

## Determination of the energy of tablet formation during compression of selected pharmaceutical powders

David P. Coffin-Beach and R. Gary Hollenbeck

*Department of Pharmaceutics, University of Maryland, School of Pharmacy, Baltimore, MD 21201 (U.S.A.)*

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### Summary

A thermodynamic evaluation of bonding in compressed tablets has been achieved providing a quantitative measure of solid particulate interaction shown to correlate with tablet strength. The evaluation was accomplished through the design and implementation of a unique compression calorimeter capable of accurate and precise determination of the heat released during powder compaction. Concomitant measurement of the work of compaction permitted an energy balance for the tableting process such that the energy difference between powder and tablet could be accurately assessed. The experimentally determined energy differences at maximum compression force (30,000 N) for 4 pure directly compressible materials (Avicel, DiTab, Fast Flo lactose, Starch 1500) indicate that the formation of a tablet is associated with a decrease in energy of the system. This decrease in energy, termed the energy of formation, is related to the dissipation of surface energy associated with bonding. The compression of a particulate system which did not form a strong tablet presented a much smaller energy of formation at maximum compression force (10.6 J for Avicel versus 0.52 J for granular acetaminophen) and thus demonstrates the potential of the compression calorimeter as a device capable of quantitatively determining energetic differences resulting from the compaction process. The tensile strength measurements for each compressible material are also shown to correlate with the energy of formation.

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*Correspondence:* R.G. Hollenbeck, Department of Pharmaceutics, School of Pharmacy, University of Maryland, 20 North Pine St., Baltimore, MD 21201, U.S.A.

## Introduction

In pharmaceuticals, the term compressibility has evolved to the point where it not only refers to the ability of a powder to be compressed into a smaller volume but also refers to the cohesive strength of the tablet. The analysis of particulate systems for compressibility has long occupied the attention of pharmaceutical researchers (Higuchi et al., 1953). Various attributes have been identified which improve this powder characteristic (Doelker et al., 1977; Hersey et al., 1967; Summers et al., 1977), but the evidence for good compressibility is most often ascribed to bonding between particles confined in the die during compaction. Although quantitative techniques have recently been developed to assess the energy input during compaction (Polderman et al., 1971), no evaluation of the consequences of this energy input or its distribution in the compacted powder bed have been reported.

The quantitative assessment of not only the work of compaction but also the thermal consequences of this energy input in the powder bed is necessary for an analysis of the compaction process from a purely energetics perspective. A novel device, the compression calorimeter, was developed to provide the necessary environment for such an evaluation.

## Materials and Methods

Details of the specially fabricated compression calorimeter are presented in Fig. 1. The housing displayed in Fig. 1 was fabricated from an acetal resin thermoplastic, Delrin. The die and punch facings were made of a durable aluminum alloy, 2024T6 designation, and the compression punches and calibration punch were machined from mandrel-formed fiberglass, G-10 grade. The materials of construction were selected based upon their inherent tensile strength in all cases, their thermal conduction characteristics in the case of the die and punch facing material, and thermal insulation properties in the case of the housing and punch stems.

Thermal measurements were accomplished using a quartz thermometer (Model 2804A, Hewlett Packard). The probe for the thermometer was positioned in the access port pictured in the calorimeter housing (Fig. 1) and was immersed in mercury which surrounded the aluminum die in the assembled calorimeter. The maximum resolution of the quartz thermometer was utilized in all experiments resulting in temperature measurements to  $1.0 \times 10^{-4} \text{ } ^\circ\text{C}$ .

The thermal data obtained from the quartz thermometer was transferred via an electronic interface (HPIB) to a computer (Model 9825T, Hewlett Packard). The data was accumulated, stored on magnetic tape, and the calculation of the process-dependent temperature change was performed utilizing a mathematical model based upon Newton's Law of Cooling:

$$dT/dt = K(T - T_0) \quad (1)$$

where  $dT/dt$  is the rate of temperature change,  $K$  is a constant termed the 'thermal

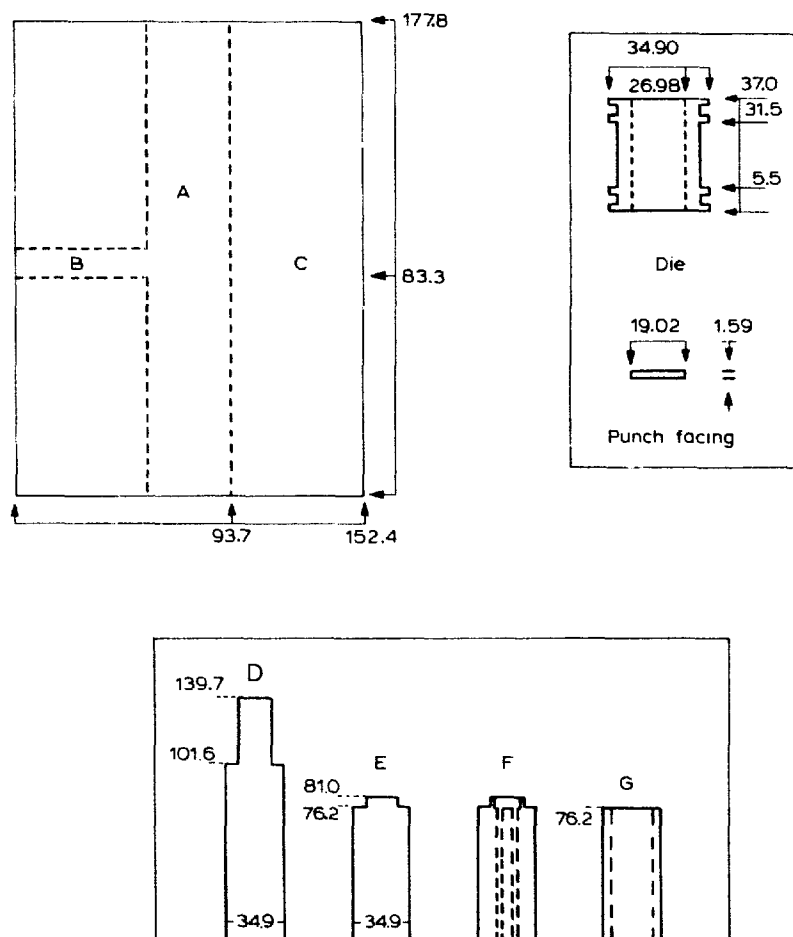


Fig. 1. Design specifications of the compression calorimeter housing (upper left), aluminum die and punch facing (upper right), and fiberglass punches and ejection jig (lower). Key: A = central channel; B = thermometer probe; C = Delrin housing; D = upper punch; E = lower compression punch; F = lower calibration punch with resistance heater, G = ejection jig.

leakage modulus',  $T$  is the temperature of the calorimeter contents, and  $T_0$  is a constant representing the temperature of the surroundings. Fig. 2 represents a set of typical temperature versus time data obtained during an experimental run with the calorimeter. The utility of the mathematical model (Eqn. 1) for the description of this data is shown by the linearity of the post-process logarithmic transformation of the data also presented in Fig. 2. The temperature change associated with any event ( $\Delta T$ ) was determined by back-extrapolation of this linear period to estimate the post-process temperature which would have occurred in a perfectly adiabatic system. The process-dependent temperature change ( $\Delta T$ ) was taken as the difference between this extrapolated value and the actual system temperature when the event was initiated ( $T_0$ ). A computer program was written to calculate  $\Delta T$  from raw temperature-time data using least-squares linear regression as the basis for the extrapolation.

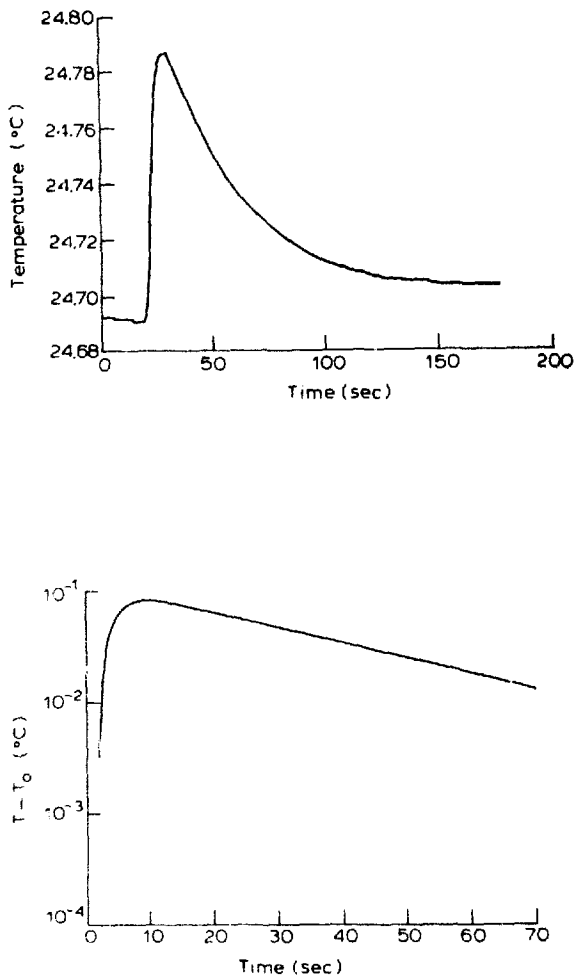


Fig. 2. Typical thermal response profile for compression of powder in the compression calorimeter: temperature vs time (upper curve) and logarithmic plot of  $(T - T_0)$  vs time (lower curve).

The calibration of the calorimeter was accomplished by replacing the lower punch with a calibration punch (F) pictured in Fig. 1. Access ports were provided for electrical supply wires attached to a nichrome wire heating element. A traditional technique involving the dissipation of a known quantity of electrical work by a resistance heating element was utilized to determine the necessary heat capacities for not only the empty system, but also for the system containing each of the materials investigated.

The measurement of the work expended during the compression process was accomplished by the utilization of a piezoelectric loadcell (Type 9061, Kistler Instruments) for force evaluation and a linear voltage displacement transducer (LVDT, Series 240, D.C.-D.C. Transducer, Trans-Tek) for the consequent displacement measurements. The output voltages from these transducers were stored on a microprocessor controlled x-y recorder (Model 8210R, Bascom Turner Instruments). A program was written which calculated the work of compression from the accu-

muated data with a demonstrated level of accuracy of greater than 0.1 J.

The compressions were performed on a Carver Press (Model C, Fred S. Carver) modified according to Fletcher (1981). The automation inherent in this modification allowed simulation of one-sided compaction similar to that obtained on a single-punch tablet press. Although the system provided adequate control of the compressive event in terms of the speed with which the platens closed upon one another, the decompression event could not be controlled. Preliminary investigations using both a compression-decompression, dynamic, methodology and a compression only, static, methodology were performed. The inability to precisely control decompression prohibited assessment of the dynamic process, and subsequent experimentation was performed utilizing the static technique exclusively. As a consequence, the data reported here represents the compression process alone, and all thermal measurements were made at constant applied pressure.

The viscoelastic nature of the punch system employed in the calorimeter resulted in measurable temperature changes resulting from the applied compression forces (2500–30,000 N). In order to partition the particulate effects of the mechanical work of compaction from the thermal effects caused by the elastic deformation of the punch system, a series of calibration experiments was performed in which no powder was added to the calorimeter. The measurement of both the work associated with punch deformation and the thermal consequences of this work were precisely determined and are presented in Fig. 3. These data served as corrections and were subtracted from the total experimentally determined work of compaction and resultant temperature change for all of the static compression experiments. Consequently, the resulting data for each powder investigated represents the net work done on the powder during compaction, and the net temperature change for this work expenditure.

The following materials chosen for investigation by this method all conformed to USP or NF standards: granular acetaminophen (Mallinckrodt), unmilled dicalcium

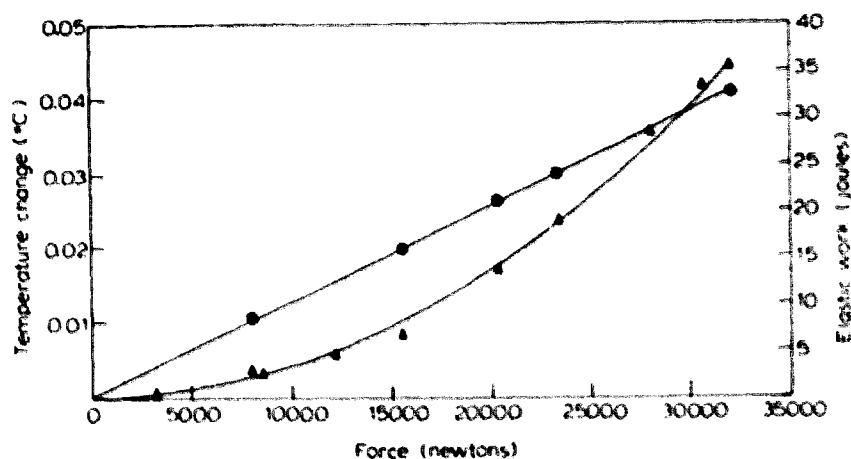


Fig. 3. Work of elastic punch deformation (▲, right ordinate) and associated thermal effect (●, left ordinate) as a function of compression force.

phosphate dihydrate (Stauffer Chemicals), lactose (Fast Flo, Foremost Foods), microcrystalline cellulose (Avicel, FMC), pregelatinized starch (Starch 1500, Col-orcon). Stearic acid (Hystrene, Humko Sheffield Chemicals) was used as a die wall lubricant and was applied to the die wall as a 2% solution in acetone prior to each compaction experiment. The materials were compacted in their 'as received' state: no preconditioning of the samples was performed prior to compaction. Accurately weighted 1.500 g samples were employed in all experiments except in the case of dicalcium phosphate dihydrate. This material required a 2.000 g sample to yield a final compact thickness (3.81 mm) comparable to the other 4 materials at maximum compression force (30,000 N).

After the compression event, each compact was removed from the die, weighed, measured for thickness with a micrometer, and fractured, if possible, using a hardness tester (Model TBH 28, Erweka Instruments).

## Results and Discussion

The term 'bonding' has a history of empirical usage, and the first objective of this discussion is to rigorously define this term and relate it to the physical process of powder compaction. In that regard, it will be useful to partition the tableting event into 2 steps:

$$\text{Solid}(\text{powder}, T_1, P_1, A_1) = \text{Solid}(\text{tablet}, T_2, P_2, A_2) \quad (2)$$

$$\text{Solid}(\text{tablet}, T_2, P_2, A_2) = \text{Solid}(\text{tablet}, T_1, P_1, A_3) \quad (3)$$

where T, P and A are temperature, pressure and surface area, respectively. The subscript 1 refers to the initial and final conditions for temperature and pressure, i.e. room temperature and atmospheric pressure, while the subscript 2 is associated with the state of compressive load. The process in Eqn. 2 is compression and the process described by Eqn. 3 is decompression; the energy changes associated with these processes are  $\Delta E_C$  and  $\Delta E_D$ , respectively. The 'surface area' of the tablet after decompression is given the special designation of  $A_3$  because the process of elastic recovery may result in an increase in this area.

The energy change associated with the tableting event ( $\Delta E$ ) is the sum of these two processes:

$$\Delta E = \Delta E_C + \Delta E_D \quad (4)$$

While an effort was made to characterize the entire process, the focus of this experimental work is the compressive event represented by Eqn. 2. In this context, bonding then represents a component of the precisely defined energy change,  $\Delta E_C$ . The first law of thermodynamics recognizes the interconvertability of heat and work as forms of energy:

$$\Delta E_C = Q - W \quad (5)$$

where  $Q$  is equal to the heat absorbed by the system and  $W$  is equal to the work done by the system.

The system of interest here is the powder confined within the die. Unfortunately, the convention of Eqn. 5 is associated with a system which does work, such as a gas expanding, while the situation under consideration here is just the opposite; work is done on the powder to form a tablet, and heat is released rather than absorbed. To avoid the confusion caused by introducing negative signs for both  $Q$  and  $W$ , the first law energy balance for the process described by Eqn. 2 may be written as:

$$\Delta E_C = W_C - Q_C \quad (6)$$

where  $W_C$  is the work done on the system, or more specifically the work of compression, and  $Q_C$  is the heat released by the system during the process. Consequently, when the work of compression is greater than the heat released in the process, the energy of the system increases ( $\Delta E_C$  is positive). Alternatively, when the heat released by the event is greater than the work of compression, the energy of the system will decrease.

The quantity  $W_C$  has been determined for a number of materials with adequate levels of accuracy and precision (Higuchi et al., 1955; Lammens, 1979; DeBlacy et al., 1970, 1974), but the quantity  $Q_C$  has never been determined by a really satisfactory method. The development of a method for measuring the heat released during compression was accomplished by using the calorimeter described previously, and from Eqn. 7,

$$Q_C = C_p \Delta T \quad (7)$$

where  $C_p$  is the heat capacity of the system and  $\Delta T$  is the process-dependent temperature change. Simultaneous measurements of the work of compression and heat released permitted determination of  $\Delta E_C$ .

Returning to the issue, bonding may now be thermodynamically identified as an exothermic component of  $Q_C$ . The initial particulate system in Eqn. 2 has more surface area and consequently more surface energy than its resultant tablet. Bonding may be associated with the elimination of surface; the commensurate reduction in energy in the system manifests itself as heat released. Note that this approach in defining bonding does not require any assumptions to be made relative to the bonding mechanism. Surface may be reduced by a melting-fusion process for a pure material or it may be reduced by the adhesion of unlike contiguous particles. Regardless of the mechanism, a reduction in energy occurs and this reduction manifests itself as heat released.

The effect of bonding may be regarded as the release of latent heat. With the exception of processes such as polymorphic transitions, bonding is the only exothermic process that is not a direct consequence of mechanical work. Die wall friction, interparticulate friction, elastic deformation, and plastic deformation are all exothermic processes which occur in the system, but the sum total of all of the heat released through these processes cannot exceed the work done on the system. It is

not possible to convert more than 100% of the work done into heat. Obviously, when  $\Delta E_C$  is negative, that is when  $Q_C$  is greater than  $W_C$ , bonding must be occurring.

Bonding may also be occurring when  $\Delta E_C$  is negligible or positive, but the exothermic bonding process is balanced or exceed by endothermic processes such as brittle fracture or deformation. A negative  $\Delta E_C$  appears to be prima facie evidence that bonding has occurred.

Based upon this hypothesis, two features of the study at hand may be anticipated. First, when bonding occurs it should be expected to be a monotonically increasing function of compression force or pressure. In general, the greater the compressive load the more void space eliminated in the compact. Also, one would expect bonding to be a capacity-limited phenomenon. When maximal consolidation has occurred and the surface area of the material has been reduced to the dimensions proscribed by the die cavity, no additional bonding can occur.

As a final point, it should be noted that while the values of  $Q_C$  and  $W_C$  depend upon the experimental apparatus used for preparing tablets, the quantity  $\Delta E_C$  does not. The same energy change will occur for the process in Eqn. 2 regardless of whether the powder is compressed on a Carver press or a high speed rotary press, as long as the initial and final states are the same.

#### *Energy transition profiles*

Fig. 4 presents data for the 4 direct compression excipients examined in this study. Since each of these plots represent the energetic process of the transition from a particulate to a compacted state, they will be termed 'energy transition profiles' for the remainder of this discussion. The ordinate in Fig. 4 is  $\Delta E_C$  so that this axis can be viewed as representing the extent to which the heat released exceeds the work of compression. The fact that this is true is perhaps one of the most significant aspects of these data. There is an applied pressure for each direct compression excipient

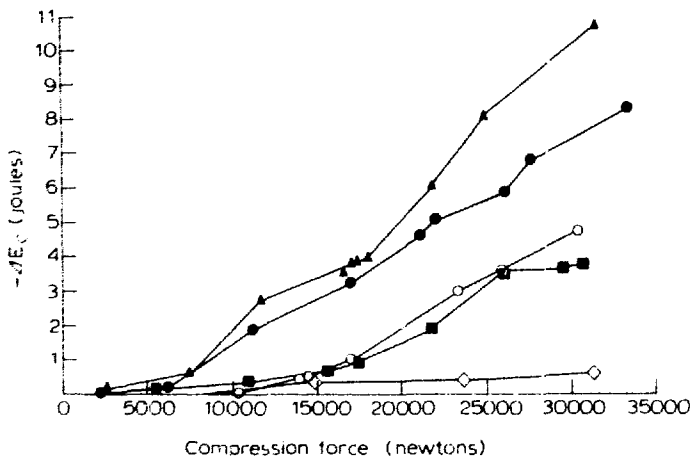


Fig. 4. Energy transition profiles for the compression of microcrystalline cellulose (▲), lactose (●), dicalcium phosphate dihydrate (○), pre-gelatinized compressible starch (■), and granular acetaminophen (◇).



where it can be shown that the compression event produces a compact at a lower energy state.

The development of the concept of an energy balance between the work done on a particulate system during compaction and the thermal consequences of this work input arises from the change of state of the system effected by compression. This process requires the expenditure of a measurable quantity of mechanical work. The tangible consequences of this input of mechanical work in compressible systems is the formation of a compact, but the thermal or energetic consequences of this energy input and the differences between various 'pure' compressible systems have not to date been quantitated. All of the particle-dependent interaction processes traditionally cited as contributing to the compressibility of particulate systems must theoretically have some energetically sound basis. These data confirm this analysis from a thermodynamic point of view; bonding has actually been demonstrated for each compressible material.

Two common features of the energy transition profiles are clearly evident. First the quantity,  $\Delta E_C$ , referred to as the energy of formation, is a function of the applied compression force. In general, there is an increase in magnitude of this quantity with increasing compression force. The hypothesis forwarded here for a pure material is that this functional relationship is due to more bonding at higher force rather than a transition to a different more intense mechanism of interaction. In this sense, the work of compression must be viewed as both an activation energy and a determinant of the extent of the reaction. The level of compression force determines the degree of consolidation of the powder through its ability to overcome or induce inter- and intra-particulate stresses. The greater the conversion of 'surface' to solid-solid interface the greater the energy of formation. The second common feature of the energy transition profiles is also related to the resistance of the powder bed to compaction. There appears to be a certain force which must be applied before a net increase in bonding is observed.

The different excipients are distinguished by the relative magnitude of the energy of formation, the minimum force required to induce bonding, and the nature of the relationship between applied force and energy of formation.

Microcrystalline cellulose (Avicel) was the first material investigated with the compression calorimeter. Among other things, the data for this material in Fig. 4 graphically demonstrates the precision of the measurement system. The 4 experimental replications performed in the 16,000–18,000 N force range show a rank correlation with increasing force. In addition, they also obviously integrate with the remainder of the continuous relationship demonstrated in the balance of the energy transition profile. The magnitude of the exoenergetic effect observed with Avicel was larger than that observed for the other direct compression excipients evaluated and measurable bonding was observed even at very low compression forces. These findings correlate well with the known compressibility of Avicel and also quantitatively reflect this material's superior compression bonding characteristics in comparison to the other direct compression excipients. Within the range of compression forces studied, there is no evidence that the bonding potential of this material has been exhausted.

The evaluation of dicalcium phosphate dihydrate (DiTab) utilized the same methodology as that employed in the preceding study and served as a contrasting study in terms of its brittle fracture compaction mechanism. A comparison of the energy transition profile for DiTab with the one obtained for Avicel demonstrates a significant quantitative difference in the energy of formation at each of the compression forces evaluated. Avicel demonstrates a predominance of exoenergetic behavior from bonding beginning at the lowest compression force evaluated (2500 N). DiTab, however, shows no evidence of this phenomenon until forces of over 10,000 N were applied. This behavior seems to indicate that at low forces the energy requirements for brittle fracture of DiTab are approximately equal to the energy released through bond formation. At the lower compaction forces the DiTab particles are undoubtedly fractured and the fractured surfaces bond, but there is a relative balance between the two processes and consequently the magnitude of the energy of formation for the process is small. When the majority of fracture within the powder bed has occurred, the particles begin to recombine and bond. From this point onward, the bonding process predominates and the magnitude of the energy of formation increases proportionately with increasing compression force. Evidence of this behavior is provided by the data presented in Fig. 4 for forces greater than 10,000 N.

Another obvious difference between the Avicel energy transition profile and the one for DiTab is the absolute magnitude of the energy of formation observed for each of the materials. At each of the compression levels investigated, the magnitude of the value obtained for DiTab is less than that for Avicel. For equal applied forces, therefore, Avicel either bonds more extensively, forms more highly energetic bonds, or both.

The energy transition profile for lactose (Fast Flo), contains several interesting features. Behavior similar to that observed for DiTab is noted at the lower range of compression forces. Here, as with DiTab, fracture of the spherical aggregates comprising the particles of Fast Flo lactose occurs and the energy of formation is low; unlike DiTab, this endoenergetic process appears to be complete at about 6000 N. From this point in the applied force range up to approximately 27,000 N, the degree of bond formation as quantitated by the energy of formation is approximately linearly proportional to the applied force. These values are of a greater magnitude than that observed in DiTab but smaller than the values obtained for Avicel.

Each of the 3 profiles examined thus far has a compression force range where bonding is very nearly a linear function of applied force. These ranges are: Avicel, 7500–32,000 N; DiTab, 14,000–30,000 N; Fast Flo lactose, 6000–27,000 N.

The profile for Starch 1500 (Fig. 4) has features similar to the others, except that when bonding occurs, the relationship between energy of formation and applied force is curvilinear. The resistance to consolidation is greatest at low force, with relatively more bonding per unit applied force as force increases. This phenomenon occurs within the range of 6000–25,000 N force. Above 25,000 N force it appears that the system experiences a maximum amount of bonding, and subsequent work of compression is expended simply in deformation of the maximally consolidated body.

The final material evaluated, granular acetaminophen, provides a striking contrast to the compressible excipients. This data is also included in Fig. 4. Granular acetaminophen is virtually incompressible, in the pharmaceutical sense, although compacts of low hardness and high friability were formed for two of the forces evaluated. The lowest levels of force application did not result in the formation of a compact. The 15,000 N force level was required to obtain a marginally coherent compact and the low value obtained for the energy of formation for the process indicates a very low level of net compression bond formation at this force level. The next higher level of force application resulted in approximately the same energy of formation while the final force level investigated resulted in a still larger value (0.52 J), although the compact formed laminated when being evaluated for tensile strength.

The overall qualitative appearance of the energy transition profile for granular acetaminophen, in addition to the quantitative values obtained for the energy of formation for each of the compression forces, clearly demonstrates the profound differences in energetic behavior between the compressible systems and incompressible system in this study.

#### *Tensile strength vs energy of formation*

A desire to establish a correlation between energy of formation and 'bonding' led to the evaluation of compact tensile strength for the tablets made in this study. With a demonstrated quantitative measure of bonding as a result of compaction, a direct correlation between this parameter and the ultimate tensile strength of the finished compact would be expected. Fig. 5 is a combined representation of the data obtained for the 5 materials investigated. The tensile strength of the finished compacts was calculated from the force required to cause tensile failure by the manner of Fell et al. (1970). The equation used to compute tensile strength was:

$$\sigma = 2F/(D\pi X) \quad (8)$$

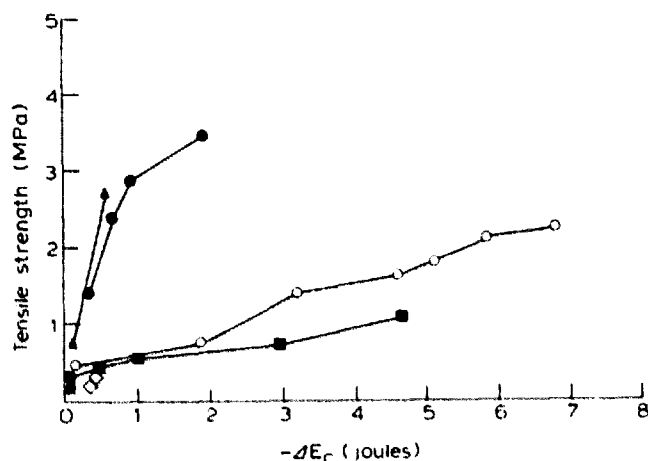


Fig. 5. Tensile strength vs energy of formation for microcrystalline cellulose (▲), pregelatinized compressible starch (●), lactose (○), dicalcium phosphate dihydrate (■), and granular acetaminophen (◇).

where  $\sigma$  is the tensile strength,  $F$  is the force needed to cleave the tablet,  $D$  is the tablet diameter and  $X$  is the tablet thickness. The tensile strength determinations reported were obtained only for those compacts which failed in tension as evidenced by splitting into halves diametrically. Any deviation from this fracture pattern was noted, and the force values obtained were not used in the subsequent tensile strength calculations. Also, it should be noted that tablets made from Avicel and Fast Flo at high compression forces could not be fractured within the range of the test device.

The correlation between compact tensile strength and energy of formation demonstrated in Fig. 5 serves to confirm that the energy of formation is a parameter which indicates the development of compact coherence through bond formation. These results graphically demonstrate the energetic differences between the compressible systems, the direct compression excipients, and the incompressible system, granular acetaminophen.

The evidence presented from the results of these studies marks an initial effort to quantitatively elucidate the energetics of the interparticulate interactions occurring during compression. The findings seem to demonstrate a logical energetic basis for the generic term compressibility, and provide a sound basic foundation upon which the further evaluation of the energetics of the compaction process may proceed.

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