Accelerated Technology Transfer for the Development of Fexuprazan Using Compaction Simulation

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PURPOSE

1. Initiate clinical development of Fexuprazan, a novel potassium-competitive acid blocker (P-CAB) for the treatment of erosive esophagitis in the U.S.
2. Identify and transfer critical process parameters (CPPs) for mixing, dry granulation, post-mixing and tableting as manufacturing steps of 40 mg strength tablets.
3. Enable process development and troubleshooting during transfer and scale-up using an accelerated and material-sparing approach.

OBJECTIVES

1. Establish the design space for manufacturing
2. Simulation of a Gerteis MINI-PACTOR® roller compactor
3. Simulation of a Fette 1200i rotary tablet press

METHODS

1. Blends were prepared based on a patented (PCT/KR2021/019265) master formula consisting of standard excipients (Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose sodium, Mg-Stearate and Iron Oxide) using a Turbula® mixer and evaluated for the true/bulk/tap density, flow properties (FT4 shear-cell) and elasticity/plasticity (Heckel analysis).
2. The intra-granular blends were roller-compacted using a simulated Gerteis MINI-PACTOR® profile on the compaction simulator (Medelpharm Styl'One Evo) with a constant roll speed=3 RPM and gap=1.5 mm. Ribbons were generated at five different solid fractions (SF= 0.55, 0.60, 0.65, 0.70 and 0.8) and milled using a Gerteis small scale hand mill (1.0 mm square screen) followed by particle size distribution analysis.
3. Subsequently, milled granules at each solid fraction were mixed with extra-granular excipients and evaluated for true density. Final blends were then compressed to 150mg tablets using a simulated profile of a Fette 1200i rotary tablet press at 30 RPM on the compaction simulator equipped with 5.1 mm x 9.2 mm oval tooling.

RESULTS

1. Table 1 summarizes the bulk and flow properties of the intra-granular blend.
2. Figure 1 shows the Heckel analysis results. Yield Pressure (Py=78.5 MPa) and % Strain Rate Sensitivity (SRS=15.9%) revealed a balanced behavior between soft ductile and moderately hard/brittle with no risks of lamination or capping.
3. Figure 2 demonstrates the Gerteis MINI-PACTOR® simulation. Transferring value of the roll force=9 kN/cm between two manufacturing facilities with major equipment differences could result in a ribbon solid fraction ~0.8. Optimum roll force values were determined targeting a solid fraction range of 0.6-0.7.
4. Figure 3 depicts the tabletability graphs generated from the simulated Fette 1200i compression profile for the final blends. Increasing dry granule solid fraction was associated with reduced tabletability in the final blends and increased granule particle size distribution (see Fig. 4).

Table.1- Density values and flowability results for intra-granular blend.

Formulation	Intra-Granular Blend
Bulk Density (g/cc)	0.53
Tapped Density (g/cc)	0.66
Hausner Ratio	1.25
Carr's Index (%)	19.7
True Density (g/cc)	1.55
Flow Function (FT4)	13.1
Dimensionless Cohesion ($^{\tau_c}/_{\sigma_1}$)	0.02

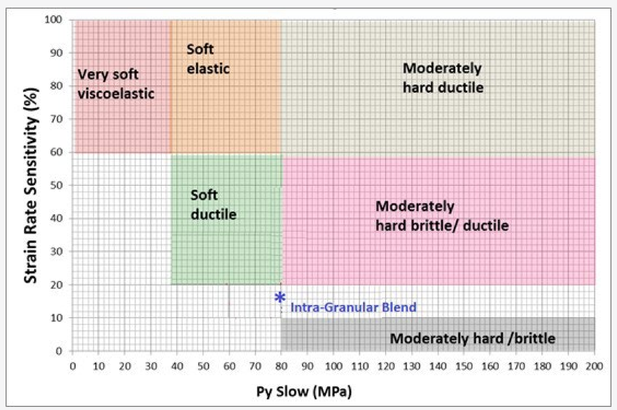

Figure 1. Elasticity/plasticity classification of intra-granular blend adapted from Roberts and Rowe[1].

[1]R.J. Roberts, R.C. Rowe, The compaction of pharmaceutical and other model materials – a pragmatic approach, Chemical Engineering Science, Volume 42, Issue 4, 1987, Pages 903-911.

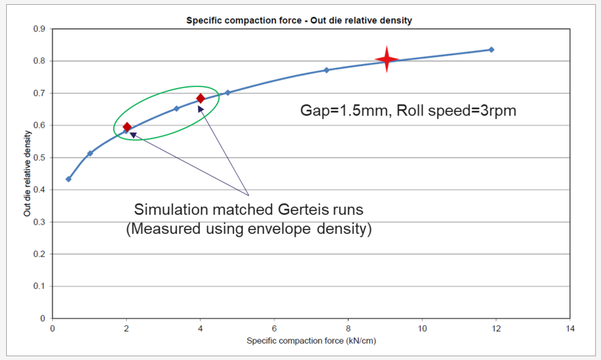

Figure 2. Predicted ribbons solid fraction as a function of actual roll-force on the Gerteis MINI-PACTOR® machine.

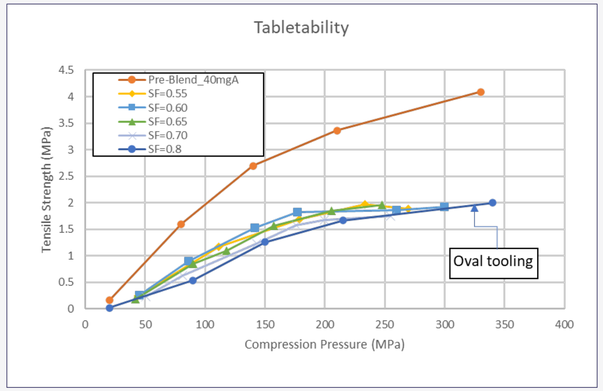

Figure 3. Tabletability profiles of the final blends based on the simulated Fette 1200i compression profile at 30 RPM.

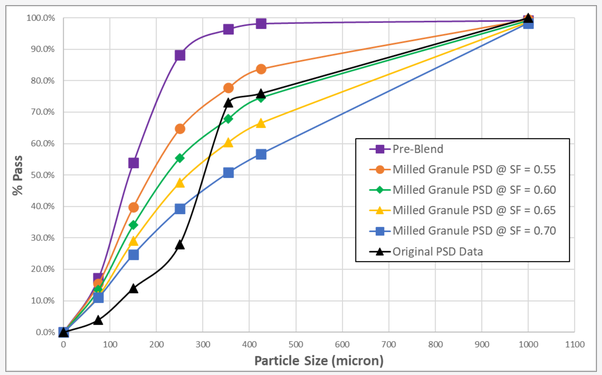

Figure 4. Particle size distribution of milled granules. Original PSD is significantly different due to different milling mechanisms (e.g., oscillating vs Comil).

5. Transferring the technology between two manufacturing facilities required additional analysis to study the hypothesis of over-lubrication during blending and tablet press feed-frame.
   - This was achieved by evaluating the loss of tabletability due to lubricant level (extra-granular Mgst ranged from 0 to 1 %w/W) and feed-frame shear, see Figure 5.
   - These analyses resulted in recommendations for decreasing lubrication level/time for CTM manufacturing.

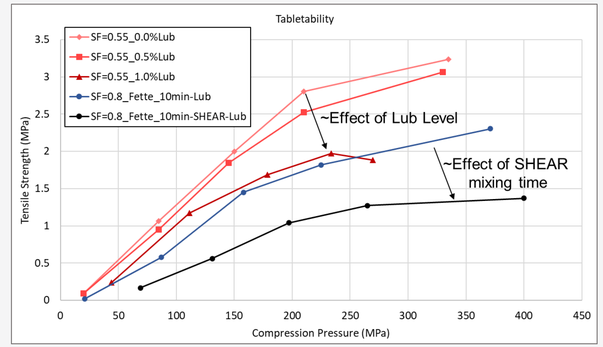

Figure 5. Effect of lubrication level and mixing time (blender and feed-frame-driven lubrication) on tablet mechanical strength.

CONCLUSIONS

1. Rapid process development and tech-transfer of 40 mg strength Fexuprazan tablets to the U.S. was successfully achieved by simulating the roller compaction and the high-speed tableting processes using Compaction Simulation.
2. The hypothesis of loss of tabletability after dry granulation and over-lubrication during blending scale-up and tablet press feed-frame was successfully investigated and confirmed.
3. These studies helped de-risk and identify the optimal process parameters for the clinical manufacturing campaign using a material-sparing approach. This provided expedited tech-transfer, scale-up strategies, and resultant timelines.

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