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Application of a Compaction Simulator to the Design of a High-Dose Tablet Formulation. Part I

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ABSTRACT

The compaction properties of an investigational drug are studied by the use of a compaction simulator. The effects of punch velocity over the range of 30–640 mm^{-1} on the compaction properties of the pure drug and a variety of formulas incorporating a high dose of the active compound have been investigated. The data were analyzed by applying the Heckel equation. The pure drug was found to have a high yield pressure at a relatively low punch velocity of 31 mm^{-1}. As the punch velocity was increased there was a decrease in crushing strength, primarily as a result of increasing yield pressure. These findings indicate that the pure drug predominantly consolidated by fragmentation and elastic deformation, with a slow plastically deforming component. The information obtained on the consolidation mechanism of the pure drug and, subsequently, on model formulas were instrumental in the design and selection of a robust formula and granulation process. The advantages of conducting dosage form design and characterization studies during the early phase of tablet formulation using means such as a compaction simulator are emphasized in this investigation.

Key Words: Compaction mechanisms; Compaction simulator; Heckel analysis; Oral dosage form development; Yield pressure.

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INTRODUCTION

Instrumented single-station and multistation tablet presses have been commonly used to characterize the compression behavior of pharmaceutical excipients and active compounds. Although instrumentation of tablet machines has provided invaluable information on the physics of the tableting process, it is not always deemed practical at very early stages of development. The data generated on an instrumented single-station press cannot invariably be correlated with the production situation, and the use of instrumented multistation tablet presses is not possible due to the unavailability of large quantities of the active compound.

Earlier work by Heistand et al. (1977) on the die wall and punch presses in compression, decompression, and recompression cycles and Augsberger's studies (1977) of time dependency phenomena were instrumental in predicting capping propensity of material. A test was developed to assess what is known as brittle fracture propensity (BFP), which is calculated as a function of tensile strengths by performing a transverse compression test of a compact with and without a hole in it. Compacts with BFP values closer to 1 will have better chances of capping than those with values closer to zero. Although the Heistand theory is very useful in classification of pharmaceutical powders, it does not integrate the stress imparted on the compact upon compression and ejection from die wall or the effect of compression speed. The latter may be responsible for the capping even if the material has low BFP.

Compaction simulators have been used to evaluate the formulation and processing of tablets, capsules, and pharmaceutical powders in recent years (Rubinstein et al., 1991; Britten & Barnett, 1991; Marshall et al., 1993; Muller & Augsburger, 1994). Introduction of compaction simulators has facilitated extensive research into the time-dependent properties of pharmaceutical materials over wide ranges of operational variables using small quantities of compounds. These advanced instrumented presses provide a powerful tool to mimic the compressional cycles of a variety of single- or multistation tablet presses and to monitor many aspects of the tableting process. The major drawbacks associated with compaction simulators are cost and maintenance. Detailed descriptions of compaction simulators have been published elsewhere and are not discussed here (Celik & Marshall, 1989; Rubinstein, 1992; Jones et al., 1985; Anon., 1993).

In recent years, increased regulatory demands and cost containment have compelled the pharmaceutical industry to focus more intensely on the early stages of formulation development. There has been an increased emphasis on initiating phase I studies using a tablet form rather than a conventional capsule or a solution/suspension to eliminate the need for a bioequivalence study between the intended market tablet formulation and the capsule or solution/suspension form at a later stage. In addition, a tablet is frequently the dosage form preferred for marketing, and tablets can often be produced more easily than capsules in the large quantities needed for late-phase clinical trials. The advent of the compaction simulator has made it possible to develop robust tablet formulations for phase I studies with minimal drug usage.

In the present investigation the effects of punch velocity on the compaction properties of a bulk drug, and a variety of formulas incorporating a high dose of active compound have been studied using the compaction simulator at the Liverpool School of Pharmacy (John Moore's University, Liverpool, U.K.). Model formulas differed in one or a mixture of variables such as: granulation method, type of binder used, amount and nature of granulating solution, and/or inclusion of a superdisintegrant. Information gathered using the compaction simulator facilitated the design and selection of the optimum formula and granulation process. This study emphasizes the advantages of conducting dosage form design and characterization studies during the early design phase of tablet formulation using means such as a compaction simulator.

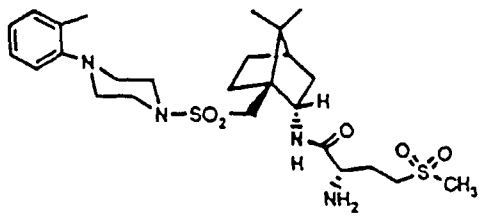
EXPERIMENTAL

Materials

Pure drug and several formulas containing a high proportion of the drug were used in the investigation.

The pure drug L-368,899, with the chemical name 1-[7,7-dimethyl-2-endo-(2*S*-amino-4-(methylsulfonyl)-butyramido) bicyclo(2,2,1) heptan-1-yl) methanesulfonyl]-4-(2-methylphenyl)-3-piperazine hemisulfate, is a salt of a primary amine (**a**). It is a crystalline, lumpy, white solid with molecular weight of 603.8 which melts at 255°–258°C. L-368,899 is extremely bulky and electrostatic with a small mean particle size, approximately 14–19 microns, and an erratic flow pattern. Microscopic examination of the bulk drug at 80× magnification indicated needle-shaped particles.

Two lots of pure drug were investigated in this study; lot I was prepared at laboratory scale, approximately 3.0 kg, and lot II at pilot scale, approximately 98 kg. The



L-368,899

a

physical properties of both lots are given in Table 1. Formulas I–III and IV were prepared using lots I and II, respectively.

The following materials were used as received from the suppliers: croscarmellose sodium (Ac-Di-Sol, F.M.C. Corporation, Newark, DE), magnesium stearate (Mallinkrodt, Saint Louis, MO), microcrystalline cellulose (Avicel PH 101, F.M.C. Corporation, Newark, DE), polyvinyl pyrrolidone (PVP 29/32, TSP Technologies, Wayne, NJ), and starch pregelatinized (Starch 1500, Colorcon Corporation, West Point, PA).

Since the final tablet contained approximately 77% active compound, it was decided to pursue a wet granulation approach for developing a tablet formulation. This process theoretically results in the particle size increase necessary to enhance the flow and compaction properties of the powders. The compositions of the formulas studied using the compaction simulator are given in Table 2.

Equipment

The compaction simulator at the Liverpool School of Pharmacy was used to produce compacts of the pure drug and various formulas. The High-Speed Compaction Simulator (E.S.H. Testing Ltd., Brierly Hill, West Midlands, U.K.) consists of a load frame for powder compression, an electric motor supplying hydraulic fluid at 4000 psi to the load frame, and an electronic console for data processing. Tablet dimensions and crushing strength were measured using a Mitutoya digital micrometer (Japan) and a Copley hardness tester (model 2E/205, Nottingham, U.K.), respectively. A Beckmann air compression pycnometer (model 930, Fullerton, USA) was used to evaluate the true volume of the materials.

Methods

To carry out the tableting process round, flat-face tooling of 7.11 mm diameter was used. Prior to compression of the pure drug, the tooling surfaces were cleaned with acetone and subsequently lubricated with

Table 1

Physical Properties of the Two Lots of the Pure Drug

Lot No.	Bulk Density (g/ml)	Tapped Density (g/ml)	Particle size (μm)
I	0.14	0.30	14.1 (95% < 32.3)
II	0.14	0.27	19.0 (95% < 41)

Table 2

Composition of Investigated Formulas (%)

Formula No.	Pure Drug	Avicel	Starch Pregel.	Magnesium Stearate	PVP 29/32	Croscarmellose Sodium	Granulating Solution (w/w)
I	76.70	11.15	11.15	1.0			30% of 25 ethanol/water mix.
II	76.70	11.15	11.15	1.0			30% pure water
III	76.70	10.15	10.15	1.0	2.0		30% of pure water[a]
IV	76.70	8.65	8.65	1.0	2.0	3	60% of pure water[a]

[a]PVP 29/32 was dissolved in the water prior to granulation process.

a suspension of 4% w/v magnesium stearate in acetone. A thin coating of lubricant covered the surfaces of the punches and die following evaporation of the acetone. Compacts of approximately 75 mg weight were produced by manually transferring the powder into the die cavity. This technique was used to prevent compact weight variation due to the poor flow characteristics of the bulk drug. Formulas I–IV were compressed using a 7.66 × 18.38 mm capsule shape and standard concave tooling. Compacts of approximately 850 mg weight were produced on nonlubricated tooling since Formulas I–IV contained lubricating agents.

The upper and lower punches of the simulator were controlled by a simple saw-tooth displacement/time profile and monitored by linear variable differential transducers (LVDTs) to an accuracy of ±2.4 μm. Punches exerted a maximum force of approximately 5 kN and 10 kN to compress formulas I–IV and pure drug, respectively. A series of compression speeds ranging from 30 to 720 m $msec^{-1}$ were used to compress the material, ad at least four tablets were produced at each speed. Tablet weight, axial and radial dimensions, and crushing strength were determined at each compression speed.

The true densities of the compacts were calculated following determination of the powder's true volume using an air comparison pycnometer. The data were analyzed by applying the widely used Heckel equation (Heckel, 1961) relating the relative density, D, of material to the compression pressure P:

$$\ln\left[\frac{1}{1-D}\right] = KP + A$$

The constant K is the reciprocal of the mean yield pressure, determined on the linear section of the Heckel plot. Constant A is the value of the intercept.

Strain rate sensitivity was calculated using the following equation (Roberts & Rowe, 1985):

$$SRS = \frac{P_{y2} - P_{y1}}{P_{y2}} \times 100$$

where P_{y1} and P_{y2} are the yield pressures at the lowest and highest compression speeds, respectively.

RESULTS AND DISCUSSION

Bulk Drug

The pure drug compacts (lot I,) were prepared at various compression speeds. A list of tablet weights, axial and radial dimensions and crushing strengths is given in Table 3. Tablet crushing strength decreased as the compression speed increased, since there was an increased tendency of the tablets to cap at compression speeds of 200 m $msec^{-1}$ and above (Fig. 1).

The true density of the pure drug (lot I) was 1.765 ± 0.05 g/cc. The Heckel plot was linear at pressures, range 20–120 MPa, which were used to determine the gradient by linear regression analysis. The calculated mean yield pressures of the pure drug at different compression speeds accompanied by their corresponding correlation coefficients are listed in Table 4. At compression speeds between approximately 31 and 362 m $msec^{-1}$, mean yield pressures of 240.5–575.6 MPa were obtained (Fig. 2), which are relatively high in comparison to those of a number of excipients and/or active compounds reported in the literature. Some examples of plastically deforming materials with yield pressures of 40–135 MPa are microcrystalline cellulose, maize starch, sodium chloride, starch 1500, and acetylsalicylic acid (Roberts & Rowe, 1986, 1987; Lloyd et al., 1992). Lactose monohydrate and dicalcium phosphate dihydrate, which consolidate mainly by fragmentation, have higher yield pressure values ranging from 177 to 297 MPa (Pedersen & Kristensen, 1994).

Table 3

Physical Properties of Compacts of the Bulk Drug L-368,899 at Different Compression Speeds (± SD).

Compression Speed (m $msec^{-1}$)	Tablet Weight (mg)	Tablet Axial Dimension (mm)	Tablet Radial Dimension (mm)	Tablet Breaking Strength (kP)
30.73 ± 0.65	75.25 ± 0.10	1.539 ± 0.010	7.138 ± 0.001	10.22 ± 1.96
125.76 ± 5.81	75.47 ± 0.50	1.563 ± 0.007	7.135 ± 0.001	9.63 ± 0.78
238.26 ± 2.12	75.30 ± 0.82	1.606 ± 0.008	7.135 ± 0.001	4.29 ± 0.89
362.11 ± 17.5	75.50 ± 0.14	1.638 ± 0.008	7.135 ± 0.002	3.09 ± 1.27
639.84 ± 21.1	75.20 ± 0.20	1.672 ± 0.010	7.135 ± 0.002	0.50 ± 0.25

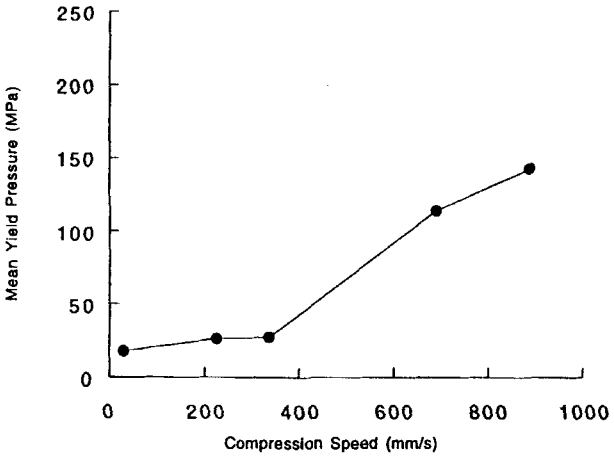


Figure 1. Mean yield pressure vs. compression speed of formula IV.

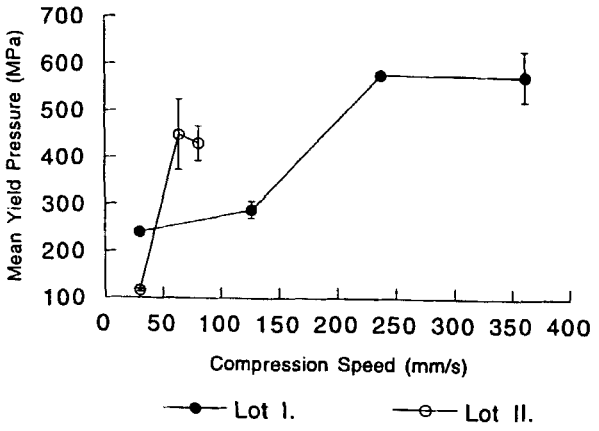


Figure 2. Mean yield pressure vs. compression speed of pure drug.

Materials which consolidate by brittle fracture display high yield pressures independent of punch velocity (Roberts & Rowe, 1985; Rees & Rue, 1978). In contrast, plastically deforming powders produce higher yield pressures as the punch velocity increases, indicating the time-dependent nature of the plastic flow. The pure drug was found to have a high yield pressure at a relatively low punch velocity of 31 m $msec^{-1}$, but the yield pressure increased with punch velocity (Fig. 2). The former suggests that the bulk drug consolidates predominantly by fragmentation while the later implicates a plastically deforming component.

Roberts and Rowe (1985, 1987) reported that materials which deform plastically are more strain rate sensitive (SRS). Strain rate sensitivity increases as the plastic deformation becomes the more dominant mechanism during the compaction process. Materials such as dicalcium phosphate and calcium carbonate (Roberts & Rowe, 1987) which compact by brittle fracture have high yield pressures independent of the strain rate. An SRS value of 58% was obtained for the pure drug (lot I) calculated using the mean yield pressures at compression speeds of 31 and 362 m $msec^{-1}$. This value was more in line with the strain rate sensitivity of materials that behave plastically under load. For example, SRS values of 46.4%, 49.3%, and 54.1% are reported for plastically deforming mannitol, maize starch, and Corvic R46/88 (copolymer: 85% vinyl chloride, 15% vinyl acetate), respectively (Roberts & Rowe, 1985).

Although pure drugs may undergo some plastic deformation during compression, the sharp decrease in crushing strength with compression speed indicated that the slow rate of plastic flow rendered bonding inadequate during high speed compression. Rees and Rue (1978) indicated that the low strength of Sta-Rx tablets was partly due to slow plastic deformation. Sta-Rx pro-

Table 4

Mean Yield Pressure of the Bulk Drug L-368,899 (Laboratory Scale) at Different Compression Speeds (± SD).

Compression Speed (m $msec^{-1}$)	Mean Yield Pressure (MPa)	Correlation Coefficient (%)
30.73 ± 0.65	240.54 ± 6.9	99.68 ± 0.17
125.76 ± 5.81	288.47 ± 17.9	99.78 ± 0.15
238.26 ± 2.12	576.40 ± 2.34	99.70 ± 0.35
362.11 ± 17.5	575.57 ± 53.6	99.9 ± 0.0
639.84 ± 21.1	—	—

duced relatively slow initial relaxation, suggesting that the consolidation of the excipient may be extremely time dependent. In addition, the excessive capping following compression of the L-368,899 drug may be indicative of a high elastic recovery upon removal of the axial pressure.

The low bulk density of the pure drug (0.14 g/ml) indicates that there must be a large amount of air entrapped between the particles. At the lower compression speed the entrapped air would have had more time to escape and this may have led to formation of better-consolidated tablets. The bulk volume reduction in this case may well have resulted from both the removal of the large volume of entrapped air and brittle fracture (i.e., high yield pressure at low speed). From compaction data at low velocity alone it is not possible to decide if there is an element of plastic deformation also. As the compression speed increased, the time for the entrapped air to escape decreased. Examination of the yield pressure data at increasing speed would lead one to assume that there was indeed a plastically deforming component to the compaction process, since yield pressure increases with speed. Additionally, since the compact tensile strength decreases with increasing compaction speed, at a constant pressure, one might also conclude that there was an element of elastic recovery. This is supported by the work of Carless and Leigh (1974), who showed that the capping of paracetamol tablets during ejection was due to the high elastic recovery responsible for the breakage of interparticulate bonds. Equally, one might evoke the argument that the shorter time for air removal from the powder sample at higher compression speeds leads to the apparently increased yield pressure.

Whichever is the correct interpretation, the conclusion is the same. Since the high yield pressure at low compaction speed (31 m $msec^{-1}$) indicates that the pure drug consolidates predominantly by fragmentation and that there is a considerable dependency of crushing strength on compaction speed, the conclusion is that to produce robust tablets, over the entire compression speed range, with sufficient strength to withstand the film-coating process (to mask the bitter taste of the active compound), the formula should include plastically deforming excipients which do not display elastic recovery. This led to the selection of microcrystalline cellulose and pregelatinized starch excipients. A further objective of the formulation design process was to increase the bulk density of the powder to minimize air entrapment and again offset the effect of high compression speeds, reducing tablet strength.

To assess the physical properties of the pure drug manufactured at a larger, pilot scale (98 kg), compacts were prepared at various compression speeds. The true density of the pure drug, 1.550 g/cc, was slightly lower than that of lot I (laboratory scale, 3.0 kg). The calculated mean yield pressures of the pure drug (lot II) at different compression speeds accompanied by tablet crushing strength are given in Table 5. At a compression speed of 127 m $msec^{-1}$, all tablets capped (Fig. 1), indicating that robust compacts of drug alone cannot be produced even on a single-punch press with a relatively low compression speed (120 m $msec^{-1}$). The mean yield pressure values obtained for the pilot-scale lot were significantly different than those of the laboratory scale lot (see Tables 4 and 5, and Fig. 2). The results above suggested that the physical properties of the pure drug were subject to significant changes as the batch size increased from laboratory to pilot scale. These changes are unlikely to be accounted for by the small differences in particle size. Because of the physical properties of both laboratory and pilot-scale drug batches (particularly the poor flow properties and low bulk density), tablet formulations were prepared by a wet granulation process.

Table 5

Mean Yield Pressure and Crushing Strength of the Bulk Drug L-368,899 (Pilot Scale) at Different Compression Speeds (± SD)

Compression Speed (m $msec^{-1}$)	Mean Yield Pressure (MPa)	Crushing Strength (kP)
30	115.75 ± 2.63	11.48 ± 0.79
64	448.9 ± 75.5	9.97 ± 1.69
81	430.0 ± 37.0	9.29 ± 1.09
127	159.44 ± 12.71	All tablets capped

Formulations

To evaluate the effect of different granulation solutions on the physical properties of L-368,899, 600 mg dose (free base equivalent) tablets, formulas I and II (see Table 2) were prepared using 25% ethanol/75% water and 100% water as granulating solution, respectively, using a pestle and mortar process. Using a Laboratory Carver Press both formulas produced tablets (850 mg in weight) of comparable and satisfactory crushing strength and disintegration time. Samples of both formulas were used to evaluate their compressional properties on the compaction simulator.

Tablet crushing strength profiles of the pure drug, formula I and formula II are given in Fig. 3. Both formulas had an improved tablet crushing strength profile, with compression speed having little effect on crushing strength, unlike the behavior of the pure drug. There was no statistical difference between formula I and II. The solubility of the hemisulfate salt of L-368,899 in ethanol and water is 0.12 and 3.9 mg/ml, respectively (expressed as free base equivalent). Using pure water as granulating solution may have enhanced the dissolution of the pure drug during granulation; however, the minimal amount of drug that might have dissolved was probably not sufficient to effect tablet crushing strength. As no differences in granulation characteristics were observed when using the hydroalchoholic solution, it was decided that pure water should be selected as the granulating solution.

Despite the improved compression speed–tablet strength profile, it was noted that there was still a tendency for tablets produced using formulas I and II to cap at compression speeds higher than that of a single-station tablet press (120 m $msec^{-1}$). The granules produced from formulas I and II were still very fine (< 100 μm mean particle size) with comparatively poor flow properties. This observation led to the inclusion of the plastically deforming binder PVP (povidone) 29/32 in formula III to further improve the mechanical strength of the tablets, increase granule particle size, and improve flow properties. It has been previously shown that at a given applied pressure, tablets of Encompress and Fast-flo lactose improve in tensile strength following incorporation of povidone or starch (Hwang & Parrott, 1993). Greater tablet tensile strength was achieved at binder concentrations higher than 1%. In the present study 2% PVP 29/32 was used to achieve satisfactory tablet hardness and increased granule size. However, although the tablet crushing strength profile at different compression speeds improved to a satisfactory level (Fig. 3) following inclusion of PVP 29/32, tablet disintegration time increased 20-fold (from less than 1.0 min to approximately 26 min). This prompted inclusion of croscarmellose sodium, a plastically deforming superdisintegrant, extragranularly, in formula IV, which produced disintegration times 10-fold lower (2.0 min) than that of formula III and an excellent dissolution profile. Formula IV was manufactured at a larger scale (2.2 kg) than the other formulas using a high-shear granulation process. Additionally, this formula was granulated using a level of granulation solution 2-fold higher than the other formulas to produce larger, more cohesive granules with better flow properties. The use of a higher volume of granulating solution led to the formation of denser granules with an improved bulk density (0.55 g/ml), which led to less entrapment of air during compression.

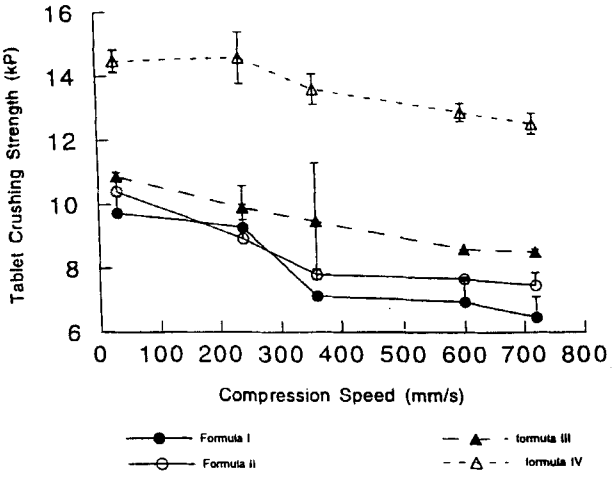


Figure 3. Tablet crushing strength vs. compression speed of formulas I–IV.

Formula IV produced the best tablet crushing strength, ranging from 14.9 to 12.5 kP with only 16% variation between the lowest and the highest compression speeds. The mean yield pressure of 17.76 MPa was obtained at the compression speed of 31 m $msec^{-1}$, which was at least an order of magnitude lower than that of the pure drug (240.5 MPa) and more comparable to that of pregelatinized starch and microcrystalline cellulose. As the punch velocity increased, formula IV produced higher yield pressures, indicating that the formulation consolidated by time-dependent plastic deformation (Fig. 4). An SRS value of 87.6% was obtained for formula IV using the mean yield pressures at compression speeds of 31 m $msec^{-1}$ and 886 m $msec^{-1}$. This high value was also similar to the strain

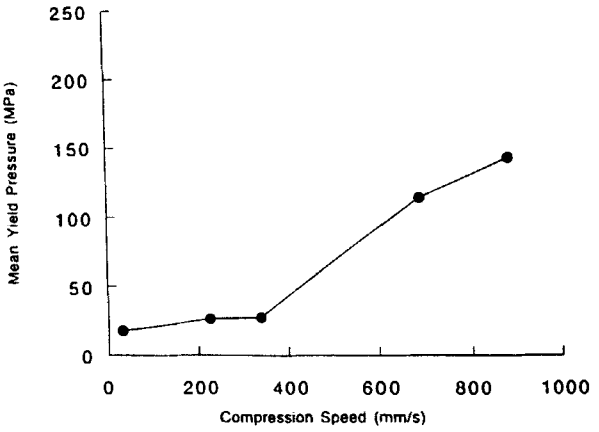


Figure 4. Mean yield pressure vs. compression speed of formula IV.

rate sensitivity of materials such as pregelatinized starch and microcrystalline cellulose that behave plastically under load. Based on these data, the final formula is predicted to scale up and transfer satisfactorily from a single-punch tablet press to a high-speed rotary press without the deleterious effects seen with the pure drug and the other formulas.

CONCLUSION

In conclusion, the compaction simulator was instrumental in the design of a robust formula at an early stage of dosage form development when only a few grams of drug were available from the laboratory-scale batch. Critical insights into the basic compaction mechanism were obtained and it was shown that the scale of manufacture of the bulk drug significantly affected its compaction behavior. The impact of formulation variables on the tablet quality was investigated in a relatively short period of time prior to initiation of phase I clinical studies, which led to the use of an optimal tablet formulation in these studies. The next step of the investigation is to conduct a statistical characterization of the granulation process at the laboratory scale to examine the effect of granulation fluid level, granulation time, and lubrication time on granule particle size, tableting behavior, and dissolution. The data so gathered will provide invaluable information on likely behavior of the formula under production conditions and, consequently, early identification and remedy of potential manufacturing problems. These data will be the subject of a second publication. Finally, there is a high possibility that if the 600-mg dose is ultimately selected for marketing purposes, no bioequivalence studies will be required during the clinical program, as formulation changes and significant process changes will have been obviated.

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