Evaluation of the Effects of Tableting Speed on the Relationships between Compaction Pressure, Tablet Tensile Strength, and Tablet Solid Fraction

CHING KIM TYE, CHANGQUAN (CALVIN) SUN, GREGORY E. AMIDON

Pfizer Global Research and Development, 7000 Portage Road, Kalamazoo, Michigan 49001

Received 24 March 2004; revised 16 July 2004; accepted 13 September 2004

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.20262

ABSTRACT: It is well known that compression speed can have significant effects on the compaction properties of pharmaceutical powders. This is a challenge during scale up and technology transfer when tableting speeds are significantly increased. This study examined the effects of tableting speed on the compressibility (solid fraction vs. compaction pressure), tabletability (tensile strength vs. compaction pressure), and compactibility (tensile strength vs. solid fraction) of four common direct compression excipients and a placebo formulation. The tabletability and compressibility of some of these materials were observed to be speed dependent whereas the compactibility of all materials tested was essentially independent of tableting speed. It is therefore proposed that the compactibility profile (tensile strength vs. solid fraction) is a predictor that is independent of tableting speed and can be used to predict tablet strength during formulation development and scale up. © 2004 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 94:465–472, 2005

Keywords: compaction; compression; excipients; mechanical properties; tableting; solid fraction; speed; tabletability; compactibility; compressibility

INTRODUCTION

The consolidation of powders into tablets is a process of reducing pores in a powder bed while creating interparticulate bonds. During compression, materials experience complex stresses. The structure of the powder bed changes and consolidation is brought about mainly by particle rearrangement, plastic deformation, and fragmentation.

The deformation of pharmaceutical materials has been recognized to be time dependent and researchers have found that the time dependency is related to a consolidation mechanism.[1–8] Under compression, brittle materials consolidate predominantly by fragmentation whereas plastic materials deform by plastic flow. It is believed that time dependency arises from stress relaxation after compaction for materials undergoing primarily plastic deformation. However, compaction of brittle materials is less speed dependent because fragmentation is rapidly achieved and prolonged exposure to the force has a more limited effect on tablet properties. Particle size has also been found to have an important part in the speed dependency of materials. This is because the predominant deformation mechanism under compression may change with particle size. Transition of brittle/ductile behavior with the change of particle size of several pharmaceutical materials has been observed.[9]

Several researchers have previously identified the utility of solid fraction in describing tablet properties. Armstrong and Palfrey[7] suggested that differences in tablet tensile strength due to tableting speed could be accounted for by porosity

Correspondence to: Ching Kim Tye (Telephone: 269-833-8100; Fax: 269-833-7290; E-mail: kim.tye@pfizer.com)

Journal of Pharmaceutical Sciences, Vol. 94, 465–472 (2005)

changes. Hancock et al.[10] found that the tablet strength and disintegration time for tablets made on an eccentric press and a rotary press were comparable when considering a comparable solid fraction. Maarschalk et al.[4] found that tensile strength as a function of tablet porosity for sorbitol was independent of compression speed.

The relationships among compaction pressure, tensile strength, and solid fraction are critical to understanding and characterizing the compaction process. The faces of the three-dimensional plot shown in Figure 1 reflect the relationship among tabletability (tensile strength and compression pressure), compressibility (compaction pressure and solid fraction or porosity), and compactibility (tensile strength and solid fraction).[11,12] The concept is also illustrated in Figure 2. The solid arrows in Figure 2 represent direct cause–effect relationships whereas the dotted arrow represents a more indirect relationship between the parameters. For example, the solid fraction of a compact is the direct result of the application of compression pressure. Similarly, the tensile strength of a compact is the direct result of its solid fraction. However, the relationship between compaction pressure and the resulting tensile strength is more indirect.

The aim of this study was to assess the hypothesis that the compactibility (tensile strength vs. solid fraction) of a powder is independent of tableting speed and, therefore, solid fraction

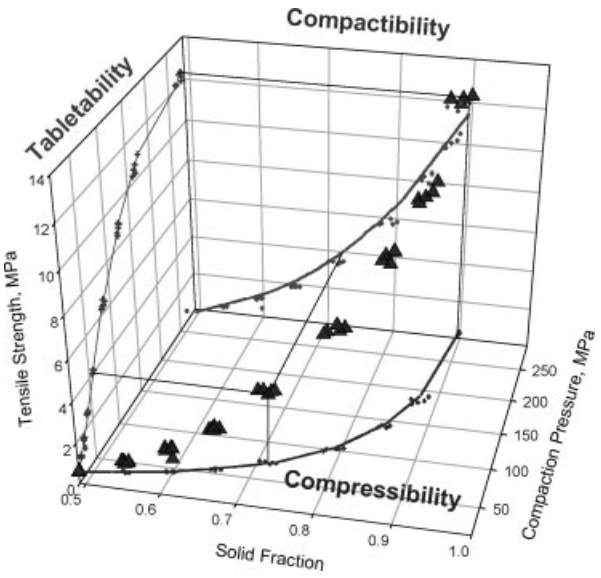

Figure 1. Three-dimensional illustration of the relationships among compaction pressure, tensile strength, and solid fraction for a hypothetical material.

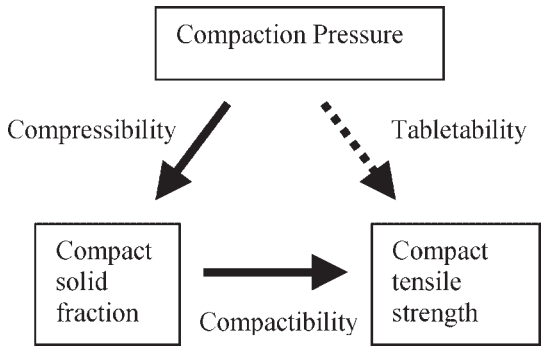

Figure 2. An illustration to show the relationships among compaction pressure, solid fraction, and tensile strength for a given powder.

can be used to predict the tensile strength of tablets prepared over a broad range of tableting speeds.

EXPERIMENTAL

The tableting behavior of four common tableting excipients—microcrystalline cellulose (MCC) (Avicel PH102, FMC, PA), pre-gelatinized starch (1500G, Colorcon, PA), lactose monohydrate (spray process, standard NF; Foremost Farms, WI), and dibasic calcium phosphate dihydrate (dicalcium phosphate) (Rhodia, NJ)—were studied. These excipients were chosen because they represented a range of materials with different mechanical properties. In response to compaction pressure, MCC is considered a ductile material,[1] lactose and dicalcium phosphate are considered brittle,[13,14] and pre-gelatinized starch is considered viscoelastic.[2,15] A simple direct compression formulation consisting of 64.5% lactose and 35.5% MCC (placebo mixture) was also studied. Each powder system was prepared by adding 0.5% w/w magnesium stearate (USP, Mallinckrodt, NJ) as a lubricant to powder and blended for 2 min at 22 rpm (Patterson-Kelley Twinshell, batch size = 500 g). The true density of each powder system was measured by helium pycnometry (AccuPyc 1330; Micromeritics Instrument Corp., Norcross, GA) in triplicate using fresh samples each time.

Tablet weights were adjusted for each material so that acceptable tablet thicknesses of 2.3–4.6 mm were obtained over the range of compaction pressure tested. Tablets were produced at four different dwell times of 8.1 ms, 27 ms, 20 s, and 90 s under pressures ranging from approximately 30 to 300 MPa. Tablets compressed at dwell times of

20 s and 90 s were produced on a hydraulic press (Autoseries 3888; Carver Inc., IN). Tablets compressed at dwell times of 8 ms and 27 ms were produced on a compaction emulator (Presster; Metropolitan Computing Corp., NJ) simulating a Kilian RTS 16-station tablet press at 100 and 30 rpm respectively using a gravity feed hopper. The compression roller diameter was 25.4 cm. No precompression was used. The graphic representation of the compression profile of the hydraulic press and the compaction emulator are shown in Figure 3. Dwell time for the hydraulic press is defined as the length of time the peak pressure was kept constant and dwell time of the compaction emulator is defined as the time when the flat portion of punch head is in contact with the compaction roll.

MCC and lactose tablets were compressed using punches of 9.57-mm diameter, flat-faced with bevel edges when 20- and 90-s dwell times were used. Correction for tablet volume was performed to account for the bevel edges for these tablets. All other tablets were produced using 10.0-mm diameter, flat-faced, round tooling. Tablets were produced at pressures ranging from approximately 30 to 300 MPa. Five tablets were tested for 8.1- and 27-ms dwell time conditions whereas three tablets were tested for 20- and 90-s dwell time conditions.

The thickness and diameter of freshly produced tablets were measured by an electronic caliper (±0.01 mm, 721B-6/150; Starrett, Athol, MA) and the weight was recorded (±0.1 mg; Mettler AE100, PA) immediately after compression. Tablet crushing strength was then measured on a conventional tablet hardness tester (Tablet Tester 6D; Schleuniger Pharmatron Inc., Manchester, NH) within 1 min after tablets were compressed.

Breaking force (F) or crushing strength is a measure of the load at which the tablet breaks under diametrical compression between two flat platens[16]; tensile strength is a fundamental measurement of the resistance to fracture.[17] Breaking force can be converted into a tensile strength value, σ, using eq. 1.

$$\sigma = \frac{2F}{\pi dh} \tag{1}$$

where d is the diameter of the tablet, and h is the tablet thickness. Equation 1 is only applicable to round flat-faced tablets[18] when tablets fail in tension (indicated by splitting cleanly into halves under diametral compression). Only tablets that failed in tension were used.[16]

The compaction pressure was calculated from the applied force and the cross-sectional area of the punch. The solid fraction (SF) and porosity (ε) were calculated based on the true density (ρ_{true}), tablet volume (ν), and tablet weight (Wt) as below:

$$SF = \frac{Wt}{\rho_{true} \cdot \nu} \tag{2}$$

SF is sometimes called relative density. The relationship between SF and ε is shown in eq. 3.

$$\varepsilon = 1 - SF \tag{3}$$

RESULTS AND DISCUSSION

The tabletability profiles, compressibility profiles, and compactibility profiles of the four excipients and placebo formulation are shown in Figures 4–14.

Tabletability is the capacity of a powder to be transformed into a tablet of specified strength under the effect of compaction pressure.[11] It is represented by a plot of tensile strength versus

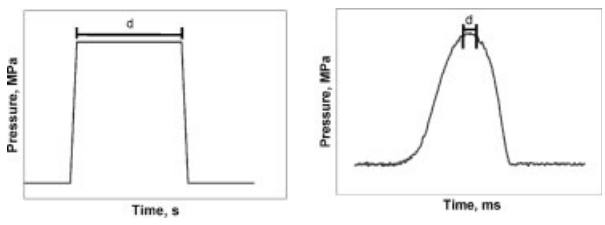

Figure 3. Representative illustrations of compression profiles of hydraulic press (Carver Press) and compaction emulator (Presster). d = dwell time.

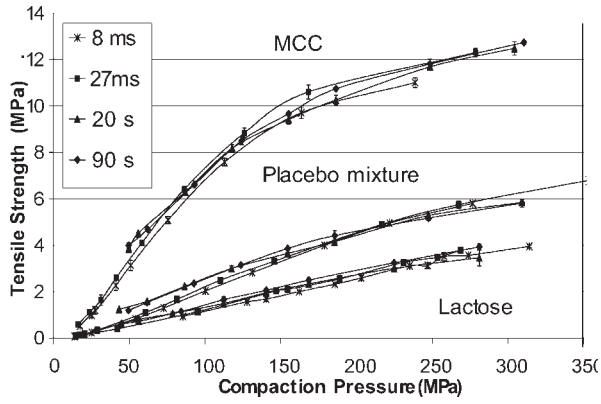

Figure 4. Tabletability profiles of MCC, lactose, and placebo mixture at four tableting speeds (dwell time = 8 ms, 27 ms, 20 s, and 90 s).

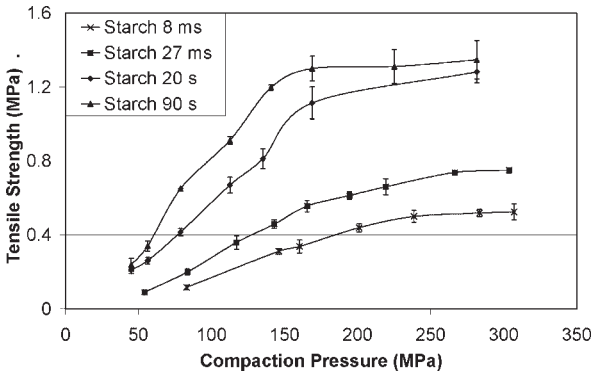

Figure 5. Tabletability profiles of pre-gelatinized starch at four tableting speeds (dwell time = 8 ms, 27 ms, 20 s, and 90 s).

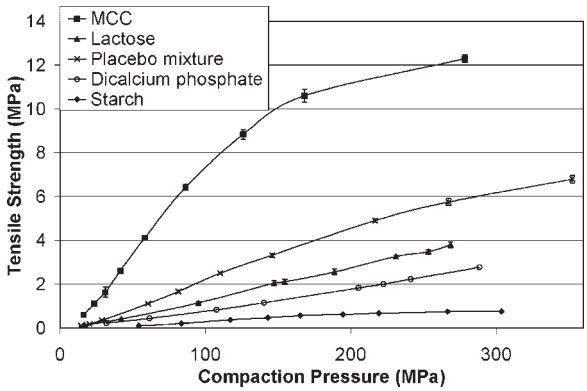

Figure 7. Tabletability profiles of MCC, lactose, pregelatinized starch, dicalcium phosphate, and placebo mixture at compression dwell time of 27 ms.

compaction pressure. Tabletability describes the effectiveness of the applied pressure in increasing the tensile strength of the tablet and demonstrates the relationship between the cause, the compaction pressure, and the effect, the strength of the compact. Normally, a higher compaction pressure makes a stronger tablet. However, this relationship is often found to be speed dependent. Also, at high pressures, some materials may have lower tensile strength because of overcompaction.[8] Characterization of the tabletability provides excellent insight into the compaction process and mechanical properties of a material.

The tabletability profiles of MCC, lactose, pregelatinized starch, dicalcium phosphate, and placebo mixture are shown in Figures 4–6. In Figure 4, it is observed that the tensile strength of MCC tablets produced at the same compaction pressure are not significantly different at any of the four different dwell times (8 ms, 27 ms, 20 s, and 90 s) studied. These results indicate that the compaction behavior of this MCC is largely independent of compression speed. As a plastic material, the compaction of MCC has been found to be speed dependent by some researchers[2,7]; however, others have found some MCC materials to be non-speed dependent.[5,8] The findings of this study agree with the latter. Ishino et al.,[5] for example, found that although MCC of 180–250 μm particle size demonstrated speed dependency, this rate dependency was reduced as the particle size decreased. Unsieved MCC was also found to be unaffected by compression speed.[5]

Figure 4 also shows the tabletability profiles for lactose and the placebo mixture. The figure shows that only a minor, if any, speed effect is observed for tablets of lactose. These results agree with the reported work of others.[1,2,7] The lack of speed dependency of lactose may be attributed to its mainly brittle properties.[13,14] Fragmentation is

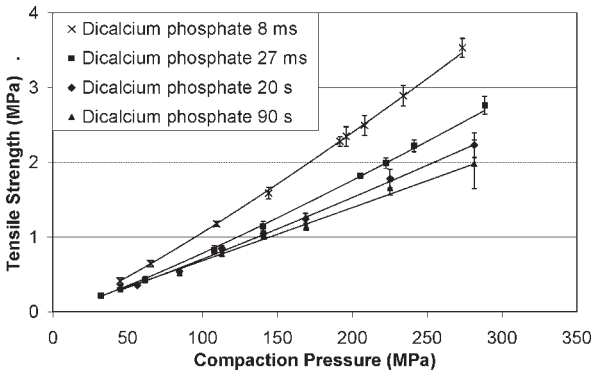

Figure 6. Tabletability profiles of dicalcium phosphate at four tableting speeds (dwell time = 8 ms, 27 ms, 20 s, and 90 s).

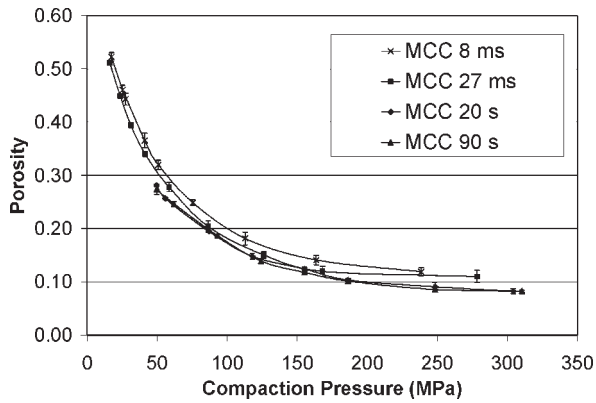

Figure 8. Compressibility profiles for MCC at different tableting speeds (dwell time).

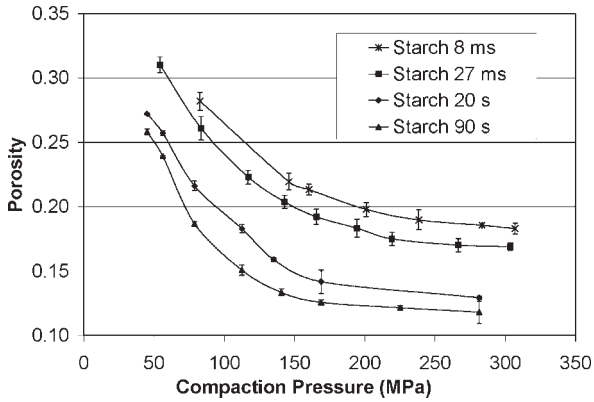

Figure 9. Compressibility profiles for pre-gelatinized starch at different tableting speeds (dwell time).

generally believed to be strain rate independent. Similarly, the strength of the placebo mixture (MCC + lactose) tablets is not significantly affected by compression speed. This may be expected because both MCC and lactose were speed independent.

Figure 5 shows that the tensile strength of pregelatinized starch tablets is substantially affected by compression speed. At the same compaction pressure, the tablet strength decreases substantially as the tableting speed increases. These results are consistent with previously reported effects of speed on the compression properties of starch.[2,6–8]

Dicalcium phosphate is considered a brittle inorganic material. Roberts and Rowe[6] ranked materials according to their strain-rate sensitivity. They concluded that plastically deforming materials were more strain-rate sensitive, and inorganic materials were insensitive to strain rate.

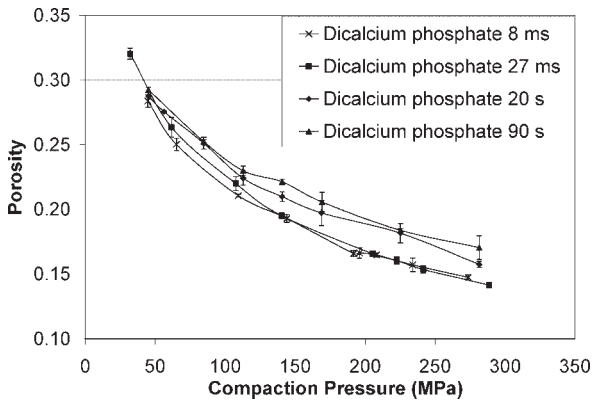

Figure 10. Compressibility profiles for dicalcium phosphate at different tableting speeds (dwell time).

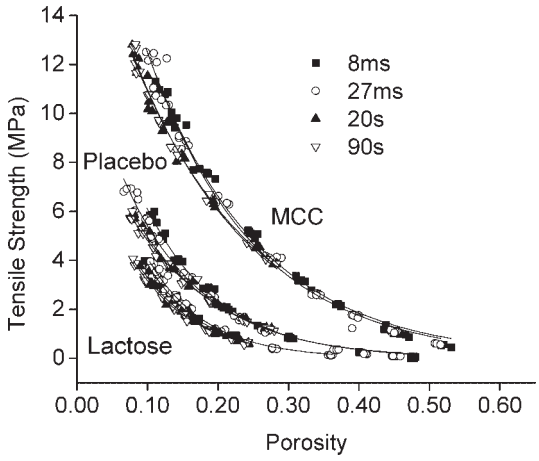

Figure 11. Compactibility profiles for MCC, lactose, and placebo mixture at four tableting speeds (dwell time = 8 ms, 27 ms, 20 s, and 90 s).

According to their ranking, calcium phosphate, calcium carbonate, and heavy magnesium carbonate are less strain-rate sensitive than lactose, MCC, or starch. One may therefore expect dicalcium phosphate tabletability to be speed independent based on published results. However, Figure 6 indicates that the tabletability of dicalcium phosphate increases as the compaction speed increases. It is interesting to note that stronger tablets were formed at higher tableting speed (shorter dwell time) under similar compaction pressure. The consolidation of dicalcium phosphate has been reported by others to be unaffected by the compression speed.[1,7] However, those studies looked over a narrower range of compression

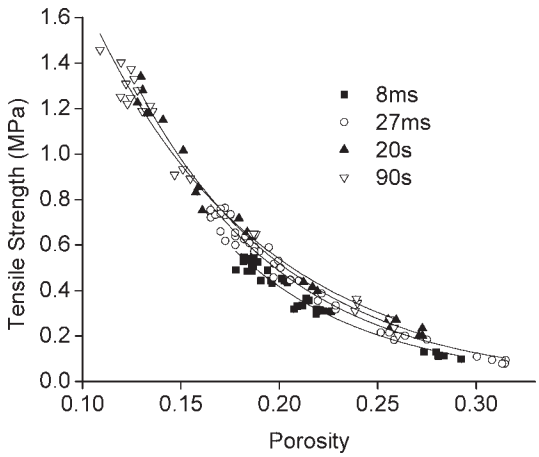

Figure 12. Compactibility profiles for pre-gelatinized starch at four tableting speeds.

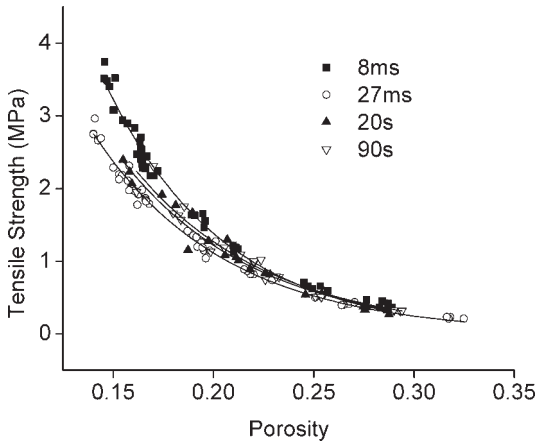

Figure 13. Compactibility profiles for dicalcium phosphate at four tableting speeds.

pressures or tableting speed than was used in the current study. One possible explanation is that higher tableting speed results in more extensive fragmentation of dicalcium phosphate particles. Consequently, a larger number of clean bonding sites may be available for bonding. The correlation between smaller particles and stronger tablets has been observed for a number of pharmaceutical solids.[19,20] This speculation is also supported by the corresponding compressibility plot (Fig. 10) in which lower tablet porosity is obtained at higher tableting speed. It is possible that finer particles pack more efficiently and result in denser tablets.

For comparison, the tabletability of all the materials studied compressed at 27 ms is presented in Figure 7. As expected, stronger tablets are achieved for all the materials studied with increasing compaction pressure. At the same pressure, MCC makes the strongest tablets, followed by the placebo mixture, lactose, dicalcium phosphate, and pre-gelatinized starch. Figure 7 also indicates that MCC is capable of producing tablets that are about 4 times stronger than lactose, and about 10 times stronger than pregelatinized starch, when compressed at comparable pressures. The placebo mixture (mixture of MCC and lactose) produced tablets with tablet strength in between pure MCC and pure lactose for all compression pressures studied.

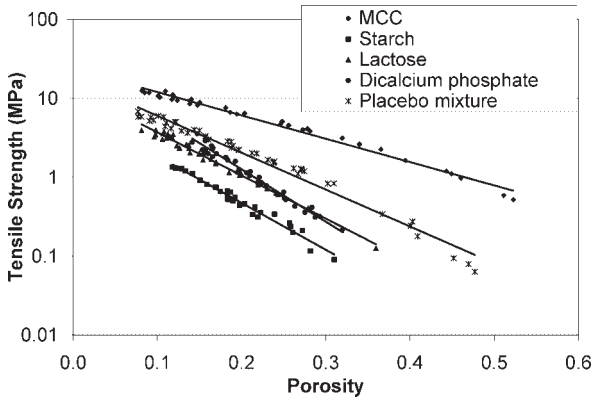

Figure 14. Log (tensile strength) versus porosity for the five powders studied compressed at dwell time of 27 ms on the Presster.

Compressibility is the ability of a material to undergo a reduction in volume as a result of an applied pressure.[11,12] It indicates the ease with which a powder bed undergoes volume reduction under compaction pressure and is represented by a plot showing the reduction of tablet porosity (i.e., the increase in solid fraction) with increasing compaction pressure. Compressibility of a powder is often described by the Heckel equation[21] or a recent modification described by Kuentz and Leuenberger.[22] Heckel plots, for example, have been widely used to assess the mechanism of deformation and as a tool to estimate yield pressure. It is also well known that tablet porosity is an important parameter, for example, in tablet disintegration and dissolution because some porosity is necessary to facilitate liquid penetration into tablets. Thus, characterization of the compressibility of a material is also valuable.[19,23–25]

The compressibility profiles for MCC, pregelatinized starch, and dicalcium phosphate are shown in Figures 8–10. The compressibility profiles for lactose and placebo are not shown but they are similar to the profile of MCC. For MCC, lactose, starch, and the placebo mixture, a longer dwell time resulted in a tablet with a higher solid fraction. More plastic flow allows greater surface contact for interparticulate bonding, and therefore tablet strength increases.[2] The improved compressibility of dicalcium phosphate at higher speeds (shorter dwell times) seen in Figure 10 was unexpected and may possibly be attributed to greater fragmentation at higher speeds that could result in finer particles and denser packing as discussed above.

Compactibility is the ability of a powdered material to be transformed into tablets with strength during densification.[11] It is represented by a plot of tensile strength versus solid fraction. The compactibility is perhaps the most valuable of the three properties because it reflects the two most important effects of applied pressure: tablet strength and solid fraction. If one can achieve an

acceptable tensile strength at an acceptable solid fraction with the application of pressure, a satisfactory tablet can be produced.

The compactibility of pharmaceutical powders can generally be described by the Ryshkewitch equation[26]:

$$\sigma = \sigma_0 e^{-b\varepsilon} \quad (4)$$

where σ = tensile strength, σ_0 = tensile strength at zero porosity, b is a constant, and ε is porosity ($\varepsilon = 1 -$ solid fraction).

In its logarithmic form, a linear relationship between solid fraction and the log of the tensile strength is predicted and this is often observed in the solid fraction range typical for pharmaceutical tablets.

The compactibility data obtained was fit to eq. 4 using nonlinear regression (Origin 7.0; OriginLab Corp., MA).

An alternative approach relating the three parameters of interest (compaction pressure, tensile strength, and solid fraction) has been proposed by Leuenberger and colleagues.[23]

The compactibility profiles for all the materials studied are shown in Figures 11–13. The data points were fitted to the Ryshkewitch equation (eq. 4) and the best-fit lines are presented in these figures. These graphs show that tensile strength decreases exponentially with increasing porosity for all dwell times studied and nicely fit the Ryshkewitch equation. For each material, the data points fall on the same general curve regardless of the compression dwell time. Apart from minor differences, these results show that the compactibility of materials is not significantly affected by compaction speed. By comparing the tabletability and compactibility profiles, it becomes clear that solid fraction (or porosity) of a tablet is a much better predictor of tablet tensile strength than compaction pressure. The differences in prediction are especially obvious for viscoelastic pre-gelatinized starch (Figs. 5 and 12). This speed independence of compactibility is to be expected if the internal structure of the compact (e.g., pore size, structure, interparticle bonding) is essentially the same at a given solid fraction regardless of the compaction speed used to form the compact. Based on this, a reliable estimate of the tensile strength of tablets produced on high-speed tableting presses can be predicted using a low-speed laboratory press that only requires a small amount of material. This information is valuable to formulation development because the amount of active drug substances available in the early phase of drug development is usually very limited.

On close examination, one can see minor differences in the compactibility curves for some of the materials tested. The data for the compactibility plots (Figs. 11–13) are generally more scattered at low porosity. This is probably due to the increase in absolute errors as the values of tensile strength increase. For pre-gelatinized starch, a slightly reduced tensile strength was observed for the highest compression speed tested (8-ms dwell time) (Fig. 12). One possible explanation is that, because of the elastic nature of this material at high speed, a high degree of elastic recovery occurs during decompression and ejection that causes additional bonds to be ruptured, resulting in further reduction in tensile strength. However, for dicalcium phosphate, it was observed that tablets compressed at the higher speed were observed to have a higher tensile strength than tablets compressed at slower speeds. This may be caused by more significant particle size reduction due to more extensive fragmentation that occurred at higher speeds for this brittle material as discussed earlier. Figure 14 shows that graph of $\log \sigma$ versus ε. Some deviation of the data from the predicted linearity of the Ryshkewitch equation is observed at porosity >0.45. Similar deviations at porosity >0.40 were also observed previously for alumina compacts.[26] However, because pharmaceutical tablets rarely have porosity >0.40, this deviation from the Ryshkewitch relationship (eq. 4) is not practically important.

CONCLUSIONS

This study shows that the relationship between solid fraction and tensile strength of tablets (compactibility profile) remains essentially the same over a wide range of tableting speeds (dwell time from 8.1 ms to 90 s) for common pharmaceutical powders of different mechanical properties (brittle, plastic, and viscoelastic). The compactibility profile is therefore a useful tool to predict the tensile strength of tablets compressed at high speeds from data obtained on a low-speed laboratory rotary tablet press or a hydraulic press. This knowledge of the relationship between solid fraction and tensile strength can be useful for tablet formulation scale up and technology transfer where compressing speeds typically vary from low speeds during early development to very high speeds in production.

REFERENCES

1. Rees JE, Rue PJ. 1978. Time-dependent deformation of some direct compression excipients. J Pharm Pharmacol 30:601–607.
2. David ST, Augsburger LL. 1977. Plastic flow during compression of directly compressible fillers and its effect on tablet strength. J Pharm Sci 66(2):155–159.
3. Roberts RJ, Rowe RC. 1986. The effect of the relationship between punch velocity and particle size on the compaction behaviour of materials with varying deformation mechanisms. J Pharm Pharmacol 38:567–571.
4. Maarschalk KV, Zuurman K, Vromans H, Bolhuis GK, Lerk CF. 1996. Porosity expansion of tablets as a result of bonding and deformation of particulate solids. Int J Pharm 140(2):185–193.
5. Ishino R, Yoshino H, Hirakawa Y, Noda K. 1990. Influence of tabletting speed on compactability and compressibility of two direct compressible powders under high speed compression. Chem Pharm Bull 38(7):1987–1992.
6. Roberts RJ, Rowe RC. 1985. The effect of punch velocity on the compaction of a variety of materials. J Pharm Pharmacol 37:377–384.
7. Armstrong NA, Palfrey LP. 1989. The effect of machine speed on the consolidation of four directly compressible tablet diluents. J Pharm Pharmacol 41:149–151.
8. Ruegger CE, Celik M. 2000. The effect of compression and decompression speed on the mechanical strength of compacts. Pharm Dev Technol 5(4): 485–494.
9. Roberts RJ, Rowe RC. 1987. Brittle/ductile behaviour in pharmaceutical materials used in tabletting. Int J Pharm 36:205–209.
10. Hancock BC, Colvin JT, Mullarney MP, Zinchuk AV. 2003. The relative densities of pharmaceutical powders, blends, dry granulations, and immediate-release tablets. Pharm Technol 27(4): 64–80.
11. Sun CQ, Grant DJW. 2001. Influence of crystal structure on the tableting properties of sulfamerazine polymorphs. Pharm Res 18(3):274–280.
12. Joiris E, Di Martino P, Berneron C, Guyot-Hermann AM, Guyot JC. 1998. Compression behavior of orthorhombic paracetamol. Pharm Res 15(7):1122–1130.
13. Duberg M, Nystrom C. 1982. Studies on direct compression of tablets. VI. Evaluation of methods for the estimation of particle fragmentation during compression. Acta Pharm Suec 19:421–436.
14. Vromans H, De boer AH, Bolhuis GK, Lerk CF, Kussendrager KD, Bosh H. 1985. Studies on tableting properties of lactose. Pharm Weekbl Sci 7:186–193.
15. Maarschalk KV, Vromans H, Groenendijk W, Bolhuis GK, Lerk CF. 1997. Effect of water on deformation and bonding of pregelatinized starch compacts. Eur J Pharm Biopharm 44(3):253–260.
16. Fell JT, Newton JM. 1970. Determination of tablet strength by the diametral-compression test. J Pharm Sci 59:688–691.
17. Jetzer WE. 1986. Measurement of hardness and strength of tablets and their relation to compaction performance of powders. J Pharm Pharmacol 38: 254–258.
18. Newton JM, Haririan I, Podczeck F. 2000. The influence of punch curvature on the mechanical properties of compacted powders. Powder Technol 107(1–2):79–83.
19. McKenna A, McCafferty DF, David ST. 1982. Effect of particle size on the compaction mechanism and tensile strength of tablets. J Pharm Pharmacol 34:347–351.
20. Sun CQ, Grant DJW. 2001. Effects of initial particle size on the tableting properties of L-lysine monohydrochloride dihydrate powder. Int J Pharm 215(1–2):221–228.
21. Heckel RW. 1961. Density-pressure relationships in powder compaction. Trans Metall Soc AIME 221: 671–675.
22. Kuentz M, Leuenberger H. 1999. Pressure susceptibility of polymer tablets as a critical property: A modified Heckel equation. J Pharm Sci 88(2):174–179.
23. Leuenberger H. 1986. Pharm Tech Conference. Cherry Hill, NJ: Hyatt Cherry Hill, pp 180–195.
24. Celik M, Ong JTH, Chowhan ZT, Samuel GJ. 1996. Compaction simulator studies of a new drug substance: Effect of particle size and shape, and its binary mixtures with microcrystalline cellulose. Pharm Dev Technol 1(2):119–126.
25. Hersey JA, Rees J. 1971. Deformation of particles during briqueting. Nature (PhysSci) 230:96.
26. Ryshkewitch E. 1953. Compression strength of porous sintered alumina and zirconia. J Am Ceram Soc 36(2):65–68.