

Development of a High Drug Load Tablet Formulation Based on Assessment of Powder Manufacturability: Moving Towards Quality by Design

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ABSTRACT: The development of a robust tablet formulation for a high dose active pharmaceutical ingredient (API) by the trial-and-error approach is challenging. To meet the growing needs of bringing drugs to market faster and with reduced costs, more targeted and efficient development practices are in demand. Here we show detailed understanding of mechanical properties of API and excipients are essential in achieving efficient development of a high API loading formulation. The loading of the experimental drug, AMG458, was 50 wt% plus accompanying 1:1 molar ratio organic acid of ~19%. We assessed manufacturability of powders based on their flow and compaction properties using a shear cell and a compaction simulator, respectively. We selected granulation process on the basis of poor flow properties of API and its blends with common direct compaction excipients. During the course of formulation development, we could quickly identify manufacturability deficiencies in the lead formulation. With detailed knowledge of the mechanical properties of excipients and formulated powders, we improved the lead formulation by overcoming manufacturability deficiencies using predictive and material sparing (<10 g) approaches. Larger batches were subsequently manufactured to confirm predictions. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 98:239–247, 2009

Keywords: manufacturability; formulation development; granulation; powder flow properties; powder compaction; tablet

INTRODUCTION

During tablet formulation development, the choice of manufacturing processes and excipients

has been largely based on personal preference and experience of formulators and by the trial-and-error approach.¹ Following the empirical paradigm, it is likely that the number of unique formulations for a new drug may be nearly as many as the number of formulators asked to develop it. Because of the empiricism, the formulation of solids dosage forms is still considered as an art rather than a science.² This empirical approach leads to not only consumption of an appreciable amount of active pharmaceutical

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ingredient (API), but also prolonged development time with significant resources required. Under the traditional paradigm, formulation development can pose a challenge because of the large number of excipients available in each functionality category.¹ The challenges are even greater when a high drug load has to be accommodated. Without a mechanistic understanding of material properties, scale up of a formulation can be problematic.² The recent quality-by-design (QbD) initiative by FDA stresses the need for applying more scientific formulation development and scale up.^{1,3} The FDA has identified, among others, two opportunities along this direction, including: (a) the establishment of formulation expert systems to assist the more efficient selection and optimization of excipient; (b) development of process simulation tools to identify optimal and efficient processes that can be easily scaled up.¹

Mechanical properties of the API and excipients determine success or failure of a tableting operation. Understanding the key mechanical properties can be extremely valuable to facilitate the rational selection of excipients and shorten the development time with minimum consumption of drug substances. Moreover, a formulation thus developed can be scaled up with more confidence. The tablet manufacturability of a powder can be reasonably assessed using the powder flow property and the compaction property. The former property dictates the readiness of powder transfer in processes, such as discharge a hopper and fill die cavity on a tablet press. The latter property dictates the quality of tablet such as tablet breaking force and friability. Powder flow properties can be assessed by the well-established shear cell measurement.^{4–6} Powder mechanical properties can be successfully assessed using tableting indices⁷ or simultaneous consideration of tabletability, compressibility, and compactibility.^{8–10} Similar information on compaction behavior of a powder may be obtained from either methodology.¹¹ By recognizing the deficiency of an API of interest, one can select appropriate excipients with known flow and compaction properties to achieve balanced powder properties for tableting. Formulated powder mixtures thus prepared are subjected to further evaluation of such properties coupled with key process variables if necessary. This process permits a rapid, efficient, and API-sparing development and optimization of the tablet formulation. Formulation development based on the described practice departs from the traditional

approach and is one step closer to the goal of scientific tablet formulation development.

AMG 458 is an experimental drug with a molecular weight of 539.6 g/mol, a pK_a of 5.67, and a projected human dose ranging 0.4–1.5 g.¹² The anhydrous crystals of AMG458 were fine needles with a volume equivalent mean particle size of 26 μm as determined by light scattering. Its solubility is $\sim 0.2 \mu\text{g/mL}$ in water (equilibrium pH 7.0) and $\sim 0.5 \text{ mg/mL}$ in a pH 2 medium.¹²

The preferred dosage form was a high drug load (50%, w/w) tablet intended for use in clinical trials. Preliminary work indicated that the presence of an acidic excipient played a critical role in enhancing the dissolution rate of AMG 458 and, therefore, improving the oral absorption of this drug.¹² As the equal molar ratio between AMG 458 and acid was desired, approximately 19 wt% acid (assuming a MW of 200) was needed to accompany the 50% AMG 458 in the tablet composition.¹² Consequently, $\sim 70\%$ of the formulation was pre-determined. This restricted the flexibility in formulation space available for other excipients. Moreover, we were challenged with an aggressive timeline and limited availability of API. Consistent with the QbD principle, we instead relied on the understanding of material properties to guide an efficient tablet formulation development in this work. To minimize the consumption of API, we identified and utilized suitable placebo surrogates based on similar mechanical properties to guide the formulation and process optimization.

MATERIALS AND METHODS

Materials

Bulk AMG458 was supplied by Chemical Process Research & Development at Amgen. All excipients were NF or USP grades purchased from respective suppliers. The list of excipients is: microcrystalline cellulose (Avicel PH102, FMC Biopolymer, Newark, DE), tartaric acid (J.T. Baker, Phillipsburg, NJ), crospovidone (International Specialty Products, Wayne, NJ), magnesium stearate, N.F. (Spectrum Laboratory Products, Gardena, CA), HPMC (K3 LV, Dow Chemicals, Midland, MI), lactose 313 (CHR Hansen Inc., Milwaukee, WI), citric acid (Mallinckrodt Inc., Hazelwood, MO), Cab-o-sil[®] (Cabot Corporation, Boston, MA). All material characterizations were performed at 20.5°C and $50 \pm 5\%$ RH.

Methods

We assessed manufacturability of powders based on powder flow properties and compaction properties. We quantified powder compaction properties using tabletability plots.^{8,10} Under identical compaction conditions, a higher tablet tensile strength indicated better compaction properties. Powder flow properties were quantified by flow function.^{4–6} A flow function describes the relationship between unconfined yield strength, f_c , and major principal stress, σ . At a given σ , a lower f_c corresponds to better flow properties. This is because a powder can initiate flow more easily since it can break under a lower stress. The lower is the flow function line the better are the flow properties. When needed, we also directly tested manufacturability of powders on a rotary tablet press (Betapress, Manesty Knowsley, Merseyside, UK) operated at 20 rpm. A gravity feeder and only two stations were used during compression.

Powder Compaction

Powder compaction of AMG458 and direct blends with excipients was conducted using an automatic hydraulic laboratory press (Model 3889; Carver Inc., Wabash, IN). The force was brought to the target value and held for 1 min before being released. The round punches were flat-faced with a diameter of 10.00 mm. A split die was used to avoid ejection step that may be problematic to poorly compressible powders.

Powder compaction of granules was carried out using a compaction simulator (Presster, Metropolitan Computing Corp., East Hanover, NJ) capable of simulating presses at various speeds as needed.¹³ The compaction rolls were 250 mm in diameter. The compaction force and ejection force were recorded for each tablet. A flat round B-tooling with a diameter of 10.00 mm was used to make tablets of ~300–400 mg in weight. Force required to break a tablet was measured using a texture analyzer (Texture Technologies Corp., Hamilton, MA). A stainless steel cylindrical probe (10 mm in diameter) was used to compress tablets against a steel platen at a rate of 0.01 mm/s until tablet fractured. Tablet tensile strength was calculated from the peak breaking force, tablet thickness and diameter.¹⁴ Powder compaction properties were quantified using tabletability plots, describing dependence of tablet tensile strength on compaction pressure. At the same compaction pressure, a higher tablet tensile

strength indicated better ability for the powder to be compressed into intact tablets. We could fully characterize compaction properties of a powder under a set of desired conditions using less than 6 g of material. If availability of a material is limited, one can conduct compaction studies using smaller toolings.

Powder Flow Properties Characterized by Ring Shear Cell

Flow properties of each powder were characterized using a ring shear cell (RST-XS, Dietmar Schulze, Wolfenbüttel, Germany) at pre-shear normal stresses of 1, 3, 9, or 15 kPa. Triplicate measurements were made at each pre-shear normal stress. The pre-shear step brought the powder to a steady state that was independent of history of the powder. Volume of the shear cell was approximately 10 mL. To prepare powders for testing, the cell was first over-filled. Excess powder was gently scraped off using a spatula to yield a flat powder surface in the plane defined by the top edges of the cell walls. Care was taken to avoid any compaction of the powder during the filling and scraping processes. This method was non-destructive and powder could be recovered at the end of each study. The shear cell data were used to construct flow function for each powder. A lower flow function line corresponds to better flow properties.

Granulation

Because of the limited amount of available API, we initially used a small food processor (MiniPrep, Cuisinart, East Windsor, NJ) to prepare wet granulation at 50 g scale for formulation screening. Water was added slowly while the powder was mixed until visually acceptable granules were resulted. Wet granules were dried in a static oven at 45°C until water content was <2.5%, determined by a loss on drying method. Dried granules were passed through a US standard sieve (# 30 mesh, 590 μ m). Sieved granules were blended with extragranular excipients in a bottle of suitable size using a Turbula shaker mixer (T2F, Glen Mills Inc., Clifton, NJ) before being compressed into tablets on a hydraulic press to supply tablets for dissolution and pharmacokinetic studies in animals.

Larger batches of granules, 250 g, of the lead formulation were prepared using a high shear

granulator (Diosna, Osnabrueck, Germany) with 1L bowl. The impeller speed was 400 rpm and chopper speed was 1500 rpm. Water was slowly added until visually acceptable granules were formed. Wet granules were dried in a convection oven at 45°C until water content was <2.5%, determined by loss on drying. Granules were passed through a comil (197S, Quadro Engineering Inc., Waterloo, OT, Canada) with a 040G screen at 1000 rpm impeller speed. The milled granules were blended with extragranular excipients in a 1 qt V-shaped blender (Patterson-Kelley, East Stroudsburg, PA) at 22 rpm for 10 min.

RESULTS AND DISCUSSION

Properties of Neat AMG458

We compared tableability of API to those of two common tablet excipients, Avicel PH102 and SD lactose. Tableability of the API was between those of SD lactose and Avicel PH102 (Fig. 1). Although tablet tensile strength was somehow more variable, AMG458 exhibited significantly better compaction properties than the SD lactose. We therefore did not expect significant problems in forming intact tablets at 50% level of API.

Flow properties of AMG458 were comparable to those of Avicel PH101, a common excipient exhibiting poor powder flow properties (Fig. 2). To develop a direct compression (DC) process, powder flow properties of blends containing 50% API needed to be significantly improved.

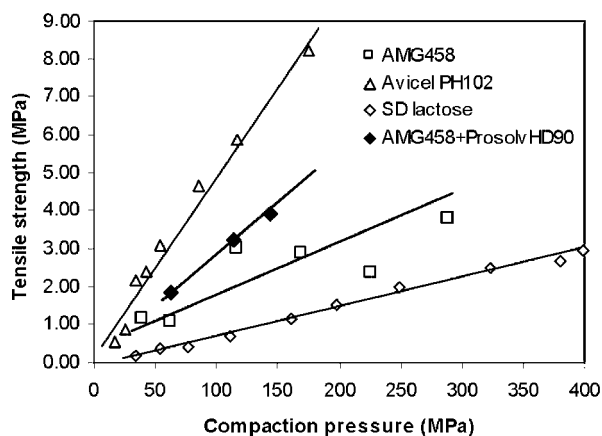


Figure 1. Compaction properties of AMG458 and its binary mixture with Prosolv HD90 compared to Avicel PH102 and SD lactose.

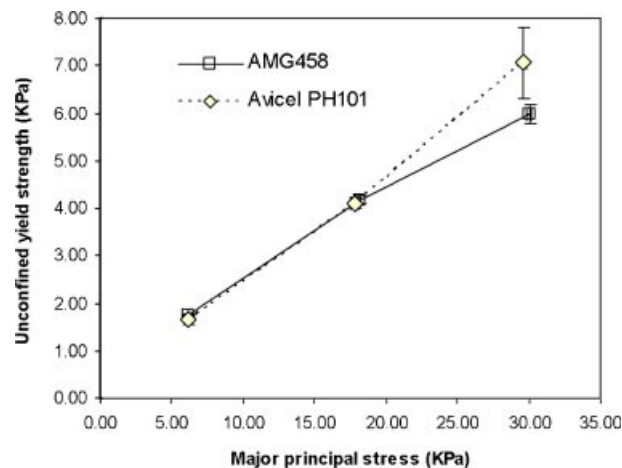


Figure 2. Flow properties of AMG458 and Avicel PH101 are nearly identical at below 20 kPa.

Properties of Simple Blends Containing AMG458

We prepared simple mixtures containing AMG458 and typical DC excipients to assess whether DC could be viable. The binary mixture between AMG458 (70 wt%) and ProSolv HD90 (30 wt%) exhibited flow properties comparable to those of the API (Fig. 3). Thus, adding 30% Prosolv HD90 did not improve powder flow properties. To improve flow properties, we prepared a mixture of AMG458 (50 wt%), Prosolv HD90 (25 wt%), and Emcompress (dibasic calcium phosphate, 25 wt%). The compositions were typical of a DC formulation. Flow properties were significantly improved over the pure API (Fig. 3). However, they were poorer than those of the Avicel PH102, a material exhibiting marginal flow properties on a typical

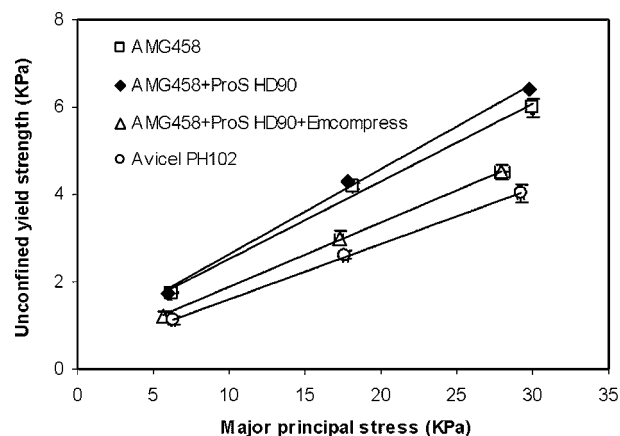


Figure 3. Flow functions of AMG458, its binary mixture with Prosolv HD90, its tertiary mixture with Prosolv HD90 and Emcompress, and Avicel PH102.

high speed tablet press (Fig. 3). There were also uncertainties with future API flow properties because of the optimization of synthetic processes.

Tabletability of the binary mixture was significantly better than that of the SD lactose and is close to that of the Avicel PH102 (Fig. 1). This asserted our early conclusion that 50% loading of AMG458 should generally not cause irresolvable problems in the tabletability of its mixtures with excipients.

To mitigate risks associated with the poor flow properties of API, we pursued granulation process. Due to a lack of suitable equipment, it was not possible for us to evaluate the process of dry granulation by roller compaction. We instead focused on the wet granulation (WG) process.

Properties of granule A

Exploratory studies based on *in vitro* dissolution studies of small batches (50 g batch size) of granulation suggested a lead formulation (Table 1).¹² A larger batch (125 g batch size) of the formulation, granule A, was prepared to explore the WG process using a granulator.

Flow properties of granule A were comparable to those of a placebo mixture containing 20% Avicel PH102, 79% SD lactose, and 1% magnesium stearate, hereafter referred as placebo A (Fig. 4). We anticipated no powder flow problem for granule A because of the excellent flow properties of placebo A.¹⁵

Despite the good flow properties, marginal tabletability of granule A rendered its overall manufacturability undesirable. Its tabletability plot is significantly below that of a mixture

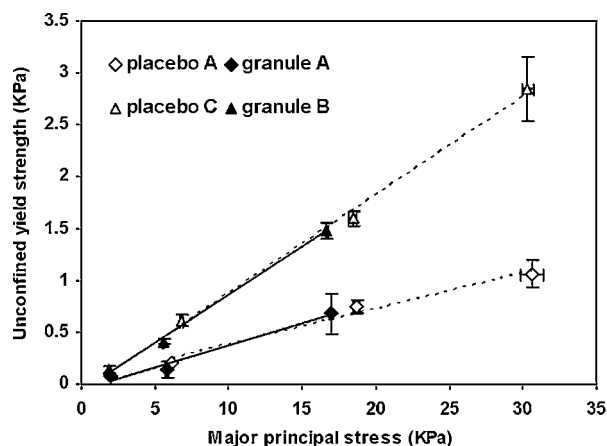


Figure 4. Flow functions of granule A, granule B, placebo A, and placebo C.

containing 59% Avicel PH102, 40% SD lactose, and 1% magnesium stearate, hereafter referred as placebo B (Fig. 5). Increasing compaction pressure would not be an effective means to improve tablet tensile strength because: (a) tensile strength had leveled off at >200 MPa (Fig. 5); (b) the maximum tablet tensile strength was lower than the minimum strength, 2 MPa, that was required for maintaining integrity of tablets when stressed during normal handling (Fig. 5).¹⁶ In search for other options to improve tabletability of granule A, we studied tabletability of two sieved fractions (<500 μm and >500 μm) of granule A. Tabletability of the finer fraction was only slightly better than that of the coarser fraction (Fig. 5). Particle size reduction was therefore also not an effective means in significantly improving tabletting properties of this material. We then focused on improving granule tabletability by changing

Table 1. Summary of AMG458 Formulation Compositions

Ingredients	Granule A (%)	Granule B (%)	Granule C (%)
Intra-granular			
AMG458	50	50	50
Microcrystalline cellulose (Avicel PH102)	16	23.5	23
HPMC K3 LV	4	4	4
Lactose 313 (impalpable)	—	15	—
Crospovidone	7	3	3
Tartaric acid	19	—	—
Extragranular			
Citric acid (anhydrate)	—	—	15
Crospovidone	3	3	3
Cab-o-sil	—	0.5	1
Magnesium stearate	1	1	1
Total	100	100	100

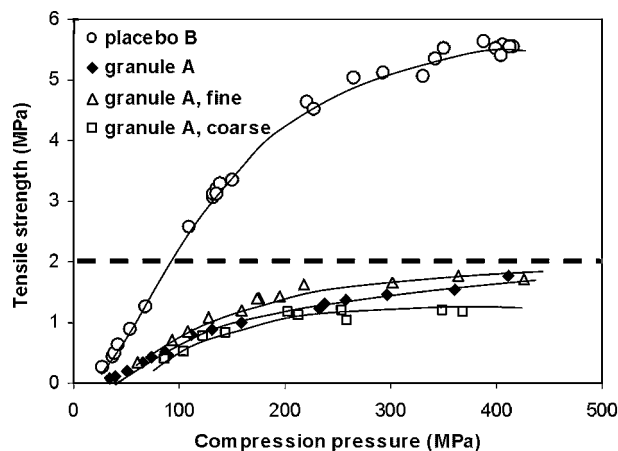


Figure 5. Tableability of *granule A* and its fine and coarse fractions in comparison to that of *placebo B*. The broken line indicates minimum tensile strength required for a tablet.

formulation compositions. Our assessment on both powder flow and compaction properties were verified by manufacturing tablets (100 mg tablet weight) using the same batch of granules on a rotary press. Tablet weight variation was small (RSD=0.5%, $n=10$) and tablet breaking force was low even at a very high compaction force during tableting.

Compaction Properties of Tartaric Acid

We investigated the origin of the poor tableting properties of *granule A*. This was a critical step towards a targeted reformulation effort for improved properties. Often, problems of this type were investigated by conducting an extensive design of experiment (DOE) study. The DOE approach would help identify sources of problems without mechanistic understanding of the nature of the problem. However, a reliable DOE required a significant amount of API and resources that were not available to us. We instead tested our hypothesis that the presence of 19% tartaric acid was causing poor tableability of *granule A*. Our hypothesis was based on the following considerations: (1) the combination of other excipients was commonly used in many other formulations at similar levels without causing tableability problems; (2) the drug exhibited good compaction properties.

The maximum tensile strength of pure tartaric acid (blended with 1% magnesium stearate) tablet was 0.15 MPa in the range of 50–400 MPa

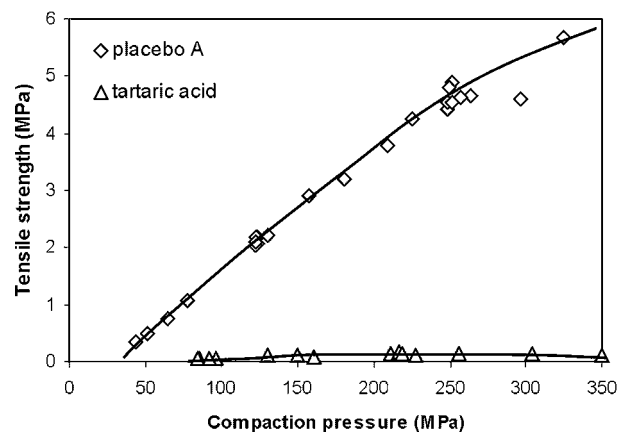


Figure 6. Tableability of the tartaric acid in comparison to *placebo A*.

compaction pressure. This was significantly below that of both *placebo A* and the minimum desired tensile strength of 2 MPa (Fig. 6). The results supported that tartaric acid was likely a source of the poor tableability of *granule A*.

Properties of *Granule B*

Once the likely origin of the poor tableting properties of *granule A* was identified, we prepared another batch of AMG458 granules, *granule B*, to confirm it (Table 1). The key change from *granule A* was the replacement of 19% tartaric acid by 15% lactose 313.

Tableability of *granule B* was significantly better than that of *granule A*, confirming our

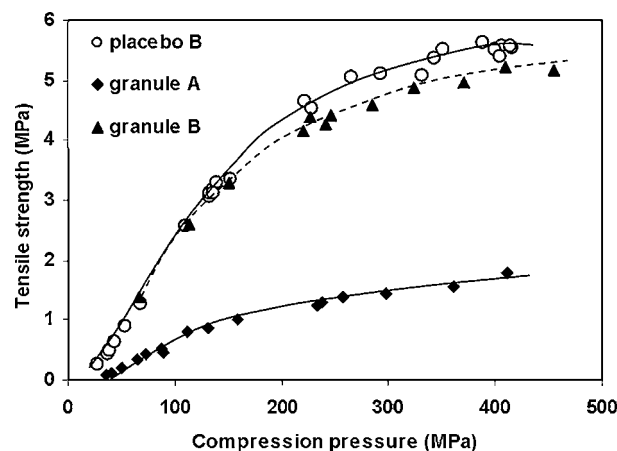


Figure 7. Tableability of *granule B* was significantly better than that of *granule A*. It is also very similar to that of *placebo B*.

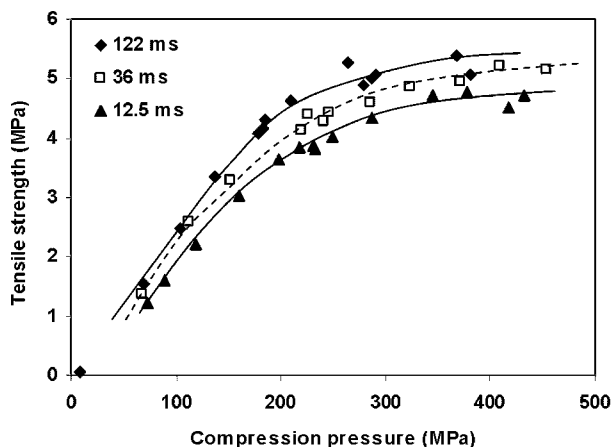


Figure 8. Compaction properties of *granule B* at three dwell times, 122, 36, and 12.5 ms

expectations. It was also nearly the same as that of *placebo B* (Fig. 7). At this point, we inquired about speed sensitivity of this formulation. We studied compaction properties at three dwell times, 122, 36, and 12.5 ms (Fig. 8). A ~ 10 -folds increase in tableting speed only resulted in less than 15% reduction in tablet tensile strength. Thus, tableability of granule containing 50% drug was robust against variations in tableting speed during manufacturing. Flow properties of *granule B* were nearly identical (Fig. 4) to those of a mixture containing 79% Avicel PH102, 20% SD lactose, and 1% magnesium stearate (*placebo C*).

Searching for Suitable Acids Using Surrogate Powder

Because organic acids were critical in maintaining acceptable dissolution and bioavailability of AMG458, we needed to identify an alternative organic acid with better mechanical properties for being used in the formulation.

Another commercially available acid with desired pK_a was citric acid, which was available as either monohydrate or anhydrate. However, limited availability of API excluded a direct comparative assessment on effects of either material in granules. Recall that *granule B* (containing no acid) exhibited almost identical compaction properties to those of *placebo B* (Fig. 7). We elected to use *placebo B* as a surrogate of *granule B* to predict potential effects of extragranular addition of citric acid on the tableability.

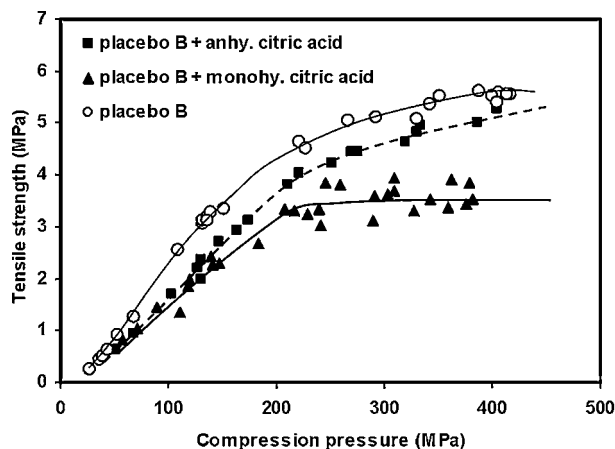


Figure 9. Tableability of surrogate blends containing citric acid monohydrate and anhydrate in comparison with that of *placebo B*.

We blended 19 wt% of either citric acid monohydrate or anhydrate with *placebo B* and tested flow properties and tableability of both blends. Flow properties of the blends containing citric acid monohydrate or anhydrate were both better than those of Avicel PH102 (data not shown). Thus, flow properties of both powders were acceptable. Below 220 MPa compaction pressure, tableability of the blend containing citric acid monohydrate was slightly lower (Fig. 9). Above 220 MPa, tableability curve of the blend containing citric acid monohydrate essentially leveled off while that of the blend containing citric acid anhydrate continued to rise with increasing pressure. Thus, incorporation of anhydrate citric acid in the formulation was more promising. The citric acid anhydrate could be added extragranularly without the need of prior particle size reduction. The particle size of commercially available citric acid monohydrate was large (>1 mm). Milling of the monohydrate would have been necessary to mitigate potential problem of segregation during handling and tableting. We suspect the higher variability in the tableability of the blend containing citric acid monohydrate (Fig. 9) may be caused by inhomogeneous distribution of the monohydrate. Moreover, a lower weight percentage of the anhydrate was needed to achieve the same impact on the local pH and because of the absence of water in its crystals.

Properties of *Granule C*

Following our learning from the surrogates, we prepared a new batch of AMG458 granules,

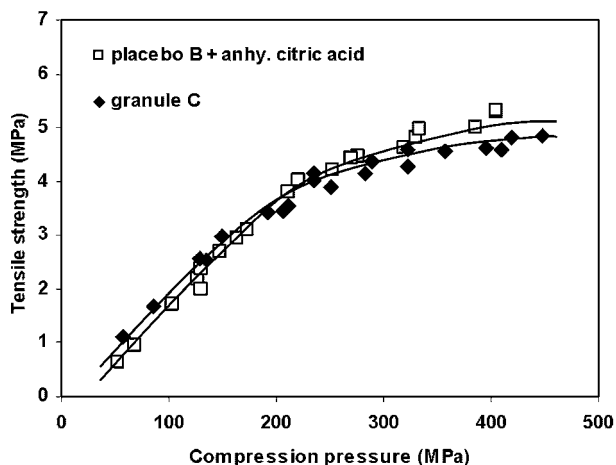


Figure 10. Tableability of *granule C* is nearly identical to that of the surrogate.

granule C (Table 1). The key change from *granule B* is the removal of 15% lactose 313 and extragranular addition of 15% citric acid anhydrate.

The tableability of *granule C* (containing 15% citric acid anhydrate) was excellent and was nearly identical to that of the surrogate powder (Fig. 10). As predicted by the surrogate studies, flow properties of *granule C* were acceptable (better than Avicel PH102, Fig. 11) for manufacturing tablets to supply clinical programs. A 1 kg batch of *granule C* was prepared and tablets were compressed on a rotary press. The tablet weight RSD was 0.43%. The breaking force of 15 kp could be easily achieved. Using the surrogate approach, we successfully overcame the deficiency in man-

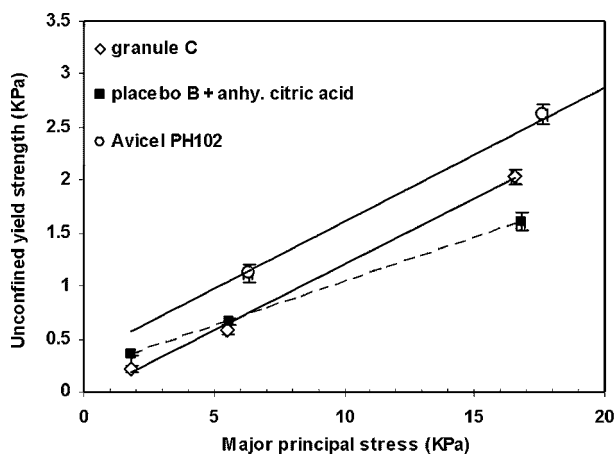


Figure 11. Flow properties of *granule C* were better than those of Avicel PH102 and similar to the surrogate.

ufacturability of the lead formulations without using any additional API.

CONCLUSIONS

Through careful characterization of flow and compaction properties of pure drug substance (AMG458), excipients, and granules, we successfully designed the tablet formulation containing a total of ~70% prefixed components (drug and organic acid) in a timely and drug-sparing manner. Based on a careful characterization of powder manufacturability, we demonstrated that surrogate placebo granules could be successfully used to guide formulation development when API was limited. We achieved significant saving in time, resources, and drug needed to develop this experimental compound. This case study demonstrates the fundamental advantage of targeted formulation development based on understanding powder manufacturability over the trial-and-error approach. Our success calls for attention to closer examination of API and excipients and seamless integration of material characterization into drug product development. Our experience also shows that results from shear cell and compaction simulator are predictive of powder manufacturability at realistic conditions.

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15. The assessment is made based on an in-house flow database where performance on a rotary press is correlated to powder flow function.
16. Based on in-house experience, we have found that the minimum tablet strength of 2 MPa is a useful criterion for tablets to exhibit acceptable friability.