A novel binder designed to enable widespread adoption of Twin Screw Melt Granulation (TSMG)

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PURPOSE

Manufacturing immediate-release granulation, especially (but not only) in the context of continuous manufacturing, is attractive as it removes the rate-limiting and energy-intensive granulation drying step, thus reducing the need for sophisticated drying equipment and reducing process and control complexity while potentially increasing productivity. There is also evidence that melt granulation with suitable binders can improve tablet strength over traditional granulation. Despite the potential benefits, concerns relating to increased in-process API degradation and impurity formation, especially in thermolabile drugs, have held back the widespread commercial adoption of TSMG.

OBJECTIVE(S)

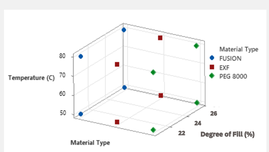
This study introduces a purpose-designed tablet binder that allows for low extrusion process temperatures (50˚ C- 80˚ C) and low shear levels at low binder level of 5%. The performance of this new binder Klucel Fusion™ hydroxypropyl cellulose (HPC) was compared against commercially available Klucel™ HPC EXF and Polyethylene glycol (PEG) 8000 using Gabapentin as an extreme example of a highly thermolabile drug.

METHOD(S)

Melt viscosity and mechanical properties of Klucel Fusion™ HPC and commercial Klucel™ EXF HPC were determined using a TA Instruments Discovery Hybrid Rheometer DHR 3 and a Dynamic Mechanical Analyzer DMA-Q800.

Binary blends of 95% Gabapentin (a thermally labile drug with poor compaction properties) and 5% Klucel Fusion™ HPC, Klucel™ HPC EXF, or PEG 8000 were prepared. The granulation was carried out on a Leistritz 18 mm twin-screw extruder, using the different polymer types at different temperatures, barrel fills, and screw speeds (Table 1). Tablets containing 600mg Gabapentin were made using each granulation and characterized for friability, hardness, and drug dissolution. The degradation product Gaba-lactam was quantified using HPLC.

Study design:



Screw configuration:

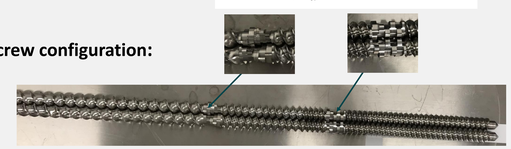


Table 1: Gabapentin tablet formulations

Ingredients	Tablet Formulation (w/w%)	Tablet Wt (mg)
Gabapentin:Polymer Granulate (95:5)	88.0	600.0
Cab-O-Sil M5P	1.0	7.18
MCC PH102	10.0	71.77
Mag. Stearate	1.0	7.18
Total	100.0	714.7

Equations to use in this study:

$$Degree\ of\ Fill\ (\%) = \frac{2\ x\ Feed\ rate\ x\ 100}{Cross\ section\ area\ x\ Pitch\ length\ x\ rpm\ x\ Density}$$

$$KW\ (appied) = \frac{KW\ (motor\ rating) x\ \%Torquex\ 0.97}{Max.rpm}$$

$$Specific\ energy = \frac{KW\ (applied)}{Feed\ rate\ (\frac{kg}{h})}$$

RESULT(S)

Figure 1: Complex viscosity & Tan delta of Klucel Fusion™ HPC vs commercial HPC grade

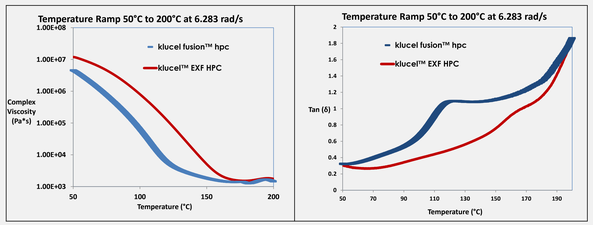
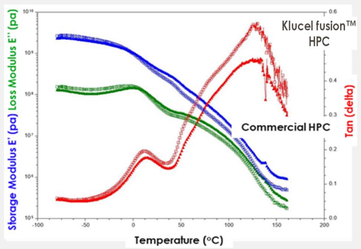


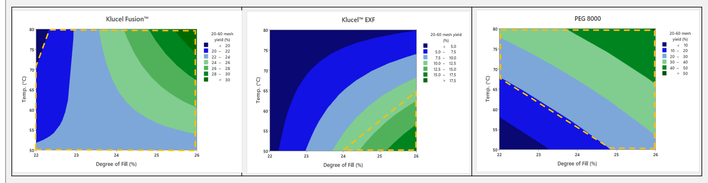
Figure 2: Dynamic mechanical analysis of Klucel Fusion™ HPC vs Commercial grade

$$\tan(delta) = \frac{loss\ (viscous) modulus}{storage\ (elastic)\ modulus}$$



This new melt granulation binder showed significantly lower melt viscosity, lower storage modules, and higher Tan (δ) than commercial HPC, indicating enhanced thermoplasticity and processability across a wide range of temperature 50-180°C compared to the commercial HPC grade (Figure 1 and 2).

Figure 3: Melt granulation performance particle size yield (> 15%)



Compared to other binders, Klucel Fusion™ HPC performed exceptionally well across a wide range of processing conditions, yielding stronger granules than HPC EXF and PEG 8000 in TSMG of Gabapentin (Figure 3).

Figure 4: Consistently higher tablet strength with less variation

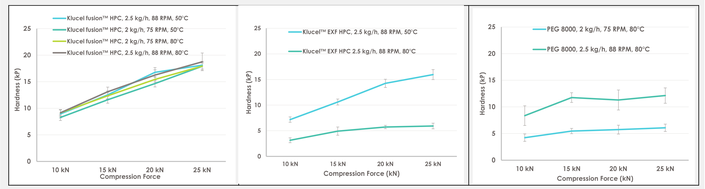
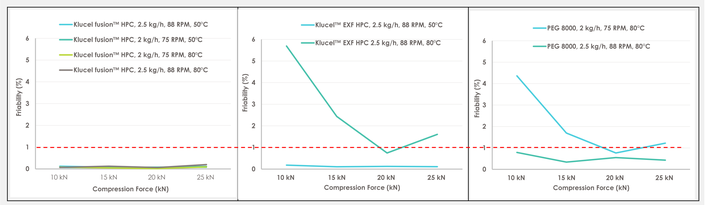
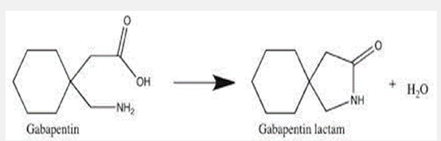


Figure 5: Friability of Gabapentin tablets



Klucel Fusion™ HPC enabled granulation of Gabapentin, a thermolabile drug, at low temperature of 50°C while the formulation with PEG 8000 was only processable at 80°C via HME. Klucel Fusion™ granulations produced under all conditions delivered the strongest tablets with acceptable friability. While formulation with PEG generated granules at 80°C via HME, PEG did not improve granule tabletability generating weaker tablets with poor friability (Figure 4 & 5).

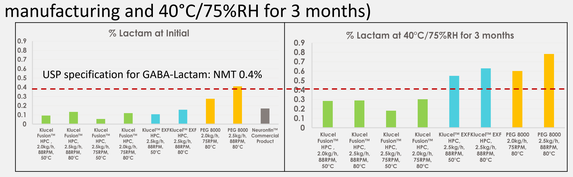
Degradation pathway of Gabapentin



Gabapentin degrades to a cyclic lactam via an intramolecular cyclization reaction triggered by a nucleophilic attack of the hydroxyl group by the nitrogen of the amino group.

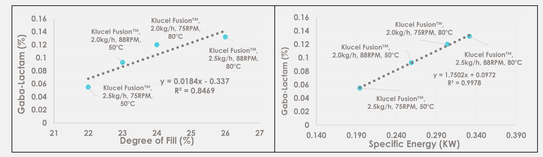
The chemical instability of Gabapentin, based on the amount of gabapentin lactam formed.

Figure 6: Gabapentin related compound A (% lactam) at the time of manufacturing and 40°C/75%RH for 3 months)



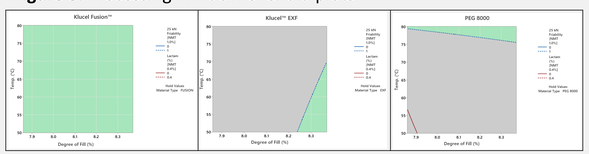
The formulation with Klucel Fusion™ not only had the lowest degradant but also lower levels than Neurontin™ (the commercial product). Even under aggressive conditions for three months, the formulation with Klucel Fusion™ had the lowest impurity level and was within the specification limit. (Figure 6).

Figure 7: Effect of degree of fill and specific energy on the Lactam impurity



The Lactam impurity increase as degree of fill of conveying elements and process specific energy increase due to mechanical stress during melt extrusion (Figure 7).

Figure 8: Processing Window overlaid plots



Klucel Fusion™ performed exceptionally well across a wide range of process parameters while yielding better granulation than EXF and PEG 8000 (Figure 8).

CONCLUSION(S)

The Klucel Fusion™ HPC exhibited better processability and stability of Gabapentin than the commercial HPC EXF grade and PEG 8000 due to its low melting temperature and complex viscosity. To move beyond traditional batch processing (e.g., wet and fluid bed granulation) to continuous processing technology using melt granulation, the Klucel Fusion™ HPC is the best polymer choice due to the ease of processing and protection of moisture-sensitive and thermolabile drugs.