International Journal of Pharmaceutics 418 (2011) 227–234

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Understanding deformation mechanisms during powder compaction using principal component analysis of compression data

Rahul Roopwani, Ira S. Buckner*

Graduate School of Pharmaceutical Sciences, Duquesne University, 600 Forbes Ave., Pittsburgh, PA, 15282, USA

ARTICLE INFO

Article history:
Received 14 December 2010
Received in revised form 20 April 2011
Accepted 14 May 2011
Available online 20 May 2011

Keywords:
Powder compaction
Compression
Principal component analysis
Deformation behavior
Plasticity
Binary mixtures

ABSTRACT

Principal component analysis (PCA) was applied to pharmaceutical powder compaction. A solid fraction parameter ($SF_{c/d}$) and a mechanical work parameter ($W_{c/d}$) representing irreversible compression behavior were determined as functions of applied load. Multivariate analysis of the compression data was carried out using PCA. The first principal component (PC1) showed loadings for the solid fraction and work values that agreed with changes in the relative significance of plastic deformation to consolidation at different pressures. The PC1 scores showed the same rank order as the relative plasticity ranking derived from the literature for common pharmaceutical materials. The utility of PC1 in understanding deformation was extended to binary mixtures using a subset of the original materials. Combinations of brittle and plastic materials were characterized using the PCA method. The relationships between PC1 scores and the weight fractions of the mixtures were typically linear showing ideal mixing in their deformation behaviors. The mixture consisting of two plastic materials was the only combination to show a consistent positive deviation from ideality. The application of PCA to solid fraction and mechanical work data appears to be an effective means of predicting deformation behavior during compaction of simple powder mixtures.

1. Introduction

Pharmaceutical tablets constitute one of the most preferred dosage forms due, partly, to their patient acceptability and their high production rate. To facilitate tablet development, information on the mechanical behavior of pharmaceutical materials used can be very important. Commercially produced tablets commonly include a number of excipients which allow for large scale manufacturing and provide for proper function of the dosage form after production. Acceptable mechanical strength and drug release from the final product are particularly important properties that must be considered during tablet development.

Despite the complex composition of many tablet formulations, understanding of how the individual components behave is important for rational development of new formulations. Characterization data for single materials can be used to guide development toward an optimum formulation, but the process frequently relies extensively on trial and error. One reason for this is that a priori understanding of how individual material properties contribute to the behavior of a mixture is limited. Therefore, predicting tableting behavior of powder mixtures based on the properties of their components is of obvious interest and value.

Many methods are employed to study deformation behavior of pharmaceutical materials including application of various compressibility models and mechanical work analysis to a lesser extent. Compressibility modeling describes changes in the relative density of a powder bed as a function of applied pressure. Parameters obtained from such models have been used as indicators of relative deformation mechanisms. One of the most widely used models for deformation characterization is the Heckel Model (Heckel, 1961a,b), which relates the logarithm of reciprocal porosity to the applied pressure. The yield pressure (P_y), obtained from a Heckel Plot, has been used to quantify a material's relative plasticity. A large P_y value is associated with low plasticity or a predominantly brittle deformation mechanism. Other models (e.g. Gurnham and Masson, 1946; Walker, 1923) have also been used to describe the compression process with varied levels of success. Studying deformation behavior by looking at tableting physics or the consumption of mechanical energy during compaction is also possible. Mechanical energy consumed in a compacted powder bed can be determined by integrating the force–displacement profile collected during the compression process (Higuchi et al., 1955). Consumption of work during compression can then be related to deformation behavior, where more work consumed is typically associated with more plastic deformation (Aburub et al., 2007; Celik and Marshall, 1989). These deformation characteri-

* Corresponding author. Tel.: +1 412 396 1006; fax: +1 412 396 4660.
E-mail addresses: roopwanir@duq.edu (R. Roopwani), buckneri@duq.edu (I.S. Buckner).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.05.040

zation approaches are known to have limitations (Higuchi et al., 1955; Sonnergaard, 1999) and it may be concluded that a single characterization method, universally applicable to the wide variety of materials used in pharmaceutical tablets, has not been identified. Hence, the basis of the work presented here is the notion that a more robust understanding of deformation and compaction behavior should rely on simultaneous analysis of diverse data types.

It has long been recognized that compression behavior is generally affected by multiple mechanical and physical properties that all play a role in determining a powder's response to the application of force. The complexity of the process has frequently been used to explain the unreliability of different compressibility models. Therefore, multivariate analysis, especially principal component analysis, offers the potential to extract the contributions of individual properties from the overall compression behavior. Early applications of multivariate data analysis to tablet compression were aimed at gaining understanding of the connection between formulation/process variables and final product properties (Jover et al., 1996; Pinto et al., 1997a,b). Multivariate methods have been recently used to analyze assortments of compression parameters derived from traditional compaction models (Haware et al., 2009a,b; Klevan et al., 2010). These studies found relationships between these parameters and different underlying properties, including deformation mechanisms and particle size (Klevan et al., 2010). However, it seems reasonable that multivariate analysis can be carried out more efficiently using the original force and displacement data without relying on any particular model's parameters. Applied force and punch displacement data collected during compaction contains extensive mechanical property information that should be quantifiable using multivariate analysis. Accordingly, the first objective of the current project was to apply principal component analysis directly to compression data collected in-die. This technique is expected to allow variation in the compression data that is associated with specific mechanical properties to be quantified. Quantifying this variability would provide a new method for evaluating the behavior of materials in terms of specific properties, such as plasticity.

Principal component analysis (PCA) is a method of data reduction and classification that transforms highly correlated, multidimensional data into a new system of variables called principal components. These new variables, which are linear combinations of the original variables, are selected so that they explain as much of the original data's variability as possible. Each principal component (PC) is uncorrelated and orthogonal to all other PCs. The first principal component (PC1) is oriented in the direction of maximum variability. Principal component 2 (PC2) is orthogonal to PC1and captures the second largest variation in the data set. Therefore, each PC represents a source of variability that is independent of the other sources. In the case of compaction data, one can image that a property, such as plasticity, is associated with some fraction of the variability observed in solid fraction and mechanical energy consumption between materials. Therefore, the principal components are expected to reflect distinct mechanical and physical behaviors, which were convoluted together in the original multivariate data.

The use of in-die compression data to characterize compaction behavior is advantageous due to the ease with which these data can be collected using a limited amount of material. However, these data can produce misleading predictions of a material's plasticity because of the complicating effects of elastic deformation (Sonnergaard, 1999; Sun and Grant, 2001). Analyzing data collected after decompression, ejection and relaxation has been used as an alternative method meant to remove elastic and viscoelastic contributions. Collection of out-of-die data is labor intensive, requires much more material and can be more difficult to properly analyze (Buckner et al., 2010a). Since the majority of reversible deformation occurs during decompression, data collected during unloading can be used to account for elastic deformation during compression. The net effect of compression and decompression will be used to approximate the irreversible response to the applied load, and should allow irreversible deformation behavior to be evaluated separate from any concurrent elastic deformation.

Once the new multivariate approach has been used to characterize a variety of individual materials, it will be applied to study how the deformation behavior of a mixture depends on the properties of its pure components. The tableting behavior of binary mixture has received significant interest in the area of powder compaction; yet predicting a mixture's properties from the behaviors of the constituent materials remains problematic. For example in work relating pressure–density relationships or tensile strength with composition, both linear and non-linear trends have been obtained (Duberg and Nystrom, 1985; Ilkka and Paronen, 1993; Sheikh-Salem and Fell, 1981; Vormans and Lerk, 1989; Wu et al., 2005, 2006; Petra and Mielck, 2005). Modeling approaches have been proposed to make these predictions (Leuenberger, 1985; Van Veen et al., 2004), but their applicability seems to be limited. It is apparent that the complex compaction process is even more complex when heterogeneous materials are taken into account. The multivariate technique discussed above will be used to study the compression behavior of binary mixtures prepared from materials with a variety of deformation mechanisms. This will be done to determine if a consistent relationship exists between the deformation behavior of individual materials and the behavior of their binary mixtures.

2. Materials and methods

2.1. Materials

Eleven tablet excipients and one active ingredient were used in this work. The materials were chosen to represent a range of materials with different behaviors including predominantly plastic, predominantly brittle, highly elastic and viscoelastic materials. Microcrystalline cellulose (Avicel PH-102, FMC Corporation, Philadelphia, PA) and hydroxypropylmethyl cellulose (Methocel CR K4M, Colorcon, Harleysville, PA) (Nokhodchi et al., 1996) represented predominantly plastic materials. Partially pregelatinized corn starch (Starch 1500, Colorcon, West Point, PA) and pregelatinized maize starch (Lycatab PGS, Roquette-Keokuk, IA) served as representatives of plastic materials displaying significant viscoelastic properties. Acetaminophen powder (USP grade, Spectrum Chemical, Gardena, CA) and two types of lactose (anhydrous lactose and lactose monohydrate, Foremost Farms; Baraboo, WI) were selected as brittle materials. Sodium chloride (Lab grade, Fisher Scientific, Fair Lawn, NJ) and two spray-dried sugars, spray-dried lactose (316 grade, Foremost Farms; Baraboo, WI) and spray-dried mannitol (Pearlitol 200 SD, Roquette-Keokuk, IA) served as materials with intermediate deformation behavior. Finally, the characteristically brittle inorganic materials dibasic calcium phosphate dihydrate (DiTab; Rhodia Inc; Cranbury, NJ) and precipitated calcium carbonate (DC grade, JRS Pharma GmbH & Co. KG, Holzmühle, Rosenberg, Germany) were used. The deformation behaviors of the materials used in the work have been widely studied. Although general consensus regarding the predominating deformation behavior of these materials can be found in the literature (Aburub et al., 2007; Buckner et al., 2010b; Klevan et al., 2010; Rowe and Roberts, 1996), the materials were selected to test the newly developed characterization methods that could be applied to new materials with unknown behaviors in the future. Table 1 gives the expected relative plasticity ranking for these materials based on the previous work published for these materials.

Table 1
Relative plasticity ranking for the twelve pure components.

Materials	Deformation behavior[a]	Relative plasticity ranking[a]
MCC (Avicel PH-102)	Soft, plastic	1
Maize starch (Lycatab PGS)	Soft, plastic (viscoelastic)	2
Methocel CR	Soft, plastic	3
Starch 1500	Soft, plastic (viscoelastic)	4
Mannitol SD (Pearlitol 200)	Soft-moderately hard, intermediate plasticity	5
Spray-dried lactose 316	Soft-moderately hard, intermediate plasticity	6
Sodium chloride	Soft, intermediate plasticity	7
Anhydrous lactose	Moderately hard, brittle	8
Lactose monohydrate	Moderately hard, brittle	9
Acetaminophen	Moderately hard, brittle	10
DiTab	Hard, brittle	11
Calcium carbonate	Hard, brittle	12

[a] Aburub et al. (2007), Buckner et al. (2010a), Klevan et al. (2010), and Rowe and Roberts (1996).

Binary powder mixtures were prepared using combinations of acetaminophen (APAP), microcrystalline cellulose (MCC), lactose monohydrate and Methocel. Given in Fig. 1 are the micrographs for these four pure components. These particles were irregularly shaped with similar sizes, although lactose monohydrate appearing to be slightly larger than the other three materials. The binary mixtures were prepared by weighing enough of each powder to produce a total batch of approximately 3 g. The two powders were then mixed with a spatula using geometric dilution. Each combination of materials was prepared in weight proportions of 1:1, 1:3 and 3:1.

All materials were used as received from the suppliers and were equilibrated at ambient temperature (typically 22–24 °C) over a saturated $MgCl_2{}^*H_2O$ solution (32–33% RH) prior to compaction.

2.2. Methods

The particle size distribution of all the twelve powders was determined as provided in Table 2. Particle size was determined using collected fractions from sieving (1000, 500, 250, 180, 150, 125, 75, 53 and 38 μm). Acetaminophen powder which formed aggregates on the sieves was analyzed with optical microscopy, measuring ferret diameter for approximately 1000 particles. The moisture content of the powders in this study (Table 3) was determined using a Computrac moisture analyzer (Max 2000, Arizona Instruments, Phoenix, AZ). Accurately weighed powders (1.72–2.13 g) were placed on aluminum pans, heated to 105 °C, and the corresponding percentage moisture content computed. Although the materials contain water, no change in water content was observed after equilibration, as the materials were stored under controlled humidity. All data should reflect the same moisture content present in the final tablets.

The true density of each pure material (Table 3) was determined by helium pycnometry (Model SPY-6DC, Quantachrome Instruments, Boynton Beach, FL). For binary mixtures, true density (particle density) was calculated using the density of the pure materials and their weight proportion in the mixture. Water-containing powders can be problematic if the water is lost during the density measurement, or if the moisture content changes afterwards. The samples analyzed in the pycnometer showed no change in water

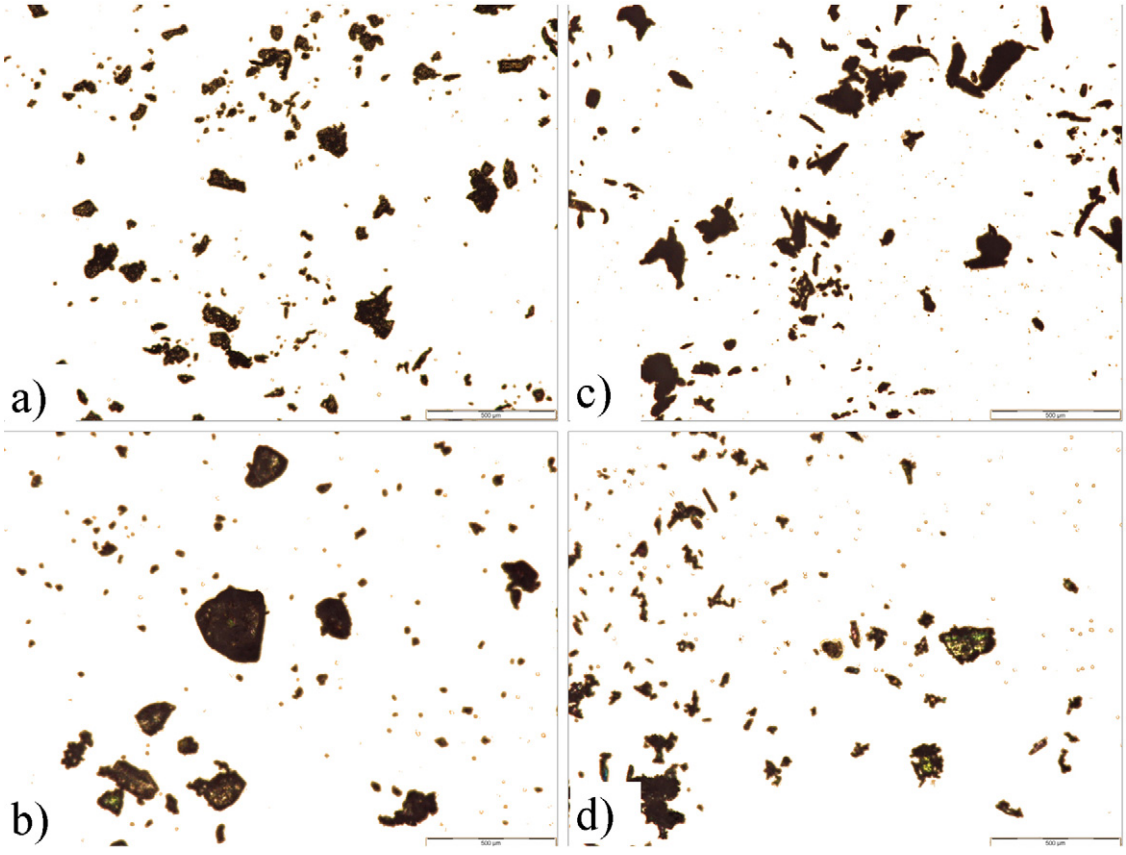

Fig. 1. Micrographs of pure components taken, as received, through a 4× objective: (a) Methocel, (b) lactose monohydrate, (c) Avicel PH-102 and (d) acetaminophen.

Table 2
Particle size distribution for the twelve pure components determined by sieve analysis.

Materials	Percentage undersize								
	<38 μm	<53 μm	<75 μm	<125 μm	<150 μm	<180 μm	<250 μm	<500 μm	<1000 μm
MCC (Avicel PH-102)	–	33.15	41.34	72.76	84.73	93.53	99.34	100	
Maize starch (Lycatab PGS)	11.19	NA	28.71	53.90	68.94	84.06	96.14	99.87	100
Methocel CR	24.84	57.49	65.82	88.54	–	–	99.76	99.89	100
Starch 1500	18.36	38.89	52.21	92.17	97.43	99.54	99.98	100	
Mannitol SD (Pearlitol 200)	0.44	1.66	3.26	40.38	68.75	91.82	99.82	100	
Spray-dried lactose 316	1.52	9.62	15.54	59.77	83.04	97.03	99.98	100	
Sodium chloride	0	0.01	0.03	0.14	0.35	0.95	3.67	41.84	100
Anhydrous lactose	3.29	12.48	17.32	49.57	64.25	79.50	96.12	100	
Lactose monohydrate	4.95	14.02	17.26	50.19	66.13	81.21	95.84	100	
DiTab	2.47	6.98	10.94	30.68	39.32	54.45	93.81	100	
Calcium carbonate	0.25	–	0.74	1.80	2.68	3.57	8.65	66.25	100
Acetaminophen[a]			D50–8 μm			D90–37 μm			

[a] Particles size analysis using optical microscopy.

Table 3
Moisture content, true density and solid fraction (after ejection) for the twelve pure components.

Material	LOD, %Moisture (S.D.)	True density[a] (S.D.)	Solid fraction post ejection
MCC (Avicel PH-102)	4.464 (0.321)	1.574 (0.004)	0.918
Maize starch (Lycatab PGS)	8.639 (0.289)	1.472 (0.004)	0.926
Methocel CR	4.700 (0.184)	1.329 (0.001)	0.939
Starch 1500	8.549 (0.140)	1.500 (0.002)	0.910
Mannitol SD (Pearlitol 200)	0.175 (0.021)	1.482 (0.002)	0.886
Spray-dried lactose 316	0.532 (0.012)	1.541 (0.001)	0.886
Sodium chloride[b]	–	2.169 (0.0002)	0.934
Anhydrous lactose	0.181 (0.005)	1.565 (0.001)	0.873
Lactose monohydrate	0.095 (0.027)	1.541 (0.001)	0.899
Acetaminophen	0.158 (0.074)	1.293 (0.002)	0.880
DiTab	2.864 (0.050)	2.342 (0.01)	0.804
Calcium carbonate	0.290 (0.043)	2.679 (0.01)	0.690

[a] Density from pycnometry.
[b] No significant moisture loss.

content during the density measurement. Furthermore, as the powder's water content remained constant throughout the formation of the compacts, the relevant density should reflect the presence of this water.

All samples were compacted using an Instron universal material testing system (Model 5869, Norwood, MA). Compaction was carried out in a stainless steel, cylindrical die (13 mm in diameter) with 500 mg of powder for each compact. Flat-faced punches were used, and the tooling was lubricated using a 3% (w/v) magnesium stearate suspension in methanol. The powder samples were compressed at a speed of 1 mm/min to a maximum load of 22 kN measured using a 50 kN load cell. For each pure component, three replicate compacts were prepared, whereas five replicate compacts were made for each binary mixture.

In-die solid fraction under load (SF) was calculated on the basis of the true density (ρ), compact mass (m, measured after ejection), diameter of die cavity (d), and powder bed thickness (t). The punch separation distance was corrected for deformation of the tooling by adding the displacement measured during compression of the punches in an empty die to the punch separation measured during compression of each sample. Eq. (1) shows the calculation,

$$SF = \frac{m}{0.25 * \pi d^2 t * \rho} \quad (1)$$

To eliminate changes in solid fraction due to the contribution of elastic deformation, the solid fraction at a given load value (f) measured during compression was corrected by subtracting the change in solid fraction that occurred during decompression from the same load. The corrected solid fraction ($SF_{c/d}$) associated with each load value can be calculated using Eq. (2),

$$SF_{c/d} = SF_c - [SF_d - SF_d(0)] \quad (2)$$

The solid fraction measured during compression (SF_c), the solid fraction measured during decompression (SF_d) and the corrected solid fraction all correspond to the same load value, while $SF_d(0)$ represents the solid fraction when load reaches 0. Applying this equation to every load value produces a function of corrected solid fraction with respect to applied load. Fig. 2 shows how these quantities relate to the collected solid fraction data. This figure also contains the corrected solid fraction for maize starch (Lycatab).

Most of the physical processes occurring during compaction consume or produce mechanical energy. Therefore, compaction energetics provide an alternate set of data, derived from force and punch displacement, that can be used to study deformation behavior. Compression work and decompression work were determined

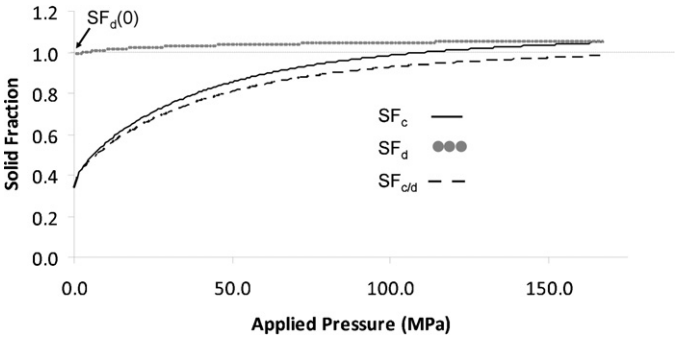

Fig. 2. A typical solid fraction versus pressure profile collected during compression (—) and decompression (●●●) and the calculated $SF_{c/d}$ (- -) profile for maize starch powder (as received). The final solid fraction before ejection of the tablet has been labeled on the graph as $SF_d(0)$.

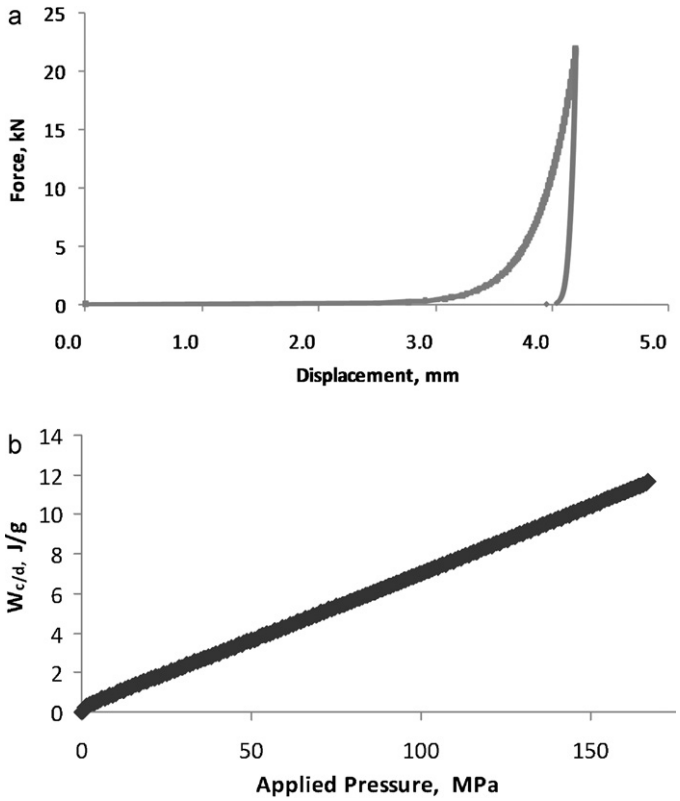

Fig. 3. (a) A typical force–displacement profile for compression and decompression of acetaminophen powder (as received) and (b) the resulting $W_{c/d}$ versus pressure profile obtained by numerical integration of the force–displacement data.

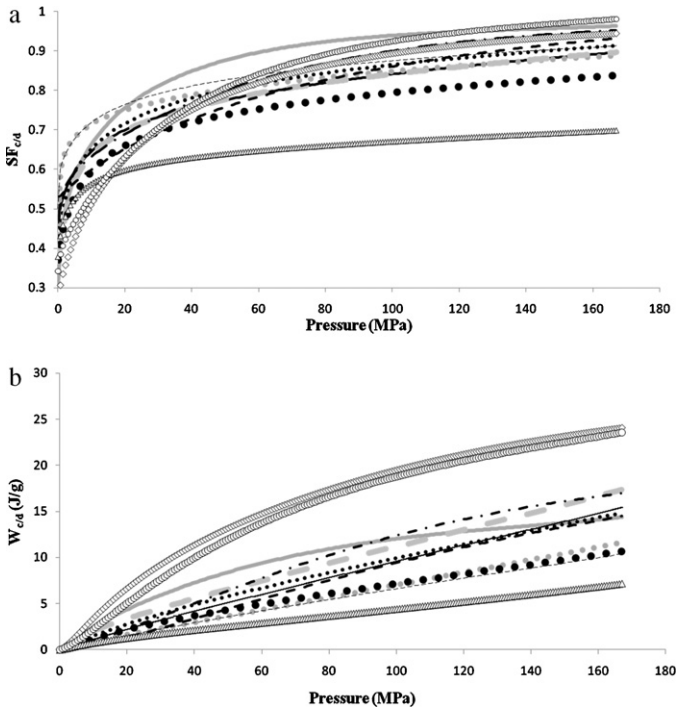

Fig. 4. Data used for principal component analysis (a) $SF_{c/d}$ versus pressure and (b) $W_{c/d}$ versus pressure for compaction of the 12 pure-component powders used in the study. Avicel PH-102 (◊), anhydrous lactose (▬▬), acetaminophen (● ● ●), $CaCO_3$ (△△△), Methocel (▬▬), maize starch (○○○), Lactose 316 (● ● ●), Pearlitol (▬ ▬ ▬), starch (▬ ▪ ▬), NaCl (▬ ▬ ▬), DiTab (● ● ●), and lactose monohydrate (- - - - -).

by numerically integrating force–displacement curves using Eqs. (3) and (4),

$$\text{Work}_c = \int_{\text{Initial}}^{\text{Maximum}} f \cdot d(\text{displacement}) \quad (3)$$

$$\text{Work}_d = \int_{\text{Maximum}}^{\text{Final}} f \cdot d(\text{displacement}) \quad (4)$$

Since the work of decompression corresponds to energy associated with reversible or elastic deformation, a parameter specific to irreversible work input during compression can be obtained by summing Work_c and Work_d. Eq. (5) shows the calculation of the work of compression/decompression ($W_{c/d}$),

$$W_{c/d} = \int_{\text{Initial}}^{\text{Final}} f \cdot d(\text{displacement}) = \text{Work}_c + \text{Work}_d \quad (5)$$

Work_c and Work_d can be determined as functions of applied pressure by repeatedly evaluating Eqs. (3) and (4) at different maximum displacements. Fig. 3a illustrates a representative force–displacement profile, while Fig. 3b shows the resulting $W_{c/d}$ function with respect to applied load for acetaminophen. A fraction of the $W_{c/d}$ will be converted to heat due to friction and other processes, and it can be informative to measure all of these values separately (Buckner et al., 2010a). However, the analysis technique used here should not be significantly affected, since the variation associated with these processes should be largely distinct from the variation related to plastic deformation.

Solid fraction and mechanical work data were obtained at force intervals of 0.1 kN between 0 and 22 kN. The measured displacement used in both solid fraction and mechanical work calculations was corrected by conducting compression experiments using an empty die. Replicate measurements were averaged at each load value prior to subsequent analysis with the relative standard deviation of $SF_{c/d}$ between replicates being <2% in all cases. For the mixtures, this provides evidence that the mixtures were relatively uniform since this standard deviation is based on tablets made from roughly 84% of the total mass of each mixture. Since almost the entirety of each powder mixture was compressed into tablets, the observed relative standard deviation indicates an acceptable level of uniformity throughout the mixture.

2.3. PCA

Principal component analysis (PCA) was performed using $SF_{c/d}$ and $W_{c/d}$ data corresponding to loads up to 22 kN. Two separate analyses were carried out. The first involved data collected during compression of single component powders. The second analysis involved the same pure components with the addition of binary mixtures made with selected materials.

The data matrix for the first analysis included the 12 pure materials, which constitute the 12 objects of the data matrix. The $SF_{c/d}$ and $W_{c/d}$ functions evaluated at 220 different loads between 0 and 22 kN constitute 440 variables for each material. Hence, the initial data matrix was 12×440. The second analysis included 21 materials (12 single components and 9 binary mixtures), producing a 21×440 data matrix. Shown in Fig. 4 are the data (pressure, $W_{c/d}$, $SF_{c/d}$) collected for all 12 pure components used in this study. In the actual application of PCA, the materials were compared over 440 dimensions, where half of those dimensions were based on $W_{c/d}$ determined at specific loads and the other half were based on $SF_{c/d}$. As PCA is meant to be a data reduction technique, this data matrix should be sufficiently large. If the number of significant principal components is much less than the number of samples, 12 in this case, meaningful information can be gained with PCA. Even as the

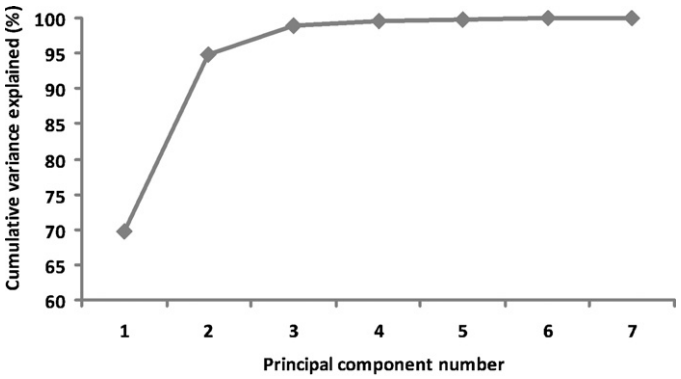

Fig. 5. Cumulative percentage of variance in $SF_{c/d}$ and $W_{c/d}$ captured by the PCA model as a function of the number of principal components.

eigenvalues of later principal components fall to zero, the earlier principal components remain valid.

Prior to analysis, the two data types were mean-centered and scaled between 0 and 1. This is a common preprocessing step that is important when attempting to interpret the first principal component. Finally, the scores and loadings of the principal components were investigated. Preprocessing and PCA related calculations were carried out using The Unscrambler® X program (CAMO Technologies, Woodbridge, NJ)

3. Results and discussion

3.1. PCA on pure components

The importance of each principal component in the overall analysis can be visualized by looking at the amount of variance present in the data that can be explained by each principal component (Wise et al., 2003). A plot of the cumulative percent variance explained by each PC is shown in Fig. 5. The plot shows that the 1st principal component explained 70% of the original dataset's total variance, and further indicates only minor reduction in error beyond two principal components. Only the 1st principal component will be discussed further.

The loading and score plots for the 1st PC are in Fig. 6a and b, respectively. Examining the loading intensity of the 1st PC for both the $W_{c/d}$ and $SF_{c/d}$ variables suggests a connection between this PC and irreversible deformation in the powder. Both of these data types show low loading at small applied forces. The loading of both $W_{c/d}$ and $SF_{c/d}$ increases as the associated force increases to a point where the loading becomes relatively constant. This shape is consistent with the expected changes in the contribution that irreversible deformation makes to consolidation as compaction progresses.

At low pressure, consolidation is dominated by particle rearrangement and fragmentation. Accordingly, the loading of the solid fraction variables is negative at the lowest applied pressures. The extent to which plastic deformation contributes to changes in solid fraction or mechanical energy consumption is likely very low, initially, where brittle fracture is a major contributor to solid fraction changes. Therefore, the loading scores show that materials with large changes in solid fraction at very low pressures are likely more brittle in nature.

As the applied pressure increases, particle rearrangement becomes hindered and much of the possible fragmentation has already occurred at lower pressures. The contribution of plastic deformation to the variability of both solid fraction and mechanical work becomes more and more significant as pressure increases. According to these loadings, materials with large changes in solid

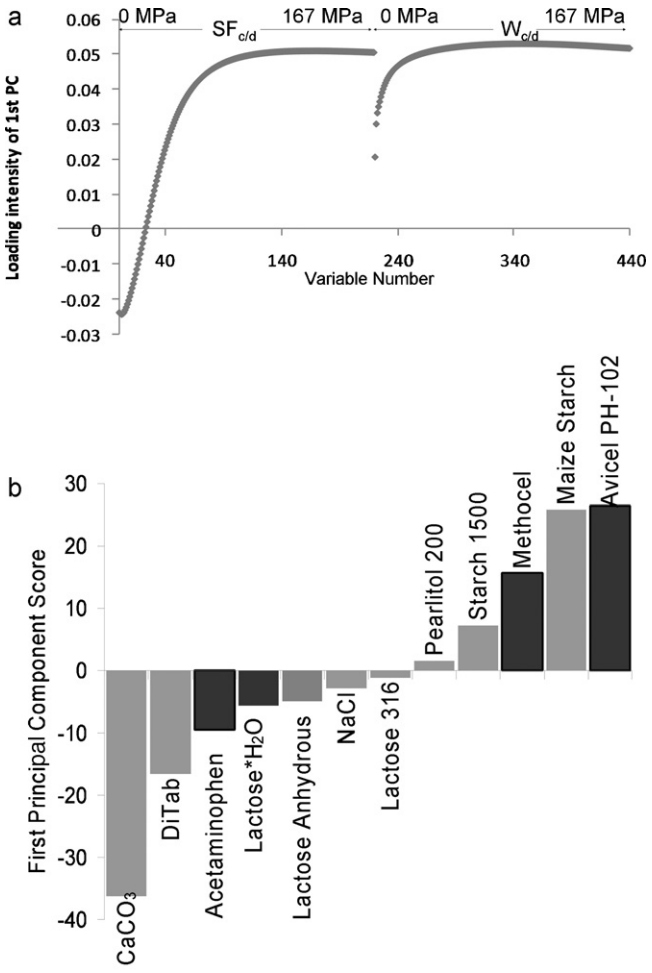

Fig. 6. Loading plot (a) and score plot (b) of 1st PC based on the 12 pure materials only. In the loading plot (a), the variables numbered 1–220 correspond to $SF_{c/d}$ values calculated between 0 and 167 MPa of applied pressure at 0.8 MPa intervals. The variables numbered from 221 to 440 are the $W_{c/d}$ values measured over the same range of pressures.

fraction and work consumption at intermediate pressures will display larger scores on the 1st PC. This is consistent with the interpretation that this score reflects primarily the propensity for plastic deformation.

Eventually, the solid fraction approaches 1, so even plastic deformation becomes improbable. At the upper end of the pressure range, the density changes result solely from elastic deformation. Elastic deformation's dominance of the compaction data variability at high pressures seems to be reflected in the leveling off of the 1st PC's loading plot. This behavior is again consistent with the conclusion that this PC is connected to plastic deformation, specifically, since both the solid fraction and work data have had the elastic contribution removed.

Although the data reflect deformation of the particles under load, the data are also affected by variation due to other processes, such as repacking of the powder. Plus, there are multiple types of deformation (both reversible and irreversible) potentially contributing to the data matrix. A connection between the relative loading of PC1 at each pressure and the relative contribution of plastic deformation to the solid fraction and mechanical energy measured has been observed. At low pressures, variation in solid fraction is most likely due to fragmentation and repacking. The PC1 scores for materials with large variation in the data at low pressure would be shifted in the negative direction, indicating less plastic

behavior. Materials with large variation in the data collected at high pressure would produce more positive PC1 scores. The loading values are, therefore, consistent with the relative contribution that plastic deformation is expected to make to the data at different pressures.

It is true that data corresponding to loading values near zero do not affect the PC1 score. However, it is just as easy to collect these data as it is to ignore them. The presence of these points in the data matrix does not detract from the results.

The first PC scores of the twelve single materials were found to have a rank order consistent with the expected relative plasticity described previously for these materials (Table 1). The agreement between the score on the 1st PC and the a priori prediction of plasticity for these common materials strongly indicates that this principal component is associated with a material's irreversible deformation behavior. In combination, the scores and loadings for the 1st PC provide even stronger support for this connection to plastic deformation.

One goal of this work was to produce a reliable way of estimating a new material's rank order plasticity or brittleness relative to commonly used tableting excipients. It is important to emphasize that the analysis depends on the inclusion of data from familiar materials with behaviors spanning the range of interest. We feel that the materials included in this study reflect a generally useful comparison set, yet the approach could easily be adjusted to include other materials or testing conditions. As with many techniques, the results are specific to the analytical details.

Quantifying a material's propensity for plastic deformation is not trivial, as the number of different methods proposed for this purpose will attest. Furthermore, the ability of $W_{c/d}$ and $SF_{c/d}$ to differentiate the materials' plasticities is not surprising as both work and solid fraction data are used with various models to characterize the predominating deformation mechanisms of pharmaceutical materials (Buckner et al., 2010b). However, the PCA approach described here has several advantages over traditional compression models. First, this approach can be applied to the entire pressure range, unlike models such as Heckel's. In general, the assumptions underlying the available models are also not required. Finally, through PCA we can simultaneously analyze multiple data types to generate a single, consistent prediction.

3.2. PCA on binary mixtures

The PCA method constructed above covered a wide range of pharmaceutical materials with diverse physical and mechanical properties. The initial PCA results were used to select materials with distinct deformation behaviors for binary mixture formation. Two predominantly brittle materials, acetaminophen and lactose monohydrate, and two predominantly plastic materials, Avicel PH-102 and Methocel, were selected. Three combinations were evaluated to look at brittle-brittle (acetaminophen/lactose monohydrate), plastic-plastic (Avicel PH-102/Methocel) and brittle-plastic (acetaminophen/Avicel PH-102) behaviors. Each mixture was prepared in weight ratios of 1:3, 1:1 and 3:1, so that 9 binary mixtures were prepared in total.

Data for the 12 pure components and the 9 binary mixtures were subjected to PCA. The 1st PC scores were used as a measure of the relative deformation behavior displayed by each sample, where large, positive values indicate more plastic deformation. Each mixture was compared to its pure components by plotting the 1st PC score with respect to weight fraction. These plots are shown in Fig. 7a–c. There appears to be a linear relationship between a mixture's PC 1 score and the weight fraction of its components, although deviations from linearity are observed in select cases.

For the mixtures containing both a plastically deforming (Avicel PH-102) and a brittle material (APAP), the relationship

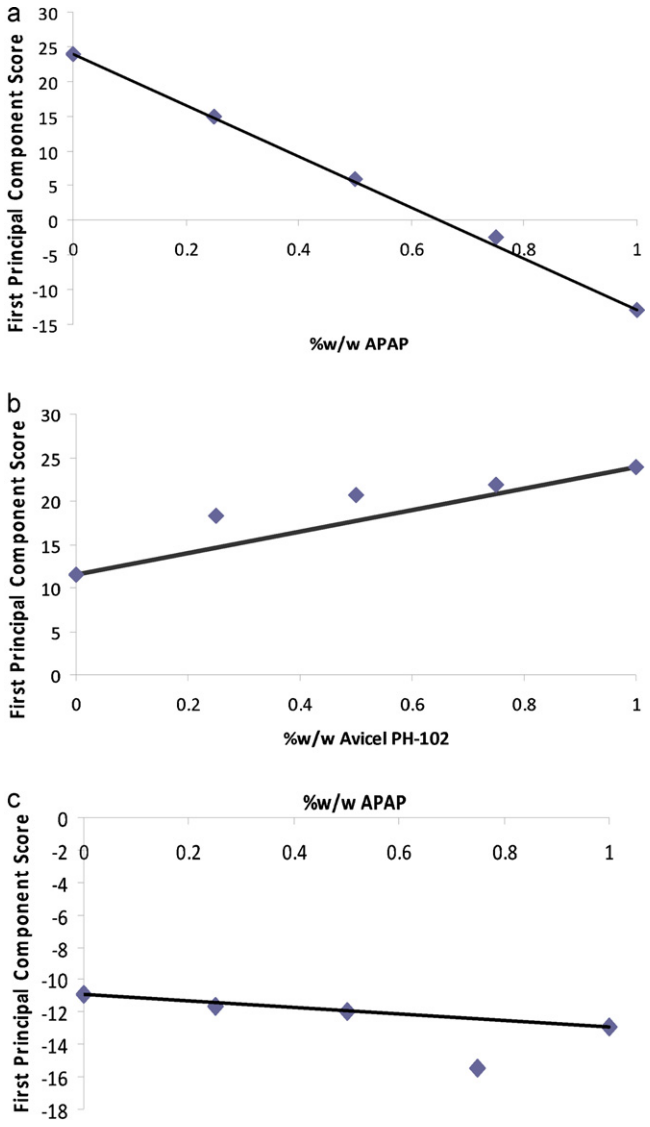

Fig. 7. First PC score versus mixture composition for three different binary mixtures composed of (a) acetaminophen and Avicel PH-102, (b) Avicel PH-102 and Methocel, (c) acetaminophen (APAP) and lactose monohydrate. The solid lines reflect weighted averages of the PC values of the pure components.

between the score values and the mixture composition was linear (Fig. 7a) over the entire composition range. When the deformation properties of a mixture's components contribute to the overall behavior strictly according to their weight proportion in the mixture, it would be classified as ideal mixing behavior. Such ideal behavior has been reported previously (Duberg and Nystrom, 1985).

For the mixtures of two plastically deforming materials (Avicel PH-102 and Methocel) a slight positive-deviation from ideal mixing behavior was observed (Fig. 7b). In other words, the mixtures appeared to behave more plastically than would be predicted from the behaviors of the components. It has been reported previously that softer materials can have a greater effect on the deformation behavior observed in mixtures than more rigid components (Busignies et al., 2006; Van Veen et al., 2000). The behavior has typically been attributed to a particulate-level effect, where the softer particles deformation preferentially and dominate the overall behavior. This would cause the softer material to contribute more to the overall behavior than its weight

fraction would indicate. Although this explanation is reasonable, the effect appears to be fairly minor in the present study. In fact, the deviation from linearity is caused mainly by the pure Methocel score, since the relationship is highly linear for the four samples containing Avicel PH-102 ($R^2 = 0.99$ between 25 and 100%). Despite the apparent, positive deviation in this combination, it does seem that the behavior of the mixture could be roughly predicted from the properties of the individual constituents nonetheless.

Shown in Fig. 7c is the score plot for the binary mixtures of primarily brittle materials (acetaminophen and lactose). These data, again, show ideal mixing behavior with the exception of the 75% APAP sample, which displayed a significant negative deviation. Due to this unusual behavior, this mixture was remade and the analysis was repeated. Very little difference was found between the first preparation of this sample and the second. Although the 75% APAP sample results were reproducible, this point seems to be an outlier. With this one exception, ideal mixing behavior between the two brittle materials appears to exist.

4. Conclusion

In the work reported here, a solid fraction parameter ($SF_{c/d}$) and a mechanical work parameter ($W_{c/d}$) were obtained in-die at 0.1 kN increments up to 22 kN of applied load. The use of these parameters was believed to reduce the effect of elastic deformation on plasticity predictions. PCA was used to find the principal component that explains the maximum variability in complex, multi-dimensional compression data. The 1st principal component of this dataset was shown to be linked to relative plasticity of the materials. The ranking of several commonly characterized materials with respect to this PC matched the expected plasticity ranking for these materials.

The application of PCA to deformation behavior studies, as described in this work, carries various advantages. PCA has the ability to separate the influence of irreversible deformation from other physical and mechanical behaviors that affect compression data. This technique can integrate similar information contained by multiple data types into a single parameter indicative of deformation behavior without focusing on a particular data range. Thus, valuable information is not lost during analysis of the collected data. Using PCA, plastic deformation can be related, specifically, to the 1st principal component of $SF_{c/d}$ and $W_{c/d}$ data. Since the effects of reversible deformation have been accounted for, in-die compression data can be used to efficiently characterize materials' deformation mechanisms.

This analysis was expanded to the study of deformation behavior in binary mixtures. The plasticity-indicating PC of binary mixtures containing at least 1 brittle component showed linear behavior with respect to weight proportion of the components. In the case of strictly plastic mixtures, non-linearity was found. Binary mixtures of Avicel PH-102 and Methocel showed a positive deviation from linearity, even thought the deviation seemed to be limited. This effect may be related to particle-level interaction between two plastically deforming materials. Nevertheless, the method described above seems to offer a very effective way to predict the deformation behavior of simple powder mixtures using a plasticity assessment based on principal components analysis of in-die compression data.

Acknowledgements

The authors are greatly appreciative of the funding provided for the research described herein by the Mylan School of Pharmacy at Duquesne University.

References

Aburub, A., Mishra, D., Buckner, I., 2007. Use of compaction energetics for understanding particle deformation mechanism. Pharm. Dev. Technol. 12, 405–414.
Buckner, I.S., Friedman, R.A., Wurster, D.E., 2010a. Using compression calorimetry to characterize powder compaction behavior of pharmaceutical materials. J. Pharm. Sci. 99, 861–870.
Buckner, I.S., Wurster, D.E., Aburub, A., 2010b. Interpreting deformation behavior in pharmaceutical materials using multiple consolidation models and compaction energetics. Pharm. Dev. Technol. 15, 492–499.
Busignies, V., Leclerc, B., Porion, P., Evesque, P., Couarraze, G., Tchoreloff, P., 2006. Investigation and modelling approach of the mechanical properties of compacts made with binary mixtures of pharmaceutical excipients. Eur. J. Pharm. Biopharm. 64, 51–65.
Celik, M., Marshall, K., 1989. Use of compaction simulator system in tableting research. Drug Dev. Ind. Pharm. 15, 759–800.
Duberg, M., Nystrom, C., 1985. Studies on direct compression of tablets: XII. The consolidation and bonding properties of some pharmaceutical compounds and their mixtures in Avicel 105. Int. J. Pharm. Prod. Manufact. 6, 17–25.
Gurnham, C.F., Masson, H.J., 1946. Expression of liquids from fibrous materials. Ind. Eng. Chem. 38, 1309–1315.
Haware, R.V., Tho, I., Bauer-Brandl, A., 2009a. Application of multivariate methods to compression behavior evaluation of directly compressible materials. Eur. J. Pharm. Biopharm. 73, 148–155.
Haware, R.V., Tho, I., Bauer-Brandl, A., 2009b. Multivariate analysis of relationships between material properties, process parameters and tablet tensile strength for α-lactose monohydrate. Eur. J. Pharm. Biopharm. 73, 424–431.
Heckel, R.W., 1961a. Density–pressure relationships in powder compaction. Trans. Met. Soc. AIME 221, 671–675.
Heckel, R.W., 1961b. An analysis of powder compaction phenomena. Trans. Met. Soc. AIME 221, 1001–1008.
Higuchi, T., Nelson, E., Busse, L.W., 1955. The physics of tablet compression 7. Determination of energy expenditure in the tablet compression process. J. Am. Pharm. Assoc. Sci. Ed. 44, 223–225.
Ilkka, J., Paronen, P., 1993. Prediction of the compression behavior of powder mixtures by the Heckel Equation. Int. J. Pharm. 94, 181–187.
Jover, I., Podczeck, F., Newton, M., 1996. Evaluation by a stastically designed experiment, of an experimental grade of microcrystalline cellulose, Avicel 955, as a technology to aid the production of pellets with high drug loading. J. Pharm. Sci. 85, 700–705.
Klevan, I., Nordstrom, J., Tho, I., Alderborn, G., 2010. A statistical approach to evaluate the potential use of compression parameters for classification of pharmaceutical powder materials. Eur. J. Pharm. Biopharm. 75, 425–435.
Leuenberger, H., 1985. Compression of binary powder mixtures and solubility parameters of solids. Int. J. Pharm. 27, 127–138.
Nokhodchi, A., Ford, J.L., Rowe, P.H., Rubinstein, M.H., 1996. The effects of compression rate and force on the compaction properties of different viscosity grades of hydroxypropylmethylcellulose 2208. Int. J. Pharm. 129, 21–31.
Petra, M.B., Mielck, J.B., 2005. The difficult in assessment of the compression behavior of powder mixtures: double layer tablets versus arithmetic additive rule. Eur. J. Pharm. Biopharm. 60, 133–145.
Pinto, J.F., Podczeck, F., Newton, J.M., 1997a. Investigation of tablets prepared from pellets produced by extrusion and spheronisation. Part I: The application of canonical analysis to correlate the properties of the tablets to the factors studied in combination with principal component analysis to select the most relevant factors. Int. J. Pharm. 147, 79–93.
Pinto, J.F., Podczeck, F., Newton, J.M., 1997b. Investigation of tablets prepared from pellets produced by extrusion and spheronisation. II. Modelling the properties of the tablets produced using regression analysis. Int. J. Pharm. 152, 7–16.
Rowe, R.C., Roberts, R.J., 1996. Mechanical properties. In: Alderborn, G., Nystrom, C. (Eds.), Pharmaceutical Powder Compaction Technology. , first edn. Marcel Dekker Inc., New York, pp. 298–304.
Sheikh-Salem, M., Fell, J.T., 1981. Compaction characteristics of mixtures of materials with dissimilar compaction mechanisms. Int. J. Pharm. Tech. Prod. Mfr. 2, 19–22.
Sonnergaard, J.M., 1999. A critical evaluation of the Heckel equation. Int. J. Pharm. 193, 63–71.
Sun, C., Grant, D.J.W., 2001. Influence of elastic deformation of particles on Heckel analysis. Pharm. Dev. Technol. 6, 193–200.
Van Veen, B., Maarschalk, K., Bolhuis, G.K., Zuurman, K., Frijlink, H.W., 2000. Tensile strength of tablets containing two materials with a different compaction behaviour. Int. J. Pharm. 203, 71–79.
Van Veen, B., Maarschalk, K., Bolhuis, G.K., Frijlink, H.W., 2004. Predicting mechanical properties of compacts containing two components. Powder Technol. 139, 156–164.
Vormans, H., Lerk, C.F., 1989. Densification behaviour of powder mixtures in relation to their binding properties. Chem. Eng. Technol. 61, 256–257.
Walker, E.E., 1923. The properties of powders. Part VI the compressibility of powders. Trans. Faraday Soc. 19, 73–82.
Wise, B.M., et al., 2003. PLS_Toolbox 3.0 Manual. Eigenvector Research Inc.
Wu, C., Best, S.M., Bentham, A.C., Hancock, B.C., Bonfield, W., 2005. A simple predictive model for the tensile strength of binary tablets. Eur. J. Pharm. Sci. 25, 331–336.
Wu, C., Best, S.M., Bentham, A.C., Hancock, B.C., Bonfield, W., 2006. Predicting the tensile strength of compacted multi-component mixtures of pharmaceutical powders. Pharm. Res. 23, 1898–1905.