SUPPORTING INFORMATION:

1. SCHEMATICS OF REACTORS

Figure S1: Configuration for 200 L reactor based on equipment schematic. Source: Buchiglas USA, Farmingdale, NY.

Figure S2: Configuration for 2000 L reactor based on equipment schematic. Source: Pfaudler, Inc, Rochester, NY.
2. CRITICAL PROCESS PARAMETERS

2.1 Wet Mill Flow Rate

The mill flow rates were adjusted by varying the circulation tube length and diameter. Lower wet mill flow rate consistently resulted in higher bulk density (0.58 g/mL versus 0.52 g/mL) and higher particle size (D90=77.3 µm versus 68.6 µm). The SEM images revealed that agglomerates generated by using a lower wet mill flow rate had smoother surfaces and were larger in size (Figure S3). This is likely due to the longer residence time in the wet mill since the residence time is inversely proportional to the wet mill flow rate. In other words, the length of time during which the slurry is in the wet mill is longer with slower flowrates. Therefore, the agglomerates would experience a greater impact energy from the wet mill for each turnover leading to an increase in agglomerate density.

Figure S3: Comparison of SEM Images of CPM Generated with Different Wet Mill Flow Rates

2.2 MTBE Addition Rate

In order to understand the impact of MTBE addition rate during the first stage of addition, two lab batches were generated by using two different addition rates (44 mL/min versus 119 mL/min) and the same number of turnovers. This was achieved by applying intermittent, rather than continuous, wet milling for one of the batches. The results showed that CPM properties were not impacted by different MTBE addition rates. On the other hand, the impact of MTBE addition rate on the mixing efficiency may be minimal compared to the impact of wet milling parameters. In order to eliminate the impact of wet milling, two lab batches were generated using two different addition rates without wet milling. The slower addition rate (44 mL/min), which was expected to result in slower polymer precipitation, generated CPM with slightly higher bulk density (0.22 g/mL versus 0.19 g/mL) and larger particle size (D90=150.2 µm versus 101.5 µm) compared to the faster addition rate (525 mL/min). There was no clear correlation between the addition rate and the CPM flow.
In order to understand the impact of MTBE addition rate during the second stage of addition, various lab batches were generated using two different addition times (10 minutes versus 60 minutes) at two different wet mill flow rates. For both flow rates, the CPM bulk density and flow were not impacted by different addition times, but the slower addition rate generated CPM with larger particle size (D90=71.7 µm versus 62.5 µm).

### 2.3 Agitation Rate during MTBE Addition

A 120-250 rpm agitation rate during the simultaneous polymer precipitation and MTBE addition step generated lower CPM bulk density (0.48 g/mL versus 0.52 g/mL) and larger particle size (D90=90.9 µm versus 68.6 µm) compared to the batches made at the 100 rpm agitation rate. There was no clear correlation between the agitation rate and the CPM flow behavior. A batch made at 40 rpm agitation rate generated large lumps that settled rapidly in the reactor and the transfer lines, which made it difficult to transfer the slurry out of the reactor. Hence, the agitation rate has a strong impact on the CPM powder properties and needs to be maintained above a certain scale specific level in order to ensure processability.

The recirculation of the process stream from the wet mill impacts the mixing efficiency of the precipitating polymer and the solvent content during MTBE addition. In order to eliminate the impact of the wet mill recirculation on mixing, two lab batches were generated using two different agitation rates (100 rpm and 225 rpm) without wet milling. The faster agitation rate generated CPM with higher bulk density (0.29 g/mL versus 0.22 g/mL) and larger particle size (D90=179.9 µm versus 150.2 µm). There was no clear correlation between the addition rate and the CPM flow. The larger particle size with increasing agitation rate without wet milling is consistent with the results obtained using a slower MTBE addition rate without wet milling. Both conditions are expected to result in more efficient mixing.

### 2.4. Hold Time before and after Decantation

The impact of time elapsed between the end of MTBE addition and decantation on CPM properties was investigated by holding batches for 4 days before decantation with and without agitation. The impeller rate was set to 150 rpm which provided enough agitation to suspend all the CPM particles from the bottom of the vessel. The batches aged for 4 days before decantation, regardless of agitation, generated CPM with lower bulk density (0.41 g/mL versus 0.48 g/mL) and higher particle size (D90=581.1-750.4 µm versus 75.9 µm) compared to a batch decanted immediately. The Malvern analysis on agitated slurry revealed that particle size increased gradually during aging (D90=93.4 µm after 24 hours, 126.2 µm after 93 hours). The SEM images confirmed that the agglomerates generated with aging were larger due to clustering of individual CPM particles. The CPM flow, potency and KF values were not impacted from aging. On the basis of these results, a maximum hold time of 15 hours post MTBE addition was recommended for the pilot plant.

The impact of time elapsed between decantation and isolation on CPM properties was investigated by isolating a portion of the batch immediately after decantation and holding the remainder for 72
hours at 100 rpm after decantation and then sampling the slurry. After sampling for Malvern particle size analysis, the remaining slurry was further held for 24 hours at 250 rpm before isolation for a total hold time of 96 hours. The main purpose of this study was to confirm that extended agitation did not cause attrition of CPM agglomerates. The particle size and SEM analyses showed that particle size did not change during aging and no attrition was observed. On the basis of these results, a maximum hold time of 96 hours post decantation was recommended for the pilot plant.

2.5 Solvent Exchange Method (Decantation versus Cake Wash)

The impact of the solvent exchange method on CPM properties was investigated by isolating a portion of a batch without any solvent exchange (i.e. filtering the sample without decantation or follow-up cake wash) and isolating the other portion after the cake wash procedure. In another batch, the same process parameters were used and decantation was utilized rather than the cake wash procedure.

The portion isolated without solvent exchange generated CPM with lower bulk density (0.47 g/mL versus 0.53 g/mL) and larger particle size (D90=87.6 µm versus 71.6 µm) compared to the portion that used the cake wash procedure for the solvent exchange. The bulk density of the portion isolated without any solvent exchange was comparable to the bulk density of the batch that used the decantation procedure, but there were a significant amount of hard lumps observed among the free flowing powder. The results suggest that inclusion of the solvent exchange step does not have a significant impact on bulk powder properties, but the step is needed to avoid lump formation.

The batch that used the cake wash procedure generated higher bulk density (0.53 g/mL versus 0.49 g/mL) compared to the batch that used the decantation procedure. On the other hand, the batch that used the cake wash procedure had lumps among the free flowing powder while the batch that used the decantation procedure displayed only a free flowing powder. The residual solvent content was not impacted by the solvent exchange method. The results suggest that the solvent exchange method may have an impact on bulk powder properties.

The lumps generated by using the cake wash method were noted upon discharging the product from the filter dryer. A small fraction of the product was observed at the bottom of the dryer below the agitator. In order to minimize the risk of damage to the filter dryer, the agitator blade did not reach the filter cloth. The resulting gap generates a layer of solids which are not washed as efficiently as the rest of the slurry during the cake wash procedure. At the end of drying, this layer of packed particles produces lumps of CPM aggregates. These lumps were observed to be soft and could be passed through a sieve and broken apart without much force.