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COMMUNICATION

Investigating the Fundamental Effects of Binders on Pharmaceutical Tablet Performance

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ABSTRACT

For solid dosage forms, a better understanding of the fundamental properties of the binders helps in developing better formulations and products. The objective of this study was to determine the effects of binder toughness and plastic flow on tablet hardness, friability, and capping. The characteristic of binder toughness was determined, and the correlation between the ejection force of the tablet and the toughness of the binder was established. Evaluation was conducted using acetaminophen tablets with different kinds of binders (i.e., hydroxypropylcellulose, methylcellulose [MC], povidone [PVP], starch, etc.). A rotary tablet press was used for tableting at three different speeds. The properties of binders and acetaminophen tablets were determined using a diametral compression test. The toughness was measured as the curve of the area under the load versus deflection. The microbehavior of these binders was also studied. The acetaminophen tablets with the binders were subjected to predetermined loads and then examined under a scanning electron microscope. The tablets that contained hydroxypropylcellulose as a binder showed the highest toughness and had the lowest ejection force. The ejection force of tablets decreased with increasing concentrations of hydroxypropylcellulose in the dosage forms. The tablets that contained other binders failed by capping and random cracking in the middle. These results show that hydroxypropylcellulose, a thermoplastic polymer, provides the best physical characteristics for the tablets. This effect could help in improving tablet manufacturing conditions (e.g., compression force and speed).

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INTRODUCTION

The characterization of pharmaceutical excipients using a materials science approach has helped in the design of drug formulations to obtain a desired set of performance properties (1,2). Binders are materials that provide the necessary bonding to hold powders together to form granules, which under compaction form a tablet. Since a binder, even a water-soluble one, will retard the disintegration of a tablet, the use of binders in a tablet formulation should be limited, not because binders are unnecessary, but because of the two-way action of the binders themselves. The granulation process is used regularly in the pharmaceutical industry to improve the properties of powders that have poor flow and compression behavior. There are many acceptable excipients used as binders in the process of granulation; these include hydroxypropylcellulose, methylcellulose (MC), povidone (PVP), starch, hydroxyethylcellulose, hydroxypropylmethylcellulose, and sodium carboxymethylcellulose (3–7).

For tablets, a better understanding of the compression properties of the binders alone and in combination with other potential components helps in developing better formulations and products (8). The fracture toughness is a material property that quantifies the ability of a material to resist crack propagation under an applied stress. For instance, thermoplastic materials have different fracture characteristics than brittle materials. Amidon (9–11) found that the mechanical properties of a material play an important role in the powder flow and compaction by influencing particle-particle interaction and cohesion, and reliable mechanical property information can be useful in (*a*) helping choose a processing method, (*b*) selecting excipients with properties that will mask the poor properties of the drug, and (*c*) helping document what went wrong.

The stress relaxation of compacts produced from viscoelastic materials was investigated by Van der Voort Maarschalk et al. (12). They suggested that the final tablet porosity is unequivocally determined by stored energy, particle attraction, and friction of the tablet with the die wall. From this observation, they concluded that porous and capped tablets suffer from the same problem, but the expression stress relaxation is different for the different materials. The use and limitations of linear-elasticity equations for describing mechanical properties of compact were investigated by Hiestand (13). He found that the use of linear elastic equations to describe stress in compacts is useful, but requires great caution. Strain rate sensitivity must be accommodated. He also addressed that, despite the complexity of the mechanics of pharmaceutical systems, mechanical property measurements provide the most systemic, rational approach to formulation design. With this in mind, the influence of binder toughness and plastic flow on tableting speed and physical properties of tablets was determined.

The objective of this study was to determine the effects of binder toughness and plastic flow on tablet hardness, friability, and capping. The characteristic of binder toughness was determined, and the correlation between the ejection force of the tablet and the toughness of the binder was established as well.

MATERIALS AND METHODS

Preparation of Tablets

The acetaminophen (acetaminophen powder USP, Rhone-Poulenc, Inc., Specialty Chemicals, Cranbury, NJ) tablets were prepared with four different binders: hydroxypropylcellulose (Klucel® EXF, Pharm, Hercules Inc., Aqualon Division, Wilmington, DE), methylcellulose NF (Methocel® A15LV, Dow Chemical, Midland, MI), povidone USP (Plasdone® K29/32, ISP Inc., Wayne, NJ), and starch (pregelatinized Starch 1500®, NF, Colorcon, West Point, PA). The rest of the materials used were magnesium stearate NF (Witco Corp., Organics Division, Chicago, IL); croscarmellose sodium (Ac-Di-Sol NF, FMC Corp., Food and Pharmaceutical Division, Newark, DE); lactose, regular grind, NF (Wisconsin Dairies, Formost Ingredient Group, Baraboo, WI); and calcium sulfate, hydrous, NF (U.S. Gypsum Co., Industrial Gypsum Division, Chicago, IL).

The formulation that contained 6% binder is listed in Table 1. The drug, binder, lactose, and calcium sulfate were preblended in a Hobart mixer at a low speed for 3

Table 1

Formulation Using 6% Binder

Ingredient	Amount (mg)	% per Tablet
Acetaminophen, USP	500	83.3
Lactose, regular grind, NF	21.5	3.58
Calcium sulfate, NF	21.5	3.58
Binder (HPC, MC, PVP, or Starch 1500)	36	6
Croscarmellose sodium, type A	18	3
Magnesium stearate, NF	3	0.50

min. The wet granulation was prepared and dried in a hot air tray dryer at 60°C to a moisture content of approximately 0.5% to 1.0%. After drying, the granulation was milled, followed by final blending with a disintegrant, croscarmellose sodium, and a lubricant, magnesium stearate. Tableting speeds of 37.5, 75, and 86 rpm were used on an instrumented 16-punch Manesty Betapress. A compression force of 15 kN was used with a 7/16-inch standard concave tooling. The tablets were examined under a scanning electron microscope.

Mechanical Experiments

The tensile behavior of the powder compacts was determined by the diametrical compression test. In this test, the flat-faced or round convex-faced compacts were subjected to two diametrically opposed point loads. The diametral compression tests (Fig. 1) were conducted at a crosshead speed of 0.05 inch/min on an Instron universal testing machine. The load-versus-deflection responses of different materials were determined. Generally, failure in the tablets occurs at the center due to tensile stress. These stresses at the center of the flat-faced tablet are

$$\sigma_x = 2P/\pi \cdot h \cdot D \quad (1)$$

$$\sigma_y = -6P/\pi \cdot h \cdot D \quad (2)$$

where σ_x is the tensile stress in the x direction, σ_y is the compression stress in the y direction, P is the compression pressure, h is the tablet thickness, and D is the tablet diameter. The compressive strength needed to be at least three times the tensile strength to ensure tensile failure, and the tests were stopped when the diameter along the loading reduced to around 50% to 75% of the original diameter.

RESULTS AND DISCUSSION

The load-deflection curves for different binders are shown in Fig. 2, and the HPC and starch tablets before and after the load-deflection tests are illustrated in Figs. 3 and 4, respectively. Numerically, the peak load and toughness for 6% binder formulations are presented in Fig. 5. The mechanical properties of binders indicate that the HPC was the toughest binder and had a very high degree of plastic flow relative to the MC, PVP, and starch samples. The povidone or starch samples showed very low strength and toughness with nearly no to very little plastic flow. The formulation that contained 6% HPC could provide the toughest and strongest tablets.

When the binder percentage in all tablets was kept at 6%, no capping or major damage was found in HPC tablets in the range of tableting speeds investigated. Failure modes of the tablets under the compression tests are shown in Fig. 6. The tablets with PVP and starch binders had extensive capping, and the tablet with MC had slight chipping. However, no capping or chipping occurred in making the HPC tablets. During the mechanical testing for breaking the tablets on purpose, the HPC tablets did not break into pieces like the rest of binders did, but were crushed and still remained intact (Fig. 7). The PVP and starch tablets showed extensive capping at 37.5 and 75 rpm, and at 86 rpm we could not make the tablets with 6% PVP or starch, and tablets with HPC binder clearly demonstrated the excellent friability performance (Fig. 8).

As shown in Fig. 9, the ejection force of tablets decreased with increasing concentrations of HPC in the dosage forms. However, the ejection force of tablets did not change with the proportion of PVP concentrations

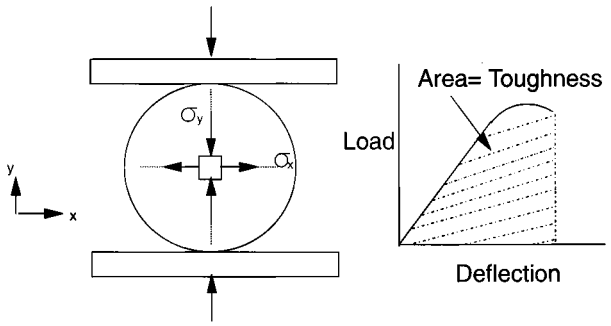

Figure 1. Diametral compression test.

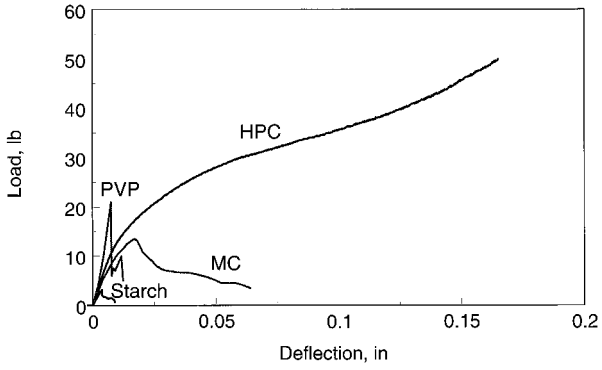

Figure 2. Load-deflection curves for binders.

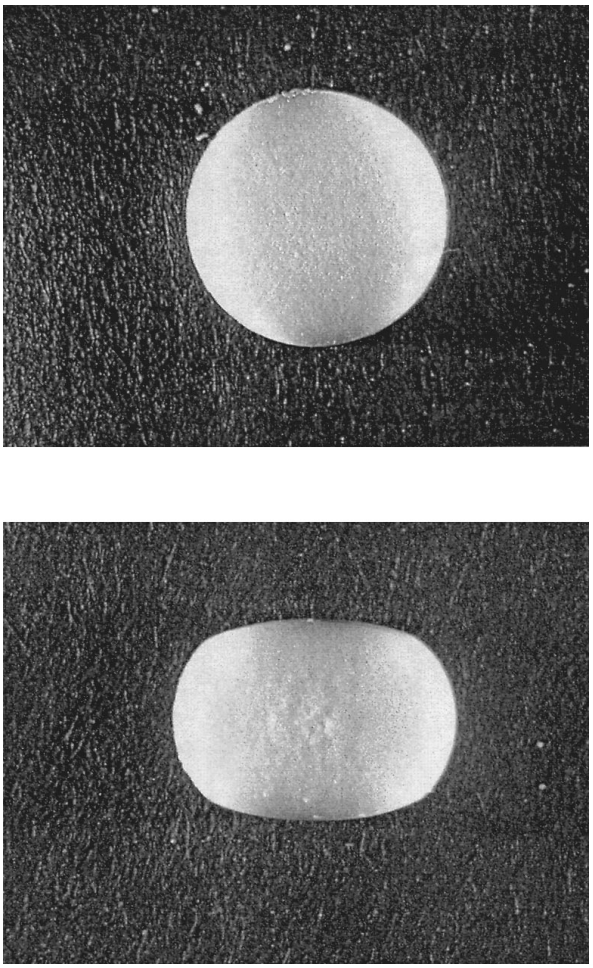

Figure 3. Hydroxypropylcellulose tablet before and after the load-deflection test.

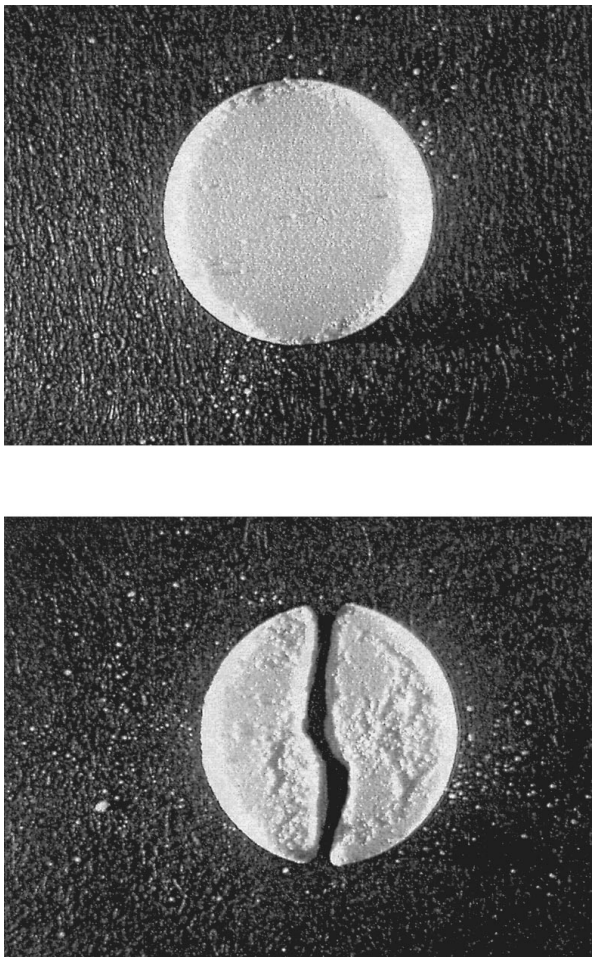

Figure 4. Starch tablet before and after the load-deflection test.

(Fig. 10), and the ejection forces of PVP tablets are higher than for HPC tablets in all the concentrations. The ejection force of tablets was found to increase with increasing rotation speed of tablet compression for both 6% PVP and 6% HPC tablets. Due to extensive capping, PVP tablets could not be made when the rotation speed was higher than 75 rpm, and no ejection force was reported after that (Fig. 11).

Toughness is the ability to absorb energy without fracturing and is the resistance of materials to the propagation of cracks. Therefore, toughness of a material is defined as the energy needed to break a material, and materials with low toughness break very easily (14–16). HPC is a nonionic, water-soluble cellulose ether with remarkable thermoplastic characteristics and has a very high degree

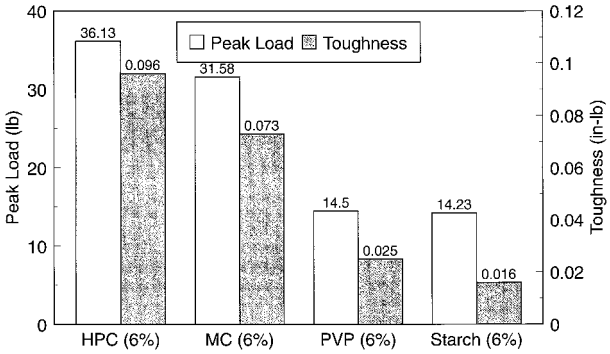

Figure 5. Strength and toughness (at peak load) of acetaminophen tablets.

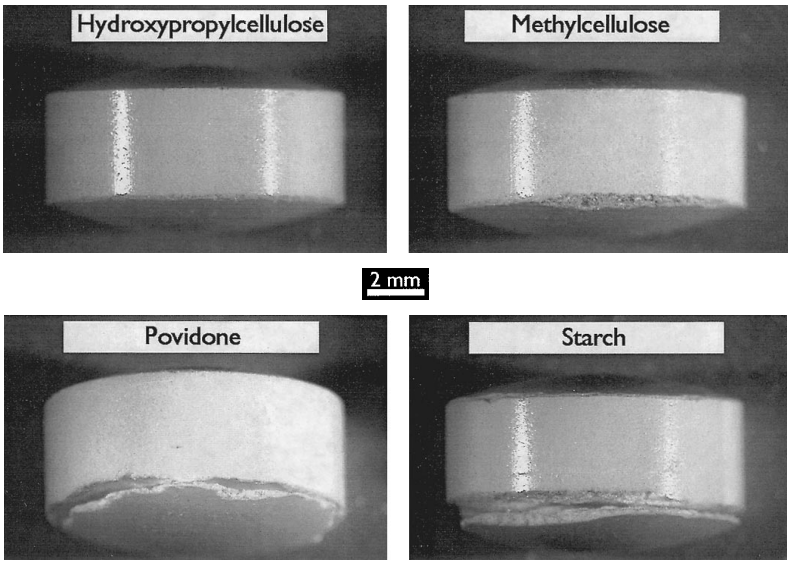

Figure 6. Conditions of tablets formed at a tableting speed of 75 rpm.

of plastic flow. Therefore, when HPC was used as a binder, it could provide strong toughness and absorb compression energy for preventing the capping of tablets. In the tableting process, a balance between the tableting speed and ejection force is important to enhance production that results in minimum tablet damage. With this in mind, the effect of ejection force on the binder amount was determined.

The ejection force, when calculated per unit contact area between the tablet and the die wall, is recommended

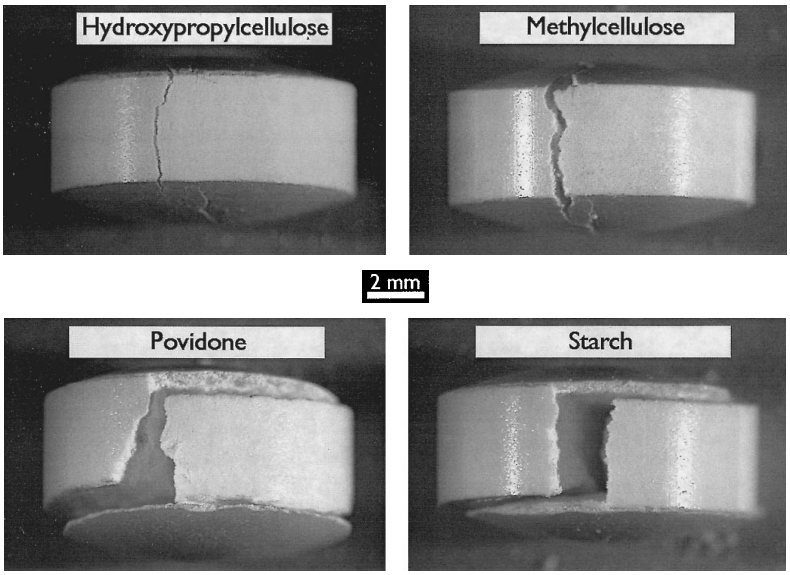

Figure 7. Failure modes induced by the compression test.

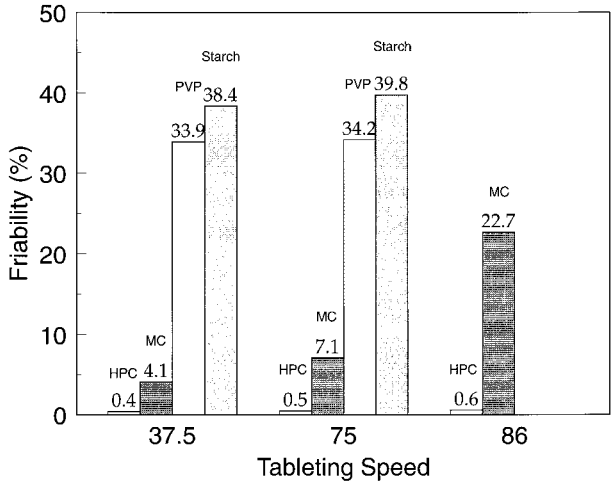

Figure 8. Friability versus tableting speed for tablets containing 6% binder.

as a good measure of friction during tableting (17–19). The friction between the tablets and the die surface dominated the ejection force:

$$F_e = k \int_0^A \mu \cdot R \cdot d\alpha \qquad (3)$$

where F_e is the ejection force, k is the process constant dependent on the process speed and die shape, μ is the friction between the die surface and tablet, R is the normal reaction force, A is the total contact area, and α is the variable for surface area. A good correlation was observed between the ejection force and the binding characteristics (binder concentration) of HPC tablets. Once again, it has been shown that HPC has strong ability (toughness) to absorb the compression energy and resist the propagation of cracks.

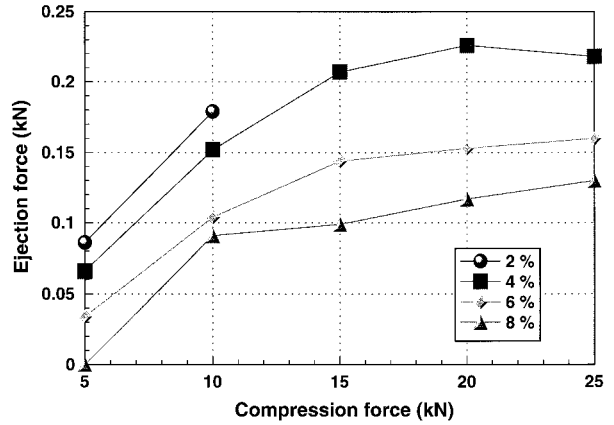

Figure 9. The ejection force of tablets that contained different hydroxypropylcellulose levels and that were made at different compression forces.

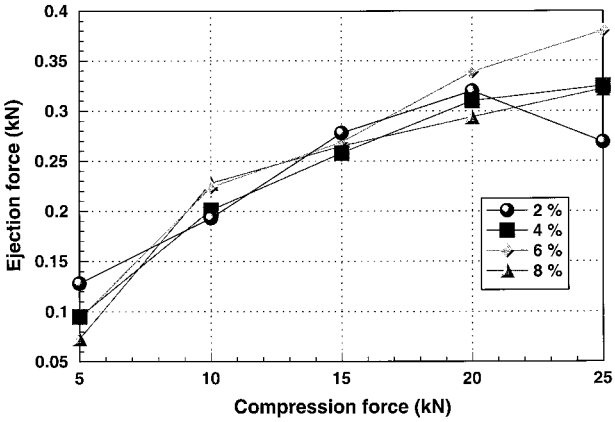

Figure 10. The ejection force of tablets that contained different povidone levels and were made at different compression forces.

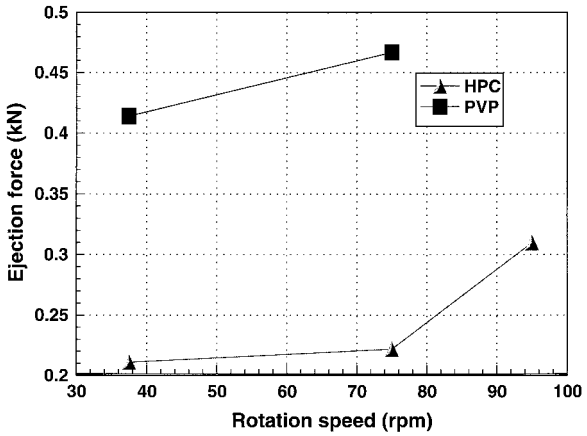

Figure 11. The ejection force of tablets that contained 6% hydroxypropylcellulose or povidone and were made at different rotation speeds.

CONCLUSIONS

These results showed that HPC, a thermoplastic polymer, provides the best physical characteristics and the lowest ejection force to tablets. This effect could help improve tablet manufacturing conditions (e.g., compac-

tion force and speed). No capping-related failure was seen in the tablets with HPC as the binder.

REFERENCES

1. A. M. Juppo, Relationship between force and pore structure of lactose, glucose and mannitol tablets, Int. J. Pharm., 127, 95–102 (1996).
2. J. L. Johnson, J. Holinej, and M. D. Williams, Int. J. Pharm., 90, 151–159 (1993).
3. W. W. Harcum, G. W. Skinner, M. Altekar, S. Joneja, P. E. Barnum, and J.-H. Guo, Modeling the effects of hydroxypropylcellulose in acetaminophen tablet formulation, Drug Dev. Ind. Pharm., 24(10), 23–30 (1998).
4. A. K. Hilton and P. B. Desay, Int. J. Pharm., 86, 79–88 (1992).
5. A. S. Hussain, R. D. Johnson, P. Shivand, and M. A. Zoglio, Drug Dev. Ind. Pharm., 20, 2645–2657 (1994).
6. D. Harris, J. T. Fell, D. C. Taylor, J. Lynch, and H. L. Sharma, Int. J. Pharm., 56, 97–102.
7. M. Efentakis, M. Vlachou, and N. H. Choulis, Drug Dev. Ind. Pharm., 23, 107–112 (1997).
8. R. C. Moreton, Tablet excipient to the year 2001: a look into the crystal ball, Drug Dev. Ind. Pharm., 22, 11–23 (1996).
9. G. E. Amidon, Physical and mechanical property characterization of powders, in *Physical Characterization of Pharmaceutical Solids* (H. G. Brittain, Ed.), Marcel Dekker, New York, 1995, pp. 281–319.
10. G. E. Amidon, Physical and mechanical property effects on powder flow, AAPS Symposium, November 1988.
11. G. E. Amidon, Mixing and flow, Proceedings of the 31st International Industrial Pharmaceutical Research Conference, University of Wisconsin—Extension, 1989.
12. K. Van der Voort Maarschalk, K. Zuurman, H. Vromans, G. K. Bolhuis, and C. F. Lerk, Int. J. Pharm., 151, 27–34 (1997).
13. E. N. Hiesstand, Mechanical properties of compacts and particles that control tableting success, J. Pharm. Sci., 86, 985–990 (1997).
14. B. R. Lawn and M. V. Swain, Microfracture beneath point indentations in brittle solid, J. Mater. Sci., 10, 113 (1975).
15. B. R. Lawn and T. R. Wilshaw, Indentation fracture: principles and applications, J. Mater. Sci., 10, 1049 (1975).
16. M. T. Laugier, New formula for indentation toughness in ceramics, J. Mater. Sci. Lett., 6, 355 (1987).
17. A. W. Holzer and J. Sjogren, Drug Dev. Ind. Pharm., 3, 23 (1977).
18. J. Kikuta and N. Kitamori, Evaluation of the die wall friction during tablet ejection, Powder Technol., 35, 195–200 (1983).
19. A. Muno-Ruiz, M. Wihervaara, M. Hakkinen, M. Juslin, and P. Paronen, Frictional work in double-sided tablet compression, J. Pharm. Sci., 86, 481–486 (1997).