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MEASUREMENT OF THE THERMAL ENERGY EVOLVED UPON TABLET COMPRESSION

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ABSTRACT

The increase in temperature that occurs when a granulation or powder is compressed into a tablet has long been of interest to pharmaceutical scientists. Not only can this rise in temperature be indicative of differences in formulations which affect their performance during the tabletting process, but it may also cause unforeseen changes in the final tablet. Exact measurements of this temperature rise and of the thermal energy released have proven to be elusive. The diversity in equipment used approximately equals the number of published studies. This is the first report in which an accurate temperature probe has successfully been placed within the powder bed being compacted. Using a measurement system of original design, both the temperature rise and thermal energy evolved have been measured for single component systems comprised of Avicel, calcium carbonate, Corn Starch USP, and sulfathiazole. Extension of this work will deal with reactive multicomponent systems.

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INTRODUCTION

The increase in temperature that occurs when a granulation is compressed into a tablet has long been of interest to pharmaceutical scientists. Not only can this rise in temperature be indicative of differences in formulations which affect their performance during the tabletting process, but it may also cause unforeseen changes in the final tablet. Exact measurements of this temperature rise and, more importantly, of the thermal energy released have proven to be elusive. The diversity in equipment used almost equals the number of published studies. This is the first report in which an accurate temperature probe has successfully been placed in the bed being compacted.

Early work in this area was performed by Nelson, Busse, and Higuchi[1] using an instrumented single punch tablet press on which both force and displacement could be measured. Integration of the resultant force-displacement curve yielded the energy of compression. A later study by Hanus and King[2] utilized an uninstrumented single punch tablet press. After allowing the press to operate for a period of time sufficient for thermal equilibrium of the equipment to be achieved, a quantity of tablets was directed into an insulated container with a known weight of liquid present. Measurement of the temperature change of the liquid and correction for the heat of dissolution, heat of wetting, and differences in heat capacities allowed the temperature change of each tablet and the thermal energy imparted to each tablet during compression to be calculated. A decade later, Nürnberg and Hopp[3] employed a portable infrared detection device to measure the surface temperatures of the tablets as they were ejected from the dies of a rotary tablet press. A recent study by Coffin-Beach and Hollenbeck[4] utilized a compression calorimeter fabricated from acetal resin thermoplastic ("Delrin"). Inside the calorimeter were two ports: one for the punches die and the other for the quartz thermometer temperature probe. The die was surrounded by liquid mercury with the probe in contact with the mercury.

There were several shortcomings to the systems described above. These included: 1) All of the systems measured temperature rise remotely; 2) Frequently, the temperature measured depended on the location of the tablet at the time it was measured; 3) Only one of the studies used an insulated compression system; 4) Compensation for all of the extra-compression thermal effects was difficult when liquid measurement systems were used; 5) The interval between readings was frequently large; 6) The surface temperatures measured by an IR detector may not have been truly indicative of the interior temperatures.

The report by Coffin-Beach and Hollenbeck[4] was the first to describe an experimental procedure in which the compression event occurred within a device which could be classified as a calorimeter. Concomitant work in our laboratory was also designed around the "compression calorimeter" concept, but a different

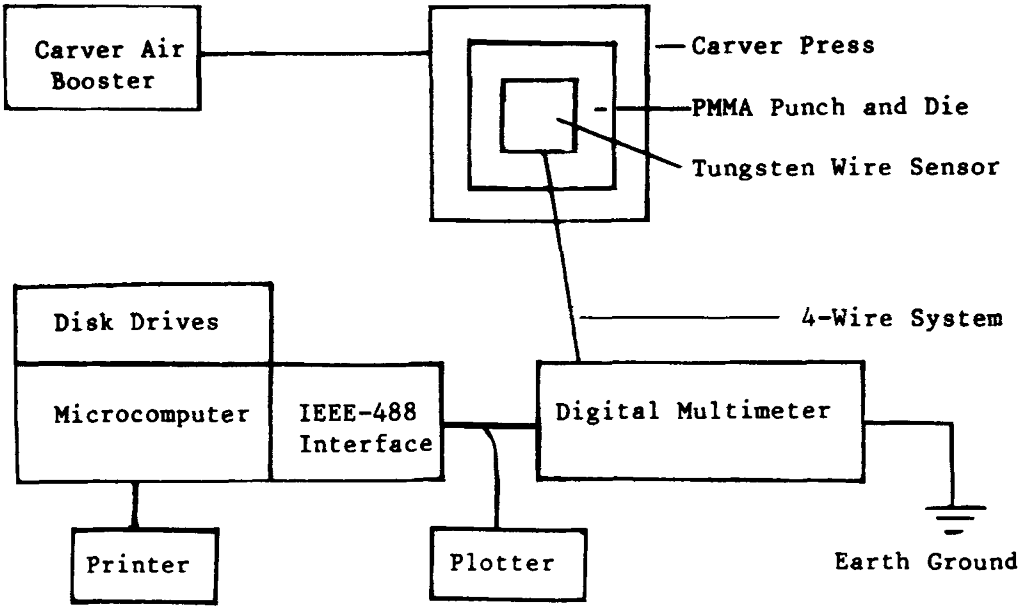

Figure 1. Schematic of the thermal energy component of compression measurement apparatus

approach was taken. This new system consists of a polymethylmethacrylate punch and die with a tungsten wire temperature probe which is in intimate contact with the die contents. Temperature measurements are made by measuring the resistance of the tungsten wire. The advantages of such a system are: 1) Thermal leakage is significantly lower than with metal punches and dies; 2) Temperature measurements can be made several times per second; 3) The probe is at the center of the material being compacted.

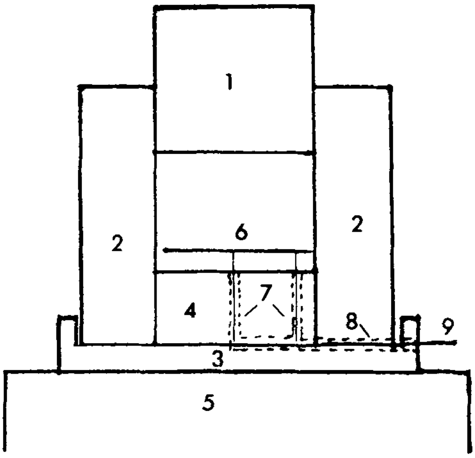

Figure 2. Cross-sectional view of PMMA punch and die assembly. 1) Top punch (shown raised for clarity), 2) Die, 3) PMMA punch and die assembly holder, 4) Bottom punch, 5) Bottom ram of Carver Press, 6) Tungsten wire sensor (planar coil), 7) Bottom punch exit ports, 8) Die and holder exit ports for wire, 9) Shielded four wire cable to DMM.

EXPERIMENTAL

A system schematic is shown in Figure 1. The compressions were performed using a laboratory press (Carver Model C) and an air operated booster (Carver No. 2735). The air booster had the advantage of being able to control the press such that compression to a specified force occurred with subsequent maintenance of that force for a desired period of time. No change in force was noted for test runs of five minutes duration.

The punch and die set shown in Figure 2 was made of polymethylmethacrylate (PMMA)(DuPont). PMMA was chosen for the following reasons: 1) Ability to withstand relatively high compressive loadings (up to 82.76 MPa);[5] 2) Easily machined to the desired shape and dimensions; 3) Low coefficient of thermal conductivity.[6,7]

The 99.98% pure 0.25 mm diameter tungsten wire sensor (Aesar, Catalog number 10408) was formed into a flat coil by weaving the wire through a 10 mesh plastic grid cut into the shape of a cross. This design allowed maximum contact of the wire with the die contents and was always placed in the center of the powder bed.

Temperature measurement was accomplished by measuring the resistance of the previously calibrated tungsten wire. A digital multimeter (Keithley Instruments Model 195A DMM) was used for this purpose and the connection was made via a four-wire configuration. The four-wire configuration eliminated lead resistance from the measurement and thereby increased accuracy.[8] The DMM's A/D converter then converted the results to IEEE-488 protocol. The DMM and the sheath surrounding the lead wires were externally grounded (true earth ground) for improved stability.

A disk drive equipped microcomputer (Radio Shack TRS-80 Model III) with an IEEE-488 interface (Scientific Engineering Laboratories Model 488-80C) acted as the data storage device, DMM controller (controlled DMM parameters via IEEE-488 signal) and data manipulation device. The computer also controlled data output devices including a printer, modem, and plotter. The DMM, microcomputer, IEEE-488 interface, printer, plotter, and modem were powered by an AC power supply (Jefferson Electric "Minigard") to further increase instrument stability and eliminate inductive back current effects caused by activating and deactivating the air booster. The data collection programs were designed to take a DMM reading and store it in memory every 300 ms. At this collection rate, rapid changes in temperature could be well characterized.

Use of the system required that the tungsten wire be calibrated. This was accomplished by replacing the top punch with the calibration insert shown in Figure 3. The punch and die were placed in a styrofoam box covered with packing foam on all sides. The power supply was set to an appropriate voltage and the system was allowed to equilibrate for at least 12 hours. When equilibrium had occured, the DMM measured the resistance of the thermistor for 30 seconds. After this, the DMM was switched to read the tungsten sensor's resistance. A 30 second stabilization period was allowed whereupon a 30 second measurement of the sensor's resistance was made. The DMM was then switched back to the thermistor position. A 30 second stabilization period was allowed after which a second 30 second measurement of thermistor resistance was accomplished. The thermistor (Yellow Springs Instrument, Number UUa35J3, 5000 ohms at 25°C) was used as a reference since the change of resistance with temperature of these thermistors has been standardized and any given resistance could be converted to temperature by a modified Steinhart-Hart equation.[9] The two thermistor reading sets were averaged to give

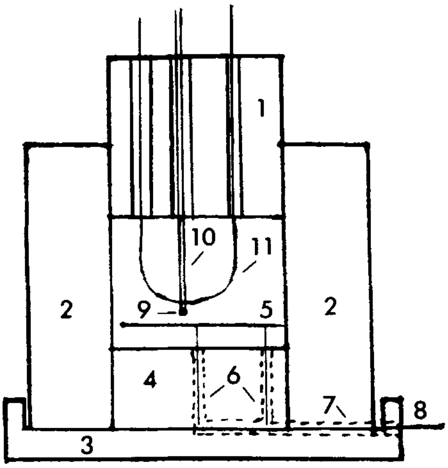

Figure 3. Cross-sectional view of PMMA punch and die assembly with tungsten wire sensor calibration insert. 1) Calibration top punch (held in raised position during calibration), 2) Die, 3) PMMA punch and die assembly holder, 4) Bottom punch, 5) Tungsten wire sensor (planar coil), 6) Bottom punch exit ports, 7) Die and holder exit ports for wire, 8) Shielded four wire cable to DMM, 9) Thermistor, 10) Thermistor lead wires (connected to 4 wire shielded cable from DMM, does not contact nichrome heater wire), 11) Nichrome heater wire (connected to DC power supply, does not contact thermistor lead wires).

the reference temperature. The tungsten wire readings were averaged to give the resistance corresponding to the reference temperature. The resulting data was regressed to fit a quadratic equation by a least-squares method using SAS (PROC REG).[10]

After calibration, each run consisted of the following steps. The die containing the bottom punch and temperature sensor was filled with a weighed amount of the material to be compressed (typically 5 g) and the top punch was inserted into the die. Four compounds were used as received in this study, Avicel PH-101

(FMC), calcium carbonate (Baker), Corn Starch USP (A.E. Staley), and sulfathiazole (Sigma). The complete setup was then placed onto the bottom ram of the press. The microcomputer program was started and data was collected for 10 seconds before the previously adjusted air booster was activated. The air-booster could be turned off independently of the computer collection program. When the run was completed, the data was stored on diskette. The data could be printed or plotted at this point. The total data collection time was 90 seconds.

The temperature change was computed by averaging the resistance values from the beginning of the run through the tenth second, converting this value to temperature, and subtracting this temperature value from the maximum temperature that occurred during the run. The blank temperature was determined by averaging the temperature rise for several compressions performed with an empty die. All compressions were carried out at a force of 21600 N (calculated pressure applied: 27.28 MPa)

The energy required to provide a given temperature change in the die cavity when occupied by the tablet components was determined by the following procedure. The die was made water tight by sealing all possible leaks with 1.5 g of heat sink compound (Dow-Corning 340 Silicone Heat Sink Compound). The bottom punch was the same as used during the compressions. Five ml of distilled water were added to the die. This volume was the approximate volume of a compressed tablet. Next, a special top punch was inserted. This special top punch had three ports: a center port for the thermistor and two other ports for lead wires from a 41.2 ohm (1% tolerance, 0.25 watt) resistor that was used as a heater. Voltage from a regulated DC power supply was applied to the resistance heater and monitored by a digital multimeter (Keithley Instruments Model 169). The voltage to be applied to reach a desired energy input rate was determined from the following equation:

$$V=[4.184E'R]^{1/2} \qquad (1)$$

where V is the voltage in volts, E' is the energy input rate in cal s^{-1}, R is the resistance of the heater resistor in ohms (41.2 ohms), and 4.184 is the calories to Joules conversion factor (since 1 watt=1 J s^{-1}). A energy input rate of 200 mcal s^{-1} was selected for use in three separate runs. Rates varying from 50 to 200 mcal s^{-1} did not appreciably affect the calculated energy requirement for a particular temperature change. Each run consisted of heating the water inside the die for 600 seconds and collecting elapsed time and temperature data (with conversion of the thermistor readings to temperature) every 430 ms. The data from the three runs were fitted to the following equation with SAS (PROC NLIN, Secant method):[10]

$$T=A[1-e^{-B(D+t)}]+C \qquad (2)$$

where T is the temperature in degrees Kelvin, A is the asymptotic fitted temperature, B is a fitted constant, D is the fitted time offset constant, C is the temperature at the tenth second (not fitted, but specific for each run), and t is the elapsed time in seconds.

The energy required to provide a given temperature change in 5 ml of water in the die cavity was obtained from the product of equation 2 solved for t and the heating rate (E', cal s^{-1}):

$$E=E'(\{\ln[1-(T^*/A)]/-B\}-D-10) \qquad (3)$$

In equation 3, E is the energy required to raise the temperature of the interior of the punch and die assembly (filled with water) T^* degrees, E' is the energy input rate in cal s^{-1}, T^* is the temperature rise in degrees Kelvin or °C, and the other constants are described above in equation 2. The -10 is compensation for the non-linear regression beginning at the tenth second instead of zero.

The specific heat capacities (constant pressure) of the materials being compressed and of the heat sink compound were determined by Differential Scanning Calorimetery (DSC) using the Boersma Differential Thermal Analysis (DTA) technique (DuPont Instruments Model 900 with DSC cell).[11] Nitrogen was used as a purge gas and dry ice was used to cool the DSC cell to slightly below 0°C before each run. Computation of the specific heat capacity was done according to technique of O'Neill[12] with synthetic sapphire (Al_2O_3) as the reference.

The specific heat capacities (constant pressure) of the resistor and of water were computed from tabled values.[7] The heat capacity of carbon was used to determine the heat capacity of the resistor since the weight of the resistor was almost entirely carbon.

Using the data above, the thermal energy component of compression was computed using equation 4 below:

$$E_{TECC}=\{[E_{eqn3,T_{mat}}-C_{p(extra)}T_{mat}+C_{p(mat)}T_{mat}]$$
$$-[E_{eqn3,T_{blank}}-C_{p(extra)}T_{blank}]\}/m \qquad (4)$$

where E_{TECC} (thermal energy component of compression) is the net thermal energy evolved upon tablet compression in cal g^{-1}, $E_{eqn3,T_{mat}}$ is the energy required to heat the interior of the punch and die assembly T_{mat} degrees when filled with water (from equation 3), $E_{eqn3,T_{blank}}$ is the heat required to heat the punch and die assembly T_{blank} degrees when filled with water (from equation 3), $C_{p(extra)}$ is the heat capacity computed from the summation of the specific heat capacities of the water, resistor, and heat sink compound multiplied by their respective weights as used in the profile study (cal K^{-1}), $C_{p(mat)}$ is the heat capacity of the material compressed obtained by multiplying the specific heat capacity of the material by the weight of the material used (cal K^{-1}), T_{mat} is the maximum temperature obtained minus the baseline temperature for the compression in °C, T_{blank} is the empty die temperature rise computed above in °C, and m is the weight of the material being compressed(g). The three values computed from equation 4 for each of the 200 mcal s^{-1} runs were averaged to give a final value for a compression.

RESULTS AND DISCUSSION

A new system has been developed and used to measure the thermal energy component of compression (TECC). This system is capable of collecting, storing and displaying the time and resistance data every 300 ms. This rapid data collection rate allows the compression event to be well characterized. Faster collection rates are possible, but at a sacrifice in measurement stability since this faster rate would require a shorter signal integration time.

Temperature changes as small as 0.07°C can be reliably measured. Greater sensitivity may be achieved by using platinum wire, since it has a greater resistivity (10.6×10^{-8}, 5.6×10^{-8} ohm-m). The temperature coefficient of resistance of platinum is slightly lower than that of tungsten (0.00393, 0.0045 K^{-1}) however.[6,7] Our tests with this material indicate that it is not well-suited for this application. Platinum wire is brittle and wire gauges small enough to give reasonable changes in resistance with temperature do not withstand the compression process. Small gauge tungsten wire survives many compressions and by adjusting the wire diameter and length, it is possible to acheive results comparable to that of platinum. Importantly, the wire and plastic grid did not inhibit bonding between particles on both sides; i.e. one compact was made not two compacts bounded by the sensor.

The PMMA punch and die assembly has proven to be surprisingly durable. After well over 300 compressions, there are no signs of crazing nor stess cracking. The compressive load prior to bursting for this material is listed as 82.76 MPa,[5] so sudden failure was not expected. The complete absence of fatigue was unexpected.

The thermal energy component of compression is the net thermal energy evolved upon compression of a powder or granulation. As can be seen from equation 4, the TECC is calculated solely on the basis of experimentally determined temperature changes and heat capacities. It is established that, for a non-reactive system, there are three principal phenomena responsible for this change in thermal energy. The most obvious of these is friction between the solid particles themselves and between the solid particles and the surfaces of the punches and die. Secondly, thermal energy is consumed during particle fracture when physical bonds are broken. Thirdly, in the process of compaction, larger particles may also be made from smaller particles. Physical bond formation must then occur with the accompanying evolution of thermal energy. These latter two phenomena can be described in terms of the formation or destruction of surface with the accompanying increase or decrease in surface free energy.

The results from the compression of Avicel, calcium carbonate, corn starch and sulfathiazole are presented in Table 1 with a representative compression event profile shown in Figure 4. A statistical comparison of the temperature changes and TECC

TABLE 1

Results of Compressions

Compound	n	Mean Temperature Change (SE) °C	Mean TECC (SE) cal gm^{-1}
Avicel	10	4.282 (0.194)	5.601 (0.507)
Blank	10	1.568 (0.092)	***
Ca Carbonate	7	4.506 (0.386)	5.620 (0.845)
Blank	6	1.171 (0.237)	***
Corn Starch	10	2.279 (0.082)	1.538 (0.113)
Blank	10	1.706 (0.058)	***
Sulfathiazole	8	3.378 (0.202)	3.025 (0.298)
Blank	8	1.597 (0.090)	***

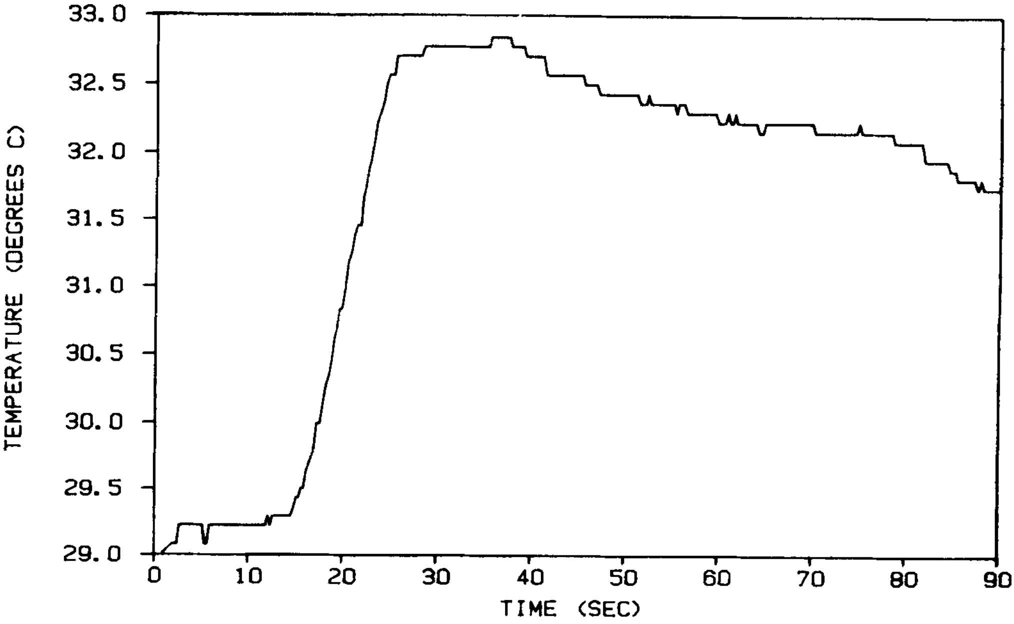

Figure 4. Typical compression profile.

TABLE 2

Statistical Comparisons of Net Temperature Changes and TECC's Between Compounds

Comparison	Temperature Change	TECC
Ca Carbonate - Avicel	-	-
Corn Starch - Avicel	+	+
Corn Starch - Ca Carbonate	+	+
Sulfathiazole - Avicel	+	+
Sulfathiazole - Ca Carbonate	+	+
Sulfathiazole - Corn Starch	+	+

\+ = significantly different at 95% confidence level
\- = not significantly different at 95% confidence level

values between compounds was performed using SAS (PROC ANOVA, Tukey-Kramer procedure)[10] and the results are presented in Table 2. All temperature changes except those for Avicel and calcium carbonate were found to be significantly different from each other and all TECC comparisions except one (Avicel-calcium carbonate) were likewise significantly different. The blank temperature values listed below each compound are the values obtained from the blank compressions. Statistical comparison of the mean blank temperature change and the mean compound temperature change for each material indicates that these quantities are statistically different at the 99% confidence level. From this result, it can be concluded that the temperature values measured for each compound are indeed due to the presence of compound during the compression event.

Compact hardness could not be evaluated in a quantitative manner since the temperature probe was imbedded in the compact. Removal of the compact from the punch and die assembly therefore necessitated breaking the compact. Subjectively, Avicel yielded the hardest compact. Comparison of Avicel with corn starch is interesting because corn starch yielded a soft compact. Since the thermal effects due to friction would be expected to be comparable between these two materials at this low compaction pressure and since their DSC-measured heat capacities are very close (0.4200 cal g^{-1} for corn starch versus 0.4268 cal g^{-1} for Avicel at 27°C), the larger temperature and TECC changes for Avicel should be due to an increased extent and/or strength of bond formation. This would demonstrate that temperature and TECC measurements can be made accurately and reproducibly enough to separate thermal effects from different sources. This is a requirement for use of this system to evaluate reactive systems.

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