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Enabling Technology

# Co-processing: Co-Precipitation Technology (CPT) for the Enhancement of Flowability and Bulk Density

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Formulating compressed tablets is one of the most widely used oral solid form dosages. However, a vital first step is choosing a suitable manufacturing approach and the right excipients to support the desired therapeutic effect.

Direct Compression is a highly efficient method of producing these compressed tablets. This process incorporates blending the API and excipients followed by compression. Unlike other common solid

formulation methods, DC does not require additional processing steps and a solvent.

The other most common solid formulation methods are dry granulation and wet granulation. Direct compression is the preferred method over wet granulation when dealing with moisture- or heat-sensitive ingredients. Another challenge for wet granulation is during its formulation workflow it needs binders and a change of chemical composition.

## Purposes

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 which have low bulk density, low flowability, etc. (1); Hence, technologies need to be developed to improve these powder properties to make the production of tablets feasible through DC. The co-precipitation technology (CPT) described below has been proven and can be used for the enhancement of powder flowability and bulk density.

When a solid phase is precipitated from solution, impurities that are normally soluble under the

conditions of the precipitation may adsorb onto nuclei or crystals and be removed with the parent solid as a single phase. This phenomenon is known as coprecipitation. Coprecipitation is a process in which normally soluble compounds are carried out of solution by a precipitate.

This technology acts as a tool to mold and figure the non-compatible traits of API such as poor flow and bulk density for the execution of direct compression to be used.

<https://www.sciencedirect.com/topics/materials-science/coprecipitation>

## Methods

Powder properties required for direct compression

The powder properties required for DC process (criteria) were proposed by Leane et al. (2) and they include the following three:

1. Particle size distribution (PSD) with D10 > 30 μm and D90 < 1,000 μm
2. The aspect ratio of < 1.5
3. Bulk density > 0.5 g/mL

Recently, quantitative improvements in terms of the bulk density and FFC (Flow Function Coefficient) value (3) have been proposed to carve an area suitable for direct compression in bulk density and FFC value map. This area, a sweet spot, includes all the API candidates when the bulk density of the coated API is greater than 0.4 g/mL and the FFC value of the coated API is higher than 7, as shown in Figure 1.

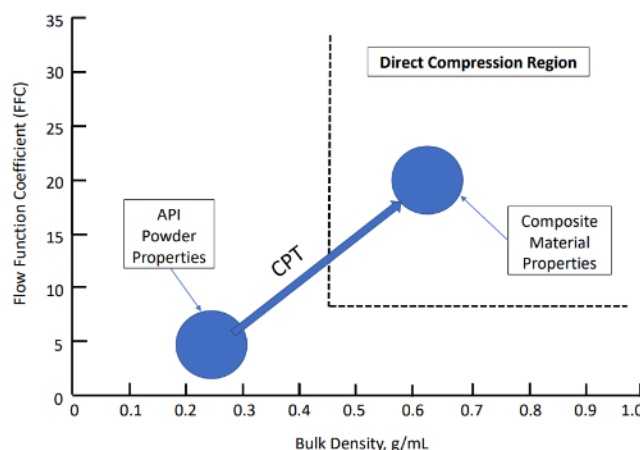


Figure 2. The sweet spot for the direct compression in the map of FFC and bulk density

Flow Function Coefficient (FFC) Value	Flowability
FFC < 1	Not flowing
1 < FFC < 2	Very cohesive
2 < FFC < 4	Cohesive
4 < FFC < 10	Easy-flowing
10 < FFC	Free-flowing

Table I. The flow function coefficient value and the flowability

## CPT Technology

The schematic process flow diagram of CPT (5) is presented in Figure 2. 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, as shown in Figure 2 (a). 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 2 (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 2 (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, as shown in Figure 2 (b).

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. Then the dried agglomerates are tested for the bulk density, flowability, and particle size distribution. If the powder properties of the dried agglomerates satisfy the criteria for DC, they are sent to a DC process for making tablets.

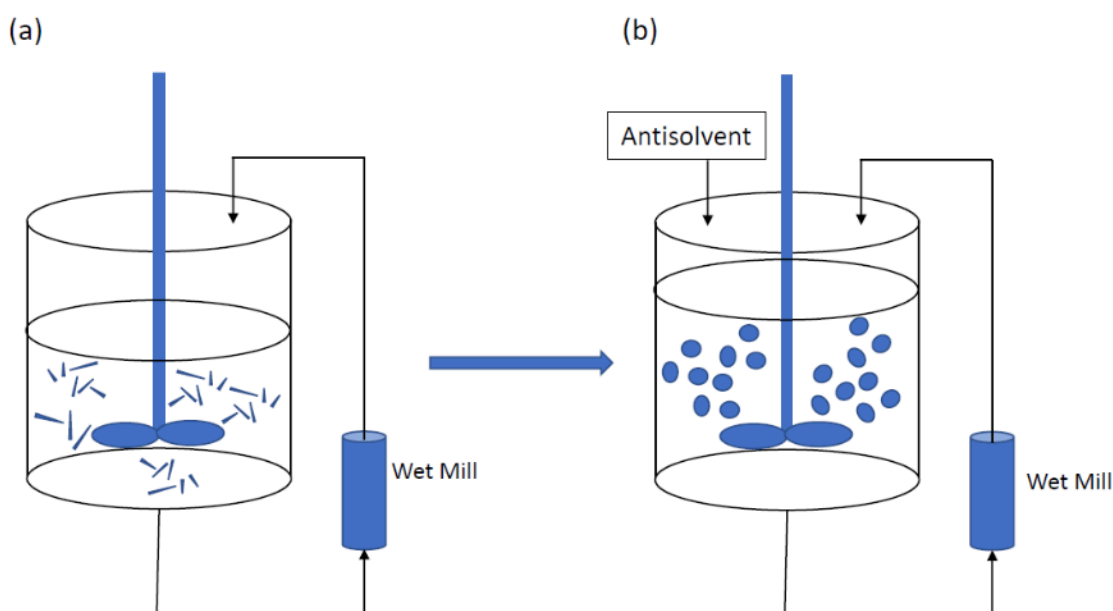


Figure 2. The Schematic Process Flow Diagram of CPT

## Results

### Enhancement of Particle Shape, Size and Distribution from CPT

The particle shape, size and distribution of raw (as-received) theophylline are not suitable for direct compression to make tablets, as shown in Table II. The aspect ratio of the raw theophylline is around 9.32, determined from the Polarized Light Microscopy (PLM), as shown in Fig. 3 (a), which is much higher than the required value of 1.5 or less for the direct compression. In contrast, the shape of CPT theophylline is close to spherical, as shown in Figure 3 (b), with the value of the aspect ratio close to 1.01.

	Properties	Raw Theophylline	CPT Theophylline
Shape	Aspect Ratio	9.32	1.01
Size (µm)	D <sub>10</sub>	35.9	44.8
	D <sub>50</sub>	146	72.5
	D <sub>90</sub>	404	147

Table II. Comparison of Shape and Size of Raw Theophylline vs. CPT Theophylline

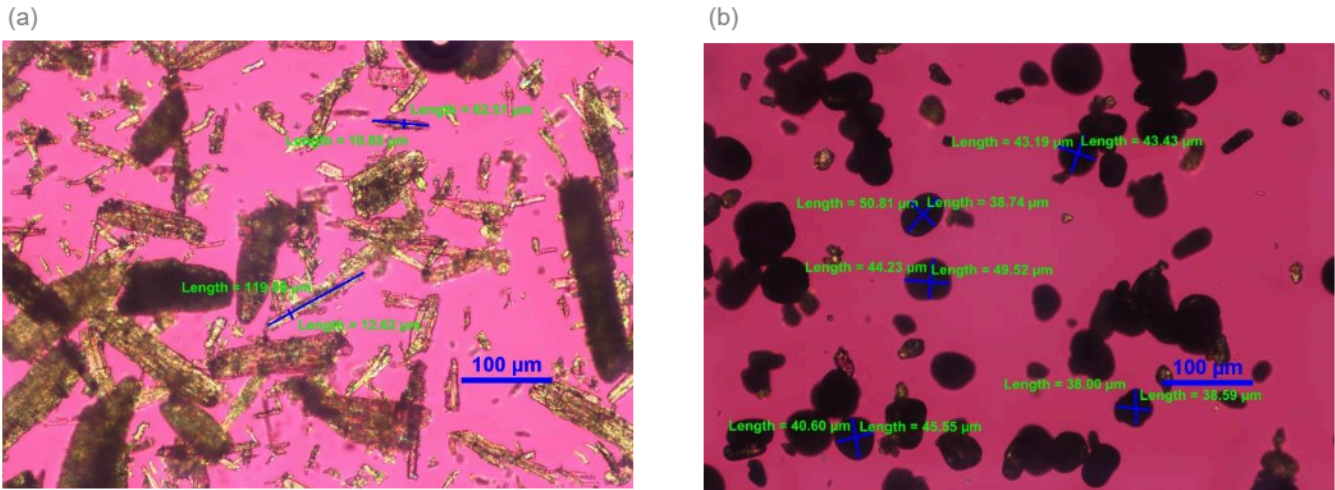


Figure 3. (a) the PLM image of as-received theophylline and (b) the PLM image of the CPT theophylline.

The comparison of the particle size distribution (PSD) of raw theophylline vs CPT theophylline, determined by Malvern particle size analyzer, is illustrated in Table I and Figure 4. The PSD for raw theophylline is very broad and ranges from 2 μm to 2,000 μm with the values of D10 = 35.9 μm, D50=146 μm and D90 =

404 μ. Although the PSD of raw theophylline is with the range of D10> 30μm and D90<1,000 μm, but its distribution is not uniform, as shown in Figure 4 (a), compared to a narrow uniform PSD for CPT theophylline, as shown in Table II and Figure 4(b).

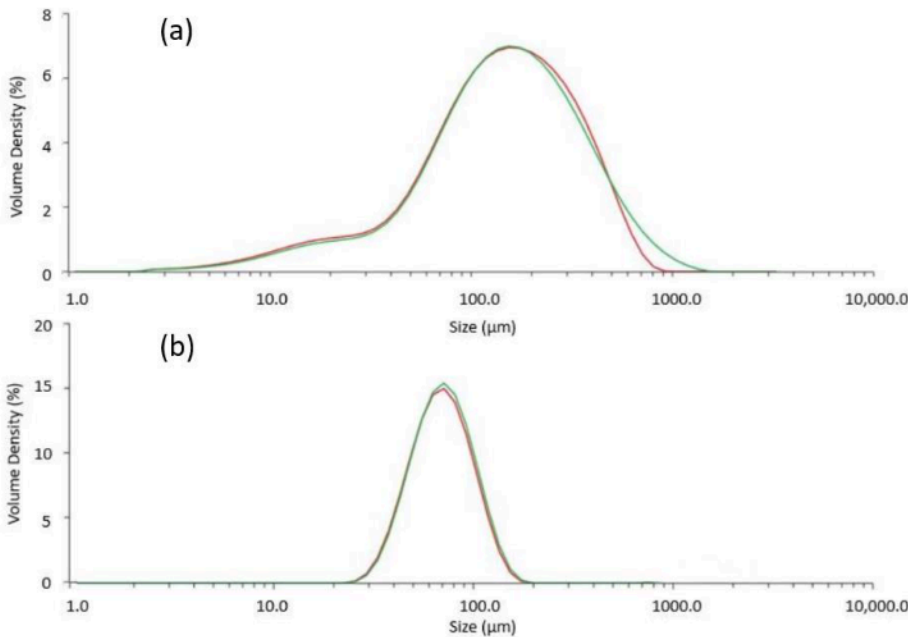


Figure 4. (a) PSD of raw Theophylline and (b) PSD of CPT Theophylline

## Impact of Wet Mill on the Coating of Theophylline

The type of wet mill used for the coating of theophylline, as shown in Figure 1, is classified as a rotor-stator device (6). This device has been applied to the areas of dispersing, grinding and mixing in chemical and pharmaceutical industry. The schematic diagram of the toothed rotor-stator device is illustrated in Figure 5. The feed to the wet mill comes from the center of the rotor and the rotor is rotating at a high tip speed ranging from 10 to 50 m/sec. The feed, a fluid with particles, subjected to a centrifugal force, is moved outward to the space between the rotor and the stator, through the slots of the rotor. During this movement, particles may collide with the wall of the rotor and are broken into smaller pieces due to the force from this collision and then escape into the space between the rotor and the stator, where a random turbulence takes place and a high shear force generated from the high tip speed of the rotor occurs at the interface between the fluid and rotor, as shown in Figure 5. Due to this turbulent and shear force, coated particles are agglomerated to form larger agglomerates and they escape from the slots of the stator to be recycled back to the vessel as shown in Figure 1.

Since the flow rate of the pump around is high, the coated particles are pumped through the wet mill more than 100 times during the coating period, resulting in the morphology change of raw theophylline as shown in Figure 6 (a) and (b) to the spherical shape of theophylline particles from this CPT process, as shown in Figure (c) and (d).

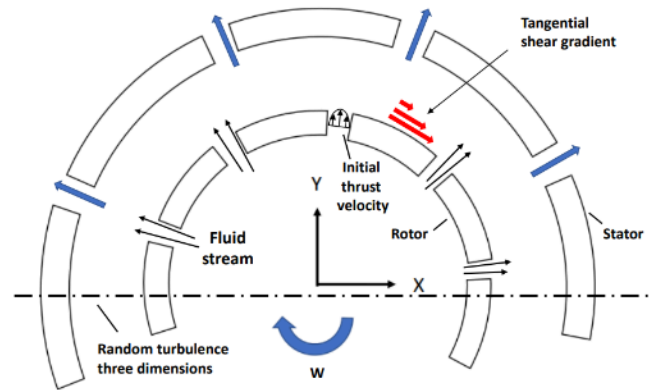


Figure 5. Schematic representation of hydrodynamics of fluid in a toothed rotor-stator device

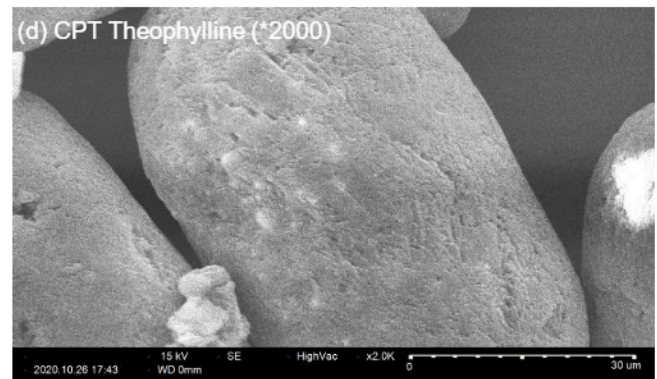
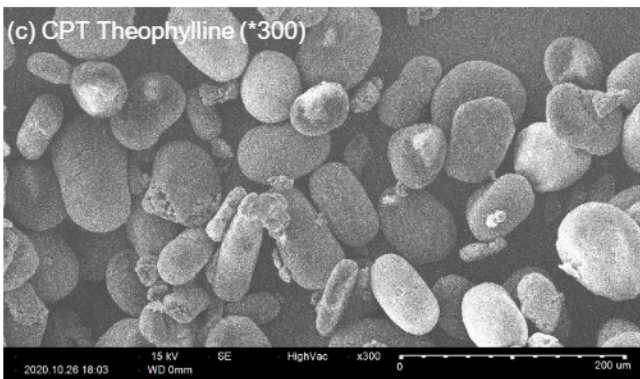
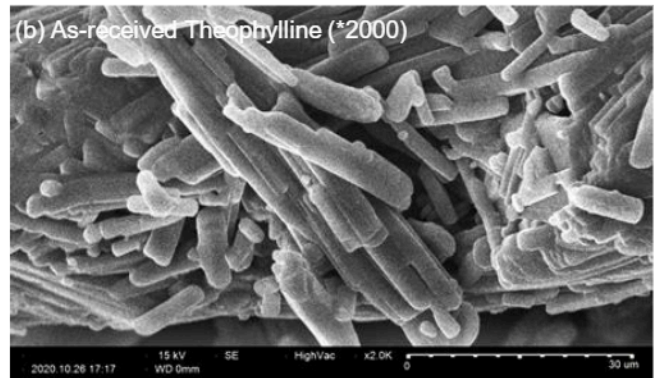
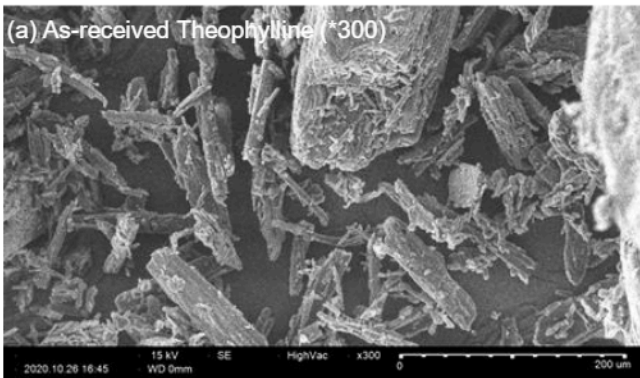


Figure 6 (a) &(b) SEM images of raw theophylline and (c) & (d) SEM images of CPT theophylline

## Comparison of Bulk Density and FFC of Raw Theophylline with CPT Theophylline

Significant improvements of bulk density and flow ability of raw theophylline are made from the CPT process, as shown in Table III. The cohesion and compressibility of the raw theophylline are

Bulk Properties	Raw Theophylline	CPT Theophylline
Conditioned Bulk Density, g/ml	0.40	0.65
Value of Flow Function Coefficient	3.87	14.50
Cohesion, kPa	0.65	0.19
Compressibility	23.80	7.15

Table III Comparison of Bulk Properties of Raw Theophylline vs. CPT Theophylline

A case study is presented to demonstrate the CPT technology and how this technology changes the shape, size and distribution of raw theophylline particles so the coated theophylline particles exhibit

## Conclusion

As discussed, only a minority of active pharmaceutical ingredients (APIs) can be made into tablets by using DC because of the powder properties of most APIs which have low bulk density, low flowability, etc. Low-dose and High-dose API's are two categories which present difficulties for use of DC in different ways.

For low-dose APIs, it may be difficult to achieve the necessary homogeneity and uniformity as segregation, de-mixing, or sedimentation of the API may occur, especially if particle sizes of the formulation components are quite different.

significantly reduced from the CPT process as well.

As the result of the CPT process, the bulk density and FFC of the raw theophylline are changed and the CPT theophylline are located in the sweet spot for the direct compression, as shown in Figure 6.

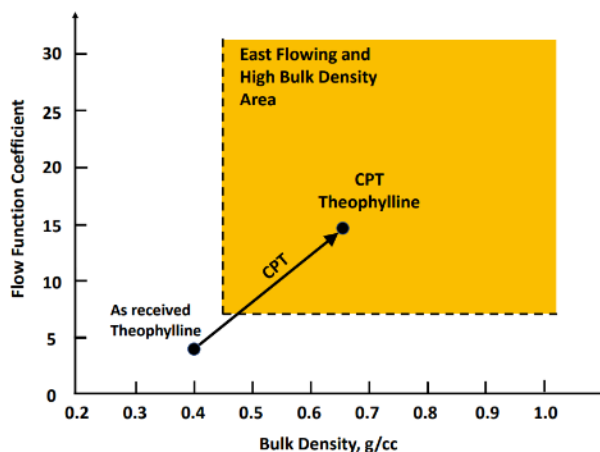


Figure 6. The sweet spot for the direct compression in the map of FFC vs. bulk density

favorable shape, size, PSD, bulk density and flowability; hence the CPT theophylline particles become the ideal candidate for direct compression to make into tablets.

In high dose formulations, where the API content can range from 50% to nearly 100%, fillers often can't compensate for poor API properties such as poor flow and compressibility

Coprecipitation is a technology that can compensate for the difficulties presented above. This method can vastly improve the flow and compressibility of API's so the efficient process of direct compression can be used for solid formulation tablets.




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Over 35 years of experience in pharmaceutical development, technology transfer in both drug substance and drug product areas.

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