Process Simplification Series No. 6

Direct Compression to Replace Roller Compaction via API Flowability Improvement

Drug Product Development, February 2021

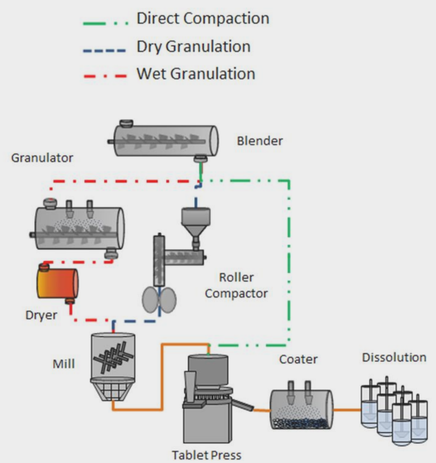
OUTLINE

Roller Compaction is one of best processing methods to improve the flowability of API. Comparatively, direct compression which skips the granulation step is more cost-effective. Our enabling techniques can significantly improve the API particles flowability, make it possible to replace roller compaction process with direct compression process, and deliver quality products while simplifying the process.

BACKGROUND

Oral solid dosage forms, mainly in the forms of tablets and capsules, still dominate the drug product market for their convenience to patients, not only for administration, but also safe and easy to compliance. In manufacturing of oral solid dosage forms, the flowability of active pharmaceutical ingredient (API), excipients used to formulate the API, and formulations play an important role, and should be assessed in the drug product development stage.

Granulation is one of the best and commonly used approaches to overcome the poor flowability of API and formulation. Basically, there are two granulation methods: wet granulation and dry granulation. In wet granulation, granulation is generally obtained via pre-mixing, adding binder solution, screen wet granulation, drying, and milling dried granulation. In dry granulation, the procedure is much simpler and enable to the continuous process because preparation of binder solution and drying are not required. Typically, the dry granulation processing steps include mixing, roll compaction and milling.



Manufacturing Processes via Direct Compression, Roller Compaction, and Wet Granulation

Roller compaction is a simple process compared to wet granulation because of eliminating the wetting and drying steps. It is particularly suitable to heat and moisture sensitive products, which has the potential capability for continuous process. However, Due to the densification, dissolution can be adversely affected, produced granulation may lost the compressibility if no external compressible excipients added to the final blend for tablet compression.

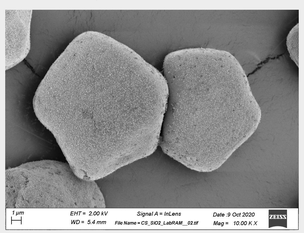
As aforementioned, direct compression is one of the most commonly used methods to produce oral solid dosage forms. Meanwhile, it is one of the simplest processes with its low cost and high throughput (see figure below). However, it has strict requirements for the physical properties of the ingredients and raw materials. For poorly compactible drugs, it will be difficult to directly compress the blend into a tablet. Therefore, some excipients that are particularly used in direct compression have been developed to satisfy the marketing needs.

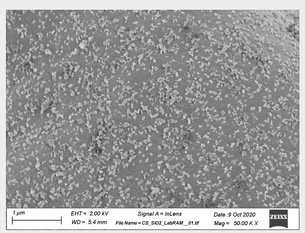
ENABLING ENGINEERING TECHNIQUES

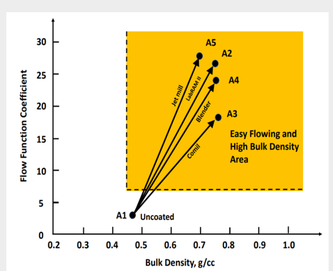
Dry Coating

Dry coating is an efficient approach to improve powder flowability by surface modification without requiring any solvents and binder. The host particles (API) are coated with the guest particles (such as SiO2) via mechanical forces. This coating can effectively increase the spacing between the host particles and the apparent surface roughness. It can reduce the cohesive forces between the hosting particles, resulting in significant benefit to pharmaceutical powder processing because the easy transport of large bulk quantities of powder through unit operations is essential to manufacture solid dosage forms such as capsules and tablets.

There are four enabled dry coating techniques that have been widely studied by researchers and industry: 1) co-milling, 2) acoustic mixing, 3) jet-milling and 4) high shear blending. Significant improvement in API bulk densities and flow function coefficient (FFc) have been achieved through dry coating which enables the API to meet direct compaction criteria.



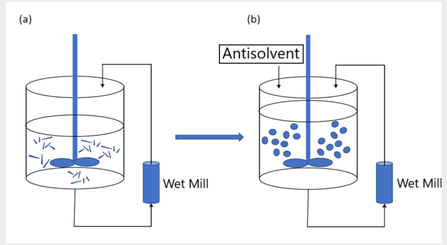




Enhancement in corn starch particles' density and flow function coefficient by acoustic mixing (Work done by DPD at J-Star)

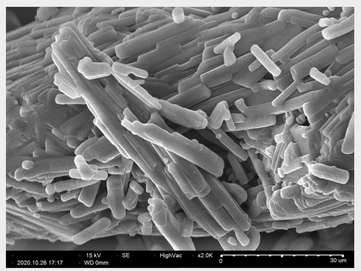
Co-Precipitation (CPT)

Co-precipitation is a technique carried out by solvent evaporation technique. 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, 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 at a controlled rate so the polymer precipitates as a binder for the agglomeration of API in the wet mill.



The Schematic Process Flow Diagram of CPT

The size of the agglomerates grows as more binder is incorporated and the shape of the agglomerate gradually becomes spherical. Successful demonstrations of CPT have been published with significant Improvement in particle aspect ratio, density and flow behavior. This CPT process is also applicable for a larger scale. J-Star Research has successfully from a lab scale to a 50 kg pilot scale.



SEM (x2000) analysis of As-received API X (Left) and CPT API X Product (Right) (Work done by DPD at J-Star)

Moisture-Activated Dry Granulation (MADG)

Moisture-activated dry granulation (MADG) is a novel and economical granulation process. It utilizes a similar setup to a high shear granulator but only requires small amount of water (1 – 5%) to activate the agglomeration formation, after which, the process uses stepwise addition and blending of the pharmaceutical ingredients that absorb and distribute the moisture, thus creating a uniform, free-flowing and compatible granules. The key for this technique is to add just enough of water to achieve particle's agglomeration rather than adding excess water that would require further drying. Given the simplicity, and cost-saving potential of MADG process, it can be a good alternative for wet and dry granulation in pharmaceutical industry.

Other Approaches

Other methods including improving the API flow characteristics by pre-mixing with excipients in the formulation or by a two-step glidant mixing process also provided insights from mixing strategies perspective. Optimized crystallization conditions and crystal habit modification have been found essential for API flow improvement as well.

SUMMARY

A poorly compactible drug substance can be modified via aforementioned enabling engineering techniques to significantly improve its flowability, which is suitable to direct compression to simplify the process by replacing the roller compaction process.

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