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The use of energy indices in estimating powder compaction functionality of mixtures in pharmaceutical tableting

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Abstract

A series of binary powder blends comprising of microcrystalline cellulose (Avicel® PH101), α-lactose monohydrate or theophylline anhydrous were prepared in order to investigate the densification of binary pharmaceutical powder mixes under compaction pressure. It is postulated that the use of derived energy parameters, as well as various evolved indices, calculated from the work expended during the fabrication and/or rupture of a compact can be employed to quantitatively predict the compaction properties of pharmaceutical powder mixes comprised of the same constituents. The relationship between the net work of compression normalized to powder volume and the resulting compact strength for mix constituents can be used to define a pharmaceutical formulation space in which compact mechanical properties can be estimated for other 'virtual mixes' of the same constituents in different proportions. The approach is successfully applied to the prediction of the mechanical properties of a ternary mix of these constituents.

Keywords: Force–displacement profile; Powder densification; Compact mechanical strength; Work of compression

1. Introduction

Many factors influence powder flow and compaction including physical and mechanical properties of the materials, environmental effects, as well as processing equipment design (Alderborn and Nyström, 1996). This, in part, is the origin of the great difficulties encountered in pharmaceutical solid dosage form formulation and technological manipulation of powders. While physical properties clearly influence powder flow and compaction, systematic research on the effects of the mechanical properties of materials has only re-

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cently been evident as a result of the rise in the use of instrumented tableting presses and compaction simulators in pharmaceutical research. This has led to a preponderance of publications dealing with the development of energy and fundamental forces during powder compaction. Several authors have attempted to identify the various stages during the compression of powders (Macleod, 1983; Jones et al., 1985; Wray, 1992). Current consensus of opinion exists regarding the following defined stages; the initial rearrangement of particles or grains, disaggregation of the grains to primary particles if the particles are aggregates, fragmentation of the particles, their plastic deformation and their elastic deformation. Contrary to previously held explanations, the observation of a strict discontinuity between these stages is unlikely. Rather, the phases arise simultaneously in powder beds depending on the applied load, each contributing to the overall physico-mechanical characteristics of a material subjected to compression force. Furthermore, certain processes appear to be more dominant than others within a specified domain of applied pressure. This dichotomy serves to confound traditional volume fraction analysis of force–displacement curves and the attempts to correlate this with the measured strength of compacts. For instance, the use of the volume fraction alone cannot explain why tablets with the same total porosity are not necessarily equivalent.

Surface energy changes and elastic deformation properties may influence individual particle true areas of contact. This in turn has direct influence on the technological potential of tableting formulations. It would seem prudent therefore, to attempt to exploit the energy characteristics of the tableting process as a tool in the mechanical evaluation of tableting formulations. Indeed, many authors have developed fundamental research in this regard with the result that an examination of the pharmaceutical literature essentially reveals two distinct trends in the approach to this problem. One is to attempt to theoretically identify parameters pertaining to the problem (Antikainen and Ylirusi, 1997; Ylirusi et al., 1997) while the other is to quantitatively analyze force–displacement profiles and compare the outcomes to practical experience (Hoblitzell and Rhodes, 1990; Ragnarsson, 1996).

The present work identifies the utility of the latter approach when used in conjunction with the former approach. The complexity of the compaction process has necessitated the use of single pure materials in the development of fundamental research on this subject. However, tablet formulations typically involve mixes of a number of ingredients which act in concert to define the compact physico-mechanical characteristics. Thus, the extension of this research to the prediction of the compaction behaviour of powder blends is of interest. It is postulated that the use of derived energy parameters, as well as various evolved indices, revolving around the work expended during the fabrication and/or rupture of a compact can be employed to quantitatively predict the compaction properties of pharmaceutical powder mixes comprised of the same constituents.

2. Background

The transformation of a collection of particles, under increasing stress, to a cohesive compact involves the formation of interparticle liaisons. These liaisons have their genesis in the intermolecular forces that arise at the surface of the particles during plastic deformation and fragmentation of the particles (Führer, 1996). The energy of compression transmitted to the consolidating powder bed is translated into the energy of adhesion by the weak van der Waals forces operating over short distances as well as the partial fusion of material at the points of particle contact. Successful powder compaction resulting in a unified cohesive structure depends on the nature of these surface interfaces as well as on the magnitude of interparticle stress relaxation that occurs upon cessation of the applied pressure. Regardless of the type of liaison existing between particles, the compression of a powdered material is manifested by a diminution of the apparent volume which is in turn reflected by the increase in relative density and the decrease in bulk porosity.

Many researchers have attempted to characterize the deformation of powders under pressure

notably Heckel, (1961) using metal powders, Cooper and Eaton, (1962) using ceramic powders, and Kawakita and Lüdde, (1971) using organic powders such as in the manufacture of pharmaceutical tablets. Their proposed relationships are described by empirical equations between the applied stress and the physical properties of the powders, that is, between pressure and volume and between internal strain and deformation.

Although the classical equation of Heckel is often employed in pharmaceutical powder compaction studies, the relationship frequently fails when applied to pharmaceutical materials subjected to pressures typically used in tableting. As a result, force–displacement profiles may be better analyzed and scrutinized for predictive purposes if energy parameters are used for exploitation of the data. This would also render the analysis closer to the energy considerations implicated in tablet formation as presented above.

Recently, a number of reports have indicated that the density of molecular crystals may also increase by compression (Ponchel and Duchêne, 1989; Dwivedi et al., 1992) resulting in apparent densities of greater than unity. The phenomenon of negative porosities was observed for ASA compacts at comparatively modest pressures of 100 MPa (Pederson and Kristensen, 1994). Experiments with polymeric materials, such as celluloses, at similar compaction pressures indicated that these materials may also exhibit increasing material density since there is pronounced upward curvature in the latter portion of the Heckel plots (Ponchel and Duchêne, 1989). Thus, these observations support the need to investigate other means of exploiting force–displacement profiles.

2.1. Densification energy quantitation

As such, compression cycles can be divided into three phases as illustrated in Fig. 1 (Fell, 1983). Each phase can be globally attributed to predominant physico-mechanical events that transpire in the course of tablet fabrication. Phase P_1 corresponds to a rearrangement and packing of the powder particles without any measurable increase in pressure. It is important to emphasize here that although a pressure increase may not be evident during this phase, this occurrence is merely a function of the sensitivity of the pressure transducer employed in the study. Indeed Gu et al. (1992) have identified this region as critically important during bulk flow of powders when particles are subjected to minimal compression stress. Typically this phase is omitted from energy parameterization of force–displacement curves, however by so doing, a significant portion of the profile is not accounted for. Phase P_2 is characterized by the augmentation of pressure until the maximum desired pressure is attained. During this phase the particles fragment, deform plastically and rearrange resulting in varying degrees of particle cohesion. Finally during phase P_3 the applied stress is progressively released whereupon the compact begins to undergo a period of elastic recovery resulting in a relative decrease in compact density.

It is possible to identify many calculable energy parameters from a force–displacement profile useful in describing and/or estimating the compactibility of a material (de Blaey et al., 1971; Antikainen and Ylirusi, 1997). These associated areas of evolved energy during the compaction process energies in relation to the aforementioned compression phases are defined in Fig. 1 as follows: E_1, energy lost due to friction between particles and surfaces of the compaction cell; E_2, energy used in the realization of a compact; E_3, energy lost by the elastic deformation of a compact with:

$$E_{\text{ideal}} = E_1 + E_2 + E_3 \quad (1)$$

The use of E_3 in derived compactibility indices must be viewed with caution since the determination of this value is inherently more uncertain than that of the other values. Equipment instability, compact cell deformation and the precision of telemetry transducers may contribute to the errors incorporated in what is typically a relatively small quantity.

These values may be further normalized to the powder mass or volume used to fill the compression cell. Standard industrial rotary tableting machines operate on the principle of constant volume filling of the tablet die in order to generate tablets of constant mass. The use of constant true

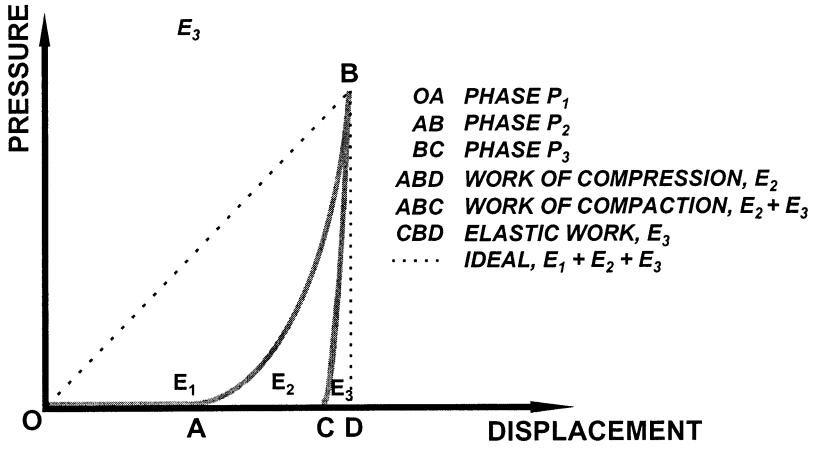

Fig. 1. Typical force–displacement compression profile defining various phase during the compression process and the resulting energies.

volume is particularly important when comparing materials since the response to punch movement (i.e. punch force) is a function of the volume of solid in the die and not its weight (Marshall, 1989).

2.2. Cohesion and mechanical strength quantitation

Since energy is needed for the compression of materials, the correlation of this energy input with

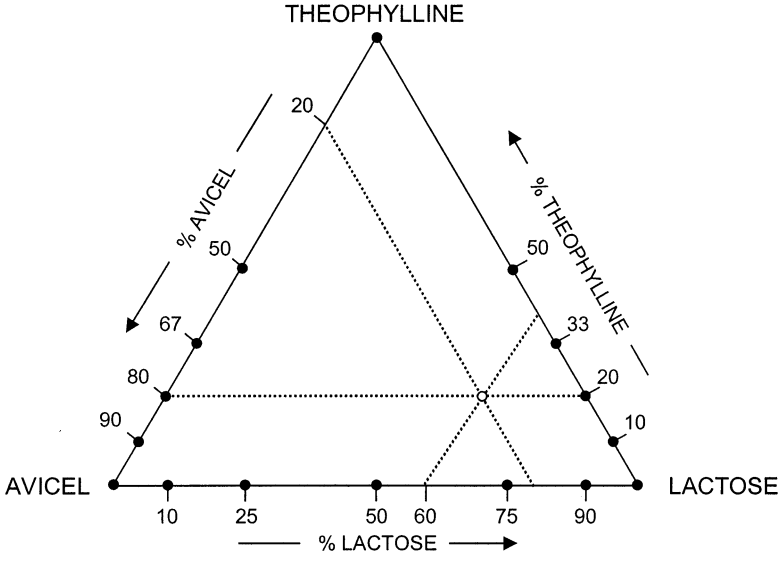

Fig. 2. Powder blends under consideration. Binary blends denoted by ● and test ternary blend consisting of 20% theophylline anhydrous, 20% Avicel® and 60% α-lactose monohydrate denoted by ○, analogous to the test binary blend consisting of 20% theophylline anhydrous and 80% cellactose.

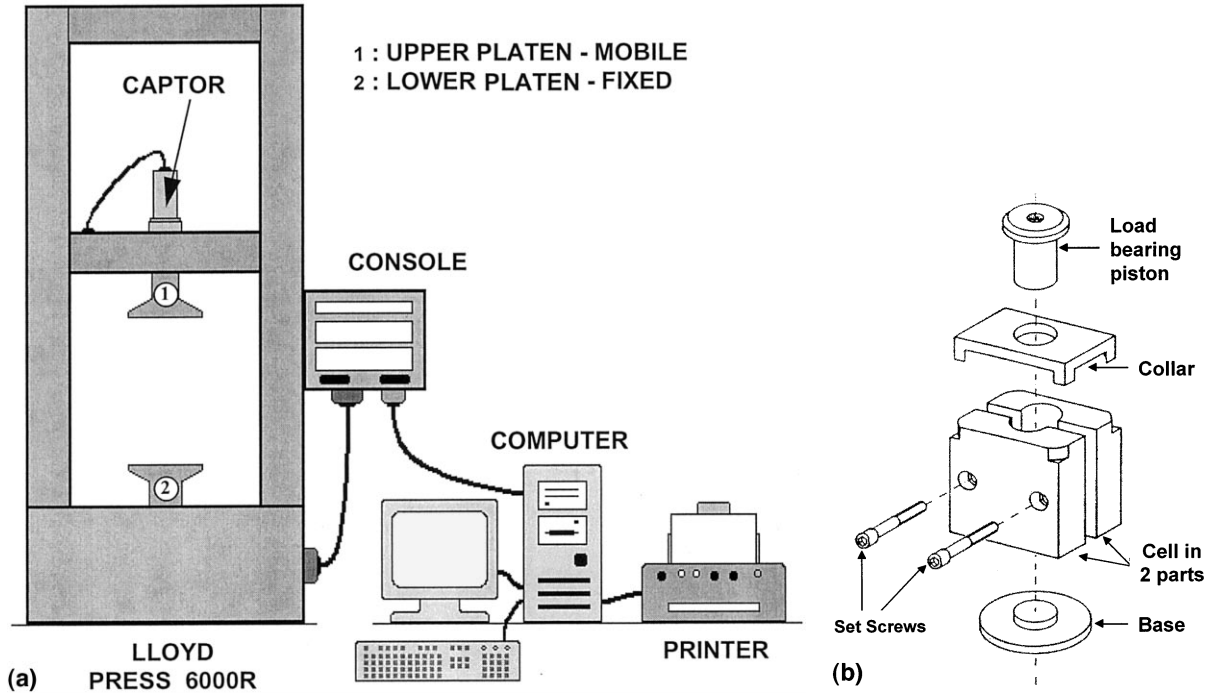

Fig. 3. (a) Lloyd uniaxial press, (b) demountable consolidation cell.

the resulting mechanical properties and ensuing energy of the compact is a logical extension (de Blaey and Polderman 1971). The importance of bonding strength on network calculations can be identified by assuming that the strength of the tablet is a reflection of the bonding that has occurred during compaction.

Tablets are known to be anisotropic. Radial tensile strengths tend to be larger than axial tensile strengths since it is a measure of the average value of the entire tablet resistance, whereas axial tensile strength is a measure of the weakest plane in the tablet (Duberg and Nyström, 1986).

It is generally known that a uniform stress is not generated in all parts of a compact during tableting, but that the stress and density in compressed powders are localized (Moe and Rippie, 1997). The result is that tablets are anisotropic in their internal structure which can lead to abherent results when orientation-specific tests like hardness measurements are used to characterize resulting tablets (Jarosz and Parrott, 1982; Doelker et al., 1989). The exploitation of the entire force–displacement curve during tablet tensile testing may alleviate this problem since the profile is reflective of the total energy dispersion that transpires during resistance of the compact to applied stress (Moschos and Rees, 1986). Nevertheless, the prudent application of these provisions still permits the classic measurement of tablet strength to be used as a marker for the extent of particle cohesion within a tablet (Fell and Newton, 1970).

The mechanical properties of a material play an important role in powder compaction by influencing the true area of contact between particles and thus powder cohesion. As a result, the assessment of the compaction performances of the formula ingredients is an important aspect of tablet product design and development. As most tablets consist of more than one ingredient, the

prediction of the compaction properties of mixtures from those of the individual components is of obvious interest.

3. Materials and methods

Materials of Pharmacopoeial grade were obtained from various commercial suppliers as follows: Avicel® PH101, microcrystalline cellulose (lot number 6551), was obtained from FMC Corporation, Newark, DE; Pharma 200/70, α-lactose monohydrate (lot number 45097), was obtained from S.A. du Sucre de Lait, Sains du Nord, France; theophylline anhydrous (lot number 223400) was obtained from Boehringer-Ingelheim, Ingelheim, Germany; cellactose 80 mesh (lot number 603) which is co-crystallized from 25% microcrystalline cellulose and 75% α-lactose monohydrate was obtained from Meggle GmbH, Wasserberg, Germany.

3.1. Preparation of mixes

Binary mixes (1 kg) of each of the three test ingredients (Avicel® PH101, α-lactose monohydrate, theophylline anhydrous) were conducted in a Turbula Type T2C (Bachofen AG, Switzerland) reciprocating tumble mixer set at 70 rpm for 5 min. The binary blends containing theophylline were restricted to 50% w/w or less of this component so as to reflect plausible industrial processes. The mixer container was charged with an accurately weighed fraction of each ingredient (Fig. 2), previously passed through a 1 mm mesh-size stainless steel screen in order to eliminate the presence of material aggregates.

A ternary test blend of the ingredients consisting of 20% theophylline anhydrous, 20% Avicel® PH101, and 60% α-lactose monohydrate was prepared in the same manner. This blend was used as a test marker of the estimation efficacy of the compression functionality test.

3.2. Density

3.2.1. True density

Gas pycnometry (AcuPyc 1330, Micromeritics Instruments Inc., Atlanta, GA) was used to determine the true density of the powders and blends.

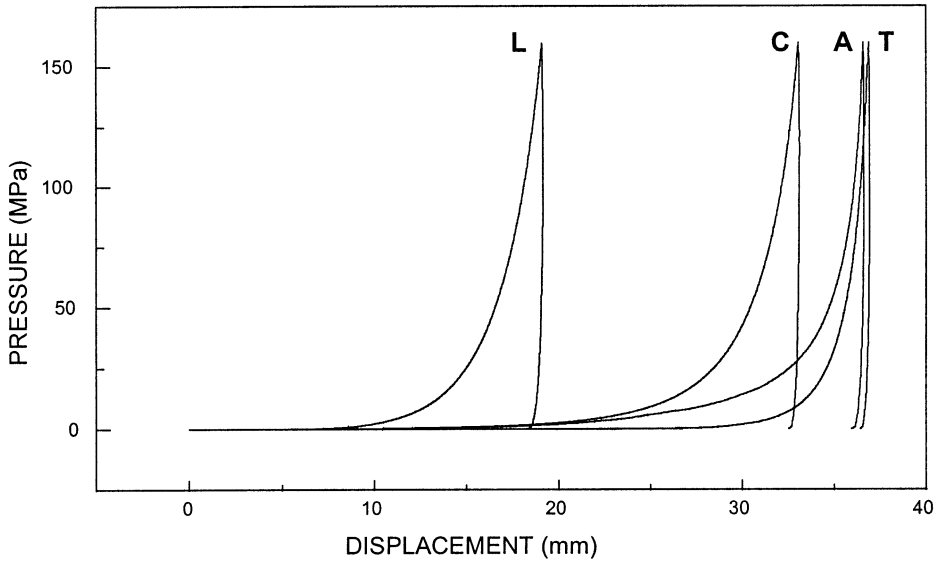

Fig. 4. Actual force–displacement profile displaying: (A) Avicel® PH101; (C) Cellactose; (L) α-lactose monohydrate; (T) theophylline anhydrous.

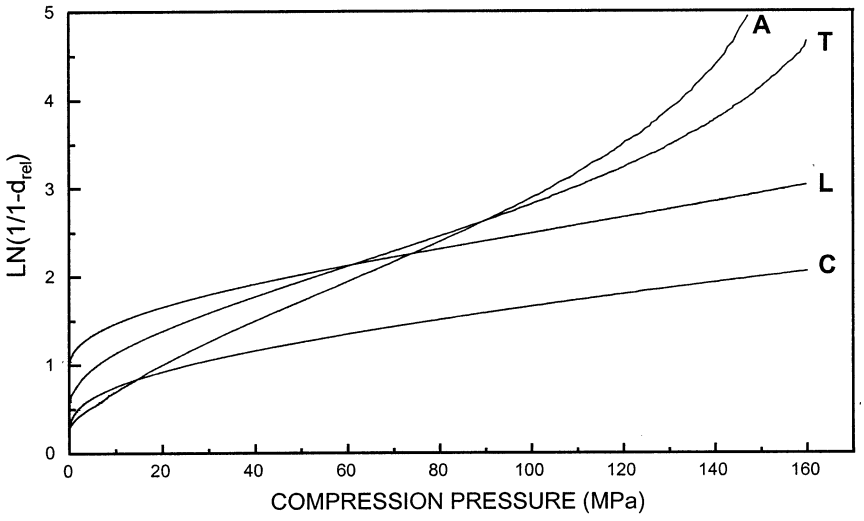

Fig. 5. Heckel plot of the densification process of materials subjected to compression stress: (A) Avicel® PH101; (C) cellactose; (L) α-lactose monohydrate; (T) theophylline anhydrous.

Known quantities of samples were degassed under vacuum for 24 h at room temperature after which ten repetitive purge/measure cycles were performed before recording the result. The analysis was performed on three independent samples. Helium was used as the displacement gas because of its preferential small molecular size.

3.2.2. Apparent density

The evolution of the apparent density of a powder bed in a volumetric cylinder subjected to successive vertical shocks (taps) was measured according to the method outlined in the Pharmacopée Européenne, 1997 utilizing the Erweka model SVM2 unit (Erweka GmbH, Heusenstamm, Germany). Analyses were performed in duplicate. The reduction in powder volume is effected by primary particles rearranging into closer contact on each tap of the bed.

3.3. Surface area

The surface area of the powders and blends under study were determined by the gas adsorption technique (Gemini 2360, Micromeritics Instruments). The method is based on the BET monolayer adsorption theory of a gas on a solid surface at reduced temperatures. Nitrogen was used as the condensable gas after the samples had been degassed under vacuum for 24 h at 50°C (VacPrep 61, Micromeritics Instruments). Samples with < 1.0 m^2/g of total surface required careful adjustment of the reference void volume in order to obtain reproducible results. Analyses were performed in triplicate.

3.4. Formation and characterization of compacts

Experimentation and analysis were carried out on the individual pure components as well as specific binary and ternary mixtures of the components. All samples were analyzed in duplicate and the mean value reported.

3.4.1. Lloyd uniaxial press

An instrumented uniaxial press (Lloyd Instruments 6000R, Fareham, England) was used to fabricate the compacts, Fig. 3a. The press consisted of two mounted platens of which the upper was potentiated and the lower fixed. The upper platen was equipped with a 30 kN captor relayed

to a microprocessor controlled workstation utilizing proprietary software; RControl (Lloyd Instruments).

3.4.2. Consolidation cell

In order to obtain compacts under different loads, a demountable consolidation cell was employed (Fig. 3b). The cell consisted of two hemicylinders, 45 mm in height, which were assembled with the aid of set screws to form a cylindrical chamber, 15 mm in diameter. The assembled cylinder was placed on a footing and fitted with a collar to facilitate the free movement of the load bearing piston within the cylindrical chamber. The surfaces of the cell that came into contact with the powder under study were lubricated with a thin film of magnesium stearate. The cell was filled with an accurate mass of powder, calculated from the apparent density of the powder, so as to correspond to the cell volume, i.e. 7951 mm^3. The cell was placed on the platen table of the press and the upper platen was brought into contact with the load bearing piston of the cell before commencing the compression. The application of the force was kept constant at 1.14 mm/min until the desired pressure was attained at which point decompression occurred at a rate of 1.14 mm/min until the platen head returned to the starting position. The rate of compaction was considered to be slow enough that the yield stress was time independent.

3.4.3. Determination of mechanical strength

The resulting compact was removed from the cell by disassembling the cell and the height of the compact was accurately determined with the aid of a micrometer. The compact was then subjected to axial compression at a rate of 0.38 mm/min until rupture occurred. The force necessary for rupture of the compact constituted a measure of the particle association responsible for the cohesion of the compact. The apparent resistance, R, or cohesion of the compact was calculated from the tensile strength, σ, according to:

$$R = \frac{\sigma}{2} \tag{2}$$

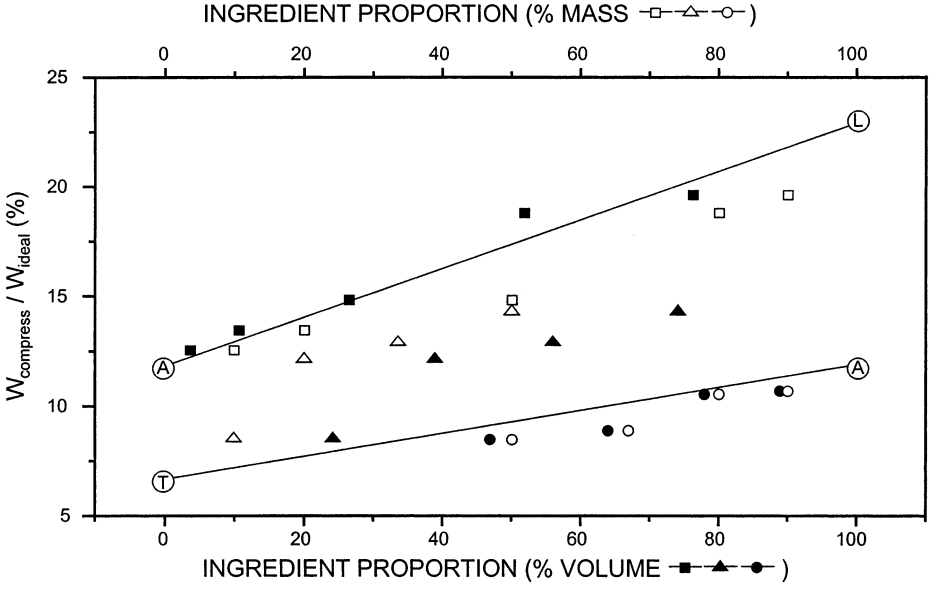

Fig. 6. Relative work vs. % composition of constituent by volume (●) or mass (○) of binary powder mixes: (A) Avicel® PH101/theophylline anhydrous -●-○-; (B) Avicel® PH101/α-lactose monohydrate -■-□-; (C) α-lactose monohydrate/theophylline anhydrous -▲-△-.

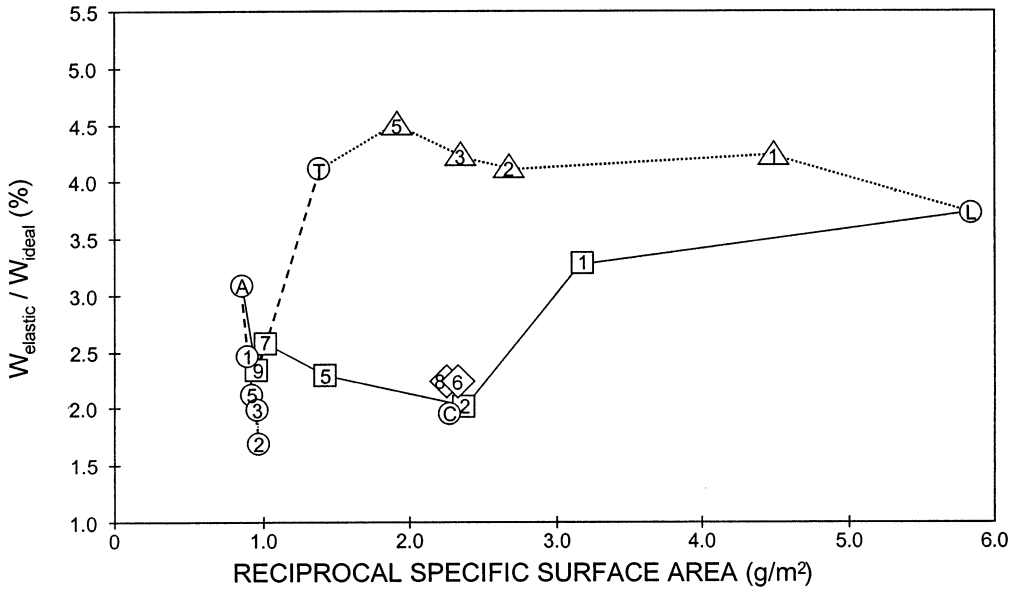

Fig. 7. Relative elastic work vs. the reciprocal of specific surface area for the pure constituents and binary powder mixes. Samples identified according to the ID Code listed in Table 1: Avicel® PH101/theophylline anhydrous ○; Avicel® PH101/α-lactose monohydrate □; α-lactose monohydrate/theophylline anhydrous △.

and, for a compressed tablet with circular axial faces, with:

$$\sigma = \frac{F}{\text{unit surface area}} = \frac{F}{\pi r^2} = \frac{F}{\pi\left(\frac{D}{2}\right)^2} = \frac{F}{\pi\frac{D^2}{4}}$$

$$= \frac{4F}{\pi D^2} \quad (3)$$

where F is the axial force exerted on the compact surface of radius, r, and diameter, D.

4. Results and discussion

Reliable mechanical property information can be useful in helping to identify a suitable processing method such as granulation or direct compression as well as selecting excipients that compliment the mechanical properties of the other ingredients in a formulation. This has been the impetus in developing predictive indices which can be applied during the pre-formulation development of tablets (Hiestand and Smith, 1991).

It is evident therefore that, a logical extension of force–displacement relationships in compaction studies is the derivation of energy parameters indicative of the system under study. Krycer et al. (1982) have noted that powders with different packing characteristics and different deformation properties will absorb varying amounts of energy. Therefore, the suggestion that the measure of the work of compaction may be a more useful measure than other characteristics has some merit. A number of researchers have obtained measures of this work phenomenon, however the methods used varied considerably (Fell and Newton, 1971; Marshall, 1989). It is important to note that the recorded forces are only the effect, not the cause, of the densification of the powder bed in the die. In this regard, comparisons of tableting to constant maximum pressure or constant weight may not be as informative as comparisons made of tablets at constant maximum relative density.

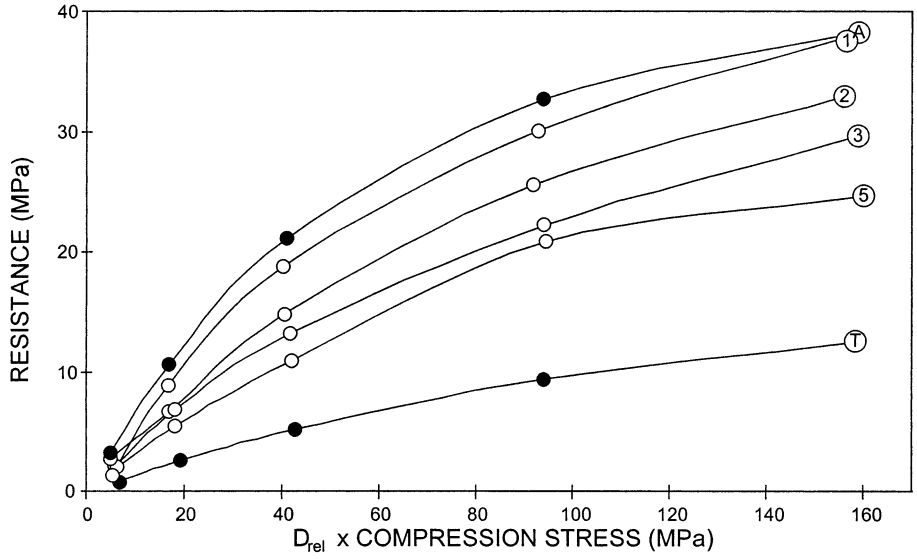

Fig. 8. Resistance vs. compresion stress normalized to powder relative density for the pure constituents and binary powder mixes of Avicel® PH101/theophylline anhydrous. Samples identified according to the ID Code listed in Table 1 where ● represents the pure constituents and ○ represents the binary mixes.

4.1. Densification

The force–displacement profiles for the pure ingredients are displayed in Fig. 4. Lactose requires a relative short consolidation period before sufficient particle rearrangement has occurred to allow the applied pressure to mount in the powder bed. Both theophylline anhydrous and Avicel® show substantial volume reduction during the compression period, however Avicel® begins to depart from the null pressure reading well before theophylline. This appears to be a result of the long acicular particles (Handbook of Pharmaceutical Excipients, 1994) interlocking in the confined dimensions of the cell and the ensuing plastic deformation of particles. The cellactose sample shows a pronounced shift away from the lactose profile toward the Avicel® profile indicating that the 25% microcrystalline cellulose component of the material profoundly affects the material mechanics.

Since the surface area of the powder bed in contact with the punch faces remains constant during one-sided uniaxial compression in the Lloyd press, the volume of the powder bed has a constant relationship to the distance between the two punch surfaces. In pharmaceutical studies of this type, the Heckel equation is most commonly used to describe this distance as a function of the developing pressure and loss of porosity. By analyzing the samples with respect to the evolving relative density in the powder bed as a function of compression stress (Fig. 5), the application of Heckel's mono-exponential empirical equation can be assessed. It appears that the relative density exceeds unity with both Avicel® and theophylline monohydrate in a similar fashion as noted by other researchers (see Section 2).

Indeed the Heckel plot is extremely sensitive to the accurate determination of the true density of the material under concern since seemingly insignificant differences greatly affect the derived mean yield pressure parameter (reciprocal of the slope) (Rue and Rees, 1978). Similar anomalous behaviour in the Heckel plots is noted for the binary blend samples as well. Although the Heckel relationship is widely used by pharmaceutical scientists, these discrepancies in applicability are perhaps to be unexpected given the assumptions that Heckel employed during his work with

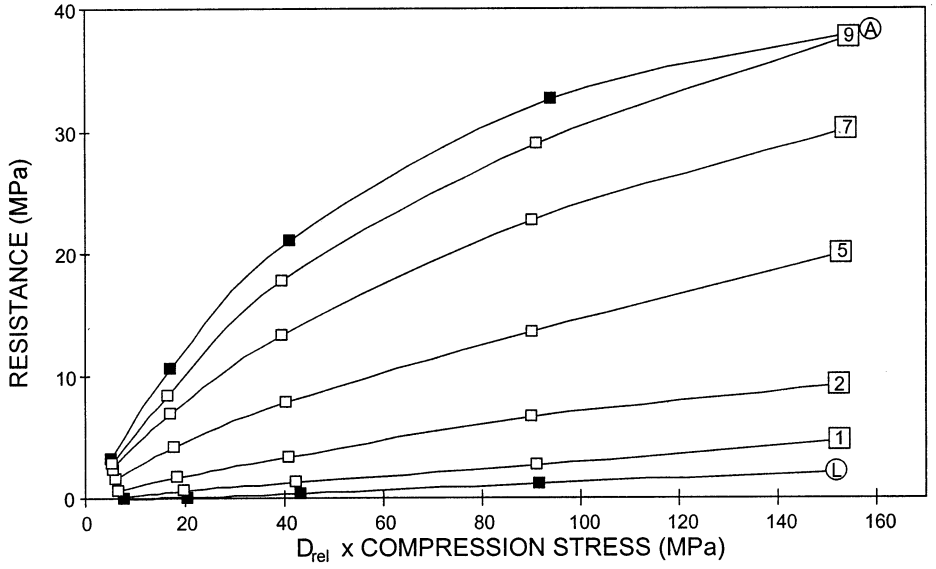

Fig. 9. Resistance versus compresion stress normalized to powder relative density for the pure constituents and binary powder mixes of Avicel® PH101/α-lactose monohydrate. Samples identified according to the ID Code listed in Table 1 where ■ represents the pure constituents and □ represents the binary mixes.

aluminum powders. The metallic powders did not display any significant fragmentation during compaction nor intragranular porosity. This is clearly not the case with many materials employed in pharmaceutical technological evaluations. Thus the use of energy relationships in densification

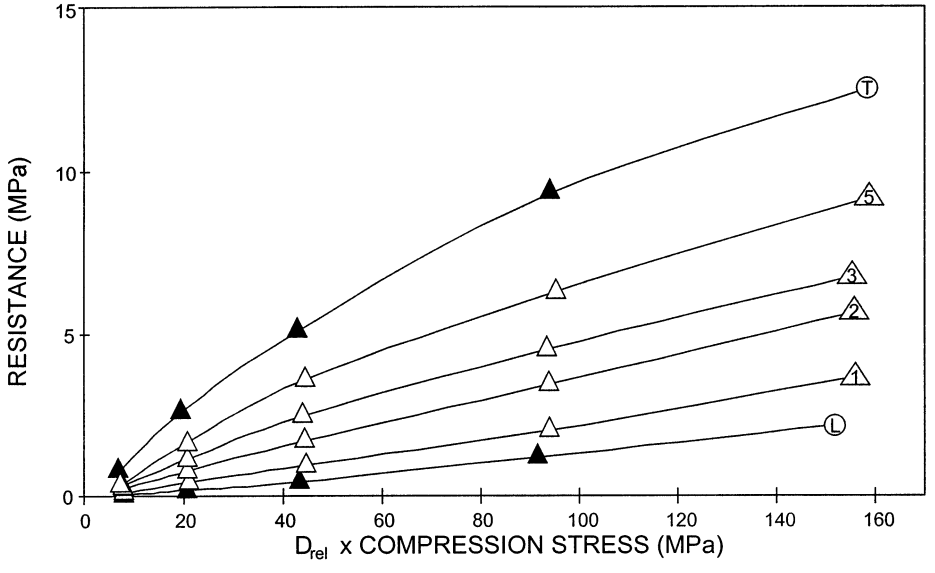

Fig. 10. Resistance vs. compresion stress normalized to powder relative density for the pure constituents and binary powder mixes of α-lactose monohydrate/theophylline anhydrous. Samples identified according to the ID Code listed in Table 1 where ▲ represents the pure constituents and △ represents the binary mixes.

Table 1
Data and parameters for compacts fabricated at 160 MPa[a]

Sample	ID code	Apparent density (g/cc)	Peak max (MPa mm)	AUC_{ideal}	$AUC_{compress}$ (MPa mm)	$AUC_{compact}$ (MPa mm)	$AUC_{elastic}$ (MPa mm)	Specific surface area (g/m^2)
Avicel®	Ⓐ	0.30	36.58	2926.00	351.8	340.9	10.9	1.17
Lactose	Ⓛ	0.84	19.09	1527.20	346.3	333.4	12.9	0.17
Theophylline	Ⓣ	0.27	36.87	2949.60	192.3	184.3	7.9	0.72
Cellactose	Ⓒ	0.38	33.04	2643.52	396.2	388.3	7.8	0.43
1T9A	①	0.29	37.13	2970.62	316.0	308.2	7.8	1.10
2T8A	②	0.30	36.99	2958.93	310.2	304.9	5.3	1.03
3T6A	③	0.28	37.04	2963.50	262.0	256.8	5.2	1.03
5T5A	⑤	0.30	37.02	2961.37	249.9	244.6	5.3	1.08
1T9L	△1	0.69	24.12	1929.25	275.9	264.3	11.6	0.22
2T8L	△2	0.62	26.07	2085.32	268.8	257.7	11.0	0.37
3T6L	△3	0.57	27.64	2211.02	268.3	257.0	11.3	0.43
5T5L	△5	0.42	32.27	2581.40	219.6	209.8	9.8	0.52
10A90L	□1	0.68	23.98	1918.53	376.5	364.2	12.3	0.31
25A75L	□2	0.57	27.70	2215.81	416.7	408.3	8.4	0.42
50A50L	□5	0.42	32.31	2584.94	383.3	374.6	8.7	0.69
75A25L	□7	0.35	34.71	2776.79	373.4	363.8	9.6	0.97
90A10L	□9	0.31	36.10	2887.80	362.4	353.9	8.4	1.04
2T8C (binary test)	◇8	0.40	32.44	2595.55	368.0	360.4	7.6	0.46
2T2A6L (ternary test)	◇6	0.50	29.88	2391.48	313.1	305.1	7.9	0.46

[a] Samples coded as: Avicel®, A; lactose, L; theophylline, T; cellactose, C. Blends consist of a number representing the % mass of the constituent letter that immediately follows, e.g. 1T9A corresponds to the binary blend of 10% theophylline and 90% Avicel®.

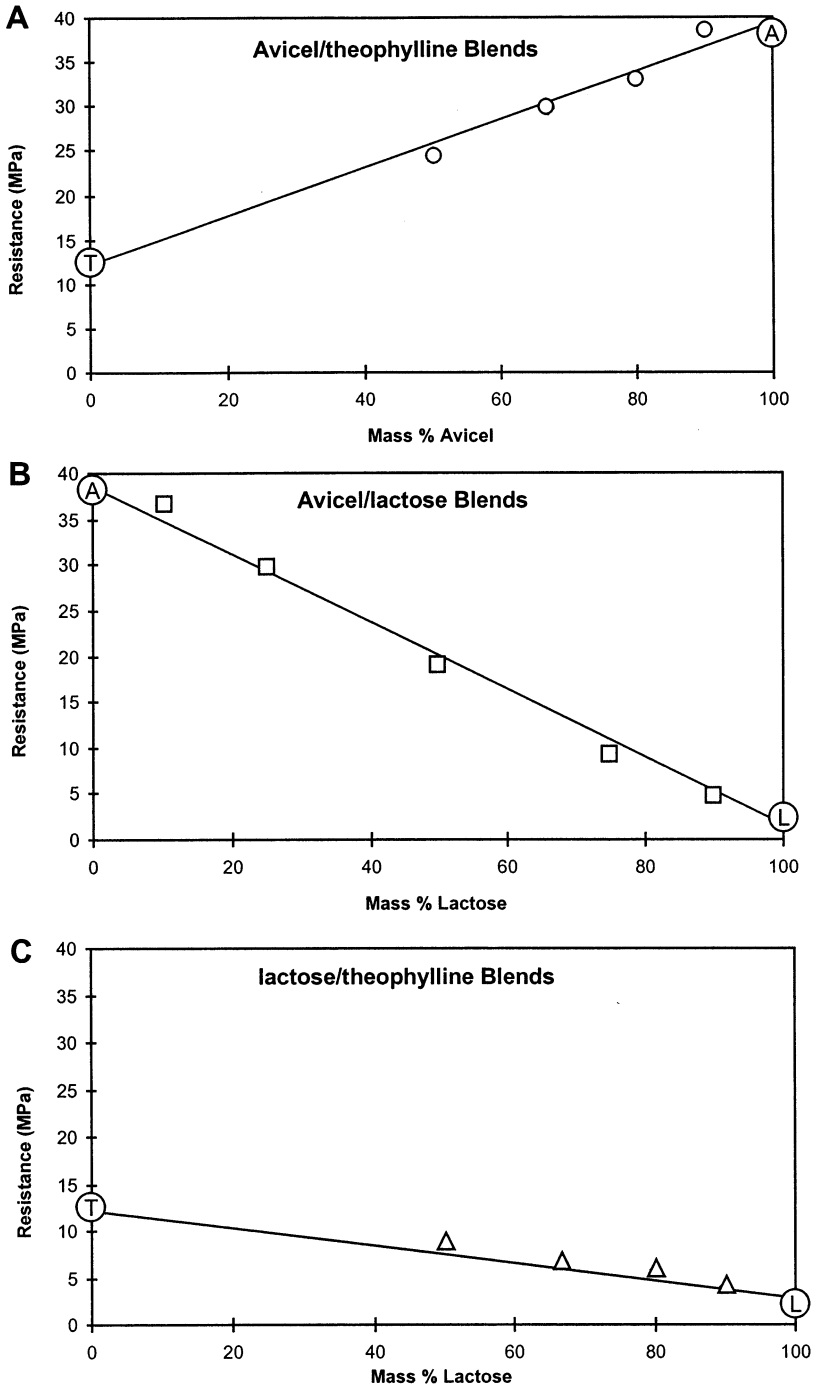

Fig. 11. Resistance vs. % composition of constituent by mass of binary powder mixes: Avicel® PH101/theophylline anhydrous ○; Avicel® PH101/α-lactose monohydrate □; α-lactose monohydrate/theophylline anhydrous △. Filled symbols represent the pure constituents.

evaluation of materials obviates the necessity of introducing further error in the analysis when using the measured parameter of material true density as is the case in Heckel-type analysis.

4.2. Energy considerations

The question of the suitability of relating physical parameters to the component ratio in a blend on the basis of mass or volume appears to be resolved by considering the evolution of energy in the system. The values for various parameters indicative of powder compaction are presented in Table 1.

Since the work of compression for each pure material and binary blend occupies a small portion of the total theoretical work, this ratio can be considered as a reflection of the apptitude of the powder to compress and consolidate. Fig. 6 reveals that a linear trend is obtained when this ratio is related to the % volume proportion of the ingredients in the Avicel®/lactose and Avicel®/theophylline blends while less apparent for the theophylline/lactose blend. Podczeck and Sharma, 1996 have shown that particle shape of the individual components in a binary mixture significantly affects volume reduction in powder mixes. In the case of the binary blends containing Avicel®, the addition of angular particles of theophylline or lactose may be held apart as a result of the bridging capabilities of the acicular Avicel® particles (Vachon and Chulia, 1998). Thus the significant apparent volume of Avicel®, which persists even under compression, is reflected in the linear relationship that evolves with respect to the utilization of compression energy and the % volume proportion of the ingredients.

By contrast, for blends of materials more prone to particle rearrangement under compression stress, a linear relationship is evident only when the % proportion of the ingredients is based on the mass. For the theophylline/lactose blends, all particles are angular in shape (Handbook of Pharmaceutical Excipients, 1994) and begin to exert significant resistance to the compression stress only when the particles have been extensively packed in the die. In this case the initial volume occupied by the powder is less a determinant than is the actual powder mass in the die. The plot may be indicative of a synergistic effect on the resulting mechanical behaviour of the blend which reduces the overall energy

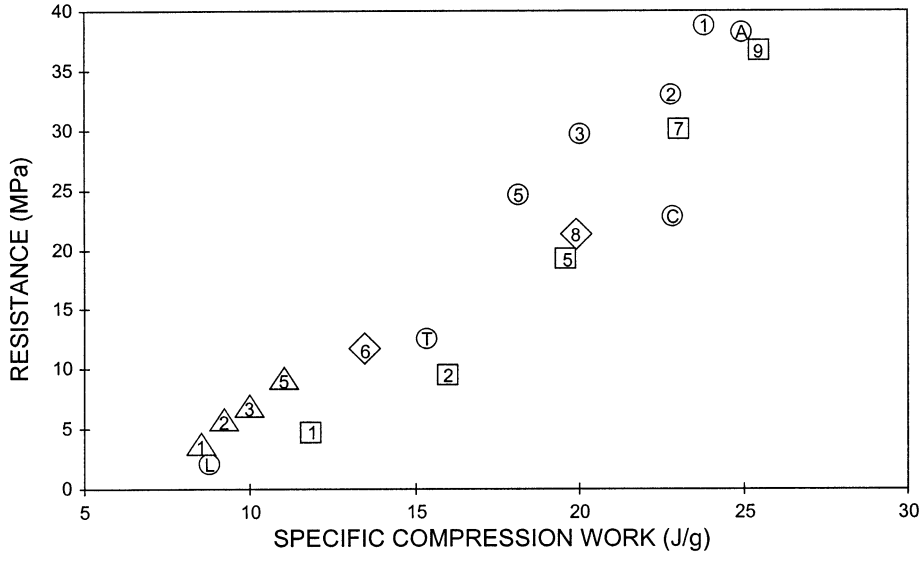

Fig. 12. Powder compression functionality plot of resistance vs. work of compression normalized to powder mass in die (Specific Compression Work) for: Avicel® PH101/theophylline anhydrous ○; Avicel® PH101/α-lactose monohydrate □; α-lactose monohydrate/theophylline anhydrous △. Samples identified according to the ID Code listed in Table 1.

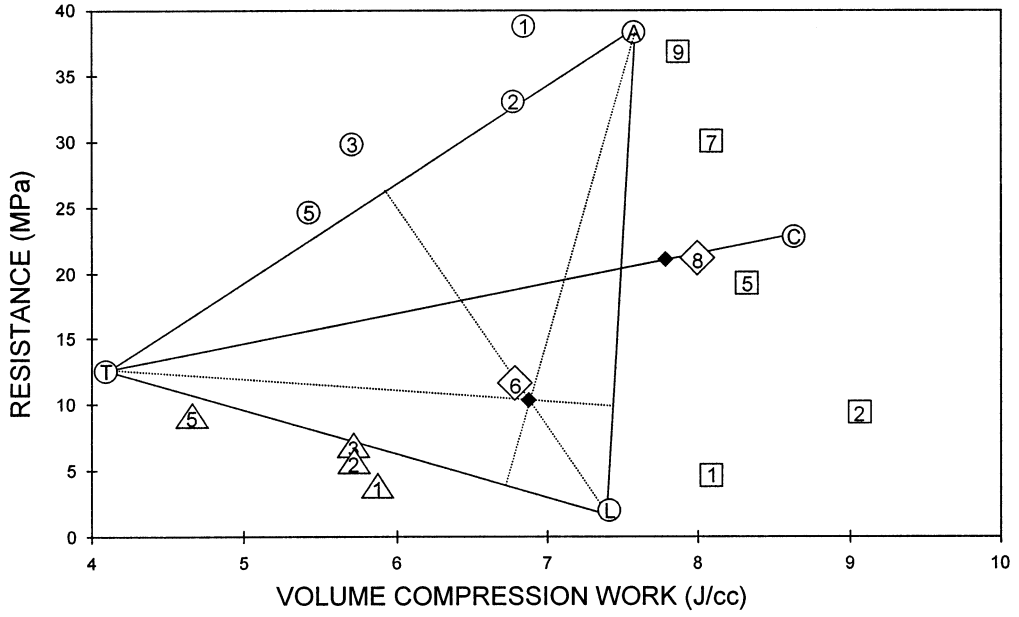

Fig. 13. Powder compression functionality plot of resistance vs. work of compression normalized to powder volume in die (Volume Compression Work) for: Avicel® PH101/theophylline anhydrous ○; Avicel® PH101/α-lactose monohydrate □; α-lactose monohydrate/theophylline anhydrous △. Samples identified according to the ID Code listed in Table 1. The theoretical points for the binary and ternary test blends are denoted by ◆.

required to realize a compact. Thus the analysis of energy data with respect to % mass or % volume ingredient proportion provides a rapid means of distinguishing the mechanical behaviour of materials under compression stress.

Since it is evident that the compressibility of a material and/or blends of material is a function of particle consolidation, particle fragmentation and, plastic deformation, the effect of specific surface area on the resulting work of the system is also of interest. Fig. 7 indicates that if the relative elastic recovery work is related to the reciprocal of the specific surface area of the starting powder, group trend behaviour is noted for the pure materials and their binary blends. In the case of lactose/theophylline blends, the elastic recovery tendency of fragmentary lactose particles is maintained while the increasing surface area associated with the small theophylline particles results in a better distribution of this elastic energy within the compact. Evidently the relatively high elastic character of lactose under compression is imposed upon all proportions of this binary composition.

In contrast, Avicel®/theophylline blends reveal that elastic energy is virtually non-significant in the blends as compared to the pure constituents. The intermingling of the small theophylline particles among the acicular Avicel® particles results in the easier consolidation of the powder bed (lower relative elastic energy). The elastic character of theophylline and Avicel® appears to have been diminished by the concomitant plastic deformation of material of differing particle morphology.

When Avicel®/lactose blends are considered, a composite of the above effects is noted whereby the relatively large specific surface area of Avicel® causes the values to collect in one region of the plot. The synergistic effect noted above is again evident when the Avicel® content in the blends is in excess of 10% w/w. The ameliorating effect of Avicel® in the blends is predominant resulting in a decreased elastic component in the compacts which is not observed in blends lacking Avicel®. This type of plot may readily identify excipients likely to enhance the consolidation properties of tableting formulations.

4.3. Compact strength

If constituents that mechanistically behave in a similar manner under compression (i.e. elastic and plastic character) comprise a powder blend, then it is likely that the compression characteristics of the powder blend will also behave in this manner. Thus an homologous series of binary blends of such constituents would be unlikely to reveal contributory effects due to any one of the constituents. Therefore the challenge was to use materials of very different compaction behaviour in an homologous series of binary blends.

By relating the foregoing discussion to the compact strength, indicative of particle consolidation, further relationships can be extracted. Tablet strength is presumably enhanced by materials possessing a low elastic component during consolidation and having a high bonding surface area capable of developing inter-molecular liaisons. Figs. 8–10 illustrate the relationship between tablet resistance to an axially applied load and the pressure required to make the tablet. In general, the crushing strength of compacts containing α-lactose monohydrate is primarily affected by the content proportion of lactose which on its own produces relatively weak compacts. Typically the highest strength compacts are obtained for Avicel® alone since interparticulate bonding occurs even under comparatively low compaction pressures. For each binary blend series, the resulting tablet strength for any particular blend consistently lies between the tablet strength of the pure constituents for all compaction pressures studied. This is in stark contrast to the relationships observed between elastic energy and blend composition. Thus tablet strength cannot simply be defined on the basis of the bond fracturing elastic character of the compacts.

Furthermore, a linear relationship is revealed when the compact resistance is related to the % mass proportion of the ingredient in the binary blend, as noted in Fig. 11 for compacts fabricated at 160 MPa for example. In this case, it is evident that overall compact strength is a result of the proportionally normalized contribution of the characteristic mechanical strength for each component in the blend. Since bond formation can only occur when particle surfaces are brought into contact, the larger the mass of material confined to a unit volume under compression stress, the more likely the imposition of its mechanical characteristics on that of the composite blend. Indeed, as further support, this linear relationship is not evident when compact resistance is related to the % volume proportion of the ingredient.

4.4. Predicting powder compaction functionality

It appears reasonable, therefore, to interpolate the mechanical attributes for binary blends of two well-characterized components. If the energy parameters extracted from force–displacement plots are selected so as to reflect the fluidity and compressibility of a powder, i.e. the aptitude to rearrange and densify, under mechanical stress then the predictive capabilities of this approach may be extended to more complex powder blends. The correlation of expended energy during tablet manufacture and the strength quality of the resulting compact can be facilitated by incorporating a cohesion parameter for the compacts into the relationship. Indeed, Delacourte et al. (1993) have recognized the utility of this approach in their definition of a Cohesion Index parameter as the ratio of compact tensile strength and work of compaction.

This approach is extended in the present work by distinguishing two normalizing variables: (i) the mass of powder occupying; (ii) a fixed volume, notably the initial cavity defined by the consolidation cell (see Section 3.4.2). Implicit in these variables is the apparent density or the packing characteristics of the components of the powder occupying the consolidation cell. The work expended during compaction of a solid is likely utilized for both particle bonding as well as volume reduction. Therefore expressing the work of compression with respect to the mass or the volume of the powder prior to undergoing compression may also reveal information. These parameters may be defined as the specific compression work, i.e. the area under the force–displacement plot per unit mass of powder and the volume compression work, i.e. the area under the force–displacement plot per unit volume of the cell.

Fig. 12 illustrates the relationship between compact strength and the specific energy of compaction expended for consolidation defined as the specific compression work. Although a general increasing linear trend in strength with compaction work is evident, there are instances where compacts of similar strength require quite differing amounts of compaction energy input. The plot is instructive in illustrating those materials that consume high energy during consolidation and thus may hasten the wear and tear of production equipment. The judicious use of these materials in tablet formulations may be prudent.

The broader relationship between composition of constituents in formulations is only revealed when the volume of the compaction cell, initially completely filled by powder, is introduced into the relationship with the use of the volume compression work as noted in Fig. 13. The same data points of Fig. 12 are now apparently scattered randomly in this plot. Closer examination reveals that the data points of the various binary blends are actually distributed along an imaginary linear path between the pure constituents, remarkably close to the % mass composition of the respective blends. For example, the data point corresponding to the 50% binary blend can be found in the vicinity midway along the path between the data points for the pure constituents.The process is challenged with another binary blend, considered as a test, which is comprised of 20% theophylline and 80% cellactose. Again, the data point for this blend is found $\approx$ one fifth of the distance along a path between the data points for the pure constituents corresponding to the % mass proportion of theophylline in the test blend. The location of the imaginary data point for this blend is denoted by a solid diamond symbol on this path.

The data point for the ternary test blend comprised of the three primary constituents in a specified composition (20% theophylline, 20% Avicel®, and 60% lactose) is also indicated in Fig. 13. In this case technological functionality of the formulation can be defined within a working space that encompasses all of the formulation constituents situated at each apex of a polygon. In the same manner, intersecting rays can be constructed which emanate from the pure constituents and cross the path between the remaining two constituents at the theoretical mass composition. When this is done in turn for each of the three constituents, the resulting rays intersect at the imaginary data point, denoted by a solid diamond symbol, very near the experimental data point for the actual blend.

Thus, this techniques has the capability of providing useful information as to the compaction functionality of various tableting formulations without having to occupy production equipment during the preformulation stages. Virtual formulations may be evaluated for suitable strength and performance based on the projected values from a similar plot of the pure constituents treated in the manner illustrated in Figs. 12 and 13. A few select formulations can then be subjected to actual compaction appraisal for further refinement. In this fashion, lead time necessary for formulation evaluation may be greatly diminished leading to more rapid tableting process optimization. Further work is underway in our laboratory to more accurately determine these derived parameters in order to reduce the deviation of the measured values from the predicted values identified in the schema of Fig. 13.

5. Conclusions

The relationship between relative work of compression and % volume proportion of blend ingredients has predictive capabilities in the evaluation of technological potential of tableting formulations. This technique may be used to diagnose material compression potential during pre-formulation evaluations thereby accelerating tableting process optimization.

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