Influence of Temperature on the Compaction and Strength of Some Pharmaceutical Excipients

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ABSTRACT

The aim of this study is to investigate the effects of temperature on the compaction behavior and mechanical properties of some common pharmaceutical powders. Two common excipients, microcrystalline cellulose (MCC) and starch-1500, were evaluated at various temperatures (25, 50, 100, and 150 °C). An Instron compression testing system with temperature controlled die and punches was employed to compact each powder into a porous tablet. Mechanical properties during and after compaction were significantly affected by temperature, primarily exhibited by differences in compactibility and tensile strength. The dependence of tablet strength on temperature for Starch-1500 was dramatic. An increase in processing temperature resulted in much larger strength values for the same compaction pressure applied at room temperature. This effect was also observed for the MCC tablets but to a lesser degree. Higher temperatures generally improved compressibility and decreased initial fill density for all materials examined. This study reveals that the compaction temperature has significant effects on the mechanical properties of pharmaceutical powders.

INTRODUCTION

Compaction transforms a loose granular assembly into a tablet of specific strength. The compaction mechanisms and affecting factors have been extensively studied\cite{1-5}. During the formation of a single tablet, temperatures of 5 ~ 30 °C above ambient are commonly observed\cite{6}. A discussion of all possible mechanisms of heat generation during tableting and a computational predictive model have been recently presented by Zavaliangos et al\cite{7}. Considering actual production, the temperature in the tablets rises even further due to the high speed of machinery and the accumulation of heat in the tools and press table. Increases of 20 - 30 °C during production have been reported. These temperature increases may not only affect the compaction behavior but also the mechanical properties of tablets after and during compaction such as the tensile strength and compressibility. Given that many pharmaceutical powders are manufactured at high homologous temperatures, it is anticipated that their mechanical properties will be significantly affected by temperature.
Britten and Pilpel studied the compaction of two representative pharmaceutical powders lactose and palmitic acid, over a range of pressure (0 - 200 MPa) and temperature (-20 – 180 °C). They found that the compactibility and strength of both materials increases with temperature in the range of 0.6 - 0.95 homologous temperatures, and this trend was attributed to the reduction of the yield stress of the powder with temperature\[8-9\]. Pilpel et al. also reported that a mixture of 15% MCC and 85% paracetamol showed reduction in lamination (capping) when the powders were heated to 70 °C\[10\]. Roueche et al. examined the influence of the temperature on the compressibility of an unspecified organic powder and observed that mechanical strength exhibited a maximum when compaction was performed in a die heated at 60 °C\[11\]. Michrafy et al. observed in their study that increasing the ambient temperature of die and punches from 20 to 57 °C increases the transfer ratio, the radial pressure, and the die wall friction\[12\]. It is also notable that in the compaction of metal powders, the technology of warm compaction (i.e., compaction of metal powders at temperatures of 100 - 150 °C) is employed to improve the compactibility and strength of metallic compactions\[13\]. Given the potential importance of the effects of temperature on compaction, mechanical properties need to be further investigated.

The present research aims to systematically study the effects of temperature on the compaction behavior and tablet properties of some common pharmaceutical excipients, microcrystalline cellulose (MCC) and pregelatinized starch (starch 1500). The experimental data generated in this study can help to fundamentally understand the compaction process and supply useful knowledge for the solid dosage formulation and compression process operation.

**EXPERIMENTS**

**Instrumentation**

The study was conducted on an Instron compression testing system with temperature controlled die and punches (Figure 1).
A 1.5 inch diameter mica band heater (OEM Heaters), PCT-2000 temperature controller (Tempco), 3-channel temperature datalogger (Extech Instruments), and precision fine wire thermocouple (Omega Engineering Inc.) were implemented to maintain an accuracy of ±2 °C. A custom A2 steel punch was manufactured with a 0.125 inch diameter hole. This drilled hole entered through the radial axis, created a channel parallel to the outer edge of the part, and terminated 3 mm from the tip face. The thermocouple was inserted into this channel and taped into position. Both upper and lower punches are flat-faced with a diameter of 9.5 mm. The compression system was programmed to compact powders at a constant strain rate with a consistent punch displacement profile. The upper punch was set to wait an allotted amount of time, approach the top of the loose powder, and then supply a constant strain rate. A typical punch displacement profile of 0.05 mm/s constant strain rate is shown in Figures 2 and 3. The lower punch was kept stationary throughout each test. The upper and lower punch load was measured by a 50kN load cell with a 0.01kN resolution.
**Materials**
The pharmaceutical powders used in this study are microcrystalline cellulose (MCC, Avicel PH 102, FMC, Newark, DE) and pregelatinized starch (Starch 1500, Colorcon, West Point, PA). They are both common pharmaceutical excipients and are employed extensively in the solid dosage formulation in pharmaceutical industry.

**Methods**
Compaction was performed at four different temperatures: 27 (Room), 50, 100, and 150 °C. During each test, the powder was poured onto the die face, the heated die hole was filled by circular arrangement, and the material was covered with the upper punch. It remained in the system for 120 seconds before compaction. This holding time corresponds to a Fourier number $F_0 = \lambda t / R^2 \approx 6$ for the radius of the die used and an estimated thermal diffusivity of $1.4 \times 10^{-6}$ m$^2$/s (derived from the published value of thermal effusivity 370 Ws, bulk density of 370 kg/m$^3$, and specific heat capacity of 890 J/(kgs)), which shows that it is adequate for heat to conduct into the powder and create a near uniform temperature field before compaction.

Samples were produced at six standard pressures for evaluation (50, 100, 200, 400, 500, and 600 MPa). After compaction, tablets formed a cylindrical geometry with a diameter of 9.5 mm and a thickness of about 2 – 6 mm. The resultant thickness is a function of the material, pressure, temperature, and initial volumetric conditions.

All experiments were conducted in an air-conditioned room in which a constant ambient temperature of 27.0 ± 2 °C was maintained. The weight and dimensions of the manufactured tablets were measured immediately after compaction using a 0.0001 g resolution scale (Sartorius) and 0.001 mm resolution electronic micrometer (Mitutoyo), respectively. A ½ tonne diametrical compression machine (Engineering Systems) was used to determine tensile strength by subjecting each tablet (with a low height-to-diameter aspect ratio) to compression across its diameter between two rigid platens. A tensile stress state develops at the center of the tablet and results in failure at a given load.

**RESULTS AND DISCUSSION**

**Compressibility**
Compressibility is the ability of a material to undergo volume reduction under pressure. Relative density, the ratio of the tablet density to the true material density, is a commonly used parameter in powder
compaction to describe the volume reduction\textsuperscript{[14]}. At a given compressive load, high relative density indicates a strong volume reduction ability of the material. The tablet relative density is calculated by the equation

$$RD = \frac{\rho_{tablet}}{\rho_{true}} = \frac{4m}{\pi d^2 h \rho_{true}}$$

(1)

where $m$ is the mass, $h$ is the thickness, $d$ is the diameter, and $\rho_{true}$ is the true density of the powder. High temperature improved the compressibility of MCC. From Figure 6, it can be seen that at lower compaction pressures (50 - 200MPa), high temperatures increased relative density by about 1 - 7% from a room temperature baseline. As pressure was increased further, the distinct relative density measurements began to converge at about 95% for all processing temperatures.

Figure 4. Relative density vs. compaction pressure for microcrystalline cellulose tablets at various temperatures
Figure 5. Log-log plot comparing pressure and porosity for microcrystalline cellulose tablets.

Figure 6. Percent change in relative density of microcrystalline cellulose tablets from room temperature at various compaction pressures.
For starch 1500, there exists a strong dependence of compressibility on compaction temperature. As shown in Figure 9, the relative density increases significantly with compaction temperature. At lower compaction pressures (50 - 200 MPa), the higher temperatures cause a large increase of 5 - 27% from the room temperature results. In addition, even as the processing pressure reaches 600 MPa, a full convergence of the relative density values is not observed, and an increase of 2 - 5% from room temperature is still present.

Figure 7. Relative density vs. compaction pressure for starch tablets at various temperatures.
Figure 8. Log-log plot comparing pressure and porosity for starch tablets.

Figure 9. Percent change in relative density of starch tablets from room temperature at various compaction pressures.
**Tensile strength**

The radial tensile strength of tablets ($\sigma_{\text{tensile}}$) was calculated from the thickness ($h$), diameter ($d$), and diametrically applied force ($F_{\text{applied}}$) using the equation,

$$\sigma_{\text{tensile}} = \frac{2F_{\text{applied}}}{\pi dh}$$

(2)

Figure 11 illustrates that the tensile strength of MCC tablets was improved by increasing compaction temperature. Again, temperature greatly affected the properties of MCC at lower pressures and steadily increased until the data began to converge around 12 – 14 MPa. Diometrical strength increased as much as 50% from the room temperature baseline at 50 MPa pressure and still remained at about 5 - 20% above the baseline at 200 MPa.

![Figure 10. Diametrical strength vs. compaction pressure for microcrystalline cellulose tablets at various temperatures](image-url)
For starch 1500, the dependence of tensile strength on the compaction temperature was also evident (Figure 13). The tensile strength was observed to be dramatically improved by raising the compaction temperature. Compared to MCC, the improvement of the strength of starch 1500 by compaction temperature was even more substantial. At lower pressures, tensile strength increased by factors ranging from 2 – 25. An increase of over 100% was observed even at higher pressures.
CONCLUSIONS
The experiments demonstrate that temperature plays an important role in the manufacturing process of pharmaceutical tablets. Tensile strength and compressibility are two important features of material design and are both greatly affected by the influence of temperature. Generally, the compactibility and tensile
strength of microcrystalline cellulose increased when processed at higher temperatures. These same outcomes are observed for starch. In the latter case, the dependence of the mechanical properties is even more substantial. The reason is attributed to the relationship between the glass transition temperature or homologous temperature of the powder and the compaction temperature.

The results are useful to solid dosage formulation and aid in the development of a fundamental understanding of compaction behavior. With an appreciation of the thermal mechanisms and their ensuing properties, new designs can be created to optimize energy efficiency.

REFERENCE