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Short communication

Improved content uniformity of tablets containing an opioid analgesic through introduction of dry granulation

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Introduction

The critical quality attributes of immediate release tablets containing a high dose (>25%) opioid analgesic are strongly influenced by the physical properties of the API and the final blend. Particularly the flowability and homogeneity of the final blend, are essential to ensure a uniform distribution of the API within the dosage form and therefore a consistent therapeutic effect.

One of the key challenges in such formulations is achieving adequate content uniformity, particularly in direct compression blends, which often exhibit poor flowability and a tendency for segregation. Inadequate flow leads to variability in tablet mass, while non-uniform blends result in uneven active substance distribution, affecting assay and content uniformity (Jakubowska and Ciepluch, 2021).

In this study, a process modification was introduced to address these challenges through the incorporation of a dry granulation step. The objective was to evaluate its impact on blend properties and critical quality attributes, with particular focus on uniformity of mass and content uniformity.

Materials and methods

Tablets were manufactured using a standard process including blending, dry granulation, and compression. Dry granulation was performed using a roller compactor (Alexanderwerk), followed by milling through defined sieve sizes to obtain granules with controlled particle size distribution.

Tablets were compressed using a rotary tablet press (Fette) under controlled process parameters. The evaluated parameters included flow properties (flow rate, angle of repose), bulk and tapped density, compressibility index, particle size distribution, blend uniformity, tablet mass variability, assay, and content uniformity.

Content uniformity and assay of the active substance were determined using a validated UV spectrophotometric method. All analytical tests were performed in accordance with the relevant European Pharmacopoeia (Ph. Eur.) methods.

Results and discussion

A batch of 10.2 kg was manufactured and evaluated during this study. Prior to dry granulation, the final blend exhibited suboptimal flow behavior, with flow rate of 24 s/100 g and angle of repose of 46°, indicating poor flow properties.

Following the introduction of dry granulation under defined critical process parameters (CPPs), including roller speed (5 rpm), roller gap (1.5 mm), roller pressure (3 kN/cm), and sieve size of 0.610 mm, improved powder behavior was observed, with flow rate reduced to 20 s/100 g and angle of repose

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decreased to 38°, indicating enhanced flowability of the granulated material.

The particle size distribution shifted toward coarser fractions after granulation, with reduced proportion of fines and increased fraction of larger particles, confirming effective agglomeration during roller compaction and the influence of the selected sieve size during milling (Marinko, et al., 2025).

Improved flow properties led to more consistent die filling during compression, resulting in reduced variability in tablet mass. Tablet mass remained close to nominal values (100 mg), with average values of 100.44 mg, 100.56 mg, and 99.97 mg across different sampling points, and low variability (RSD 1.07%, 0.99%, and 0.80%, respectively), indicating a stable and capable process. Blend homogeneity showed reduced variability after dry granulation, with RSD decreasing from 2.9% to 1.8%, indicating improved distribution of the active substance.

The reduction in mass variability contributed directly to improved assay and content uniformity. Content uniformity results showed an overall average of 99.0%, with minimum 95.25% and maximum 102.63%, and low variability (RSD 1.7%).

These results demonstrate that the introduction of dry granulation improves flow properties and reduces mass variability, which in turn leads to improved assay and content uniformity (Peddapatla et al., 2021).

Conclusion

The introduction of a dry granulation step significantly improved the physical and functional properties of the tablets containing an opioid analgesic. Enhanced flowability and reduced proportion of fines resulted in more consistent die filling, leading to improved tablet mass uniformity. Improved blend homogeneity contributed to more uniform distribution of the active substance, resulting in excellent content uniformity with low variability and high process capability.

These findings confirm that dry granulation is an effective strategy for improving both process performance and critical quality attributes in tablet formulations containing opioid analgesics.

References

Jakubowska, E. and Ciepluch, N., 2021. Blend Segregation in Tablets Manufacturing and Its Effect on Drug Content Uniformity—A Review. Pharmaceutics, 13(11), 1909. https://doi.org/10.3390/pharmaceutics13111909

Marinko, N., et al., 2025. Effects of roller compaction on dissolution of granules and tablets captured in the development of pharmaceutical formulations. AAPS PharmSciTech. https://doi.org/10.1208/s12249-025-03217-1

Peddapatla, R. V. G., et al., 2021. Process model for predicting tablet weight variability in direct compression. Pharmaceutics, 13(7), 1033. https://doi.org/10.3390/pharmaceutics13071033