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🔑 *Keyphrases*

Dermatological lotions—rheological properties

Rheology, lotion—changes during aging

Brookfield viscosimeter—shear stress values

Metered bottling machine—rheological effect

Viscosity—shear rate relation

Thixotropy—agitation type, duration

Thermodynamic Effects in the Compression of Solids

By EDWARD J. HANUS* and LOUIS D. KING

The temperature changes of solids undergoing compression were determined. Compounds of known heat capacity were compressed into tablets at varying speeds and pressure and collected into thermally insulated vessels containing a suitable liquid. The resulting increase in temperature of the liquid was measured after equilibrium was established, and it was found that the increases in temperature were directly related to speed of compression and to compression pressure. Extrapolation of the data provided a technique for predicting tablet temperatures at time of compression. Thermal energy was converted to its mechanical equivalent thus providing a means for estimating the energy expended in the tablet compression process. The use of thermochromic indicators qualitatively supported the validity of the conclusions and quantitative confirmation was obtained by direct heating of samples.

MEASUREMENT OF thermal energy developed in a dynamic operation such as the compression of solids with a tablet machine is a difficult and challenging problem. The reasons are numerous: (a) the heat content of a compressed compact is very quickly dissipated to its environment, (b) the high pressures applied during compression would crush ordinary temperature measuring devices such as thermometers or thermistors, and (c) during compression, the granulation is virtually encased within a steel chamber consisting of the die and punches, and thus is not physically accessible at the moment when temperatures are at a maximum.

In the compaction of powders, the following processes contribute to the total energy of compression (1, 2).

(a) Packing—Initially within a bed of powder there is essentially only one point of contact between two neighboring particles. As pressure is applied, consolidation takes place by the particles sliding one over the other and heat is generated. The extent to which this occurs is influenced to a large degree by the frictional properties of the two sliding surfaces (3, 4).

(b) Elastic and plastic deformation—In this phase of compression, most of the energy is consumed in the deformation of particles and by die-wall friction.

(c) Cold working with or without fragmentation—When fragmentation occurs, the specific surface area of tablets increases directly with pressure to a maximum and then decreases (5).

(d) Removal of the upper punch from the die after compression.

(e) Tablet ejection.

Nelson *et al.* (2), using an instrumented single punch tablet machine, found it possible to estimate the energy expended in the tablet compres-

sion process by considering the magnitude and relation between compression variables (upper and lower punch force, ejection force, upper punch displacement), and the linear dimension of the die cavity. Using granulations of sulfathiazole, Nelson calculated a probable temperature rise of about 5° by constructing force–displacement curves and measuring the area under the curve with a planimeter. However, there appears to be a need for a relatively simple and inexpensive method for determining the total heat generated by solids undergoing compression in order to study the tableting process. It was for this reason that the current study was initiated.

The simplest approach to the problem originally appeared to be to include some material in the tablet granulation that would change color in such a way as to give a true indication of the maximum temperature produced during compression. However, results from this portion of the study were only qualitative in nature and a more precise thermometric method was developed.

EXPERIMENTAL

Thermochromic Method—Samples of Thermochrom temperature indicating crayons[1] and Detecto Temp temperature indicating pigments[1] were obtained for evaluation. The exact chemical identity of these highly complex metallic salts could not be provided. When the specified temperature is maintained for 1 or 2 sec. a gas, such as carbon dioxide, ammonia, sulfur dioxide, or water vapor is liberated and the chemical structure and color of the salts undergo changes (6). Eighteen Thermochrom crayons provide temperature measurements from 65°–670°. Thirty-six pigments cover a measurement range from 40 to 1350°; accuracy is estimated to be ±5°. Reportedly changes in air pressures affect all compounds in that the color change temperature thresholds are displaced upward or downward (7). At 5–10 mm. mercury, the materials change color from 5–20% below the temperatures they would indicate under normal atmospheric pressure and when used under vacuum or pressure, suitable calibrations are recommended.

The lowest available temperature indicating crayons of Thermochrom 915–1015 (65°) and 915–1016 (75°) were shaved with a razor blade to small fragments, passed through a No. 40 sieve, added to separate samples of sodium chloride (40/60 mesh) at a concentration of 1%, and mixed for 15 min. by tumbling in a wide-mouth glass bottle. Three-gram tablets were then prepared using a hydraulic press at a pressure of 10,000 lb. Duplicate runs revealed no change in color from gray to blue (65°) or gray to green (75°) in either sample, therefore, it was tentatively concluded that the average temperature of the sodium chloride tablet was less than 65°. However, it was noted that the crayons appeared to contain a waxy base which would

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[1] Trademarked by the H. V. Hardman Co., Inc.

undoubtedly act as a lubricant and possibly alter experimental results. For this reason, the Thermochrom crayons were abandoned and attention was directed toward the Detecto Temp pigments which were available as fine powders and could readily be incorporated in tablet granulations.

The first pigment to be examined was Detecto Temp 915–0900 which was reported to change from pink to blue after 2 sec. at 40°. A 5% triturate of sodium chloride (40/60 mesh) was prepared and then compressed into 3-Gm. tablets of $^3/_4$ in. diameter using a flat-faced upper tablet punch and a smooth flat stainless steel plate as a support for the die in lieu of a lower tablet punch. Tablet pressure was brought up rapidly and maintained at 10,000 lb. for 15 sec. and then quickly released. It was noted that tablets made in this manner changed in color from pink to blue indicating that an average tablet temperature of approximately 40° or higher had been attained.

The pigment available at the next higher temperature was Detecto Temp 915–0923 which was reported capable of undergoing two color changes, *i.e.*, pink to lilac at 55° and lilac to blue at 85°. Tablets prepared in the manner described above showed a very faint lilac color which was difficult to distinguish with certainty from the original pink color of the pigment. In order to establish confidence in the observations, tablets were prepared at pressures of 5,000, 10,000, and 30,000 lb. on the basis that increasing pressures might produce higher tablet temperatures. This was borne out in the experimental results which showed no color change at 5,000 lb. pressure, a very faint color change at 10,000 lb., and a definite color change at 30,000 lb.

The experiment was repeated with Detecto Temp 915–0901 which changes from light green to blue at 60°. Pressures of 10,000 and 30,000 lb. were employed; no change in color was observed indicating that a temperature of 60° was not reached regardless of pressure. Tablets containing the 60° pigment (915–0901) were placed in an oven at 80° for $1^1/_2$ hr. A pronounced color change from green to blue was noted indicating that the pigment was operative.

Thus, using a pressure of 30,000 lb., sodium chloride tablets were found to rise in temperature to about 55°, and an increase in thermal energy appeared to be directly related to an increase in pressure.

The temperature developed at points in the compress was probably much higher than the indicated temperature. However, no measure of the maximum temperatures which may have developed was possible because of the time required for the pigments to undergo changes and the possible reversibility of the reactions. Only average temperature changes for the total compress were observed.

Effect of Reduced Pressure—A vacuum pellet die, usually used with infrared procedures, was employed to prepare $^1/_2$-in. flat-faced tablets under reduced pressure. One-gram tablets of sodium chloride were compressed at a pressure of 3,000 lb. while a vacuum of 2 mm. mercury was maintained for 30 min. Two pigments were tested at a concentration of 5%, *i.e.*, 915–0901 (60°) and 915–0924 (65°) and no color change was noted with the 65° pigment while a nonuniform color change from green

TABLE I—COLOR CHANGES OBSERVED IN TABLETS OF SODIUM CHLORIDE USING THERMOCHROMIC INDICATORS

Thermochromic Indicator	Color Change and Temp.	Pressure of Hydraulic Press[c]				Time Period of Applied Vacuum	
		3	5	10	30	2 min.	30 min.
Crayon 915–1015	65°–gray to blue			—			
Crayon 915–1016	75°–gray to green			—			
Pigment 915–0900	40°–pink to blue			+			
Pigment 915–0923[a]	55°–pink to lilac		—	+	+		
	85°–lilac to blue		—	—	—		
Pigment 915–0901	60°–lt. green to blue			—	—		
Pigment 915–0901	60°–lt. green to blue	b				—	+
Pigment 915–0924[a]	65°–lt. pink to lt. blue	b				—	—
	145°–lt. blue to lt. brown	b				—	—

[a] Has two color changes. [b] Vacuum applied. [c] Gauge pressure $\times 10^3$.

to blue was observed with the 60° pigment. The sides of the tablets were mostly blue whereas the upper and lower face of the tablet still showed some evidence of the original green color. Reducing the time period for applying vacuum from 30 min. to 2 min. resulted in no color change in tablets prepared with either one of the pigments. This indicates that the thermochromic materials change color significantly below the temperatures that they would under normal atmospheric pressure. A summary of the above findings is presented in Table I.

Dynamic Compression—The behavior of the thermochromic materials under dynamic conditions of compression using a Stokes model E single punch tablet machine equipped with $1/2$-in. flat-faced punches was studied. Two pigments, 915–0900 (40°) and 915–0293 (55°) were added at a level of 5% to a number of common pharmaceutical compounds; no tablet lubricant was used. Approximately 10 to 50 tablets were compressed depending on the severity of binding or capping experienced because of the absence of lubrication. In all cases, the tablets were made as hard as practical. However, hardness, tablet weight, and thickness measurements were not attempted because the resulting tablets were not satisfactory *per se.*

As shown in Table II, sodium bicarbonate, alumina, citric acid, lactose, and sodium chloride attained average temperatures of about 40°, representing a temperature rise of about 16° above room temperature (24° ± 2°); polyethylene glycol did not exhibit a comparable rise in temperature which is not unexpected considering its lubricating properties (low coefficient of friction) and its relatively low yield value.

Thermometric Method—A single punch Stokes Tablet Machine model E as shown in Fig. 1 was con-

verted to a variable speed tablet press by the use of appropriate pulley arrangements. Other modifications included the use of $1/8$ in.-Teflon laminated to the bottom of the feed shoe in order to reduce friction and heat transfer between the feed shoe and die table. In addition, the hopper and die table were ringed with a combination of copper and rubber tubing, covered with aluminum foil and then connected to a constant temperature bath. The granulation, die table, punches, and die were maintained at constant temperature by circulating water through the system. The hopper was covered and a thermometer was inserted into the granulation with the bulb centered 1 in. from the bottom of the hopper. An additional thermometer was attached to the die table in close proximity to the punches and die in order to monitor possible temperature changes in that area of the tablet machine which was critical to the operation. A closed chute was prepared of cardboard and polyethylene and attached to the tablet machine in order to permit transfer of tablets to a Thermos bottle with a minimum loss of heat. Flat-faced punches of $1/2$ in. diameter were used throughout the study.

Granulations—Calcium carbonate and sodium chloride, two common materials of known heat capacity, were selected for study. The first was formulated into granules by a wet granulating technique whereas the latter, which can be compressed directly into tablets, was used in its pure form. The calcium carbonate granulation was prepared as follows:

Calcium carbonate USP........	10.000 Kg.
Magnesium stearate...........	0.105
Cellulose acetate phthalate	0.465
Acetone USP..................	2.068
Methanol.....................	6.204

The cellulose acetate phthalate (CAP) was slowly added with stirring to the acetone. After solution was effected, the methanol was added with stirring until the solution was homogeneous and the solution was then filtered through gauze.

The calcium carbonate was weighed, transferred to a pony mixer, and the granulating solution was added slowly with blending until the mixture was sufficiently wet. The wet mass was forced through a No. 8 mesh screen, air-dried for 18 hr., and then dried at 40° for a period of 40 hr. The dry granules were forced through a No. 14 screen and transferred to a steel drum. Magnesium stearate was added to an equal weight of 60 mesh fines, blended for 15

TABLE II—COLOR CHANGES IN TABLETS OF PHARMACEUTICAL COMPOUNDS USING THERMOCHROMIC INDICATORS

Compound	Pigment 915–0900 Color Change[a]	Pigment 915–0923 Color Change[b]
Sodium bicarbonate	+	—
Alumina	+	—
Citric acid	+	—
Lactose	+	—
Polyethylene glycol 4000	—	—
Sodium chloride	+	—

[a] Changes at 40° from pink to blue. [b] Changes at 55° from pink to lilac.

Fig. 1—Modified Stokes model E tablet machine.

min., and then added to the calcium carbonate granulation and mixed for 30 min. to form a homogeneous mixture.

One 25-lb. lot of sodium chloride was used throughout this study. Results of particle size analyses are recorded in Table III.

All operations were conducted in a sealed, air-conditioned room in which a constant temperature of 24° ± 1° was maintained at all times. Wide-mouth Thermos bottles were tared and 160 Gm. of distilled water was added. The bottles were capped and allowed to come to equilibrium for a period of time not less than 15 min. The speed of the tablet machine was then checked with a stopwatch, and the tablets collected were checked for initial weight, thickness, and hardness. Ten tablets were weighed to obtain an average weight; thickness was measured with a pair of vernier calipers and hardness was determined with the Monsanto tablet hardness tester. The plastic cap was removed from one of the Thermos bottles and quickly replaced with a square of Lucite (5 × 5 × ½ in.) to prevent any changes of temperature. A Beckman differential thermometer was inserted through a hole in the Lucite cover into the water to a point ¹/₂ in. from the bottom of the container. The temperature of the water was

measured after allowing a period of 5 min. for equilibration. The Thermos bottle was then transferred to the tablet machine and inserted snugly under the tablet chute equipped with a round plastic adapter. The tablet machine was activated and approximately 350 tablets each weighing 500 mg. were collected directly into the Thermos. The bottle was immediately capped and allowed to come to equilibrium for 30 min. Exact tablet weight was determined by weighing the Thermos again at this point. At the end of a 30-min. period, the container was gently tumbled for 1 min. and the temperature of the mixture measured. All determinations were made in triplicate at machine, speeds of approximately 27, 40, 60, 80, 100, 120, and 140 tablets/min. Temperatures of the granulation, the room, and the die table were recorded at the beginning and end of each run.

As a control, tablets prepared as previously described were allowed to cool, and then stored at 24° for 15 hr. in preweighed quantities of exactly 175 Gm. The stored tablets were quickly added to the Thermos bottle containing 160 Gm. of distilled water. Temperature changes were measured using the exact procedure described above.

To check the accuracy of tablet temperatures predicted, 175 Gm. of preweighed 500-mg. tablets were stored in sealed glass bottles and heated in a constant temperature oven at a mean temperature of 45.60°. The heated tablets were quickly transferred to the Thermos bottles following precisely the procedure described above and appropriate temperature measurements made.

The procedure employed with sodium chloride was identical to that reported above for calcium carbonate with the following exceptions: (a) Two hundred 700-mg. sodium chloride tablets weighing 140 Gm. were compressed and collected in each

TABLE III—PARTICLE SIZE ANALYSIS OF
CALCIUM CARBONATE AND SODIUM
CHLORIDE GRANULATIONS

Particle Size, μ	Calcium Carbonate, %	Sodium Chloride, %
840	24.0	5.1
420–840	33.3	65.2
177–420	21.4	29.6
177	21.3	0.1

Thermos bottle containing 150 Gm. of carbon tetra-chloride. (*b*) In checking the accuracy of the method, the sodium chloride tablets were heated at a mean temperature of 32.06°.

Effect of Pressure—Although an instrumented tablet press, equipped with a strain gauge for measuring pressure was not available, it seemed desirable to determine the effect of pressure on thermal effects developed during tablet compression. In this connection, the pressure adjustment screw was measured; the circumference was calculated and found to be 8.3254 cm. The screw was then suitably calibrated so that each quarter turn of the screw would move through a distance of 2.0814 cm. Using sodium chloride as the test material, tablets were compressed at 8 different pressure settings ranging from 0 to 2.5 turns of the pressure adjustment set screw. All determinations were conducted in triplicate using the process detailed heretofore.

CALCULATIONS

The temperature of a tablet at a given machine speed was calculated from the thermal capacities of the tablet material and the liquid to which the tablets were added. Heat capacity values utilized are listed below (8):

Calcium carbonate granulation....... 0.206
Sodium chloride.................... 0.220
Distilled water.................... 1.000
Carbon tetrachloride............... 0.202

The following equation was used for calculating the increase in thermal energy of the compressed solid.

$$\Delta T = \frac{\Delta T_L W_L C_L}{W_t C_t}$$

where ΔT is the measured increase in temperature (°C.) of the tablets as a result of compression, ΔT_L is the increase in the temperature of the liquid

(°C.), W_L the weight of the liquid, C_L the heat capacity of the liquid, W_t the weight of tablets, and C_t the heat capacity of the tablet granulation.

The calculated temperature (T) of the tablet just before striking the surface of the liquid was determined by summing ΔT and T_f and making a correction for the heat of wetting, mixing, dissolution, *etc.* (T_w) as follows:

$$T = (\Delta T + T_f) - T_w$$

where T_f represents the final temperature of the tablet-liquid mixture after equilibrium is established.

It was not feasible to collect a predetermined exact weight of tablets because of normal tablet weight variations, and practical counting difficulties. Thus, temperature readings were adjusted for a common weight, *i.e.*, 175 Gm. for the calcium carbonate granulation and 140 Gm. in the case of the sodium chloride. Temperature increases obtained with the unheated control tablets (T_w) were subtracted from the calculated temperature (T) in the case of the calcium carbonate granulation only since the T_w for the sodium chloride was found to be insignificant. This correction factor was 4.90° for the $CaCO_3$.

RESULTS AND DISCUSSION

Tables IV and V present a summary of the results obtained with the calcium carbonate and sodium chloride granulation, respectively. These data show that as the speed of the tablet machine increases, the temperature of the tablets collected also increases. In all cases, temperature ranges were not more than 1.61° indicating excellent reproducibility of results considering the nature of the experiments.

As can be observed, tablet hardness was reasonably well maintained throughout the study since variation in pressure imparts significant effects on tablet temperature. The relationship of tablet temperature to machine speed, Fig. 2, is almost

TABLE IV—TEMPERATURES OF COMPRESSED 500-mg. CALCIUM CARBONATE TABLETS AS A FUNCTION OF SPEED OF COMPRESSION IN °C.

Speed (Tablets/Min.)	Temperature Increase (T)	Tablet Temperatures[a] (T)	Range (°C.)	Tablet Hardness,[b] Kg.	Tablet Thickness,[b] cm.
26.74	16.27	36.42	36.26–36.61	10.6	0.248
40.32	17.69	38.32	37.48–39.08	10.5	0.247
61.43	19.70	40.84	40.48–41.53	10.6	0.245
77.72	20.47	41.79	41.43–42.14	10.5	0.247
100.00	21.28	42.74	42.11–43.34	10.2	0.245
122.95	22.13	43.67	43.00–44.17	10.1	0.248
140.85	22.20	43.74	43.66–43.82	10.7	0.242

[a] Average of 3 experiments—corrected for T_w. [b] Average of 30 measurements.

TABLE V—TEMPERATURES OF COMPRESSED 700-mg. SODIUM CHLORIDE TABLETS AS A FUNCTION OF SPEED OF COMPRESSION IN °C.

Speed (Tablets/Min.)	Temperature Increase (T)	Tablet Temperatures[a] (T)	Range (°C.)	Tablet Hardness,[b] Kg.	Tablet Thickness,[b] cm.
25.64	2.69	28.69	28.67–28.88	7.5	0.269
39.47	4.18	31.89	31.16–32.36	7.8	0.261
60.00	5.41	34.21	33.49–34.58	7.5	0.261
81.97	6.32	35.13	34.85–35.32	7.4	0.261
102.74	7.04	36.30	36.11–36.51	7.4	0.261
140.87	7.11	36.51	36.35–36.82	7.4	0.257

[a] Average of 3 experiments. [b] Average of 30 measurements.

linear at low speeds, whereas at high speeds the temperature values tend to become constant. This indicates that a limiting value was approached and that relatively little thermal energy is lost to either the tablet press or atmosphere at the highest attainable machine speed.
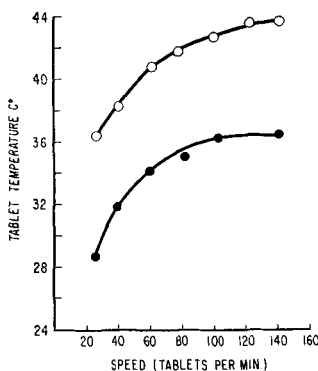

Fig. 2—*Tablet temperature as a function of machine speed. Key: ●, 700-mg. sodium chloride tablets; ○, 500-mg. calcium carbonate tablets.*
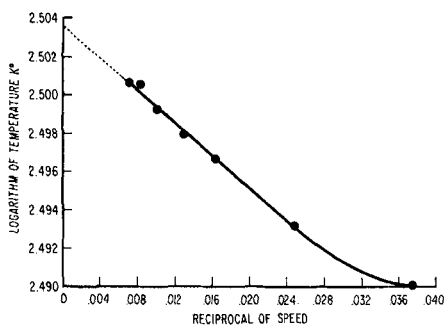

Fig. 3—*Relationship of the logarithm of tablet temperature in degrees Kelvin (K.°) and the reciprocal of machine speed for tablets of calcium carbonate.*

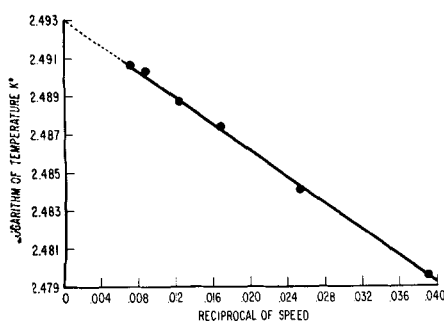Fig. 4—*Relationship of the logarithm of tablet temperature in degrees Kelvin (K.°) and the reciprocal of machine speed for tablets of sodium chloride.*

Plotting the logarithm of the tablet temperature in degrees Kelvin (°K.) against the reciprocal of machine speed produced a linear relationship as shown in Figs. 3 and 4. Extrapolation of the plot to the y axis gave the predicted temperature of the solid at the instant of maximum compression. At this theoretically infinite speed, losses in thermal energy by conduction to the tablet machine or radiation to the atmosphere approached zero. Thus, were it possible to run a tablet press at infinite speed, the enthalpy of the compressed compact would be completely transposed to the liquid in the thermally insulated collecting vessel. Some slight departure from linearity was noted only in the case of the calcium carbonate granulation at a slow speed of 27 tablets/min. The temperature of the compressed sodium chloride and calcium carbonate tablets was then determined at time of compression from their respective plots and is reported in Table VI.

The average increase in temperature as a result of the tablet compression process was found to be 20.9° for calcium carbonate and 14.2° for sodium chloride. The local temperatures in the granulation at the points of contact during compaction may momentarily be several hundred degrees, thus the temperatures reported above actually represent the mean tablet temperature immediately after compression.

In order to establish further confidence in the procedure, tablets were first heated to an exact temperature and subjected to the experimental method detailed above. Predicted and observed temperatures were compared and are reported in Table VII. The observed and predicted temperatures for calcium carbonate are in good agreement. However, there is a difference of approximately 9% between the 2 values for sodium chloride. This difference appears to be due to difficulty in obtaining exact values for the specific heat in the indicated temperature range and slight inherent errors in the experimental methods. Variability within individual experiments was not more than 0.16° in all cases.

Pressure has a profound thermodynamic effect on materials undergoing compression as can be deduced from Table VIII. At a low pressure mea-

TABLE VII—A COMPARISON OF CALCULATED AND OBSERVED TEMPERATURES USING PREHEATED TABLETS OF CALCIUM CARBONATE AND SODIUM CHLORIDE

Tablet Identification	Predicted Temperature, °C.	Observed Temperature, °C.	Temperature Difference, °C.
Calcium carbonate tablets, 500 mg.	44.9	45.6	0.7
Sodium chloride tablets, 700 mg.	38.2	35.0	3.2

TABLE VI—PREDICTED TABLET TEMPERATURES AS THE RESULT OF COMPRESSION

Tablet Identification	Predicted Tablet Temperature °K.	Predicted Tablet Temperature °C.	Temperature of Hopper Granulation, °C.	Increase in Temperature as a Result of Compression, °C.
Calcium carbonate tablets, 500 mg.	317.9	44.9	24.0	20.9
Sodium chloride tablets, 700 mg.	311.2	38.2	24.0	14.2

TABLE VIII—EFFECT OF PRESSURE ON 700-mg. TABLETS OF
SODIUM CHLORIDE AT A CONSTANT TABLET MACHINE SPEED[a]

Pressure, cm. [b]	Tablet Temperature [c] (T), °C.	Range, °C.	Increase in Temperature, °C.	Tablet Thickness,[d] cm.	Tablet Hardness,[e] Kg.
0.0000	25.51	25.32–25.48	1.51	0.335	e
4.163	27.40	27.30–27.42	3.40	0.315	e
6.244	27.48	27.41–27.58	3.48	0.310	e
8.325	28.29	28.23–28.40	4.29	0.300	e
10.407	29.37	29.29–29.43	5.37	0.290	e
12.488	30.77	30.56–31.04	6.77	0.280	4.0
16.651	32.38	31.81–32.72	8.38	0.270	5.9
20.814	35.12	34.67–35.42	11.12	0.260	7.1

[a] 81.97 tablets/min. [b] Each half turn (180°) of pressure set screw equals 4.163 cm. [c] Average of 3 experiments. [d] Average of 15 measurements. [e] Too soft to measure accurately.
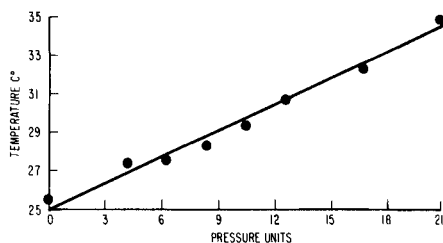

Fig. 5—The relationship of tablet temperature and applied pressure during the compression of sodium chloride tablets.

sured as 0 "cm." the tablet formed was observed to be extremely fragile however its shape was retained; the temperature increase noted was only 1.51°. On the other hand, when the pressure was grossly increased to a near maximum at 20.814 "cm." pressure, the increase in thermal energy was more than seven fold. Plotting pressure as represented by calibrated pressure adjusting screw *versus* temperature, produced a linear relationship as shown in Fig. 5. The reproducibility of the individual experiments at various pressure was excellent with the range of results being not more than 0.91° in all cases. As expected, tablet thickness was found to be inversely related to pressure and tablet hardness directly related.

Having determined tablet temperature as a result of compression, the heat in calories input, was then obtained from the following relationship:

$$Q = \Delta TCM$$

where Q is calories of heat, ΔT the increase in temperature, C the heat capacity, calorie/degree/Gm. of the granulation, and M the weight of one tablet in Gm. As shown in Table IX, it was found that the increase in heat per tablet for the calcium carbonate and sodium chloride tablet was 3.0 and 2.0 cal., respectively. Observing the law of conservation of energy and assuming that all the

useful energy expended in the compression process appeared as heat, the mechanical equivalents of heat appearing in Table IX were derived from the following relationships: (9)

1 cal. = 4.1858 × 10⁷ ergs = 4.1858 abs. joules

Thus by determining the increase in thermal energy in powdered solids as a result of compression, it has been possible to estimate the total useful energy expended in the tablet compression process.

SUMMARY AND CONCLUSIONS

The thermal changes occurring in powdered solids undergoing compression have been studied. Granulations of calcium carbonate and sodium chloride were compressed into tablets at varying machine speeds and pressures and collected into a thermally insulated vessel containing a suitable liquid. The resulting increase in temperature was measured after equilibrium was established. It was found that the increases in temperature were directly related to speed of compression and to the applied pressure. Plotting the reciprocal of time *versus* the logarithm of the temperature provided a linear relationship. An extrapolation provided techniques for predicting tablet temperature at the time of compression. Good agreement was observed between predicted tablet temperatures and results obtained by heating tablets by direct means. Further qualitative confirmation was obtained by the use of thermochromic materials which changed color at predetermined temperatures.

The measured thermal energy was converted to its mechanical equivalent thus providing a means for determining the useful work required for the tablet compression process. It is felt that the techniques reported here should find future utility as a tool in more quantitatively evaluating various parameters in tabletting technology related to the study of lubricants, excipients, glidants, particle size, moisture, and hardness.

TABLE IX—ENERGY REQUIREMENTS PER TABLET FOR THE
COMPRESSION OF CALCIUM CARBONATE AND SODIUM CHLORIDE GRANULATIONS

Tablet Identification	Temperature Increase,[a] °C.	Thermal Energy Increase, Cal.	Mechanical Energy Expended—— ergs × 10⁻⁷	abs. joules
Calcium carbonate tablets, 500 mg.	20.9	3.0	12.6	12.6
Sodium chloride tablets, 700 mg.	14.2	2.0	8.5	8.5

[a] From Table VI.

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⟨◦⟩ *Keyphrases*

Compression—solids

Thermodynamic effects—compression

Tablets—heat of compression

Temperature indicating pigments—heat of compression

Heat of compression, measured—water temperature change

Pressure relation—thermal effects

Speed of compression—thermal effects

Notes

Synthesis of Several Dibasic Acid Esters of 3-Quinuclidinol as Potential Pharmacological Agents

By HILLEL LIEBERMAN and SAMUEL ELKIN

Eight new dibasic acid esters of 3-quinuclidinol have been synthesized and isolated as their free bases using an alcoholysis reaction. A ninth compound, 3-quinuclidinyl hydrogen homophthalate, could not be isolated with sufficient purity to obtain an elemental analysis. However, this compound showed characteristic ester bands and gave a positive hydroxamic acid test. In a preliminary pharmacological evaluation in dogs, 3-quinuclidinyl hydrogen phthalate and 3-quinuclidinyl hydrogen 2,3-pyridinedicarboxylate gave a substantial increase in blood pressure and produced central stimulation as evidenced by a marked increase in respiration. Five compounds showed varying degrees of local anesthetic activity.

SERIES OF ESTERS of 3-quinuclidinol have been prepared by Sternbach and Kaiser (1) and by Mikhlina and Rubtsov (2). All of these esters produced marked spasmolytic activity. Of great interest was the observation that many of these esters showed a much higher antiacetylcholine activity than the analogous esters derived from diethylaminoethanol and other generally used basic alcohols. One of the most active of the series was 3-diphenylacetoxyquinuclidine.

Many other therapeutically active quinuclidine derivatives have been synthesized and pharmacological activity has been found in both mono- and disubstituted products. Several 3-substituted derivatives of quinuclidine have been reported by Grob (3) to stimulate the central nervous system. A series of 2-aminomethyl quinuclidines has been prepared and tested by Rubtsov *et al.* (4). Some members of the series were found to have strong ganglionic blocking activity while one member, diethylaminoethylquinuclidine-2-carboxylate (5), was found to be a good hypotensive. Ganglionic blocking was also noticed with 2,3-disubstituted derivatives (6). Perrine (7) has synthesized a series of 4-phenyl substituted compounds for investigation as possible analgesics.

The research involved in this work devotes itself to the synthesis of a series of dibasic acid esters of 3-quinuclidinol and the preliminary pharmacological testing of these products. These compounds evoked one or more of the following pharmacological responses: local anesthetic activity, respiratory and vasomotor stimulation.

Eight new compounds were synthesized and are represented by the general formula, I. All products