W1130-10-079

Excipient consistency is key to de-risk formulation development and manufacturing

Sunil Kumar N, Bastiaan HJ Dickhoff, DFE Pharma, Goch, Germany

Contact information: dfepharma.com

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Purpose

Continuous manufacturing (CM) gains more and more interest in the pharmaceutical industry. The International Conference of Harmonization (ICH) states in its Q8 'Pharmaceutical Development' guideline that the manufacturer of pharmaceuticals should have an enhanced knowledge of the product performance over a range of raw material attributes, manufacturing process options (including continuous manufacturing) and process parameters.

Stringent controls on Particle Size Distributions (PSD) of starting materials are of key importance in continuous manufacturing of granules. For this purpose the PSD of Pharmatose® CM (a new excipient) has been evaluated in comparison with custom made grades of the fine and coarse ends of Pharmatose® 200M. Furthermore, Pharmatose® CM was chosen to identify the influence of variation in the excipient PSD on the final granule size and on tablet properties.

Objective(s)

To showcase the consistent performance of continuous wet granulation with granules from three batches of Pharmatose® CM (a new excipient grade) along with a fine and coarse end of Pharmatose® 200M, these batches were analyzed for Bulk Density (BD), Tapped Density(TD), Particle Size Distribution (PSD) and tabletability.

Method(s)

Pharmatose® 200M was used to map the influence of the excipient variation on the processing behavior of a Twin screw Extruder (TSE). Three batches of Pharmatose® CM having consistent PSD characteristics along with custom made fine and coarse end of Pharmatose® 200M supplied by DFE Pharma were used. The different products were processed using TSE from Leistritz , model-ZSE 18 HPe-VA. The product (solid) was fed to the TSE using a loss in weight twin screw feeder (K-Tron, K-PH-CL-24-KT20). The binder-water 8,25%w/w, was fed using a peristaltic liquid feed pump (Watson Marlow, 520Du) and TSE was run at solid feed addition rate of 5kg for 30min. The granules obtained were dried using Rapid dryer (Retsch, Germany). Dried granules were sieved using a 800µm sieve and the undersize granules were lubricated by blending with 0.5% Magnesium Stearate using Turbula mixer for 2 min at 90 rpm. Lubricated granules were tableted using 9mm round flat faced punch sets.

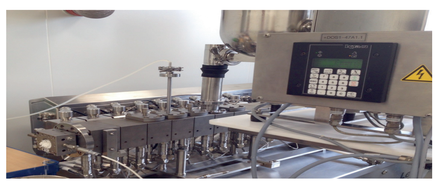

Fig 1: Manufacturing of granules using Leistritz ZSE 18 HPe-VA

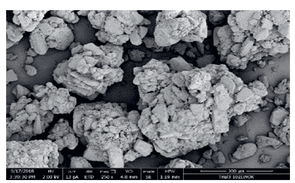

Fig 2: Typical SEM of Pharmatose ® CM granules using TSE

Result(s)

An example of continuously produced typical Pharmatose® CM granules is visualized by SEM in Fig 2. Pharmatose® CM showed the most consistent granulation performance in terms of BD, TD, and PSD; where BD of granulations were within limits from 0.60 to 0.67 and TD varied from 0.82 to 0.92. The three tier PSD ranged as follows: X10 - from 47 to 60µm; X50 - from 188 to 289µm; and X90 - from 735 to 885µm. Fig 3 shows the cumulative volume distribution. The green line and the green dotted line represents the starting material and the granulated fine end of Pharmatose® 200M, respectively. The blue line and the blue dotted line represents the starting material and the granulated coarse end of Pharmatose® 200M , respectively. The orange line shows the starting material, whereas the dark orange line represents the granulated Pharmatose® CM.

Interestingly, magnitude of the variation in PSD as seen in the starting materials is not seen in the granulated products. Probably this is due to the fact that the granules were sieved using 800µm and this may have caused the discriminative power between the products in terms of PSD to diminish. Pharmatose® CM granules shows good tabletability (Fig 4, orange line). The black dotted line represents granulated Pharmatose® 200M fine end, whereas black line represents granulated Pharmatose® 200M coarse end.

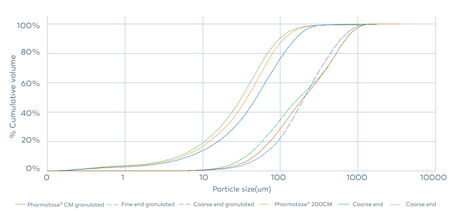

Fig 3: Cumulative PSD graph of Pharmatose® CM along with fine and coarse end

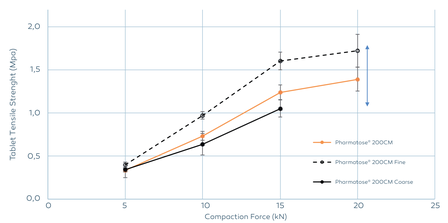

Fig 4: Tablet tensile strength vs Compaction force data of lubricated granules

Conclusion(s)

Utilizing excipients with tight particle size and density ranges are of benefit in Continuous Manufacturing, as these products will ensure a consistent output in end product behaviour. Excipients with wide size / density ranges, as described in this study as fine and coarse end are expected to cause a wide output product behavior.

DFE Pharma offers QbD support and consistent pharmaceutical excipients for pharmaceutical development and manufacturing and suitable for Continuous Manufacturing.

SuperTab® 21AN DFE Pharma was used in the same way and gave comparable results.

Acknowledgement

The authors would like to thank Kathrin Nickel and Albert Huber from Leistritz Extrusiontechnik GMBH; without their help this work would not have been possible.

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Contact information

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