Thermophysical Properties of Some Pharmaceutical Excipients Compressed in Tablets

Jarkko Ketolainen,[1,3] L'udovit Kubičár,[2] Vlastimil Boháč,[2] Marián Markovič,[2] and Petteri Paronen[1]

Received May 2, 1995; accepted August 3, 1995

Purpose. Thermophysical properties of three tableting excipients; microcrystalline cellulose, lactose and dicalcium phosphate dihydrate were observed to evaluate their ability to resist temperature induced changes in tablet form.

Methods. Two thermophysical parameters, thermal diffusivity and specific heat, were measured by a pulse heating method. The materials were also evaluated by differential scanning calorimetry (DSC).

Results. Microcrystalline cellulose in tablet form was found to be rather insensitive to heating and cooling treatments, even though the tablets seemed to remain in a stressed state four weeks after tableting. This stress, indicated by low temperature anomalies, was observed by the pulse method, but not by DSC. When magnesium stearate was incorporated as a lubricant within the microcrystalline cellulose powder, the thermophysical parameters indicated that the internal structure of the tablets changed with heating and cooling. Magnesium stearate eliminated the low temperature anomalies as well. The heat treatment changed the thermophysical properties of tablets made of the crystalline excipients lactose and dicalcium phosphate dihydrate, permanently causing irreversible structural changes.

Conclusions. The melting of the lubricant together with enhanced stress relaxation in the structure of microcrystalline cellulose most probably caused the improved thermal diffusivity. The observed thermophysical changes with the crystalline excipients were due to changes in tablet's structure and material. The combination of methods used was found to be an accurate and reliable way to obtain useful information on the structural changes and material relaxations of intact tablets during temperature treatment and age-related changes in material properties.

KEY WORDS: thermal diffusivity; specific heat; tablets; structural relaxation; pulse method; differential scanning calorimetry.

INTRODUCTION

In manufacturing of pharmaceutical tablets, the particulate materials are subject to strong mechanical stress, and during compression powder compacts are warmed up. This rise in temperature is dependent on several process and formulation related factors. Thermophysical properties of pharmaceutical powders have usually been studied by differential thermal analysis and differential scanning calorimetry. Several studies have examined the thermodynamics of tableting processes (e.g., 1,2). Some studies have investigated the effects of temperature on the mechanical properties of pharmaceutical powders (e.g., 3,4). However, studies on changes in the thermophysical parameters of tablets, due to aging or structural relaxation phenomena, have not been reported. The method used in this study, namely the pulse heating method, in which the studied objects; e.g., tablets, need no special treatment and remain intact, has previously been used to study structural relaxation of metallic systems and carbon based composites (5,6).

Various composite systems; e.g., glasses, ceramics and polymers, typically undergo structural changes during aging or annealing to reach a more stable thermodynamic state, and such transformations cause changes in the physical properties of these materials (6). In principle, two basic types of structural changes exist: structural relaxation and structural phase transformation. The former can occur at lower temperatures or shortly after the production procedure and is most probably correlated with the weak attraction mechanisms; e.g., cohesion forces (often dependent on water content), and intermolecular forces; i.e., Van der Waals forces, hydrogen bonds or electrostatic forces, created during the plastic deformation or fragmentation of particles (7). In the case of compressed powders, the particle surface is the most dynamic component of structural relaxation, where relaxation is a function of the attractive forces between individual powder particles. The second type of relaxation, structural phase transformation, can occur at higher temperatures and is related to a structural rearrangement with longer distance mechanisms (6). The structural phase transformations found at higher temperatures are most often caused by the processes like dehydration, melting or recrystallization of materials in the compacts. All structural changes are functions of time and temperature, and the higher the temperature, the shorter the time needed for certain changes in physical properties. Thus, the thermal diffusivity and specific heat of a material are modified through structural changes induced by heat treatment or aging.

In this study the thermophysical properties of some pharmaceutical excipients compressed to tablets were evaluated by a pulse heating method in combination with differential scanning calorimetry (DSC). Also, attention was paid to the physical stability and structural relaxation of tablets. The applicability of pulse heating method with DSC to study tableting materials and tablets is also discussed.

MATERIALS AND METHODS

Materials

The excipients studied were microcrystalline cellulose (Avicel® PH102, FMC Co., Philadelphia, Pennsylvania, USA) with and without magnesium stearate (Ph. Eur., 2% w/w) as a lubricant, along with α-lactose monohydrate (Lactose M80, DMV, Veghel, The Netherlands) and dicalcium phosphate dihydrate (Emcompress®, Mendell Co., Patterson, New York, USA), both without a lubricant. Avicel® was considered as a partially crystalline material with plastic flow properties, while lactose and Emcompress® as more or less fragmenting crystalline materials. Magnesium stearate

[1] Department of Pharmaceutics, University of Kuopio, POB 1627, FIN-70211 Kuopio, Finland.

[2] Institute of Physics, Slovak Academy of Sciences, SVK-84228 Bratislava, Slovak Republic.

[3] To whom correspondence should be addressed.

0724-8741/95/1100-1701$07.50/0

was used to demonstrate the effect of a typical lubricant on the thermophysical parameters of Avicel® tablets.

The material densities of the compressed powders were determined by a pycnometer method (Multipycnometer MVP-1, Quanta Chrome, Syosset, New York, USA), using helium as an inert gas. The density of Avicel® without the lubricant was 1.60 g/cm^3 and with the lubricant, 1.59 g/cm^3. Lactose and Emcompress® had densities of 1.55 and 2.33 g/cm^3, respectively.

Water contents, determined with a Mettler DL35 Karl Fischer titrimeter (Mettler-Toledo AG, Switzerland) as a mean of three measurements, were 4.9, 5.2 and 0.4% for Avicel®, lactose and Emcompress®, respectively.

Sample Preparation

All powders studied were compressed into tablets with a hydraulic compaction simulator (PuuMan Oy, Kuopio, Finland) using flat-faced punches (10 mm in diameter) and a compression time of about 500 ms. A one-sided sine-wave was used as compression profile. The compaction simulator was adjusted to produce tablets with a constant thicknesses of 3.0 and 4.5 mm at a constant porosity of 15%. The mean weights of the 3.0 mm Avicel® tablets, without and with the lubricant, were 320 and 318 mg, respectively, and for lactose and Emcompress® were 314 and 471 mg, respectively. Tablets of 4.5 mm were used to obtain a geometry of the experimental set up closer to the ideal one for the pulse heating method.

Methods

The pulse method employed for measuring thermophysical properties of the tablets had a planar heat source, which generated a dynamic temperature field inside the sample. Thermal diffusivity and specific heat were calculated from the time (t_m) and the magnitude (T_m) of the maximum temperature response to the heat pulse. The sample set consisted of three pieces (tablets) having thicknesses of 4.5, 3.0 and 4.5 mm, respectively. The planar heat source (a thin metallic foil) was placed between the first and the second piece of the sample set, while a thin thermocouple was placed into a small groove made into the contact surface of the third piece of the sample. A thin layer of thermoconductive silicone paste (Midland Silicones Ltd, England) was used to improve the thermal contact between the individual parts of the sample set. The heat pulse was generated by the passage of an electrical current (I) through the metallic foil for 6 sec (t_0). Thermal diffusivity, a, was calculated as described by equation 1 (8):

$$a = h^2/2t_m, \quad (1)$$

where h is the distance between the heat source and the thermometer (3.0 mm), and specific heat, c, as described by equation 2:

$$c = Q/(2e)^{1/2}h\rho T_m, \quad (2)$$

where ρ is the apparent density, Q the energy of the heat pulse (2.3 J/m^2), and e a constant (2.71). Q can be presented as:

$$Q = RI^2t_0, \quad (3)$$

where R is the electrical resistance of the heat source.

All measurements were made under a gentle vacuum (10^{-3} Pa), which prevented the possibility of adsorbed water to the surface of tablets. When the termophysical parameters were measured, the temperature was kept constant for a short period of time during both heating and cooling phases. The measurements were started from the temperature of 10°C and after reaching a sample temperature of 200°C, sample sets were cooled to room temperature. The heating and the cooling rates were typically 0.8°C/min, and near room temperature rates were less than 0.1°C/min.

By the pulse method, five sets of samples from each tablet batch were measured and all the measurements were begun four weeks after tableting, to avoid possible effects of rapid elastic recovery. A typical experimental error for the pulse method was found to be between 4–6%.

Differential scanning calorimetry (DSC 7, Perkin-Elmer Co., Norwalk, Connecticut, USA) was used for all the studied materials in powder and tablet form (i.e., a small piece of broken tablet) to compare the two methods and give more information on the anomalies observed in tablets by pulse heating measurements. All DSC measurements were performed under a dry nitrogen atmosphere (flow 23 ml/min) with a heating rate of 2.0°C/min. Sizes of the samples sealed in aluminum pans with holes ranged from 2–4 mg for powders, and 3–8 mg for pieces of broken tablets.

RESULTS AND DISCUSSION

Unlubricated Avicel® Tablets

The thermal diffusivity, a, and specific heat, c, of Avicel® tablets without a lubricant are presented in Fig. 1 as a function of temperature. At temperatures below 40°C some anomalies were found in both of the thermophysical parameters studied. A heat treatment up to 40°C eliminated these anomalies. In a temperature range from 40 to 190°C, both thermophysical parameters were analogous during heating and cooling of the sample sets.

Two types of structural relaxation were evident. The first one, a function of short-time relaxation, was responsible for anomalies observed near room temperature. This low temperature anomaly was observed by the pulse method, but not with DSC. These anomalies in thermal diffusivity and specific heat were possibly due to a partial release of energy which was stored in the tablets during the tableting process. Thus, the unlubricated Avicel® tablets seemed to remain in a stressed state for at least four weeks after compression. Microstresses are known to modify intermolecular forces, and could be responsible for these observed effects since the surfaces of individual powder particles are the most dynamic areas for material deformation during tableting. Only a modest heat treatment was needed to overcome the energy barrier of the observed stress in our measurements. This was proved by a later measurement of the same sample set, where no low temperature anomaly was observed. Tablets tend to seek more thermodynamically and structurally stable states via relaxation of induced short-range microstresses, and recovery of the respective deformation of microcrystalline cellulose particles.

The second type of structural relaxation of Avicel® tablets was observed at higher temperatures. These were seen

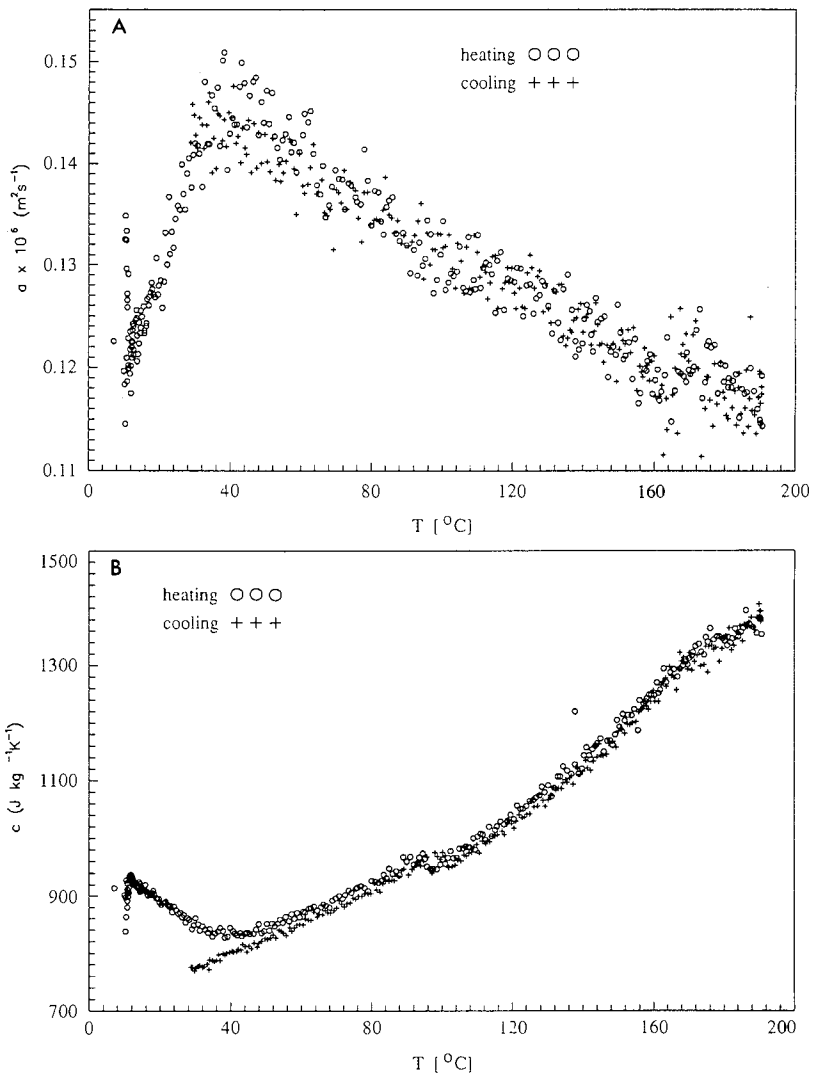

Fig. 1. Thermal diffusivity, a (m^2s^{-1}), (A) and specific heat, c ($J\ kg^{-1}\ K^{-1}$), (B) of unlubricated Avicel® tablets as a function of temperature (°C) during the heating (○) and cooling (+) phases of pulse method measurements.

as longterm, age-related changes in the material's property, and analogous during both the heating and cooling phases (Fig. 1). Thus, the changes in thermophysical properties were practically reversible and no permanent changes in structure remained. It is evident that the water content of the microcrystalline cellulose tablets decreased due to heat treatment. Water evaporated easily, even from pieces of tablets, at temperatures well below 100°C, according to DSC. Instead of coordinated water in a crystalline lattice, the water molecules in the amorphous parts of microcrystalline cellulose may be more diffuse as randomly absorbed water. This notion is supported by the broad DSC endotherms of low intensity. Obviously, the effect of water on the thermophysical properties of microcrystalline cellulose tablets, is fairly negligible. The thermal movement of chain structures in cellulose seems to be independent of the amount of water in a tablet, as reflected by the similar changes in thermal diffusivity and specific heat during the heating and cooling phases. Perhaps due to the amorphous parts in the structure of microcrystalline cellulose coupled with its great tendency towards plastic deformation, as well as its ability to form bonds by mechanical interlocking (7), thermophysical changes resulting from treatment by heat are more or less reversible with Avicel® tablets.

Lubricated Avicel® Tablets

The thermal diffusivity, a, and specific heat, c, of Avicel® tablets with 2% w/w of a lubricant are presented in Fig. 2 as a function of temperature. Thermal diffusivity of lubricated tablets clearly behaved differently than with unlubricated tablets (Figs 1 and 2). The lubrication of Avicel® tablets eliminated the anomalies related to short-time relaxation. Due to lubrication, the die wall and interparticulate frictions were reduced, and thus the rearrangement of particles was enhanced. The deformation of particles may also have been more homogeneous with magnesium stearate, and thus decreased the stress differences inside the compact. The incorporation of magnesium stearate has also been reported to partially disrupt the strong interparticulate bonding

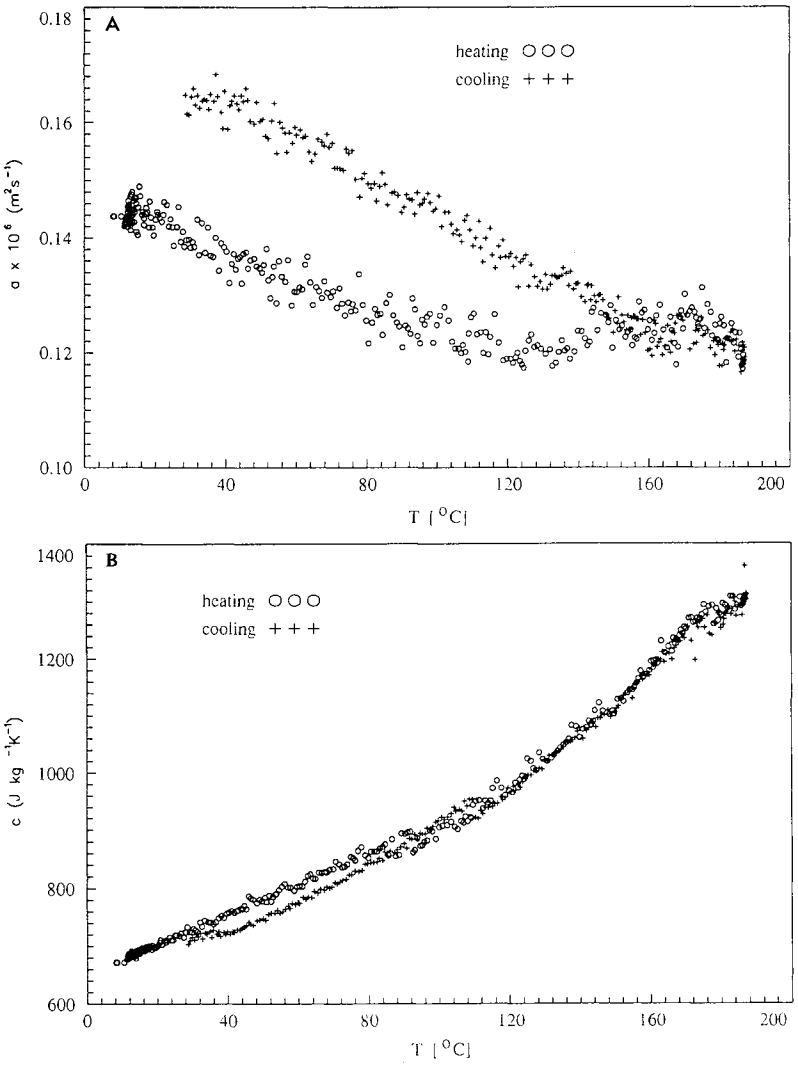

Fig. 2. Thermal diffusivity, a (m^2s^{-1}), (A) and specific heat, c ($J\ kg^{-1}\ K^{-1}$), (B) of lubricated Avicel® tablets as a function of temperature (°C) during the heating (○) and cooling (+) phases of pulse method measurements.

between microcrystalline cellulose particles (9). Therefore, the lubricated tablets could be considered as more structurally and thermodynamically homogeneous than unlubricated tablets, where a stressed state prevails after compression. A strong hysteresis was found in the thermal diffusivity during heating and cooling (Fig. 2A). Slow dehydration and melting of magnesium stearate above 90°C, and its possible recrystallization in a different physical form during cooling, may have improved the thermal diffusivity, and thus caused the hysteresis. Therefore, we suggest that the melting of magnesium stearate probably changed the tablet structure by enabling the formation of solid bridges between individual particles during cooling, which resulted in improved interparticulate contacts. No differences at high temperatures were observed between data obtained from the heating and cooling regimes, most probably due to the likelyhood that magnesium stearate was molten within the microcrystalline cellulose matrix.

The values for specific heat from lubricated tablets matched those from unlubricated tablets (Figs 1A and 2A). The trivial decrease in specific heat, found at low temperatures with lubricated tablets, is also most probably due to the evaporation of diffuse water from the sample, as seen by DSC. These results underscore the sensitivity of thermal diffusivity for detecting changes in a tablet's internal structure; e.g., changes in interparticulate contacts, and the sensitivity of specific heat as indicator of change in the material.

Lactose Tablets

Figure 3 shows the thermal diffusivity, a, and specific heat, c, of lactose tablets as a function of temperature. The data of both thermal diffusivity and specific heat show a strong hysteresis and two clear transformations could be seen in them (Fig. 3). The first significant structural change started above 80°C and ended around 150°C, and was composed of at least four smaller structural changes clearly seen in the specific heat gram (Fig. 3B). All these changes were connected by dehydration. Apparently the compression of particulate material modified water bonds in the structure

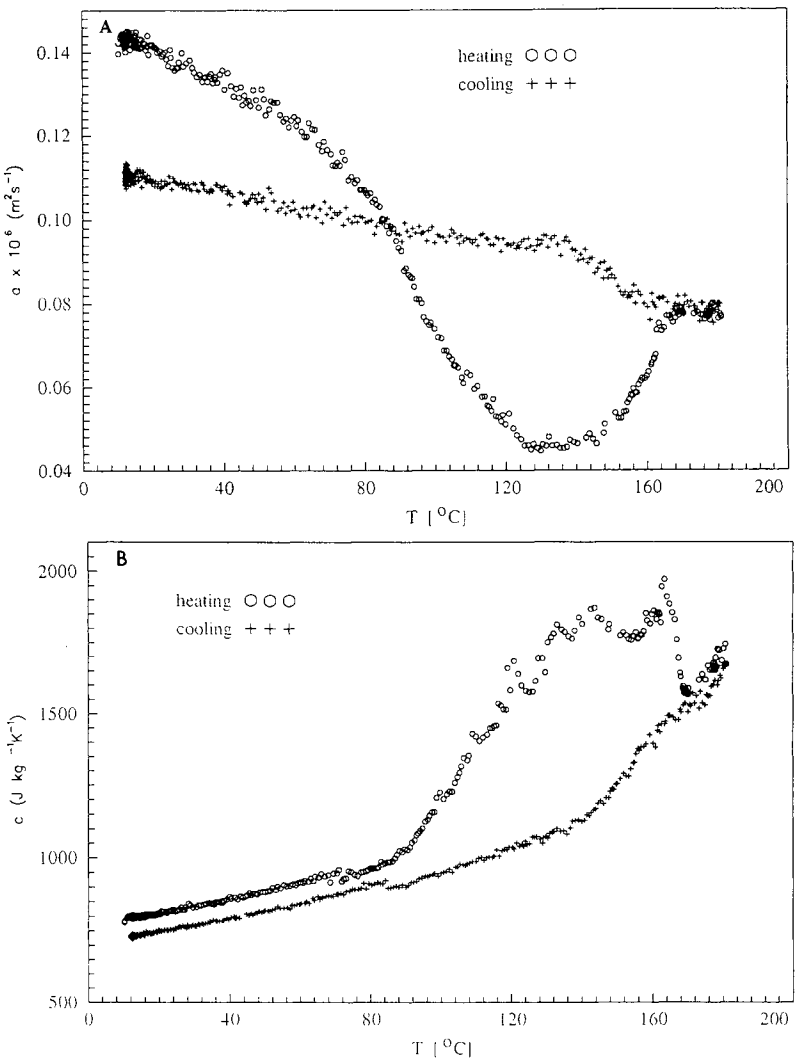

Fig. 3. Thermal diffusivity, a (m^2s^{-1}), (A) and specific heat, c ($J\ kg^{-1}\ K^{-1}$), (B) of lactose tablets as a function of temperature (°C) during the heating (○) and cooling (+) phases of pulse method measurements.

and, consequently, allowing the water to escape from the system at lower temperatures and over a wider range of stages than normal (10–12). The release of water may also have changed the degree of crystallinity of lactose monohydrate (13). The second significant structural change was found near 160°C, and it is probably related to the recrystallization of anhydrous α-lactose (12). This transformation seemed to enhance the solid-solid interactions in the compact and consequently, improve the thermal diffusivity. Both thermal parameters, thermal diffusivity and specific heat, changed considerably due to heating and cooling, indicating changes in tablet's structure and material, respectively, especially due to the changes in lactose-water interactions.

Hüttenrauch and Keiner (13) have stated that with hydrous forms of lactose the evaporation of water creates a large number of defects, which is not welcome due to the detrimental effects on the physical and biopharmaceutical properties of the tablets. On the other hand, Lerk et al. (14) have stated that the thermal dehydration of α-lactose monohydrate strongly increased binding properties with decreasing water content. According to our results, the thermal diffusivity of lactose tablets decreased due to the dehydration. However, after a heat treatment at temperatures high enough, the recrystallization compensated the decrease. The studies of Hüttenrauch and Keiner (13) and Lerk et al. (14) together with the present one raises the question about the putative role of water in tablets; whether or not it takes part in the formation of bonds, or reduces the attraction forces between particles.

The observed transformation temperatures with pulse heating differed from those observed with DSC. In the DSC thermogram of the powder, dehydration of α-lactose began near 90°C and the main dehydration peak was observed at 140°C, whereas recrystallization could be seen at 170°C. Also in the DSC thermogram of a piece of a tablet, only one sharp endotherm was seen at 135°C. The rather significant shift in observed transformation temperatures was mainly due to the differences in the methods; e.g., heating rates, heat transfer and in the nature of the sample (powder or dense compact).

Emcompress® Tablets

Both the thermal diffusivity, a, and specific heat, c, of Emcompress® tablets show a clear hysteresis and two transformations (Fig. 4). The first transformation began near 100°C, while the second above 180°C. In the DSC thermogram of powder, three different transformations were observed; at 80, 120 and 180°C, but only two transformations were seen in the thermogram of tablet. The anomalies around 120 and 180°C, as measured by DSC, corresponded those observed by the pulse method and are due to dehydration of dicalcium phosphate dihydrate (15). Dehydration changed totally the thermophysical properties of Emcompress® tablets. During the cooling phase, the thermophysical parameters remained relatively unchanged, especially the thermal diffusivity, implying that the solid-solid interactions were weakened more dramatically by dehydration than with lactose and lubricated Avicel® tablets. This underscores the importance of hydrate water in the molecular structure of dicalcium phosphate dihydrate.

The pulse method was found to be a potentially informative method for characterizing thermophysical properties of tablets. This method gives useful and practical information on tablet stability; i.e., structural relaxation and material aging of tablets. The transformation temperatures of tablets observed with DSC were generally in better agreement with the pulse method measurements than with the DSC measurements of powders. Together with the DSC, the pulse method forms a powerful combination for the investigation of thermophysical phenomena.

ACKNOWLEDGMENTS

Financial support was provided by the Technology Development Centre of Finland, Pharmacal Research Foundation, Finland and University Pharmacy, Finland. The skillful technical assistance of Ms. M. Laakkonen, Ms. M. Simonen, Mr. V. Viitasaari and Mr. M. Wihervaara (University of Kuopio, Finland) are gratefully acknowledged. The authors wish also thank Prof. J. Lanik (Slovak Academy of Sciences, Bratislava, Slovak Republic) for making this study possible and Dr. J. C. Callaway for revising the language.

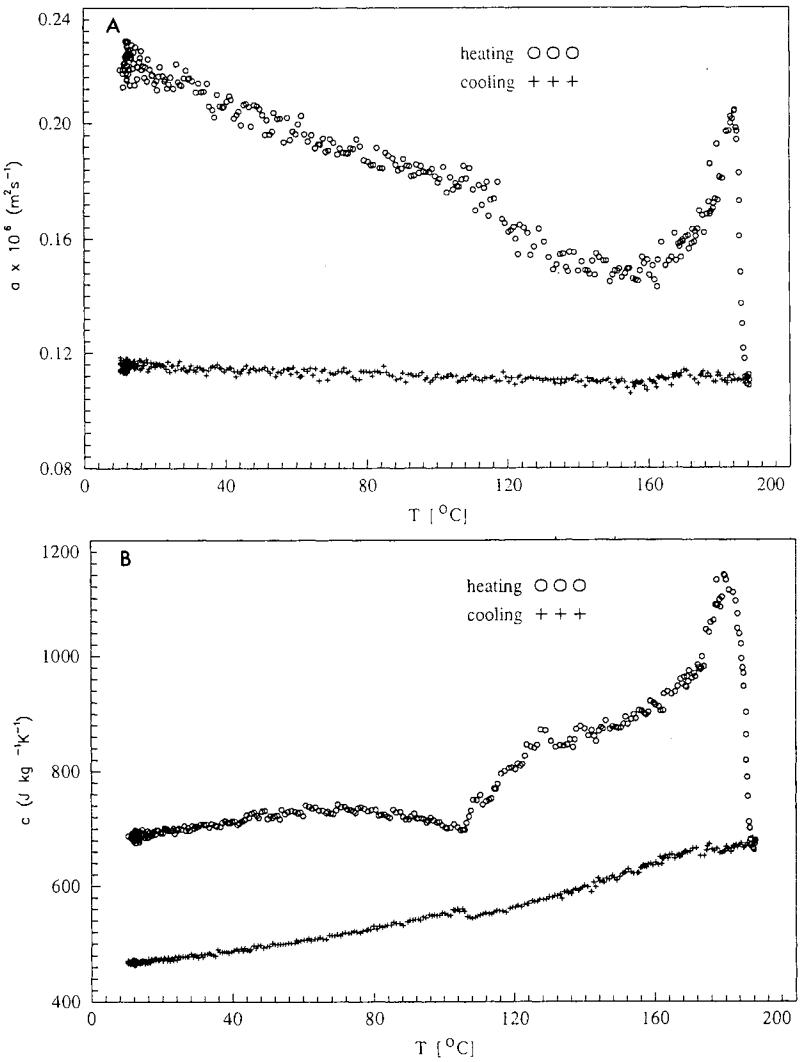

Fig. 4. Thermal diffusivity, a (m^2s^{-1}), (A) and specific heat, c ($J\ kg^{-1}\ K^{-1}$), (B) of Emcompress® tablets as a function of temperature (°C) during the heating (○) and cooling (+) phases of pulse method measurements.

REFERENCES

1. E. Nürnberg and A. Hopp. Temperature measurement during tableting. *Pharm. Technol.* **168**:81–101 (1981).
2. J. Ketolainen, J. Ilkka, and P. Paronen. Temperature changes during tabletting measured using infrared thermoviewer. *Int. J. Pharm.* **92**:157–166 (1993).
3. J. R. Britten and N. Pilpel. Effects of temperature on the tensile strength of pharmaceutical powders. *J. Pharm. Pharmacol.* **30**:673–677 (1978).
4. S. Esezobo and N. Pilpel. The effect of temperature on the plasto-elasticity of some pharmaceutical powders and on the tensile strength of their tablets. *J. Pharm. Pharmacol.* **38**:409–413 (1986).
5. L. Kubicar. Applications of the pulse method. In G. Svehla (ed.), *Pulse method of measuring basic thermophysical parameters*, Elsevier, Amsterdam, 1990, pp. 231–267.
6. L. Kubicar, J. Spisiak, and D. Krivankova. Investigation of the structural relaxations of materials. *High Temp. High Press.* **23**:249–254 (1991).
7. C. Nyström, G. Alderborn, M. Duberg, and P.-G. Karehill. Bonding surface area and bonding mechanisms—Two important factors for the understanding of powder compactability. *Drug Dev. Ind. Pharm.* **19**:2143–2196 (1993).
8. L. Kubicar and J. Spisiak. Measurement of thermophysical properties of solids by the pulse method, *High Temp. High Press.* **20**:619–626 (1988).
9. S. W. Hoag and E. G. Rippie. Thermodynamic analysis of energy dissipation by pharmaceutical tablets during stress unloading. *J. Pharm. Sci.* **83**:903–908 (1994).
10. I. Krycer and J. A. Hersey. Detection of mechanical activation during the milling of lactose monohydrate. *Int. J. Pharm. Tech. Prod. Mfr.* **2**:55–56 (1981).
11. H. Vromans, A. H. de Boer, G. K. Bolhuis, C. F., Lerk and D. D. Kussendrager. Studies on tableting properties of lactose; The effect of initial particle size on binding properties and dehydration characteristics of α-lactose monohydrate. *Drug Dev. Ind. Pharm.* **12**:1715–1730 (1986).
12. P. Di Martino, S. Martelli, A.-M. Guyot-Hermann, J. C. Guyot, M. Drache, and P. Conflant. The batch-to-batch nonreproducibility of the compression ability of lactose. Reasons and detection. *S. T. P. Pharma Sci.* **3**:436–441 (1993).
13. R. Hüttenrauch and I. Keiner. Producing lattice defects by drying process. *Int. J. Pharm.* **2**:59–60 (1979).
14. C. F. Lerk, A. C. Andreae, A. H. de Boer, G. K. Bolhuis, K. Zuurman, P. de Hoog, K. Kussendrager, and J. van Leverink. Increased binding capacity and flowability of α-lactose monohydrate after dehydration. *J. Pharm. Pharmacol.* **35**:747–748 (1983).
15. M. Landín, R. Martinez-Pacheco, J. C. Gomez-Amoza, C. Souto, A. Concheiro, and R. Rowe. The effect of country of origin on the properties of dicalcium phosphate dihydrate powder. *Int. J. Pharm.* **103**:9–18 (1994).