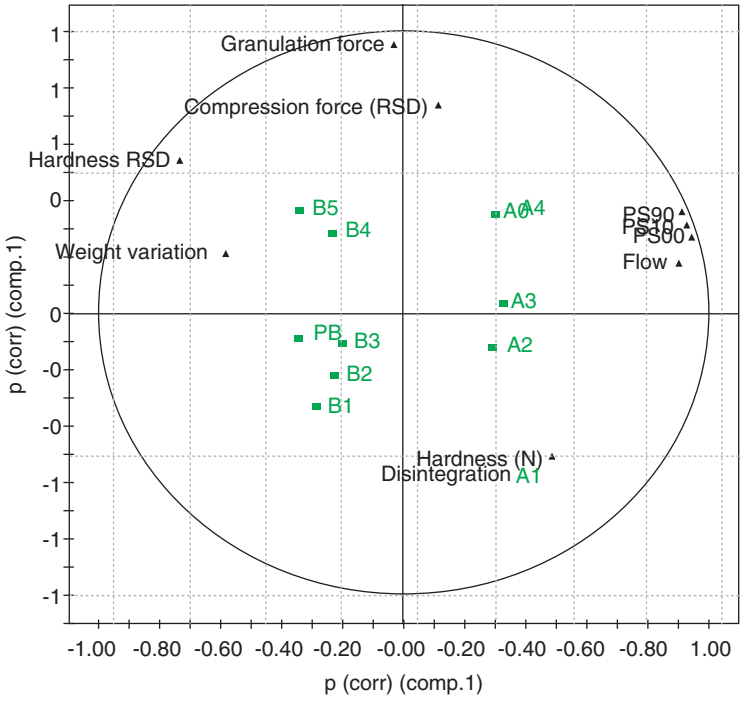

Figure 7. A data overview using a principal component analysis correlation plot. The plot shows the clustering of roller compacted (B-series) and PDG (A-series) batches of the metformin formulation. In general, a batch that is closer to a given property (marked with black triangles) the higher its value for that property. E.g., A3 which is closer to the 'Flow' response has better flow (g/s) properties than the corresponding RC batch B3.
Compression force RSD: Relative standard deviation of compression force during tableting; Flow: Powder flow g/s; Hardness RSD: Relative standard deviation of tablet hardness; PB: Ungranulated powder blend; PDG: Pneumatic dry granulation; ps10/ps50/ps90: Particle size diameters; RC: Roller compaction.

solving the problem of formulation-dependent fines and recompactibility requires a different approach. PDG has potential to provide such an alternative. When considering the issue of the high amount of fines and leakage, the classifying unit of the pneumatic granulator addresses this problem by recycling the fines and the small granules, and by collecting only the larger granules. Due to the low compaction forces used, PDG makes it possible to retain more binding forces between and within the granules thus minimizing the loss in compactibility.

All formulations that result in compacts with a tensile strength of ~ 0.5 MPa can be dry granulated using PDG, resulting in a flowable granulate. Whether these PDG granules still can be compacted to tablets with sufficient mechanical strength will depend on the amount of bonding sites left after the RC process. At large roll compaction forces, or more precisely at large solid fractions of ribbons, especially plastically deforming substances may result in granules with poor compactibility because of too much bonding sites being used during the RC step. Therefore, and this is generally valid, during RC the forces should be as low as possible for obtaining a sufficiently flowable granulate. Because sufficient flowability will be achieved with PDG at lower roll compaction forces (lower solid fractions) compared to just roll compaction, PDG enables the use of high drug loads of 70 – 100%, which quite often results in formulations with poor compactibility. And this extends the application of dry granulation considerably.

As described above, PDG has potential to improve RC and has shown to lend itself to high drug loadings; however, there are still open questions and challenges regarding the technology that current research activities are looking into. Some of the open questions include:

- the influence of recycling on the particle and granule properties
- with low dose formulations: does the process have an inherent risk of process-induced segregation due to the recirculation of uncompacted fines, rich in non-compactible active pharmaceutical ingredient (API), which potentially could lead to content uniformity issues
- what is the lower limit for drug load where this becomes negligible
- is friability an issue for PDG granules for being blended in a large scale
- influence of and sensitivity to raw material (API and excipients) variability.

Declaration of interest

Niklas Sandler is an external scientific advisor to ATACAMA Labs, who develop pneumatic granulation technology commercially.

Rob Lammens is ATACAMA's CTO (Chief technical officer) and consultant to both the pharmaceutical industry and the manufacturers of pharmaceutical manufacturing equipment, whilst also being a senior lecturer at the department of Pharmaceutical Technology at the University of Bonn.

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