ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 43 (1997) 95–100

European Journal of Pharmaceutics and Biopharmaceutics

# Influence of micronization on the compaction properties of an investigational drug using tableting index analysis

Marcelo O. Omelczuk[a,*], Chen-Chao Wang[b], David G. Pope[1,a]

[a]*Sandoz Research Institute, Sandoz Pharmaceuticals Corporation, East Hanover, NJ 07936-1080, USA*
[b]*Drug Dynamics Institute, The University of Texas, Austin, Texas 78712, USA*

Received 18 December 1995; accepted 5 May 1996

**Abstract**

Tableting index analysis was used to study the compaction properties of two lots of an investigational drug substance alone and in combination with excipients in tablet formulations. Lot A was pin-milled while lot B was micronized using a fluid energy mill. Light scattering analysis demonstrated a median particle size of 23.4 and 5.0 $\mu$m for lots A and B, respectively. Results from tableting index analysis indicated a significantly higher average tensile strength and bonding index for the micronized material at solid fractions of 0.80, 0.85, and 0.90. The enhanced bonding could be attributed to approximately a five-fold increase in particle surface area and associated increase in the true contact areas between the micronized particles. Brittle fracture index testing demonstrated slightly higher brittle propensities for the pure micronized compacts at each solid fraction. Tableting index analysis was also performed on tableting formulations containing milled and micronized drug at both the 30 and 65% level. The formulation containing 65% micronized drug demonstrated a significantly higher bonding index over the equivalent formulation containing milled drug. However, there was minimal difference in the bonding index between the formulations containing 30% micronized and milled drug substance. Results suggested that the incorporation of micronized drug could significantly increase the bonding propensities of high dose formulations in comparison with formulations containing conventionally milled drug substance. In addition, tableting index analysis was shown to be a very useful technique to quantitatively study the effect of micronization on compaction properties of tableting formulations. © 1997 Elsevier Science B.V. All rights reserved

*Keywords:* Tableting indices; Tensile strength; Bonding index; Brittle fracture index

## 1. Introduction

Micronization refers to the reduction of a powdered substance to particle sizes of approximately 10 $\mu$m or less. This rapid and relatively efficient process employs a fluid energy mill which reduces the particle size by impact and attrition using a high velocity stream of air. Micronization takes place immediately because of the very high speed collisions between the particles suspended within the stream of air [1,2]. In most cases, micronization is used to maximize the particle surface area in order to improve the rate of dissolution and bioavailability of a poorly soluble active drug substance [3]. Although micronization offers this advantage, it can precipitate formulation processing problems because of high dust, low density, and poor flow properties as compared with conventionally milled powders. In addition, past studies have shown that the particle size and shape can have a significant effect on the physical-mechanical properties of compacts [4–11]. Huttenrauch reported that smaller particles generally tend to yield higher tablet strengths as compared with coarse particles [4,6]. His observation was explained by his molecularly based activation theory which postulated that smaller particles exhibit larger surface areas,

* Corresponding author. Schering-Plough Research Institute, 2000 Galloping Hill Road K-2 F31A, Kenilworth, NJ 07033, USA.
[1] Present address: Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950, USA.

0939-6411/97/$17.00 © 1997 Elsevier Science B.V. All rights reserved
*PII* S0939-6411(96)00002-1

as well as higher frictional and internal energies, leading to an activated state. This activated state results in tablets of higher mechanical strength when compressional forces are applied.

The major objective of this present study was to investigate the influence of micronization on the compaction properties of an investigational active compound alone and in combination with formulation excipients using tableting index analysis. The tableting indices, which include the bonding index and brittle fracture index, are dimensionless parameters which are used to quantitatively characterize the tableting performance of individual components and mixtures [12–21].

## 2. Materials

Various excipients were utilized in this study: microcrystalline cellulose (Avicel Ph102), (FMC, Princeton, NJ); pregelatinized starch (Starch 1500®), (Colorcon, West Point, PA); crospovidone (Polyplasdone-XL®), (GAF, Wayne, NJ); magnesium stearate, (Mallinckrodt, St. Louis, MO); and colloidal silicon dioxide (Cab-O-Sil®), (Cabot, Tuscola, IL).

The drug compound investigated had the following physical properties: molecular weight, 257; melting point, 115°C; solubility (water/25°C), 23.5 μg/ml; and a true density of 1.25 g/ml. Two lots of the drug were used: lot A was pin-milled while lot B was micronized using a fluid energy mill. Lots A and B exhibited bulk densities of 0.28 and 0.15 g/ml, respectively.

## 3. Methods

### 3.1. Formulation

Several formulations containing 0, 30, and 65% of both the micronized and milled drug lots were prepared, as shown in Table 1. The excipients in the formulation included microcrystalline cellulose, starch, crospovidone, magnesium stearate, and silicon dioxide. The microcrystalline cellulose, starch, and crospovidone were pre-mixed in a 10 l Collette Gral® (Machines Collette, Antwerp, Belgium) for 2 min. With the exception of the placebo formulation, the active was incorporated into this preblend and mixed for an additional 3 min. Silicon dioxide and magnesium stearate were each then successively added to the blend and mixed for 30 s. As shown in Table 1, equivalent percentages of each excipient were employed in all formulations, with the exception of microcrystalline cellulose and starch. The amounts of microcrystalline cellulose and starch were adjusted to complete (q.s.) the balance of the formulation while keeping their ratio constant at 0.87. The true density of the pure drug substance and the dry blends was determined using a helium pycnometer (Micromeritics Instrument, Norcross, GA). The true density was used to calculate the solid fraction (SF) of the compacts: SF = (apparent density/true density) = (1 − porosity).

Table 1
Compact formulations

| | Formulation (%) | | |
|---|---|---|---|
| | A | B | C |
| Drug (log A or B) | 0.0 | 30.0 | 65.0 |
| Micorcrystalline cellulose[a] | 44.0 | 30.0 | 13.7 |
| Pregelatinized starch[a] | 50.5 | 34.5 | 15.8 |
| Crospovidone | 4.0 | 4.0 | 4.0 |
| Colloidal silicon dioxide | 1.0 | 1.0 | 1.0 |
| Magnesium stearate | 0.5 | 0.5 | 0.5 |
| Total | 100 | 100 | 100 |

[a] (% microcrystalline cellulose/% starch) = 0.87.

### 3.2. Particle size analysis

Particle size analysis of the pure drug lots was performed utilizing a light scattering diffraction apparatus (MasterSizer®, Malvern Instruments, Worcestershire, UK) attached to a Malvern computer data processor. The drug samples were saturated in a 0.1% Tween 80 solution and were subsequently filtered and sonicated for 50–60 s. The dispersions were measured using a light beam of 2.4 mm length [1].

### 3.3. Tableting indices

Both lots A and B of the pure drug substances were each compressed into compacts with sufficient force to achieve solid fractions of 0.8, 0.85, and 0.9 using a Carver® press modified with a load cell. Each compact weighed 3.0 g and was compressed using a 1 $cm^2$ die with two square flat-faced punches. The die was split along a line through one diagonal and was capable of triaxial decompression. One set of compacts was compressed with a 1 mm axially oriented hole. The hole served as a stress concentrator for tensile strength testing. Compacts were also compressed to a solid fraction of 0.80 for formulations containing 0, 30, and 65% of both the milled and micronized drug. An average of four compacts was used for each of the following determinations. The coefficient of variation was less than or equal to ± 5% for all results reported.

Tensile strength testing was achieved using an Instron® equipped with a 1 kN load cell. Both sets of compacts, with and without a stress concentrator, were transversely compressed between two platens until a tensile fracture was observed. The speed of the platens was adjusted to maintain a time constant of 10 s

between the maximum force and $1/e$ times that force. The maximum force required to produce the tensile fracture was recorded as the tensile strength.

Dynamic indentation hardness was determined using a pendulum impact apparatus. The compacts were held in a die with one side exposed to the path of the sphere of the pendulum. A ballistic sensor measured the velocity before and after impact which was then converted to the height of the sphere before and after impact, respectively. The chordal radius of the resulting dent in the compact was measured under the low power objective of a microscope. The values of the initial height of the sphere '$h_i$', rebound height '$h_r$', and chordal radius '$a$' were used to calculate the indentation hardness '$P$' as follows:

$$P = [(4mgrh_r)/(\Pi a^4)](h_i/h_r - 3/8)$$

were '$m$' is the mass of the sphere, '$g$' is the gravitational constant, and '$r$' is the sphere radius. The indentation hardness serves as an indicator of the shear strength of the compact under a compressive load.

The brittle fracture index (BFI) is defined as:

$$\text{BFI} = [T_s/T_{so} - 1]/2$$

where '$T_s$' is the tensile strength without a stress concentrator and '$T_{so}$' is the tensile strength with a stress concentrator. The BFI indicates the ability or inability of a compact to relieve stresses caused by plastic deformation. A BFI value of 0 indicates no brittle behavior, while a BFI of 1 indicates high brittleness.

The bonding index (BI) is defined as $T_s/P$: the ratio of the tensile strength of the compact after decompression to the shear strength under a compressive load. It indicates the fraction of strength that survives the decompression process. This index is based on the premise that bonding is dependent on the true areas of contact formed between particles and that the success of this bonding depends on the areas of true contact that survive the decompression process [12–21].

## 4. Results and discussion

The data in Fig. 1 show the cumulative frequency plots for particle size distributions of drug lots A (milled) and B (micronized). The median particle size of lot A was 23.4 $\mu$m with 90% less than 55.8 $\mu$m, while the micronized lot B had a median particle size of 5.0 $\mu$m with 90% less than 12.0 $\mu$m. The reduction in particle size was inversely related to an approximate increase in surface area from 0.6 to 3.2 $m^2$/cc.

Results of tableting index analysis indicated that the compacted micronized lot had a significantly higher average tensile strength at each solid fraction tested, as shown in Fig. 2. Indentation hardness results for both the milled and micronized compacts showed relatively

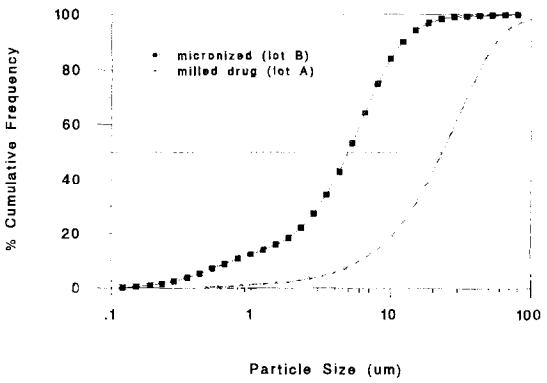


Fig. 1. Cumulative frequency plot of particle sizes from micronized versus pin-milled drug.

similar hardness values, except at the highest solid fraction (0.9) where the micronized lot demonstrated a higher hardness (Fig. 3). The ratio of the tensile strength to the indentation hardness was used to calculate the bonding index, as shown in Fig. 4. The results demonstrated that the compacted micronized lot had a significantly higher average bonding index than the compacted milled lot at each solid fraction tested. The higher bonding indices could be attributed to the fivefold increase in surface area and associated increase in surface energy of the smaller micronized particles. The enhanced bonding was a manifestation of the larger contact areas between the smaller particles which survived the decompression process [16]. The differences between the tensile strengths with and without the stress concentrator also indicated that the micronized compacts had slightly higher brittle fracture index values than the compacts containing the milled particles (Fig. 5). However, experience suggests that a brittle fracture index of less than or equal 0.25 generally

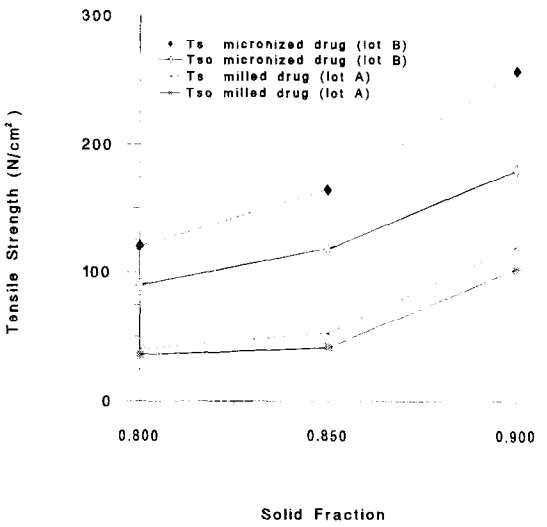


Fig. 2. Influence of micronization on the tensile strength, with ($T_{so}$) and without ($T_s$) a stress concentrator, of pure drug substance.

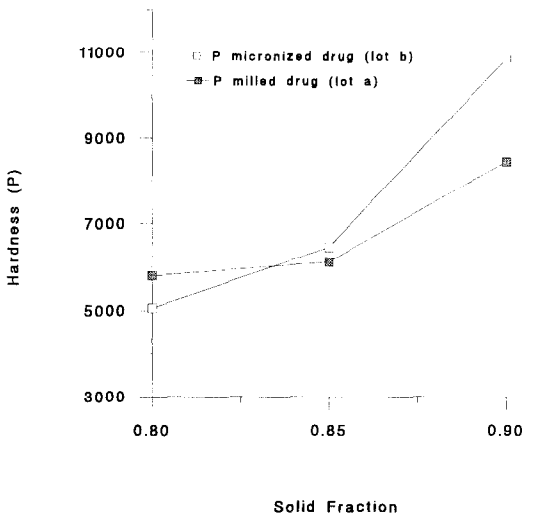


Fig. 3. Influence of micronization on the hardness ($P$) of pure drug substance.

implies that a material has an inherently low propensity to cause fracture problems.

Analysis of scanning electron micrographs (S.E.M.) of the pure drug substances (Fig. 6) demonstrated the significant size differences between the micronized and conventionally milled drug particles. In comparing both S.E.M., the micronized active displayed a significantly higher degree of agglomeration than the milled active. Since the micronized particles have larger surface areas and are highly energetic, they tend to agglomerate in such a way to reduce their total surface area and surface energy [22]. As pointed out by Huttenrauch [4,6], this agglomeration or cohesiveness generally increases the true contact areas between particles and produces tablets of higher mechanical strength. Similar observations were also reported in a study by Akbare-

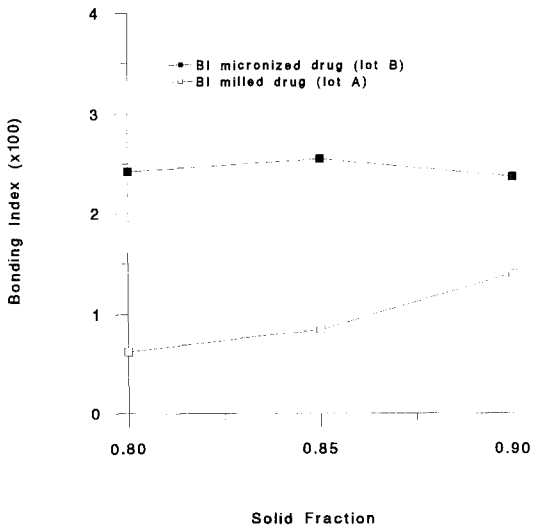


Fig. 4. Influence of micronization on the bonding index (BI) of pure drug substance.

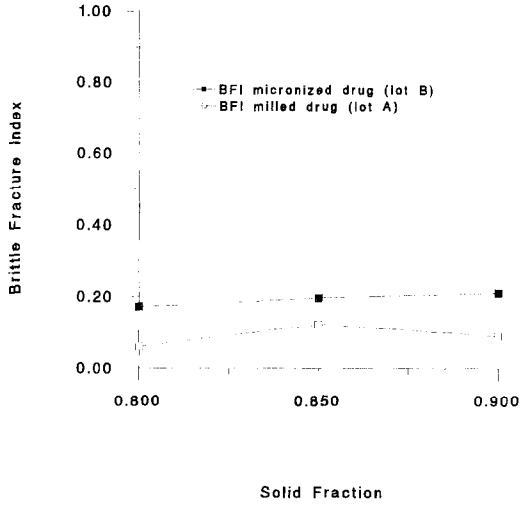


Fig. 5. Influence of micronization on the brittle fracture index (BFI) of pure drug substance.

ich and Tawashi [5].

The data in Fig. 7 show the combined influences of micronization and percentage of drug substance on the bonding index of the tableting formulations. As was demonstrated by the pure drug substance, the compacts

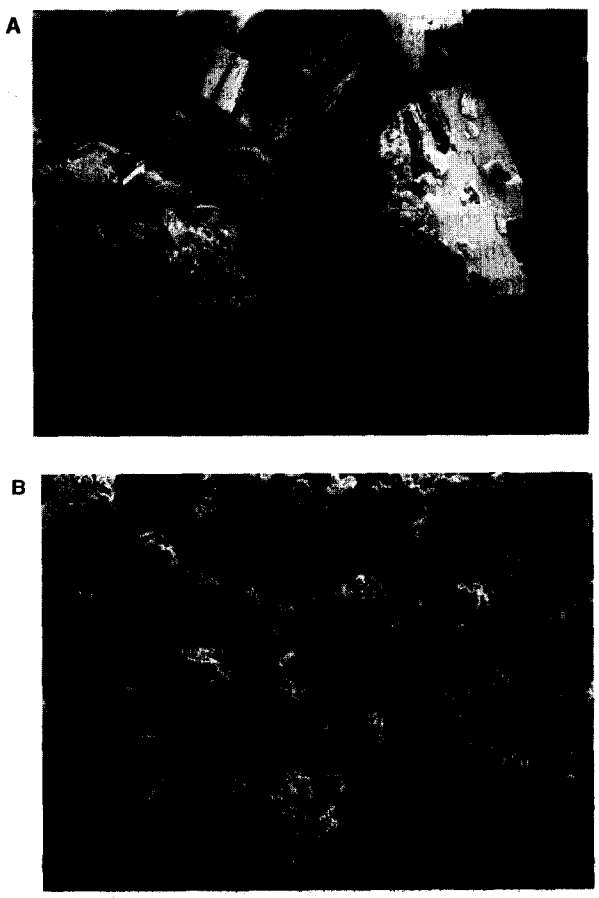


Fig. 6. Scanning electron micrographs of the milled (lot A) and micronized (lot B) drug particles.

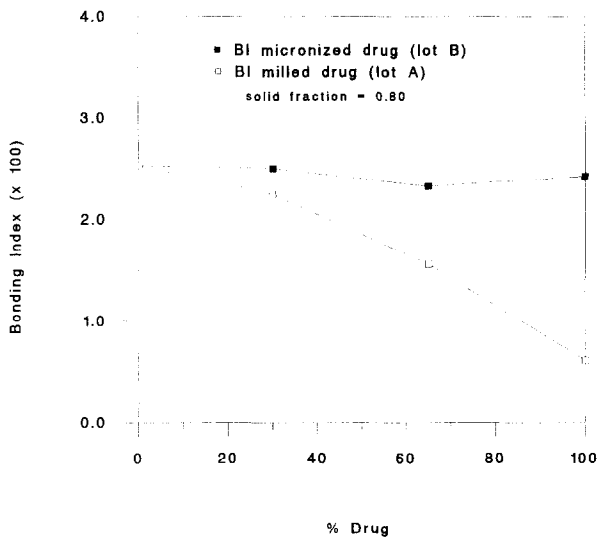


Fig. 7. Influence of micronization on the bonding index (BI) of formulations containing 0, 30, 65 and 100% drug.

containing 65% micronized drug exhibited a higher average bonding index relative to compacts containing 65% milled drug. This result could be attributed to the micronized drug which in its pure state demonstrated a significantly higher bonding propensity than the milled drug substance. In contrast, there was minimal difference between the average bonding index of compacts containing 30% micronized and milled drug substance. These results suggested that the bonding index could be significantly improved by incorporating micronized drug at higher levels in the formulation.

The lack of significant differences between the ratios of the average tensile strength of compacts with and without a stress concentrator resulted in similar brittle fracture indices for formulations containing 0, 30, and 65% of the micronized or milled drug (Fig. 8). However, the index results did suggest that the incorporation of excipients decreased the slightly higher brittle propensity exhibited by the pure micronized drug. This reduction could be attributed to the addition of microcrystalline cellulose which itself has an extremely low brittle fracture index of 0.04 [16].

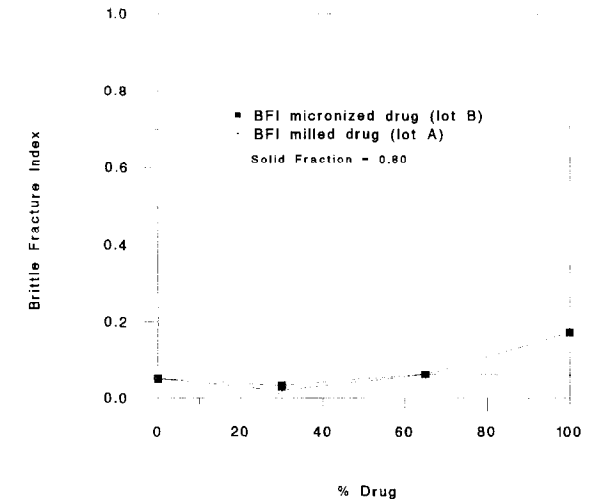


Fig. 8. Influence of micronization on the brittle fracture index of formulations containing 0, 30, 65 and 100% drug.

In addition to comparing milled versus micronized formulations, the data in Fig. 7 also show the effect of adding excipients to the pure drug. As the milled drug was diluted with excipient to 0%, the bonding index progressively increased. This trend was expected since the major excipient components were composed of two highly compactable materials, pregelatinized starch and microcrystalline cellulose. The bonding indices for pregelatinized starch and microcrystalline cellulose are $1.5 \times 10^{-2}$ and $4.0 \times 10^{-2}$, respectively [21]. In most cases dealing with powdered mixtures, the effect of adding a material can be qualitatively predicted from the index values of pure materials [16]. The dilution of the pure micronized drug with excipients did not significantly increase the bonding index. Since the bonding index of the pure micronized drug was approximately equal to that of the placebo formulation, the addition of excipients was not expected to improve the bonding index.

In conclusion, the results of this study demonstrated that particle size reduction due to micronization significantly influenced the compaction properties of the pure drug. The higher tensile strength and bonding index results for the micronized lot could be attributed to an increase in surface area and true contact areas between the particles. Tableting index analysis on formulations containing 0, 30, and 65% of both micronized or milled active suggested that the bonding index could be significantly improved by using micronized drug at higher levels. Overall, the results of this study also indicated that tableting index analysis can be a useful technique to quantitatively study the effect of drug micronization on the compaction properties of solid formulations.

## Acknowledgements

The authors wish to thank Dr James W. McGinity for his technical assistance and the use of the compaction equipment for tablet index analysis.

## References

[1] Lantz R. Size reduction. In: Lieberman H, Lachman L, Scharwtz JB, editors. Pharmaceutical Dosage Forms, Vol. 2. New York: Marcel Dekker, 1990:113.
[2] Parrott E. Milling of pharmaceutical solids. J. Pharm. Sci. 1974;63(6):813–28.
[3] Stavchansky S, McGinity JW. Bioavailibility in tablet technology. In: Lieberman H, Lachman L, Scharwtz JB, editors. Phar-

maceutical Dosage Forrns, Vol. 2. New York: Marcel Dekker, 1990:453.
[4] Huttenrauch R. New concepts in pharmaceutics. Labo-Pharma-Probl. Tech. 1983;31:644–55.
[5] Akbarieh M, Tawashi, R. Morphic features of solid particles after micronization in the fluid energy mill. Indian J. Pharm. 1987;35:81–9.
[6] Huttenrauch R. Modification of starting materials to improve tableting properties. Pharm. Ind. 1983;45:435–40.
[7] Krycer I, Pope D. The role of intra-granular porosity in powder compaction. Powder Tech. 1982;33:101–11.
[8] Pesonen T, Paronen P. The effect of particle and powder properties on the mecahnical properties of directly compressed cellulose tablets. Drug. Dev. Ind. Pharm. 1990;16(1):31–54.
[9] Vromans H, DeBoer AH, Bolhuis GK, Lerk CF. Studies on the tableting properties of lactose: part 1, the effect of initial particle size on binding properties and dehydration chracteristics of lactose. Acta Pharm. Suec. 1985;22:163–72.
[10] McKenna A, McCafferty D. Efect of particle size on the compaction mechanism and tensile strength of tablets. J. Pharm. Pharmacol. 1981;34:347–51.
[11] Summers MP, Enever RP, Carless, JE. Influence of crystal form on tensile strength of compacts of pharmaceutical materials. J. Pharm. Sci. 1977;66(4):1171–5.
[12] Omelczuk MO, McGinity JW. The influence of polymer glass transition temperature and molecular weight on the drug release from tablets containing poly(D,L-lactic acid). Pharm. Res. 1992;9:26–32.
[13] Omelczuk MO, McGinity JW. The influence of thermal treatment on the physicalmechanical and dissolution properties of tablets containing poly(D,L-lactic acid). Pharm. Res. 1993;10(4):542–8.
[14] Omelczuk MO. An investigation of the chemical, physical-mechanical, and dissolution properties of controlled release tablets containing poly(D,L-lactic acid). Dissertation. The University of Texas at Austin, Austin, Tx, 1991.
[15] Hiestand EN, Wells JE, Poet CB, Ochs CF. Physical process of tableting. J. Pharm. Sci. 1977;66:510–9.
[16] Hiestand EN, Smith DP. Indices of tableting performance. Powder Technol. 1984;38:145–59.
[17] Hiestand EN. The practical applications of the tableting indices. Pharm. Tech. 1989;13:(9):54–66.
[18] Williarns III RO, McGinity JW. The use of tableting indices to study the compaction properties of powders. Drug. Dev. Ind. Pharm. 1988;14:1823–44.
[19] Schulze MD, McGinity JW. Physical-mechanical properties of spray-dried and milled acrylic resin polymers in combination with a brittle or plastic drug. S.T.P. Pharma Sci. 1991;1:165–71.
[20] Omelczuk MO, McGinity JW. A comparative investigation of the compaction and dissolution properties of tablets containing poly(D,L-lactic acid) as a binder and retardant polymer. S.T.P. Pharma. Sci. 1994;5(3):181–6.
[21] Hiestand EN, Johnson BW, Smith DP. Use of tableting indices. Paper presented at the Arden House Conference, Harriman, NY, Jan 21–Feb 1, 1985.
[22] Hartley PA, Parfitt GD, Pollack LB. The role of the Van Der Vaals Force in the agglomeration of powders containing submicron particles. Powder Technol. 1985;42:35–46.