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Addressing Formulation and Process Challenges for a Needle-Shaped API: From Wet Granulation to Roller Compaction

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Purpose

API particle morphology strongly influences processability in solid dosage form development. Needle-shaped particles with high aspect ratio are associated with poor flow, non-uniform die filling, and mechanical instabilities during compression **[1,2]**.

This study aimed to develop a robust tablet formulation and manufacturing process for a needle-shaped, poorly soluble API by systematically addressing morphology-induced challenges. Early characterization revealed elongated crystals with low packing efficiency and limited suitability for wet granulation. Based on these findings, a Quality by Design (QbD)-guided formulation strategy was applied to balance flowability, compressibility, and tablet integrity.

Materials & Methods

The unprocessed, needle-shaped API was provided by the customer *(↗ Figure 1)*. In addition, a portion of the API was micronized using a spiral jet mill (performed externally, *↗ Figure 2*) and used for selected experiments within the study. A previously established wet-granulation (WG) formulation was transferred to the CDMO Rottendorf Pharma. The formulation based on cellulose, starch, povidone and magnesium stearate served as the initial baseline. In a next step, a dry granulation (DG) formulation based on microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate was developed. Process train and equipment for both formulations are shown in *↗Figure 3*.

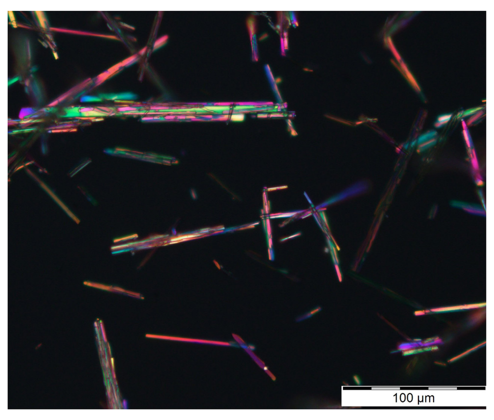

Figure 1: Light microscopy image of unprocessed API

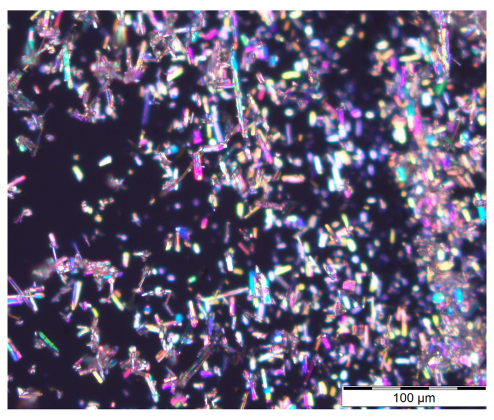

Figure 2: Light microscopy image of micronized API

Figure 3: Process train and equipment for wet granulation (first column) and dry granulation process (second column)

Results & Discussion

Development initially focused on a wet-granulation approach with varying binder levels, granulation endpoint, impeller speed, and liquid addition rates. Despite process optimization, granules exhibited insufficient mechanical strength, and tablets showed pronounced capping and lamination, likely caused by elastic recovery of the needle-shaped API particles during decompression. *(↗Figure 4)* **[2]**.

API micronization reduced particle size and partially destroyed the needle morphology, resulting in a narrower particle size distribution. However, only marginal improvement in compaction behavior were observed, indicating that morphology-related deformation constraints persisted.

A shift towards roller compaction using the unprocessed API was therefore proposed to enhance particle densification and reduce air entrapment. Process parameters such as specific compaction force, roller gap, and flake milling speed were optimized to control granule size distribution and bulk density. The transition to roller compaction significantly improved tablet quality *(↗Figure 5)*.

The final blend of the optimized granules showed uniform particle size distribution and increased bulk density *(↗Figure 7)*.

Compression trials confirmed consistent tablet weight and high mechanical robustness without capping across varying press speeds. These findings confirmed that the densification achieved via roller compaction effectively mitigated morphology-induced process limitations. Microscopic analysis confirmed a clear transformation from elongated, needle-shaped API crystals to compact, irregular agglomerates of API and excipients with reduced aspect ratio *(↗ Figure 6)*. This morphological change directly translated into improved compactability and process robustness.

Tensile-strength profiles of the tablet cores highlighted pronounced differences between the granulation approaches *(↗ Figure 8)*. Wet-granuled material, with both unprocessed and micronized API, remained below the 2.0 MPa robustness target.

In contrast, dry-granulated material exceeded this threshold with increasing compression force, demonstrating enhanced consolidation and reduced elastic recovery.

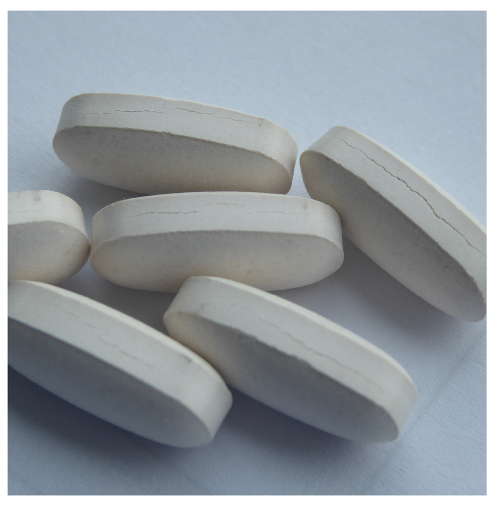

Figure 4: Tablets from wet granulation process showing cracks on the band

Figure 5: Tablets from roller compaction process

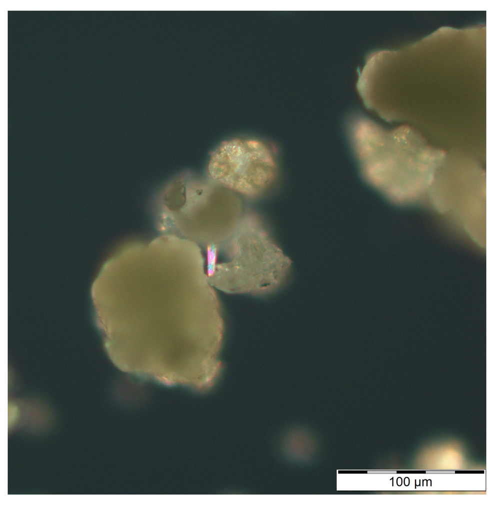

Figure 6: Light microscopy image of roller-compacted granules

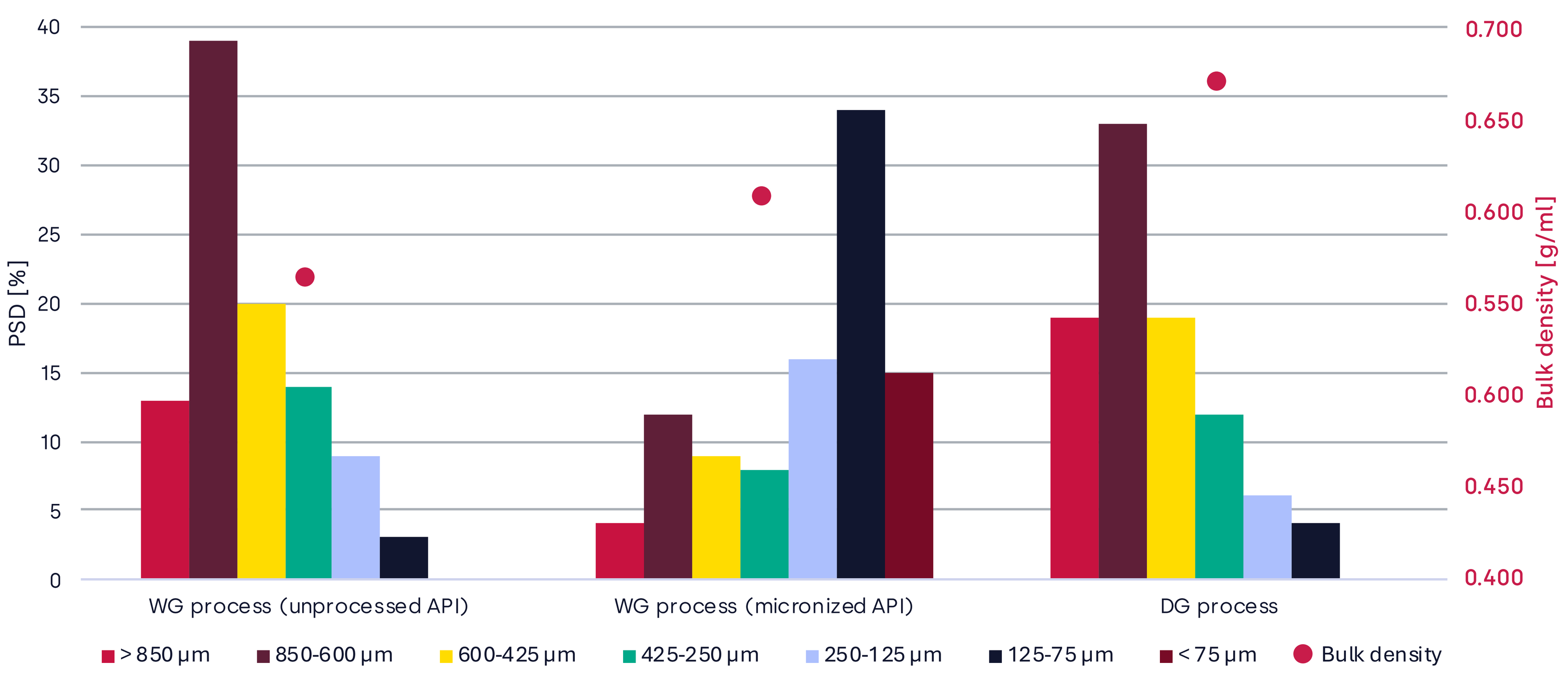

Figure 7: Powder data of final blends

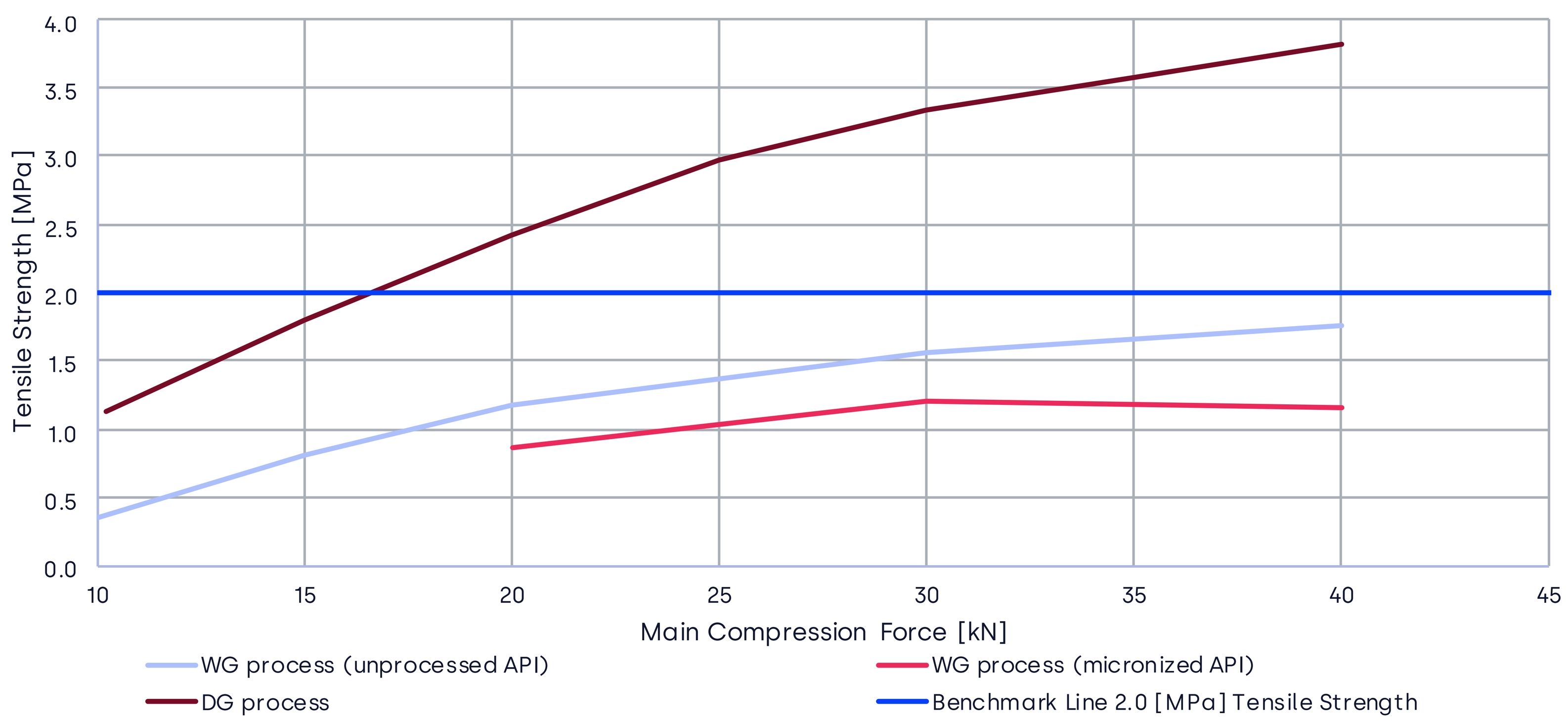

Figure 8: Tensile strength of core tablets

Conclusion

Needle-shaped API morphology limited the effectiveness of wet granulation and caused mechanical instabilities during tableting. Roller compaction overcame these limitations successfully by improving particle morphology, consolidation behavior, and process robustness. The results highlight the importance of addressing early morphology assessment and morphology-driven process selection in pharmaceutical development.

References:

[1] Azad, M., et al., Impact of Critical Material Attributes (CMAs) – Particle Shape on Miniature Pharmaceutical Unit Operations, *Int. J. Pharm.*, 2021.

[2] Kwak, H.-S., et al., Compaction Behavior of Paracetamol Powders of Different Crystal Shapes, *Drug Dev. Ind. Pharm.*, 2018.

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