Granule Strength Determination and Compactibility of Granules of Varying Density

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Purpose: As in-line process analytics are becoming more widely accepted, it is important to illustrate that a measurement of interest will provide the expected outcome if that control point has reached a desired level. This methodology is especially true for novel applications. The purpose of this work was to investigate the role of densification during high shear granulation and the resulting impact on the compaction properties of the prepared granules. Additionally, the structural dependence of granule strength on the compaction phase was investigated to establish the validity of controlling granule density during high-shear wet granulation to ensure reproducible compaction properties.

Methods: Wet granulations were performed in a Diosna six-liter high-shear granulator equipped with a bottom driven impeller and side mounted chopper. Granulations consisted of 500 grams of Avicel PH 102 and utilized distilled water as the binder. To vary the density of prepared granules, granulations were carried out with impeller speeds of 175, 250 and 500 RPM at water levels corresponding to 50, 60, 70, 80, 90, 100 L/S%. At the 90 L/S% level, wet massing times were varied corresponding to 0, 500 and 7500 impeller revolutions. The chopper speed remained constant at 1000 RPM for all granulations. After drying the granulations, sieve fractions were prepared in order to minimize the effects of size distribution during further analysis. Envelope density of the sieve fractions (16, 20, 30, 40 mesh) was measured using the GeoPyc 1360 (Micromeritics, Norcross, GA). The 12.7mm ID sample chamber was chosen to perform

all tests. The corresponding tight fitting piston was utilized with a compression load of 28N and a conversion factor of 0.1284 cm^3/mm. To determine the average granule strength a uni-axial confined compression method was employed as it simulates a compaction process that would be encountered during a compaction phase of tablet manufacture. Granule fractions were charged into the tooling with pre-lubricated die walls by volume. Uni-axial compression occurred using ½" flat-faced tooling (Natoli Engineering) on an MTS Sintech 30D load frame equipped with a 20,000lb load cell. Average compressive granule strength was derived using Kawakita analysis[1]. The compression stage was continued beyond the region necessary for Kawakita analysis to prepare compacts. After the compression stage, ejected compacts were allowed to elastically recover for a minimum of three days. Dimensions and weights were recorded prior to hardness testing using diametric compression. The tensile strength (σ) was derived from the compact hardness tests using Fell and Newton analysis[2] (Equation 1).

$$\sigma = \frac{2H}{\pi D t} \qquad \text{Eq. 1}$$

Where H is the force necessary to cause tensile failure (compact hardness), D is the diameter of the compact and t is the thickness of the compact.

Results: To model the relationship between granule density and granule strength, existing models were tested. The simplest model examined was the Ryshkewitch-Duckworth equation[3] (Equation 2).

$$\sigma = \sigma_0 \exp(-BP) \qquad \text{Eq. 2}$$

Where σ_0 is the strength of a non-porous sample, P is the sample porosity and B is the slope of the ln σ vs P line. This model was originally derived empirically to describe the relationship between the porosity of sintered ceramics and the compressive strength of samples. In the field of granulation, Rumpf proposed his famous model for relating the strength of agglomerates to the presence of pores in the sample[4] (Equation 3)

$$\sigma = \frac{1-\varepsilon}{\varepsilon}\frac{F}{d^2} \qquad \text{Eq. 3}$$

Where F is the mean tensile strength per unit cross-sectional area, d is the diameter of the primary particles and ε is the porosity of the agglomerate. By investigating Rumpf's model of granule strength, it can be found that the strength of a granule is affected by the strength of the bonds within the granule and the amount of void space in the granule. The strength of solid systems has been found to be reduced by flaws and all solids contain imperfections. It is the propagation of these flaws that allow materials to fail. The strength reduction of a material has been quantified by Griffith in his well known work[5] (Equation 4).

$$\sigma = \sqrt{\frac{2E\gamma}{\pi a}} \qquad \text{Eq. 4}$$

Where E is the elastic modulus, γ is the surface energy of the crack per unit area and a is the size of the flaw. Building on the model of Rumpf, Kendall[6] integrated the work of Griffith[5] to derive Equation 5.

$$\sigma = 3.7(1-\varepsilon)^4 \frac{F}{d\sqrt{da}} \qquad \text{Eq. 5}$$

Where a is the flaw size as stated in Griffith's Model (Equation 4), F, d and ε are the mean tensile strength per unit cross-sectional area, diameter of primary particles and the agglomerate porosity as stated in Rumpf's Model. Granule strength-density relationships were found to be well modeled using the Ryshkewitch-Duckworth model for all prepared granules[3] (Figure 1).

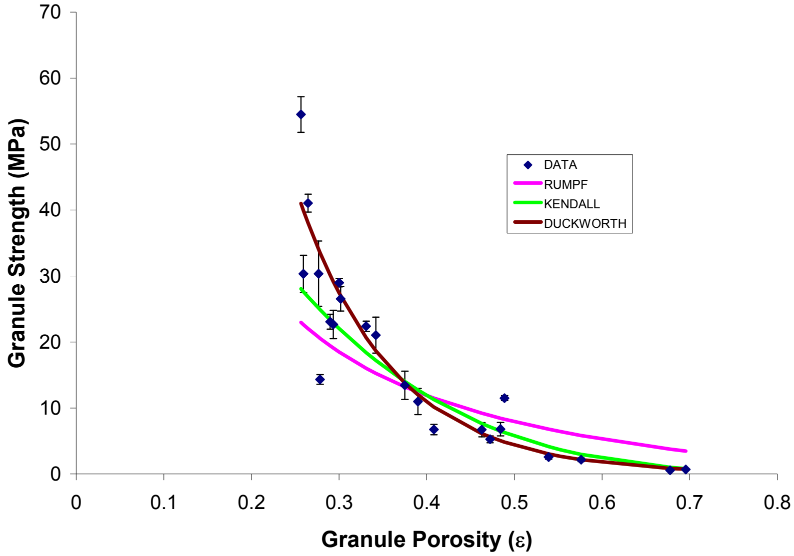

Figure 1 Application of models used to quantify granule strength dependence on granule density on 40 mesh granule data

A power law relationship was found between granule strength and compact strength for all prepared granules (Figure 2).

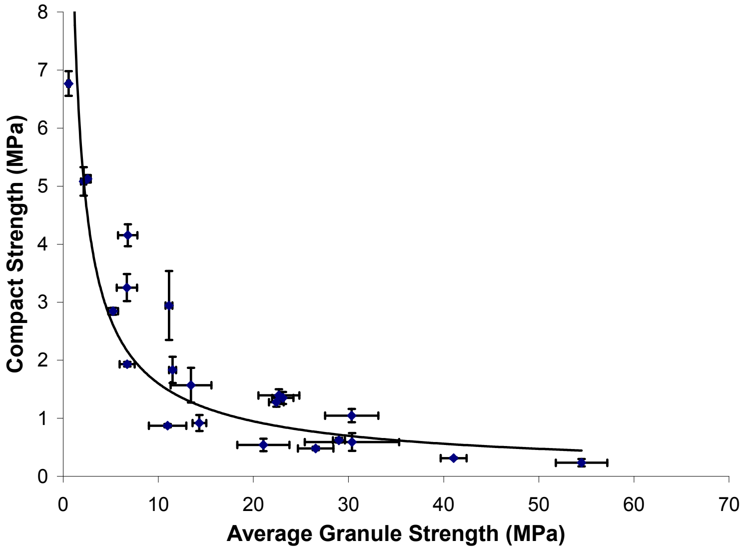

Figure 2 Power Law Model of Compact Strength versus Granule Strength (40 Mesh)

Upon truncation of granules which yielded poor compacts, Kendall's model was most applicable to describe the granule strength-density relationship and a narrowly linear relationship existed between granule strength and compact strength.

Conclusions: For the current system, the method of preparation did not influence the strength and compaction dependence on granule density. Illustrating that the desired compaction properties can be obtained solely by controlling granule density is quite significant. The method of granule density attainment did not influence the density-strength-compaction relationship. This illustrates the feasibility of controlling granule density during HSWG to arrive an end-point in terms of compaction characteristics. This systematic approach to process understanding is necessary to advance the transition from traditional, time-based granulation methods to the ideal platform of ensuring product quality during processing.

References

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