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Original Research Paper

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

Tim Freeman [a], *Harmut Vom Bey* [b], *Michael Hanish* [b], *Katrina Brockbank* [a,*], *Brian Armstrong* [a]

[a] *Freeman Technology, 1 Miller Court, Tewkesbury, Gloucestershire, GL50 3RP, UK*
[b] *Gerteis Maschinen + Processengineering AG, Stampfstrasse 74, 8645 Jona SG, Switzerland*

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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

* Corresponding author. Freeman Technology, 1 Miller Court, Severn Drive, Tewkesbury, Gloucestershire, GL50 3RP, UK. Tel.: +44 1684 851551; fax: +44 1684 851552.
E-mail address: katrina.brockbank@freemantech.co.uk (K. Brockbank).
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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.