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## General Commentary

# Crystal and Particle Engineering Strategies for Improving Powder Compression and Flow Properties to Enable Continuous Tablet Manufacturing by Direct Compression

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## ABSTRACT

Continuous manufacturing of tablets has many advantages, including batch size flexibility, demand-adaptive scale up or scale down, consistent product quality, small operational foot print, and increased manufacturing efficiency. Simplicity makes direct compression the most suitable process for continuous tablet manufacturing. However, deficiencies in powder flow and compression of active pharmaceutical ingredients (APIs) limit the range of drug loading that can routinely be considered for direct compression. For the widespread adoption of continuous direct compression, effective API engineering strategies to address powder flow and compression problems are needed. Appropriate implementation of these strategies would facilitate the design of high-quality robust drug products, as stipulated by the Quality-by-Design framework. Here, several crystal and particle engineering strategies for improving powder flow and compression properties are summarized. The focus is on the underlying materials science, which is the foundation for effective API engineering to enable successful continuous manufacturing by the direct compression process.

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## Introduction

The state of pharmaceutical tablet manufacturing is witnessing a strategic shift in the recent years. There is a conscious effort across the pharmaceutical industry to transform the traditional and, somewhat, empirical pharmaceutical development process into a science-based approach that is focused on product quality and process robustness, as stipulated by the Quality-by-Design (QbD) framework.<sup>1-3</sup> The paradigm of a QbD filing for regulatory approval of new drug products is no longer a “nice-to-have” for the pharmaceutical industry, as illustrated by the recently published policy from U.S. Food and Drug Administration, MAPP 5016.1, which outlines its expectations for applying International Council on Harmonization ICH Q8(R2), Q9, and Q10 during product development and regulatory review of new drug applications.<sup>4</sup> Fundamental to the successful QbD implementation in pharmaceutical

development is building the understanding of the relationship between the structure and properties of materials as well as manufacturing process relevant to the quality of drug products.<sup>5</sup>

In addition to embedding the QbD principles, the switch from the traditional batch manufacturing into continuous manufacturing, operated with integrated model-based controls, is another aspect of pharmaceutical development that is receiving significant attention. Continuous manufacturing is defined as a process where a continuous flow of input raw materials is transformed into finished products under a state of control, with any product manufactured outside the control limits diverted.<sup>6,7</sup> Continuous manufacturing of pharmaceuticals has recently been categorized as an advanced manufacturing technology area of emerging priority by the U.S. Federal Government.<sup>8</sup> Continuous manufacturing offers a wide spectrum of advantages and has the potential to significantly reduce operational costs and capital costs by: (a) increasing efficiency and shortening development and manufacturing timelines, (b) significantly reducing product losses, (c) reducing operational footprint, (d) increasing consistency of the manufacturing process, and (e) enhancing quality of the product.<sup>6,7,9</sup>

A true continuous manufacturing line requires every step in the process to be continuous and seamlessly integrated. In many cases,

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the design of the continuous line is semicontinuous, having a combination of continuous and batch process steps. Tablet manufacturing by both granulation (wet or dry) and direct compression are amenable to continuous manufacturing. A twin screw granulator or a continuous high shear granulator enables continuous wet granulation.<sup>10,11</sup> Continuous dry granulation can be achieved using roller compaction, which is inherently a continuous process. These continuous processes can be integrated with other unit operations to form a continuous manufacturing line. However, direct compression is the most suitable process for continuous manufacturing of pharmaceutical tablets, because of the reduced number of unit operations that need to be integrated for continuous manufacturing. In this case, the input powder blend is directly transformed into a tablet without any intermediate process steps of granulation, drying, and granule size reduction. In addition to the shortened manufacturing time, the reduced number of manufacturing steps, and thus fewer critical process parameters to monitor, ensures process robustness and consistent quality of drug products. Finally, direct compression also eliminates under- or over-granulation problems associated with any granulation process. These advantages have led to a heightened recent interest in the strategies to enable continuous direct compression in both the industry and academia.<sup>12-16</sup>

The 2 fundamental material properties that impact the manufacturability of tablets are powder tabletability and flowability. The key impediment in the implementation of continuous direct compression is often the sub-optimal compression and flow properties of the active pharmaceutical ingredient (API). The loading of API in a majority of pharmaceutical tablet formulations usually falls in the 10%-80% range depending on the dose. A wider range may be expected if all tablets are considered. At that level, the API compression and flow properties will influence final product manufacturing robustness, especially if the drug loading in the formulation is very high. Therefore, API engineering with the objective of improving the compression and flow characteristics is an effective strategy to enable continuous tablet manufacturing by direct compression, eliminating the need of using significant quantities of excipients to address compression and flow deficiencies of API. The objective of this commentary is to outline API engineering strategies to enhance the powder compression and flow properties of pharmaceutical materials. The current understanding of the fundamental relationships between the structure of materials and their compression and flow properties is summarized. Of course, these engineering strategies are equally applicable to enhance manufacturability during traditional batch processes.

## Powder Compression

### *The Physics of Powder Compression*

For a given material, the net mechanical strength of tablets directly depends on the bonding area formed between particles due to permanent particle deformation.<sup>17</sup> Tablets would retain integrity only if an adequate area of the interparticulate bonding is preserved after the removal of the compression stress at the conclusion of the compression cycle. The development of bonding area among particles is influenced by particle size, shape, surface texture, moisture content, as well as crystal mechanical properties, which are influenced by crystal structure.<sup>17</sup> When the total bonding area is the same, tablets with higher bonding strength are stronger. It is the interplay between bonding area and bonding strength that dictates the tablet compression properties of a powder.<sup>18</sup> Thus, particle or crystal engineering for improving bonding area, bonding strength, or both can effectively solve problems related to tablet compression.

To effectively design appropriate crystal and particle engineering strategies for improving the compression properties of an API by influencing bonding area and bonding strength of materials, it is important to understand the fundamental relationships among a material's structure, mechanical deformation, and compression properties.<sup>19-21</sup> For a solid material, the key mechanical deformation mechanisms under the application of an external mechanical stress include elastic deformation, plastic deformation, viscoelastic deformation, and fragmentation. Elastically deformed particles undergo complete recovery once the external stress is removed. For perfectly elastic materials, the contact area between particles developed during compression is lost after stress removal. Powders of such materials cannot form intact tablets by compression. For this reason, materials with high elasticity have poor powder compression properties and tend to laminate on decompression due to insufficient bonding area as a result of extensive elastic recovery.

Plastic deformation is the most important mechanism for creating a permanent bonding area under compression stress. Irreversible plastic deformation is necessary for retaining the bonding area during the decompression phase of powder compaction and, therefore, for producing robust tablets. Since elastic deformation is inevitable, the compression performance of a powder is largely determined by the relative magnitude of the elastic and plastic deformation. The plasticity of crystals depends on the crystal packing.<sup>19,22,23</sup> It has been well documented in the literature that the presence of rigid flat molecular layers in crystals enhances the compression properties of materials by increasing plasticity. These flat layers serve as active slip planes, which are crystallographic planes that have the weakest inter-planar interactions in a crystal. These in turn allow facile movement of dislocations in crystals under mechanical stress, a prerequisite for plastic deformation. A well-known pharmaceutical example of the relationship between crystal structure, plasticity, and powder tabletability is acetaminophen. Acetaminophen polymorph I, having a corrugated herringbone (zig-zag) crystal packing, displays extremely poor powder compression properties. However, acetaminophen polymorph II exhibits flat hydrogen-bonded layers and higher plasticity compared with polymorph I. Consequently, polymorph II exhibits superior compression properties to polymorph I.<sup>24</sup> The effectiveness of improving tabletability through enhancing crystal plasticity by introducing flat rigid layered crystal structure is also illustrated in several other polymorphic systems.<sup>25-27</sup> Contrary to flat slip layers, a crystal with molecules packed in a 3-dimensional hydrogen-bonded network structure exhibit more resistance to plastic deformation, and thereby have poor compression properties.<sup>19</sup> When multiple mechanisms of slip are possible in a crystal, crystal plasticity is further improved compared with the simple layered structure. An example of such a material is theophylline, whose crystal structure has flat layers that are formed by stacking hydrogen-bonded V-shaped rigid columns. Slipping between columns is even easier than between rigid layers. In addition, columns between adjacent layers are oriented at an angle of 111.61°, thus making them crystal capable of accommodating the compression stress at 2 different orientations to further improve plasticity. This results in exceptional tablet compression properties.<sup>19</sup> Other examples of good crystal plasticity and tabletability corresponding to such stacking column structures were also reported.<sup>28</sup> Recent work has suggested that ladder-like molecular packing in theophylline monohydrate is responsible for its superior plasticity to theophylline anhydrate.<sup>29</sup>

Such understanding of the fundamental relationship among the structure, mechanical properties, and tableting behavior at the crystal and tablet levels can now be applied to tailor the compression properties of APIs by crystal and particle engineering.

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