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Letter to the Editor

On the mechanism of reduced tabletability of granules prepared by roller compaction

Abstract

In a recent paper published in this journal, authors were perplexed by their results seemingly conflicting with our earlier findings [Sun, C.C., Himmelspach, M.W., 2006. Reduced tabletability of roller compacted granules as a result of granule size enlargement. J. Pharm. Sci. 95, 200–206]. After carefully reviewing the two studies, we conclude that results in the two studies are actually consistent with each other.

Keywords: Roller compaction; Dry granulation; Granule size; Tabletability; Powder compaction

Dear Sir,

In a recent paper published in this journal, Herting and Kleinebudde (2007) suggested some of their results contradicted our earlier findings (Sun and Himmelspach, 2006). After carefully reviewing the two studies, we have concluded that results in the two studies were demonstrably consistent with each other.

Both papers addressed the phenomenon of reduced tabletability of granules prepared by roller compaction (RC). Using microcrystalline cellulose (MCC), we showed that this phenomenon could be explained by granule-size enlargement for plastic materials but not by work-hardening (Sun and Himmelspach, 2006). We arrived at this conclusion partly based on the following observations: (1) smaller sieve cut of RC granule exhibited better tabletability than larger sieve cut from the same batch; (2) tabletability of granule with similar size distribution was similar and was independent of size of the primary particle size; (3) tabletability of RC granules with adequately small size was higher than that of the virgin powder; (4) tabletability of repeatedly roller compacted granules decreased with increasing granule size but not with the increasing total number of RC.

Herting and Kleinebudde studied mixtures of MCC and theophylline. They observed that larger granules of a mixture containing smaller primary MCC particles formed stronger tablets under the same compaction conditions, i.e., exhibiting better tabletability. This, on the surface, contradicted our second observation mentioned above.

Besides the fact that different materials were used in the two studies, a key difference between the two studies was the lubrication of granules. We explored effects of granule size enlargement on tabletability of lubricated MCC granules since pharmaceutical powders are invariably lubricated prior to tableting. The presence of a layer of magnesium stearate on surface of granules leads to significantly lower strength of intergranular bonding than that of intragranular bonding. In Herting and Kleinebudde's work, granules were not lubricated. Thus, intragranular bonding strength is comparable to the intergranular bonding strength.

To clearly demonstrate the effects of granule size enlargement on tabletability pertaining to formulation development, following two conditions must be satisfied: (1) original difference in granule size is preserved during compaction by the avoidance of extensive fragmentation; and (2) intergranular bonding strength is lower than intragranular bonding strength. A correlation between reduction in granule tabletability and granule size enlargement may not be observed when either condition is not met. The first condition is necessary because extensive fragmentation of granules can effectively minimize or even eliminate any difference in the original size prior to compaction. This was shown in our more recent work where tabletability of brittle materials was essentially independent of granule size (Wu and Sun, 2007). The second condition is necessary to ensure that propagation of fracture plane during tablet tensile failure is along the surfaces of granules and not through them.

The use of lubricated MCC granules in our earlier work satisfied the two conditions and we were able to clearly demonstrate granule size effect. Granule size effect was failed to be shown in Herting and Kleinebudde's study because neither condition was satisfied.

The following facts suggest that fragmentation of granules likely occurred in the early stages of compaction in Herting and Kleinebudde's study.

(1) Plasticity of the mixtures of MCC and theophylline is lower than that of pure MCC.

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(2) Granule porosity was high, ranging 19–41%. Porous granules of even relatively plastic material may fracture when compressed. That is to say they behave like brittle particles.[1]
(3) Herting and Kleinebudde observed more profound effect of primary MCC particle size for more porous granules, suggesting more porous granules fractured more extensively.
(4) Tensile strength ratio between tablets compressed from granules and original powder ranged 0.68–1.04. The higher the granule porosity, the higher the ratio. A near unity ratio suggests that fragmentation is so extensive that granules are largely reduced into primary particles in early stages of compaction.

Even if some granules may not have extensively fractured, the lack of lubrication to the RC granule would result in the breach of the second requirement. In absence of the lubricant layer, boundary along granule surfaces cannot be discerned from boundary among primary particles within granules after being compressed into tablet. Tablet tensile strength would be lower as observed in both studies (Herting and Kleinebudde, 2007; Sun and Himmelspach, 2006) if primary particles are larger. It is therefore not surprising that granule size did not correlate with tabletability but it did correlate with primary particle size of MCC.

In summary, granule size enlargement remains an important factor in causing reduced tabletability of plastic and lubricated RC pharmaceutical granules. Results in the study of Herting and Kleinebudde and ours are in fact consistent. Both are in agreement with the proposed effects of particle size on the reduction of tabletability after RC granulation of pharmaceutical powders.

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Changquan Calvin Sun *
Amgen Inc., Materials Science Laboratory, Small Molecule Pharmaceutics, One Amgen Center Dr. 21-2-A, Thousand Oaks, CA 91320-1799, United States

* Tel.: +1 805 313 5581; fax: +1 805 447 3401.
E-mail addresses: ccsun@amgen.com, sunx0053@yahoo.com

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[1] Two outcomes may be anticipated if extensive fracture of granule occurs: (1) variations in granule porosity do not influence powder compaction properties because granules are essentially reduced into primary particles; (2) granule size is not relevant to compaction property of granules.