Infrared Imaging of Pharmaceutical Materials Undergoing Compaction

Simon R. Bechard[1,2] and G. R. B. Down[1]

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The goal of this study was to use infrared thermography as a new technique to investigate the heat released during compaction and consolidation of pharmaceutical powders and granules. Real-time temperature measurements without physical contact with tablets were provided by a highly sensitive (±0.1°C at 30°C) infrared camera (Agema Infrared Systems, Model 470 with CM-SOFT software). High-resolution images were captured at the takeoff point, i.e., less than 1 sec after compaction, stored on floppy disks, and then analyzed on a regular PC equipped with a VGA color monitor. Thermal surface profiles of tablets were obtained with high geometric and temperature resolution. Reproducibility of the camera readouts was better than 3%. The model granulation used was a direct compression blend of microcrystalline cellulose, spray-dried lactose, and magnesium stearate. This blend was compressed using an instrumented Korsch PH106 rotary press fitted with 1 station of 19.1 × 7.9-mm (0.750 × 0.312-in.) capsule-shaped tools. The effects of compaction force (6–20 kN), rate (130- to 360-msec contact time), and lubricant level (0.5 and 1.0%) on postcompaction temperature rise, caused by heat released during compaction, were investigated. The presence and location of nonhomogeneous heat distribution were assessed as well. Results have shown that the heat released during compaction increases with compaction force. Tablet surface temperatures of 33.8 ± 0.7°C were observed at 20 kN compaction force in contrast to 29.5 ± 0.3°C at 6.7 kN. The compression rate, as determined by the upper punch contact time did not have any significant effect on the heat released during compaction at 15-kN force. However, magnesium stearate level had a significant effect on the heat released during a compaction run. Tablets lubricated with 1.0% magnesium stearate had surface temperatures of 39–40°C after a 20-min run time, as opposed to 50–51°C for tablets lubricated with 0.5% magnesium stearate. Hot spots were seen at tablet edges where the die-wall friction occurs. Tablet cross-sectional thermal profiles revealed a 3–4°C temperature gradient across the tablet. These experiments show that infrared imaging is a unique tool for semiquantitative evaluation of heat released during compaction because it provides direct visualization with good temperature resolution of the heat evolved during the process.

KEY WORDS: pharmaceuticals; powder consolidation; compaction; infrared imaging/thermography; interparticulate friction.

INTRODUCTION

Theoretical treatment of heat transfer applied to the compaction of pharmaceutical solids (1) revealed that during compaction, localized high-temperature areas created by interparticulate friction could possibly attain the melting point of many compacted materials. Several methods have been described in the literature for evaluating the heat released during compaction. Using materials of known heat capacities, changes in temperature after compaction were determined by collecting tablets into thermally insulated vessels containing a fluid of known heat capacity (2). Temperature changes were found to be directly proportional to speed and force of compaction. Average temperature rises as high as 22°C were reported for calcium carbonate tablets. Surface temperature of tablets were later determined (3) by employing a portable infrared spotmeter detection device that measured the temperature of tablets as they were ejected from the dies of a rotary tablet press. Tablets having surface temperatures up to 50°C were observed under certain conditions. The amount of heat released during compaction was also determined by using a compression calorimeter (4–6). The authors associated the formation of a compact with a decrease in the energy of the system. This decrease in energy was correlated with the heat dissipation caused by a reduction in surface energy associated with particle bonding. Another technique (7) involved the introduction of a temperature probe within the powder bed being compacted. All these investigations showed that compaction may induce temperature increases as much as 25°C above ambient temperature. However, studies describing the use of infrared imaging for evaluating compaction-induced temperature changes and gradients have never been reported.

Infrared thermography is a technique that allows real-time temperature measurements without physical contact with a heat emitting object. Infrared radiation can be detected by scanner units that convert them into an electrical video signal. The scanner produces a TV-like real-time thermal color image of the object surface. Highly sensitive (±0.05°C at 30°C) infrared cameras available on the market can record high-resolution images and store them on a magnetic medium or tape. Recorded sequences can be transferred to a software package for both static and dynamic thermal pattern analysis. Infrared and microwave thermography/imaging has been used in medicine to detect breast cancer (8), in rheumatology (9) and dermatology (10,11), and to assess the inflammation associated with oral lesions (12). However, the technique was neglected by pharmaceutical scientists, even though many heat and mass transfer processes are involved in basic research or during the development phase of a product.

A knowledge of compaction-induced thermal events is needed for a better understanding of the mechanisms involved in the bond formation of solid dosage forms. Further, heat-induced physical changes after compaction can have an impact on the physical stability of solids (13,14). Because infrared imaging provides a direct visualization of infrared radiation evolved during compaction, it is believed that it will constitute a unique tool for the evaluation of thermal events during compaction. The goals of this study were therefore (i) to demonstrate the suitability of infrared thermography to evaluate thermal events occurring during compaction and (ii) to show that infrared thermography can be used for semiquantitative assessment of the heat of compaction by investigating the effects of compaction force, rate, and lubricant level on thermal energy released during compaction of a model granulation.

[1] Merck Frosst Centre for Therapeutic Research, Pharmaceutical R&D, P.O. Box 1005, Pointe-Claire-Dorval, Quebec, Canada H9R 4P8.

[2] To whom correspondence should be addressed.

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MATERIALS AND METHODS

Thermal Measurements and Analysis

A highly sensitive (0.1°C at 30°C) infrared camera (Agema Infrared Systems, Model 470, Ontario, Canada) equipped with a 12 × 12° lens was used to monitor thermal events. The region of interest was the die table at the takeoff point. A focused image was generally found when the camera was located at about 0.5 m from the table. Thermal measurements were performed by recording an image and then storing it on a floppy disk. The image was later transferred from the magnetic medium and analyzed for its thermal profile on a regular PC equipped with a VGA monitor using CM-SOFT extended version 1.10 software (Agema Infrared Systems). Reported values represent the maximum temperatures found on tablets. All experiments were carried out by using the same object emissivity value of 0.9, an ambient temperature of 23 ± 0.5°C, and a relative humidity of 23–24%. The reproducibility of measurement was assessed by recording images of several tablets and was found to be better than 3%.

Model Granulation

The model granulation used was a direct compression blend of microcrystalline cellulose (Avicel PH102, Lot 2014, FMC Corp.) and spray-dried lactose (DCL11, Lot 19257, Mallinckrodt Canada Inc.) at a 35:65 ratio. Magnesium stearate was used as the lubricant at levels of 0.5 and 1.0%.

Microcrystalline cellulose and lactose were introduced into a twin-shell blender and blended for 3 min. Magnesium stearate was sieved through a 60-mesh sieve, added to the powder blend, and then blended for 3 min at 35 rpm. The mixture was not equilibrated to ambient moisture level before compaction runs.

Compaction Studies

Compaction studies were performed on an instrumented Korsch PH106 rotary tablet press (Korsch Tabletting, NJ) fitted with one station of 19.1 × 7.9-mm (0.750 × 0.312-in.) capsule, deep concave tools. The granulation was gravity fed. Upper punch and ejection forces vs time profiles were collected for all experiments as well as tablet weight, thickness, and hardness (Key International, NJ, Model HT300). During preliminary experiments, it was noted that the press structure acts as a heat sink and becomes warmer as a function of run time. The press was therefore equilibrated to ambient temperature for 15–20 hr before any set of experiments was initiated.

Temperature vs Time Profiles

The suitability of the infrared camera to monitor temperature changes on tablet surfaces was assessed. Five tablets were compacted at 15-kN force and 305-msec contact time and infrared images collected over time. For that experiment only, the tablet press had not been equilibrated to ambient temperature.

Effect of Compaction Force and Rate

Tablets were compacted at four levels of compaction forces: 20, 15, 10, and 7 kN. Fill weight and press speed (45 rpm, 200-msec contact time) were kept constant. Tablets were also compacted at three rates: 136-msec (60 rpm), 213-msec (40 rpm), and 363-msec (20 rpm) contact times. The total upper punch contact time was determined from force vs time profiles. Compaction force was kept at a constant value of 14–15 kN throughout the experiment. Fill weight was adjusted at each speed to keep a constant tablet weight. Thermal data were collected with the press running, and therefore, data acquisition was independent of turret speed. The difficulty involved at high speeds was to coordinate the image capture with the course of the tablet entering camera's field of vision.

For these two sets of experiments, press thermal history effects on heat of compaction were minimized by starting at the highest compaction force and speed. Furthermore, in order to minimize any thermal interference from the press structure, fewer than 30 tablets were compacted for each trial and a 15-min cooling period was allowed between trials. For each compaction force and rate, infrared images were collected on five tablets between completion of ejection and takeoff.

Effect of Lubricant Level

Tablets were compacted at 0.5 and 1.0% lubricant level

Table I. Compaction and Tablet Physical Parameters

	Upper, kN	Ejection, N	Contact, msec (rpm)	Weight, mg[a]	Thickness mm[a]	Hardness, N (range)
1. Temp. vs time	15.3	201	305 (30)	890 (6)	6.66 (0.05)	264 (256–271)
2. Temp. vs force	6.7	129	204 (45)	985 (4)	8.04 (0.04)	150 (144–160)
	10.3	185	—	992 (5)	7.59 (0.04)	221 (215–228)
	13.6	216	—	988 (5)	7.28 (0.03)	275 (267–285)
	19.6	245	—	991 (7)	6.96 (0.05)	>295
3. Temp. vs rate	14.8	240	363 (20)	919 (2)	6.78 (0.03)	275 (248–289)
	14.5	200	213 (40)	911 (9)	6.74 (0.05)	261 (226–270)
	15.0	180	136 (60)	912 (20)	6.78 (0.07)	252 (241–257)
4. % lubricant						
0.5	13.2	N/A	137 (60)	859 (28)	6.50 (0.08)	225 (187–246)
1.0	13.6	210	137 (60)	860 (12)	6.54 (0.05)	202 (165–227)

[a] Mean ± SD (n = 10).

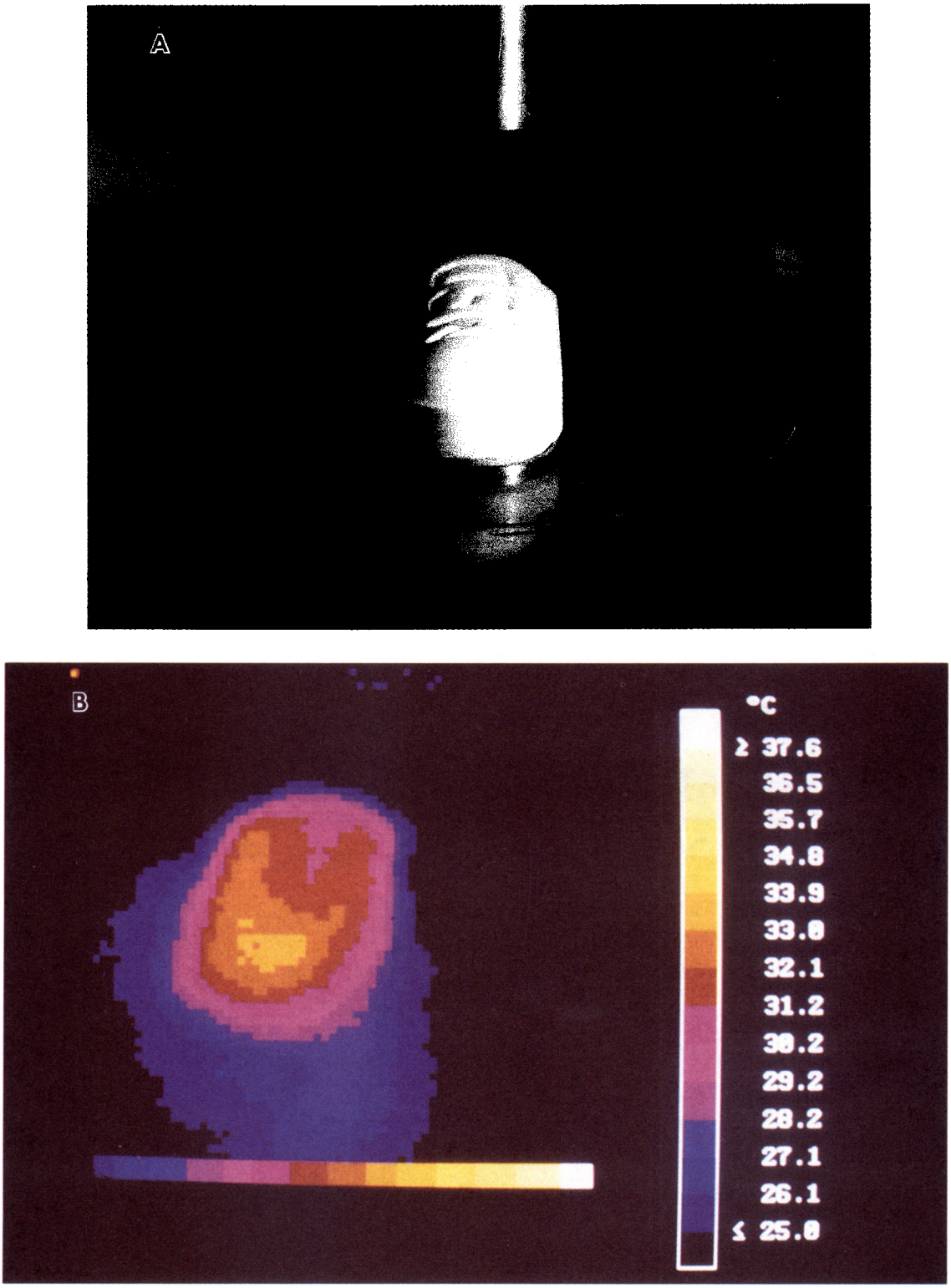

Fig. 1. Thermogram of a tablet surface before takeoff (20-kN force). (A) Photograph of the actual compact after ejection; (B) infrared image of a tablet after ejection. Note that images were taken at slightly different angles (see text).

for a total of 20-min run time. Compaction force was adjusted to 13 kN at 60 rpm (137-msec contact time). Infrared images were captured at different time points during the run in order to generate profiles of tablet surface temperatures as a function of time. Tablets lubricated with 1.0% magnesium stearate were sampled at the end of the run, then fractured into two halves, and cross-sectional thermal measurements were collected.

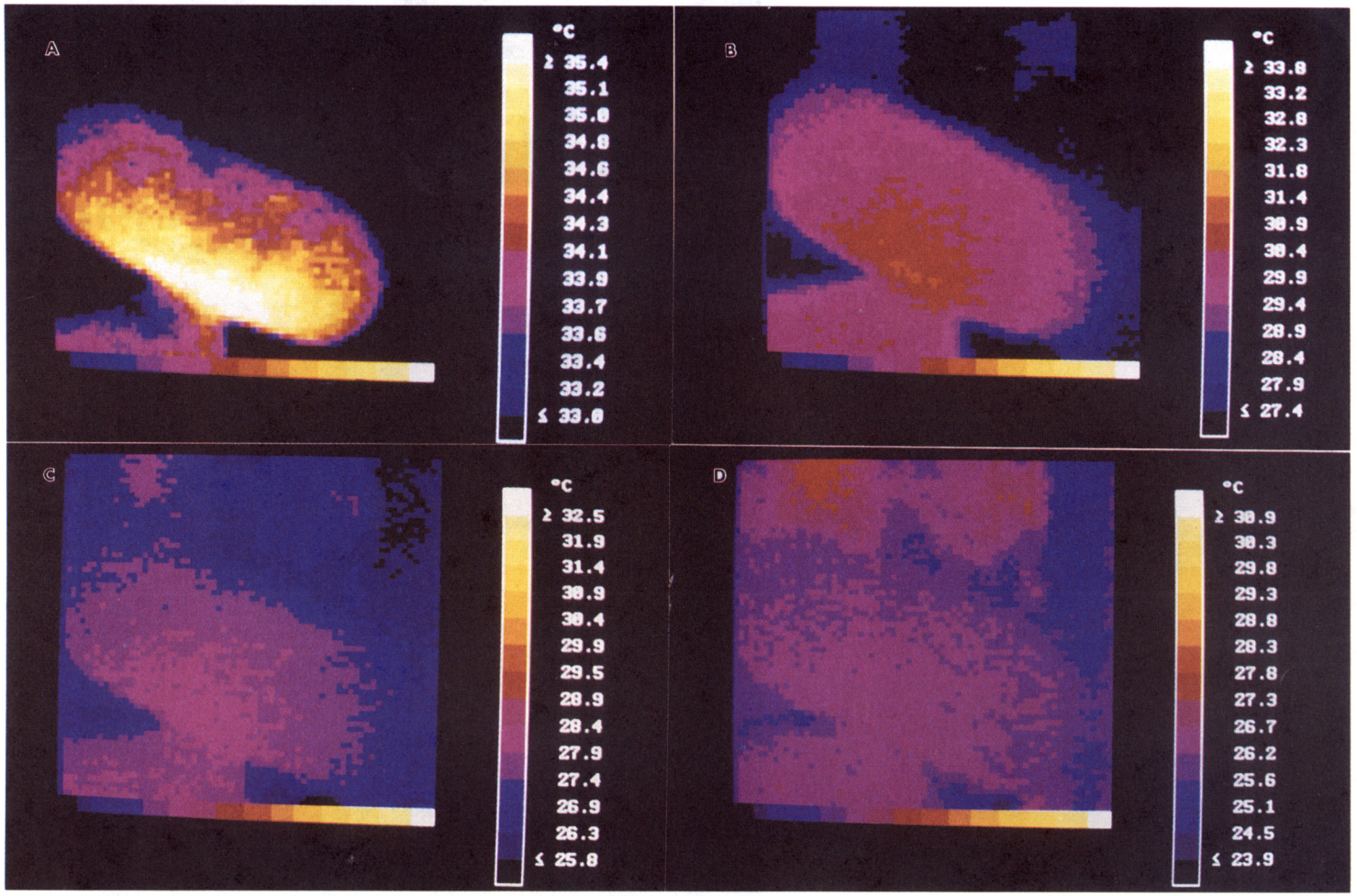

Fig. 2. Thermal profiles as a function of postcompaction time for one tablet compacted at 15-kN force: (A) 5 sec, (B) 1.1 min, (C) 2.0 min, and (D) 3.0 min (see text for tablet orientation).

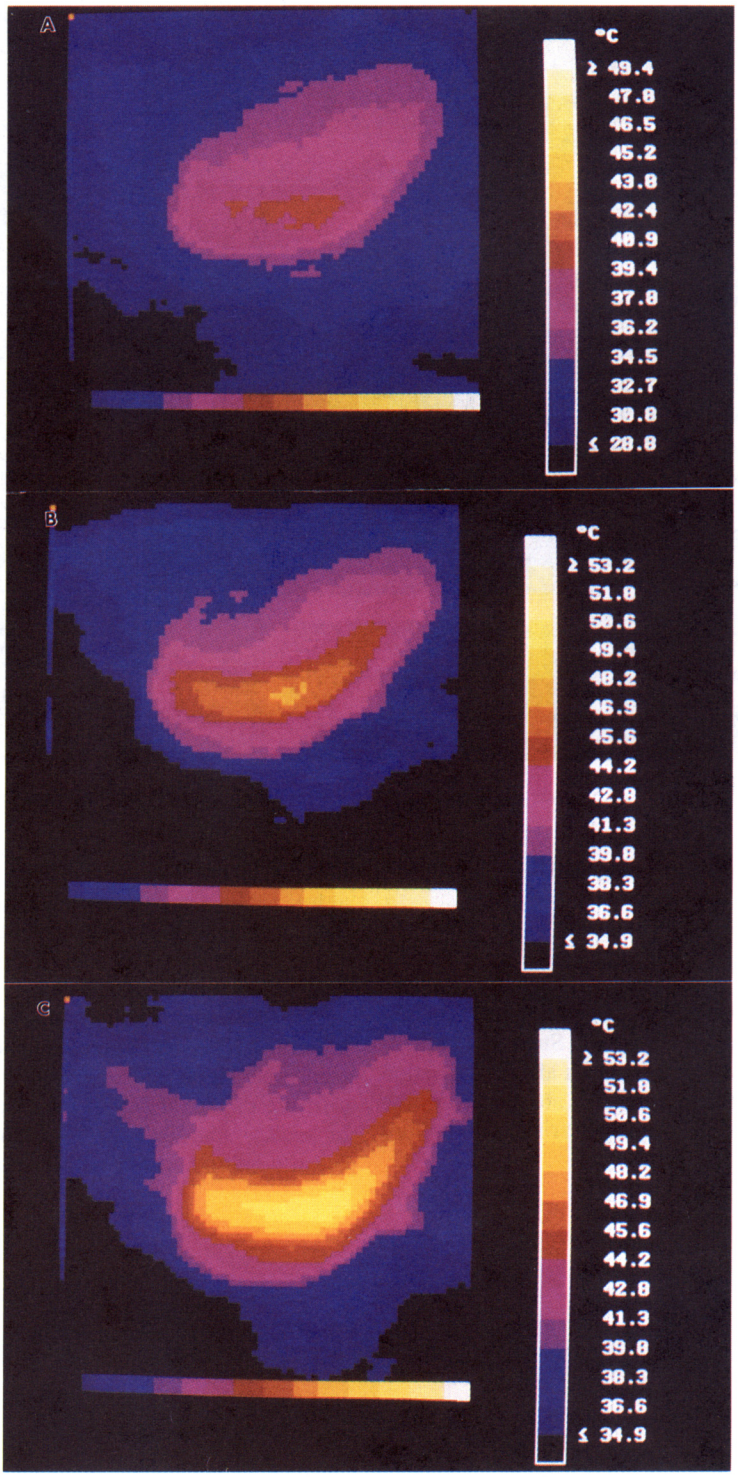

Fig. 3. Thermograms of tablet surfaces lubricated with 0.5% magnesium stearate at different time points during a run: (A) 3.5 min, (B) 12.9 min, and (C) 17.5 min (see text for tablet orientation).

RESULTS AND DISCUSSION

Compaction forces and rates as well as tablet physical parameters are given in Table I for each set of experiments. Infrared images of tablets compacted under various conditions are shown in Figs. 1–4. Figures 1A and B show, respectively, a photograph and a typical thermogram of a tablet just before takeoff. Note that the tablet configuration is approximately the same in both cases, except that images were taken at slightly different angles. The tablet contour can be easily depicted on the thermogram. This will facilitate

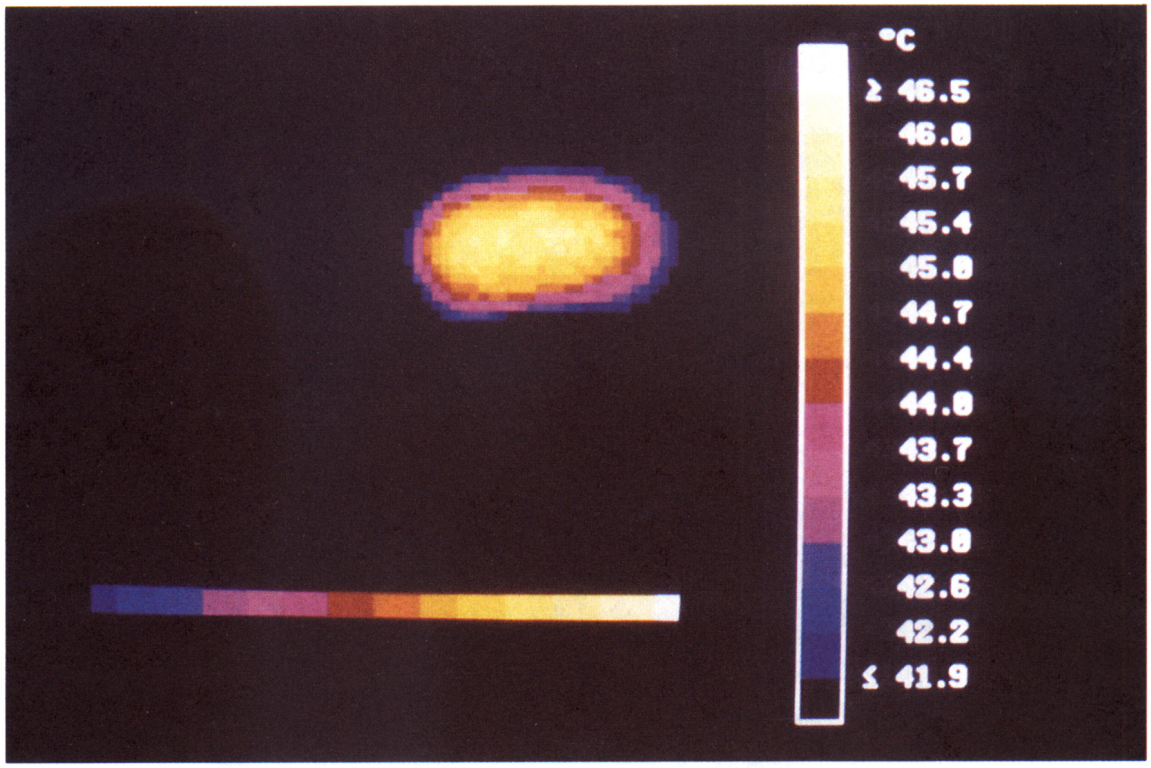

Fig. 4. Thermogram of a tablet cross section after a 20-min run time. The lubrication level is 1%.

the interpretation of the other thermograms with respect to tablet orientation.

Temperature vs Time Profiles

Figure 5 shows tablet surface temperatures as a function of postcompaction time for five tablets. Surface temperatures of 35–36°C are achieved few seconds after compaction and decrease to 26–27°C after 3 min. This clearly shows the suitability of infrared imaging for monitoring temperature changes on the surface of tablets. Figures 2A to 2D show the actual tablet temperature as a function of postcompaction time, indicating good temperature and geometric resolution. Thermal images were taken from a top view of the tablet located on the discharge chute. This resolution cannot be achieved by any other method previously described in the literature. The manufacturer specifications for accuracy of measurements is 2°C at 30°C. Figures 2A to 2D clearly demonstrate the suitability of infrared imaging for the detection of small temperature gradients on tablet surfaces. Under the set of conditions used in this study, temperature resolution

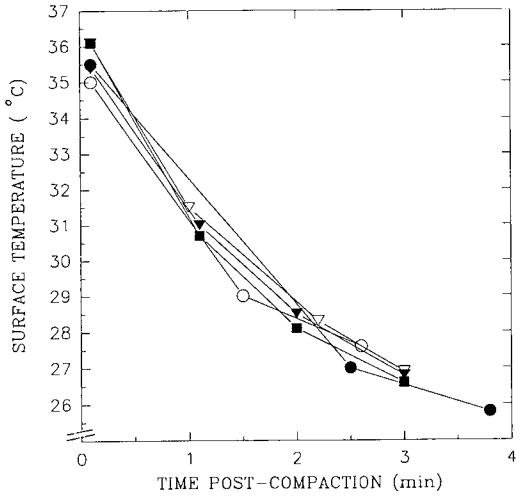

Fig. 5. Temperature as a function of postcompaction time for five tablets after ejection. Tablets were compacted at 15-kN force and 305-msec contact time (30 rpm). The ejection force was 200 N.

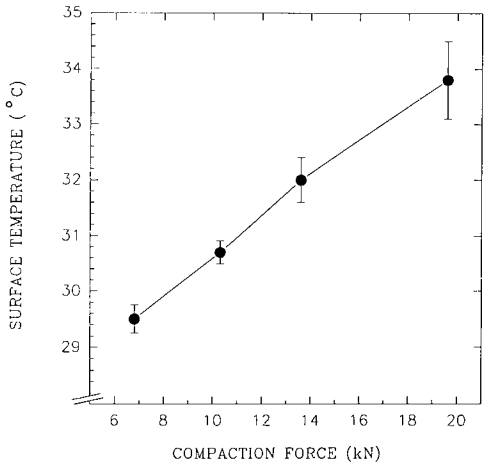

Fig. 6. Tablet surface temperatures as a function of compaction force. Values represent the mean ± SD (n = 5). See Table I for tablet physical parameters.

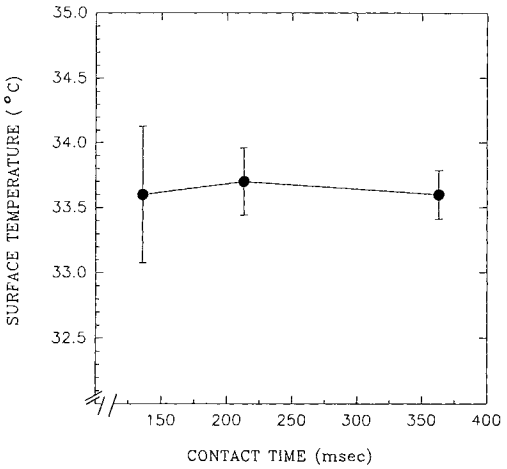

Fig. 7. Tablet surface temperatures as a function of compaction rate. Values represent the mean ± SD (n = 5). See Table I for tablet physical parameters.

was about 0.2–0.5°C onto tablet surfaces. However, the camera is capable of an higher resolution of 0.1°C.

Effect of Compaction Force and Rate

Figure 6 shows a plot of surface temperature as a function of compaction force. The higher the compaction force, the higher the tablet surface temperature. At 6.7 kN, tablet surface temperatures of 29.5 ± 0.3°C are achieved, as opposed to 33.8 ± 0.7°C at 19.6 kN. These findings are in agreement with reports that have previously described (2–4,6,7) this phenomenon. Higher forces generate more heat due to an increase in friction and plastic/elastic deformations. The dissipation of surface energy as heat resulting from particle bonding could also be involved (4,6).

It is convenient to look at postcompaction temperature rise as a result of the heat generated from interparticulate and die-wall friction as well as plastic/elastic deformations. It has been reported (15) that, at most, only 10% of the mechanical energy imparted during compaction is stored as mechanical-deformation energy inside the tablet. A large portion is therefore converted to heat. Initially, the thermal energy is not distributed homogeneously throughout the tablet but concentrated in regions where these frictions occurred. This heat is then transferred throughout the anisotropic solid and the surroundings by conduction and radiation, respectively. These areas of friction are called the true area of contact, which represents the fraction of the total area in actual contact. A recent study (16) described measurements made of the tensile strength of some pharmaceutical powders compacted over a range of temperatures from 20 to 200°C. The tensile strengths increased with temperature. The relative contribution of plastic deformation and/or melting at areas of friction to the tensile strengths of tablet was not resolved. Nevertheless, it was believed that temperature changes have a significant influence on the mechanism and extent of bonding.

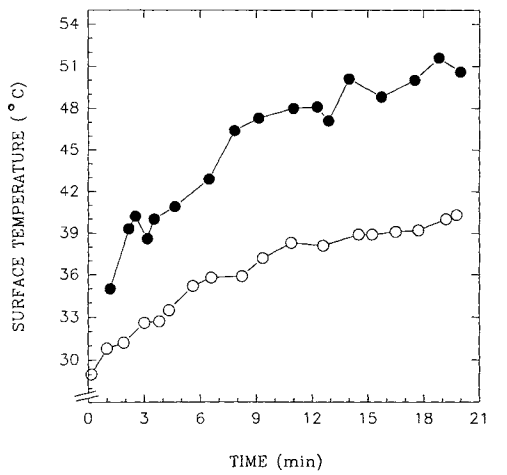

Fig. 8. Tablet surface temperatures as a function of run time for granulations lubricated with 0.5% (●) and 1.0% (○) magnesium stearate.

Compaction rate, as expressed by the upper punch contact time with the granulation, did not have any effect on tablet surface temperatures over the range tested as shown in Fig. 7. This indicates that the rate at which the mechanical energy is transferred to the system does not affect the heat generated by die-wall and interparticulate frictions as well as plastic/elastic deformations.

Effect of Lubricant Level

Figure 8 shows tablet surface temperature as a function of run time for granulations lubricated with 0.5 and 1.0% magnesium stearate. The lubricant level has a significant effect on both the rate of heating and the temperature values. Tablet surface temperatures as high as 51°C were seen after 19 min of compaction, as opposed to about 39–40°C for tablets lubricated with 0.5 and 1.0% magnesium stearate, respectively. Lubricants are used to decrease interparticular friction and, therefore, in the case of magnesium stearate, appear to be very effective in decreasing heat of friction. In this particular case, the extent of bonding was not compromised by using 1% magnesium stearate. Figure 3 shows thermal patterns of tablets lubricated with 0.5% magnesium stearate at 3.5, 12.9, and 17.5 min, showing the effect of run time on temperature increase. Thermograms were captured at an approximately 45° angle from the die table and at about a 30° angle from the tablet main axis. A few minutes after the beginning of a run the die table became visible on the camera. The heat released during compaction is transferred to the steel structure, which gets warmer over time. The temperature will rise until a thermal equilibrium is achieved. For lactose-based granulations compacted on a rotary press at different forces and rates (3), most of the temperature increase occurred within 30 min and a state of equilibrium was achieved after 90–120 min. The rate of heating as well as the equilibrium temperature depends on the amount of heat released per compaction cycle, the compaction force, and the press operating speed. The energy released per compaction cycle depends on the formulation and its degree of lubrication. The press speed should be looked at in terms of the amount of energy generated per unit time and not in terms of punch speed or dwell time, which in this particular study, had no impact on the amount of heat released per compaction cycle. Time-zero temperatures cannot be determined

exactly because of the time-dependent nature of heat transfer. This is the reason why the thermal energy released could be calculated only for semiquantitative purposes, knowing the heat capacity of the material being compacted.

These findings imply that postcompaction heat-induced physical changes could be minimized by proper formulation and process development. The relationship between the temperature at which a material is undergoing compaction and the tensile strength or extent of bonding of the resultant tablet has been demonstrated (16). More knowledge is therefore needed concerning the thermal behavior of drugs and excipients undergoing compaction since temperature plays an important role in the mechanism and extent of interparticle bonding. This also suggests that for poorly compactible formulations, operating the press at a higher temperature could be beneficial from a bonding point of view.

Figure 4 shows a thermogram of a cross-section of a tablet lubricated with 1.0% magnesium stearate after a 20-min run time, indicating a 3–4°C temperature gradient across the tablet, the center being warmer. This indicates that temperature elevations were not due solely to die-wall friction but also to frictions that occurred inside the tablet. Surface temperature gradients of less than 4–5°C were typically seen at the beginning of a run. However, this gradient increased to 8–9°C over time. Areas of tablets that were in contact with die-walls were found to be warmer. The press steel structure acts as an heat sink. When the press is activated, the heat generated by compaction is transferred to the sink at a rate that decreases until thermal equilibrium is achieved. Since the structure becomes warmer over time, the temperature gradient between the tablet and the steel decreases, and so the heat transferred. The overall effect is detected by the infrared camera as warmer tablet edges.

This study has shown that infrared imaging is a unique tool for monitoring infrared radiation evolved after compaction with good reproducibility (3%) and accuracy (±2–3°C at 30°C). However, infrared imaging does not provide any measure of the actual temperature at the contact points during compaction but provides an average surface temperature profile. It is a technique that allows direct visualization of thermal events occurring during compaction, with good temperature and geometric resolutions, and warrants further investigation for semiquantitative determination of thermal energy released during compaction and for a better understanding of the mechanisms involved in bond formation. Furthermore, it is a very sensitive tool for the determination of lubricant efficiency and the effects of compaction variables on thermal energy released. Finally, it is a noninvasive technique, is easy to operate, and can be utilized both in a research and in a production setting for monitoring compaction runs.

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