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Assessment of Intragranular and Extragranular Fracture in the Development of Tablet Tensile Strength

Biplob Mitra [1, 2, 3, *], Jon Hilden [2, 4], James Litster [5, 6]

[1] Drug Product Development, Celgene Corporation, Summit, New Jersey 07901
[2] Small Molecule Design and Development, Eli Lilly and Co., Indianapolis, Indiana 46285
[3] Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, Indiana 47907
[4] School of Materials Engineering, Purdue University, West Lafayette, Indiana 47907
[5] Department of Chemical and Biological Engineering, University of Sheffield, Sheffield, UK
[6] School of Chemical Engineering, Purdue University, West Lafayette, Indiana 47907

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ABSTRACT

When a tablet is compacted from deformable granules and then broken, the fracture plane may cleave granules in 2 (intragranular fracture) or separate neighboring granules (extragranular fracture). In this study, a novel method was developed to quantify the extent of intragranular versus extragranular fracture by compacting tablets from multicolored ideal granules and evaluating fracture surfaces. The proportions of intragranular and extragranular fracture were quantified and modeled in light of a new metric; the deformation potential, Δ, reflecting the solid fraction increase as an initial granule bed is compressed into a final tablet. Results show that a measurable tablet strength is achieved at $\Delta > 0.18$, but intragranular fracture is not observed until $\Delta > 0.21$. At very large Δ, tablets experience almost exclusively intragranular fracture, yet the tablet tensile strength is considerably lower than that of a tablet compacted from raw powders versus precompacted granules. Thus, secondary compaction of granules appears to weaken the granule matrix, leading to reduced tablet tensile strength even in the presence of strong extragranular bonding.

Introduction

Pharmaceutical tablets can experience a range of mechanical stressors from multiple sources including the tumbling action inside a tablet coating pan, vibration and impact during bulk transport in bottles, or from being forcefully pushed through the foil backing of a blister pack. In these cases, it is desirable to avoid tablet fracture. Fracture not only affects tablet elegance but can also increase the risk of unintended exposure to caregivers in cases where the tablet coating helps contain the medicine within. A mechanistic understanding of tablet fracture is therefore highly desirable.

The transformation of powder into a coherent tablet structure is essentially an interparticle bonding process. However, the majority of pharmaceutical powders fed to a tablet press are not primary particles, but granular, porous secondary particles. Powders are often converted into granules via various granulation techniques and then forward processed into tablets to achieve desired quality attributes of the final product (such as mechanical strength, content uniformity, dissolution) and to improve process performance. Tablets prepared from granules can be described as granules bonded together. In addition to the mechanical properties of the primary particles and granules, the physical changes that occur to granules during the confined compression process are also important in evolution of the tablet structure. In the development of a quality tablet dosage form, a balance between physical (e.g., appearance) and mechanical (e.g., solid fraction [SF], tensile strength [TS]) properties of tablets and their performance (e.g., disintegration time, dissolution) must be maintained. The use of mechanistic understanding in selecting material attributes and process parameters to design a tablet product can potentially ensure robustness of the product quality attributes.

To mechanistically explain the strength of tablets formed from granules, the process of fracture has attracted considerable interest. The TS of pharmaceutical tablets has been explained in view of the phenomena that generally occur in metal (Hall-Petch

* *Correspondence to:* Biplob Mitra (Telephone: 1 908 673 9126).
E-mail addresses: bmitra@celgene.com, bkmitra@yahoo.com (B. Mitra).

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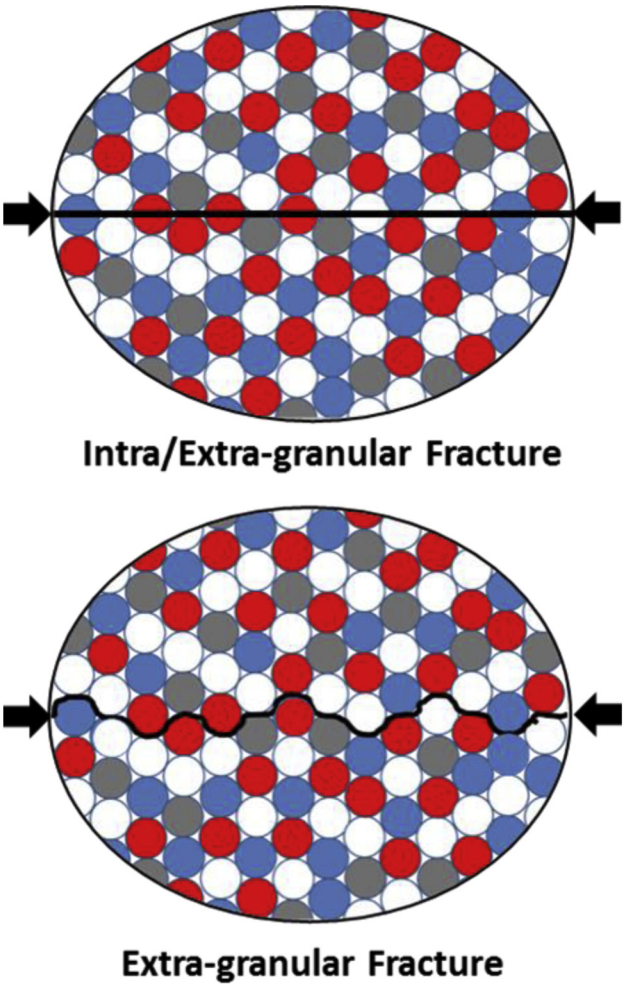

Figure 1. Illustration of the approach to quantify intragranular and extragranular fracture of tablets.

relationship[1,2]) and ceramic compacts (Griffith's crack criterion[3-5]). In fact, Sun et al.[6] and others[7-9] have used milled granules of microcrystalline cellulose (MCC) and showed that larger granule sizes lead to lower tablet TS. Relationships between TS, critical stress intensity, and crack size have also been reported in literature.[10-12] However, mechanical properties of pharmaceutical materials such as ductility and brittleness are generally ranked between metal and ceramic materials. It is not clear whether the Hall-Petch relationship nor fracture mechanics can be applied to pharmaceutical materials such as MCC. Dislocation glide is not the expected deformation mechanism in MCC. Fracture of an MCC tablet by crack propagation is also less likely to occur because of the potential blunting of the crack tip by plastic deformation.[13] Moreover, the crack length is a critical parameter that cannot be easily determined.[14] The largest crack is not necessarily located on the fracture plane.

The TS of tablets have also been modeled using the bond summation concept which is based on Rumpf's[15] theory of strength of agglomerates. The TS of a tablet is governed by the interparticular bonding force and the bonding area in a given cross-section that fails under an applied stress.[16,17] Johansson et al.[18] showed that low and high SF MCC pellets achieved larger and smaller bonding area in the tablet, respectively. For the bond summation concept to work, it is critical to determine the actual bonding surface area and the bonding force. However, it is difficult to quantify them directly.

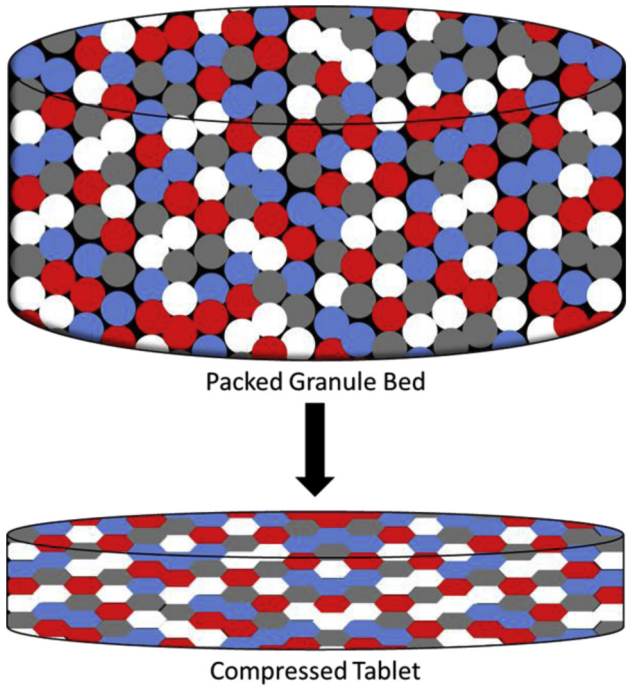

Figure 2. Illustration of deformation of granules during compression.

In literature,[18-21] there is a common perception that the fracture plane of tablets prepared from granules is created between the neighboring granules. In contrast, our previous study[22] demonstrated that high SF tablets prepared from low SF granules fracture indiscriminately both intragranularly and extragranularly and produce a smooth fracture plane. Conversely, low SF tablets prepared from high SF granules fracture extragranularly by separating neighboring granules. A common perception also exists that intragranular bonding strength is higher than extragranular bonding strength in a tablet.[18,21]

In this work, a mechanistic model of tablet compression and strength evolution is proposed and explored experimentally by examining the fracture planes on matching halves of broken tablets prepared from novel, multicolored monodisperse granules. The model explores basic phenomena that transpire as a bed of porous granules is compressed into a tablet and then broken. This includes the densification of individual granules with increasing compaction stress and associated evolution of granule strength as well as the formation of bonds between granules and the associated evolution of extragranular bond strength. The novel use of multicolored monodisperse granules in this work permits the experimental quantification of intragranular fracture versus extragranular fracture when compacted tablets are broken. These fracture areas are examined under different conditions of initial granule SF and final tablet SF. Analysis of these results leads to the identification of a new variable, the deformation potential, as being critical to the formation of extragranular bonds and the evolution of tablet strength. Results also suggest that the inherent weakening of granules due to repeated deformation (first in the granulation process and then again in the tablet compaction process) is the dominant factor leading to decreased tablet TS.

Mechanistic Model to Predict Tablet TS

The fracture of tablets comprising compressed granules can occur along 2 possible paths. The first occurs when the fracture