Advantages of Co-precipitation Technology (CPT)
Part I: Enhancement in Particle Morphology and Flow

Drug Product Group at J-Star Research Inc.

BACKGROUND AND OBJECTIVES

Direct compression (DC) process is the preferred method for tablet production because it is both simple and energy saving. However, only a minority of active pharmaceutical ingredients (APIs) can be made into tablets by using DC because of the powder properties of most APIs (low bulk density, low flowability, etc.). Hence, technologies that can improve these powder properties are essential for DC.

The co-precipitation technology (CPT) described below has been proven efficient for such powder flow improvement.

METHODS

The schematic process flow diagram of CPT is presented in Figure 1. The equipment consists of a tank reactor and a wet mill. The tank reactor is filled up with API, polymer and a solvent for the polymer. The mixture of the API and the polymer solution is pumped around by the wet mill.

The shape of the API could be needles as shown in Figure 1 (a), which is the worst for the powder flow and for the filtration. After a few minutes of the pumping around, the antisolvent for both API and polymer is added to the tank reactor as shown in Figure 1 (b) at a controlled rate so the polymer precipitates as a binder for the agglomeration of API in the wet mill.

The size of the agglomerates grows as more binder is incorporated and the shape of the agglomerate gradually becomes spherical.

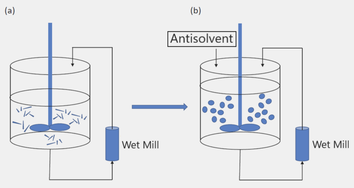

Figure 1. The Schematic Process Flow Diagram of CPT

At the end of the CPT operation, the slurry from the tank reactor is pumped into a filter dryer to separate the solid from the liquid and the wet agglomerates are dried under a vacuum at moderate high temperature.

According to the criteria of powder properties for DC process The aspect ratio of <1.5

1. Bulk density > 0.45 g/mL
2. Flow Function Coefficient > 7.0
3. Particle size distribution (PSD) with D10 > 30 µm D90<1,000 µm

RESULTS

Aspect ratio, bulk density, flowability, and particle size distribution were tested using polarized light microscopy (PLM), Freeman Technology Rheometer (FT4) and Mastersizer 3000 for both original material and the dried CPT product to quantify the improvement in particle morphology and flow. Results are shown below:

1. Aspect Ratio

Aspect ratio of the crystalline of as-received API X and CPT API X product were tested using polarized light microscopy (PLM). Figure 2-1) shows an example of PLM image of as-received API X and 2-2) shows an example of PLM image of the CPT API X product. The aspect ratio results were calculated by the average of 10 randomly selected clear crystals from multiple PLM images. Figure 3 shows the comparison of aspect ratio results between both materials.

2-1) 2-2)

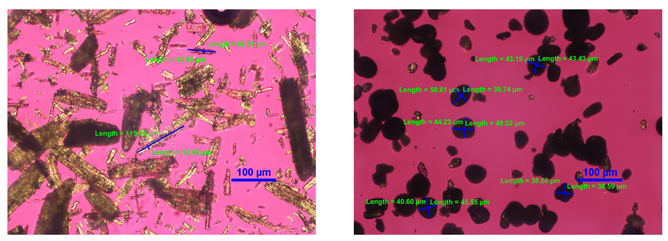

Figure 2. 2-1) shows an example of PLM image of as-received API X and 2-2) shows an example of PLM image of the CPT API X product.

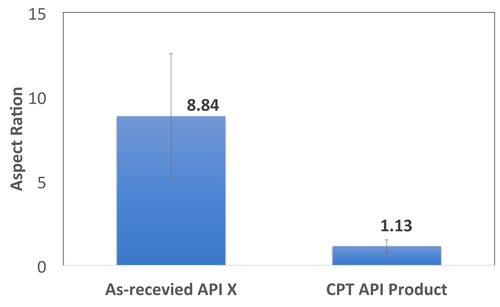

Figure 3. Aspect ratios of As-received API X and CPT API X product.

Besides the PLM images, scanning electron microscope (SEM) analysis were also performed to provide a detailed view of the as-received and post-CPT particles, as shown in Figure 4.

4-1) 4-2)

4-3) 4-4)

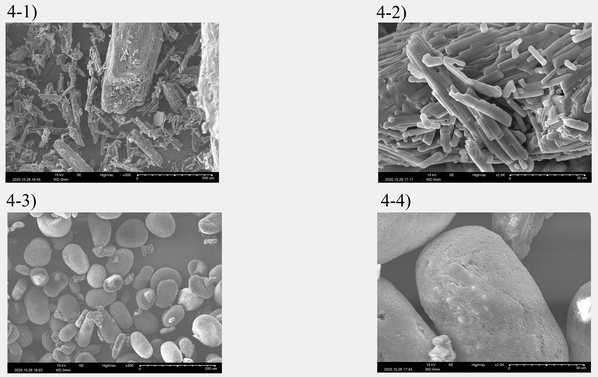

Figure 4. SEM analysis for 4-1) As-received API X (*300), 4-2) As-received API X (*2000), 4-3) CPT API X Product (*300), 4-4) CPT API X Product (*2000)

2. Bulk Density and Flow Function Coefficient (ffc)

The bulk density and flow function coefficient of the as-received API X and CPT API product were obtained from the compressibility and shear cell tests by Freeman Technology Rheometer (FT4).

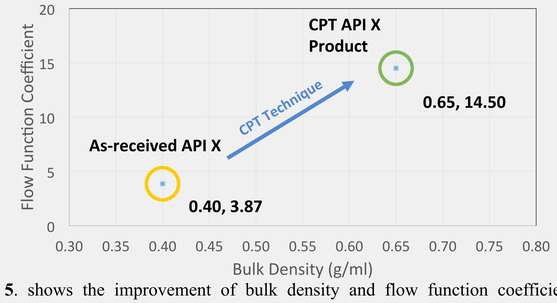

Figure 5. shows the improvement of bulk density and flow function coefficient results between two tested materials.

3. Particle Size Distribution (PSD)

The particle size distribution of the particles were tested using Mastersizer 3000 with a dry method in which around 600 mg of solids were analyzed with the dispersion pressure set to 0.5 psi.

Table 1. Particle Size Distribution Results for As-received API X and CPT API X product

Material	D10 (µm) (RSD)	D50 (µm) (RSD)	D90 (µm) (RSD)	Span (D90-D10)/D50
As-received API X	35.9 (8%)	146 (2%)	404 (7%)	2.52
CPT API X Product	44.8 (1%)	72.5 (0.4%)	147 (14%)	1.41

6-1) 6-2)

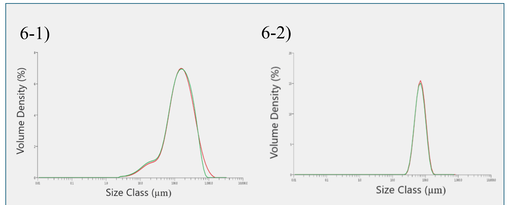

Figure 6. Particle Size Distribution of 6-1) As-received API X and 6-2) CPT API X product.

CONCLUSIONS

Table 2. Enhancement in Aspect Ration, Bulk Density, Flow Function Coefficient and Span (PSD) for API X by Co-precipitation technique.

Material	Aspect Ratio	Bulk Density	FFc Value	Span (D90-D10)/D50
As-received API X	8.84	0.40	3.87	2.52
CPT API X Product	1.13	0.65	14.50	1.41

- As shown in Table 1, the as-received API X particle has been greatly improved in different aspects in terms of morphology and flow by Co-precipitation techniques performed by Drug Product Group at J-Star Inc.
- J-Star drug product group has the equipment, talent and experience in carrying out this Co-precipitation (CPT) technique for our clients.

REFERENCES

1. Li, Zhe. et al. Composite particles based on particle engineering for direct compaction. International Journal of Pharmaceutics 2017, 519, 272
2. Leane, M. et al. A proposal for a drug product Manufacturing Classification System (MCS) for oral solid dosage forms. *Pharm Dev Technol* 2015, 20(1), 12.
3. Schulze, D. 2007, Powders and bulk solids. Behavior, Characterization, Storage and Flow, 2nd edn, Springer Verlag.
4. Erdemir, Deniz. Et al. Design and scale-up of a co-processing technology to improve powder properties of drug substances, OPR&D 2019, 23(12), 2685

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