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# DOES TEMPERATURE INCREASE INDUCED BY TABLETING CONTRIBUTE TO TABLET QUALITY?

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## Abstract

The aim of this paper is to determine temperature and structural changes caused by tableting and to deduce from the combination of temperature measurement and the determination of structural changes whether temperature increase induced by tableting contributes to tablet quality. Tablets were produced of microcrystalline cellulose (MCC), spray-dried lactose, pregelatinized starch, and dicalcium phosphate dihydrate (DCPD) with an instrumented single punch tableting machine. The temperature pattern at the surface of the tablets was measured starting directly after tableting with an infrared thermoviewer and an infrared sensor. Powder and tablets were analyzed by FT-Raman spectroscopy, the tablets were analyzed directly after tableting and after one month of storage. The crushing force of the resulting tablets was determined. For all materials a temperature increase (TI) induced by tableting was determined with both methods used. The order of the temperature increase was the same for both methods used: TI (MCC)>TI (spray-dried lactose)>TI (pregelatinized starch)>TI (DCPD). The order was also identical for the crushing force of the tablets. The extent of differences in the spectra followed the same ranking. In conclusion, the temperature increase contributed to the changes in material structure and thus temperature increase is one factor which determined crushing force and thus tablet properties.

**Keywords:** crushing force, excipients, FT-Raman spectroscopy, tableting, temperature

## Introduction

Generally, a tablet is produced with the aim to transfer a loose powder into a tablet with a coherent form. The material properties are assumed to stay the same. However, structural changes in tablets can be caused by tableting, the material becomes mechanically activated [1]. This mechanical activation can lead to practical problems during processing and storage of the tablets. For example, materials with low glass transitions or melting points or materials with different polymorphic forms can change their physico-chemical properties [e.g. 2–5]. In cases when the mechanical stability of the tablet is improved, a mechanical activation can be of advantage. Polymorphic and structural changes in materials, which can be analyzed by spectroscopic methods such as FT-Raman spectroscopy result from this mechanical activation. Un-

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til now, no detailed examinations are available on the influence of the temperature on the molecular structure and the tableting behavior of pharmaceutical materials.

The mechanical activation is induced by the pressure applied during tableting. But not only pressure is applied, additionally a significant temperature increase can evolve. The applied pressure is partially transformed into heat, and the increase in temperature is caused either by friction of the particles [6], by friction between particles and machine components, or by material stresses inside the tablet [1, 7–9]. A temperature increase of 5 to 70 K was determined. Hot spots of several 100°C are discussed [10].

Several methods have been applied to determine the temperature increase with thermal sensors which are installed in the punches, inside the die, or the powder bed. A temperature increase of 5 K [11–13], but with epoxide punches also a temperature increase up to 30 K could be measured [14]. By calorimetric measurement an increase of 10 up to 30 K [15] and by infrared measurement an increase of 10 K was determined [16]. Beissenhirtz measured a temperature increase of 30 K indirectly by measuring conductivity which arose during tableting with conductive materials [17]. Energy calculations indicate a temperature increase of more than 30 K caused by tableting [16, 18–19]. Partial melting of drugs could be analyzed for materials whose melting temperature is as high as 94°C [3], and the reversible transgression of a glass transition temperature of 80°C was determined [2]. The temperature increase depends on the material.

The aim of this paper is now to determine temperature and structural changes caused by tableting for excipients and to deduce from the combination of temperature measurement and the determination of structural changes whether temperature increase induced by tableting contributes to tablet quality.

### *Materials*

The materials used were microcrystalline cellulose (MCC, Avicel PH 101, Lot # 6911C, FMC Corp., Princeton, NJ, USA), spray-dried lactose (FlowLac 100, Lot # S0047, Meggle GmbH, Wasserburg, Germany), pregelatinized starch (Starch 1500, Lot # 606009, Colorcon, West Point, PA, USA), and dicalcium phosphate dihydrate (DCPD, Emcompress, Lot # R 19 K, Mendell, Patterson, NJ, USA).

## Methods

### *Test conditions*

All experiments were performed at 21±1°C and 45±2% RH in a special climate room.

### *Tableting*

Tableting was performed on an instrumented single punch tableting machine (EK0/DMS, No. 1.0083.92, Korsch GmbH, Berlin, Germany) with 11 mm diameter flat faced punches (Ritter GmbH, Hamburg, Germany). For analysis with an infrared sensor 300 mg powder were tableted at different compaction pressures of the upper punch: 50,

130, and 210 MPa. Five single tablets were produced at each condition. For the analysis of the ejected tablet with an infrared thermoviewer, tablets with a defined porosity of 5% (dicalcium phosphate dihydrate 15%) and a tablet height under load of 3.00 mm were produced. The amount of material necessary for each tablet was calculated. Previously the true density ($\rho_{true}$) of all materials was determined by helium pycnometry (Accupyc 1330, Micromeritics, Norcross, GA, USA). All tablets produced for temperature measurement did not contain any lubricant. For determination of crushing strength five tablets were produced at four different pressures. Magnesium stearate was added in the case of DCPD as the lubricant. In all cases, the depth of filling was held constant at 12 mm. The production rate was 10 tablets per min. The powder was manually filled into the die and one compaction cycle was performed. Displacement of the punch faces was measured using an inductive transducer (W 20 TK, Spectris GmbH, Langen, Germany). It was corrected for elastic deformation of the punches. Forces were measured by the calibrated strain gages. Data acquisition was performed by a DMC-plus system (Spectris GmbH, Langen, Germany) with BEAM-Software (AMS, Flöha, Germany). Force, time, and displacement were recorded for each compaction cycle.

*Temperature measurement*

*Infrared thermoviewer*

The infrared thermoviewer (Thermacam PM 695, FlirSystems, North Billerica, MA, USA) was positioned in front of the tableting machine and allowed collecting thermographic sequences of the tablet directly from the moment of ejection of the tablet until cooling down to room temperature. The position of the infrared thermoviewer was the same in all experiments. The temperature of the tablets was analyzed as the mean value over the central circular area at the surface of the tablet.

Infrared sensor

The infrared sensor (Sensytherm IR-C, ABB AG, Mannheim, Germany) was positioned with a special holder at the die holder (Fig. 1, construction University of Halle-Wittenberg, Halle, Germany). Temperature was measured from the time of ejection until cooling down to room temperature.

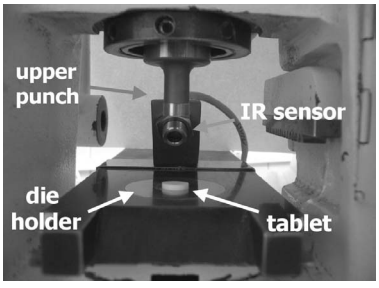


**Fig. 1** Positioning of the infrared sensor at the die holder inside the tableting machine

*FT-Raman spectroscopy*

Pure materials and tablets were analyzed using FT-Raman spectroscopy. The spectra were collected on a Bruker RFS 100/S FT-Raman spectrometer (Bruker Optik GmbH, Ettlingen, Germany) using a diode-pumped Nd:YAG with an operating wavelength of 1064 nm. Typical spectra were acquired with 200 scans and a laser power of 125 mW at the sample location. The interferograms were apodized with the Blackman–Harris four-term function and subjected to Fourier transformation to give spectra with a resolution of 4 $cm^{-1}$.

Powder samples were placed in glass test tubes. The tablets were broken and the laser beam was focused on the fractured surface. The tablets were measured directly after tableting and after 1 month of storage. Between the measurements the samples were stored in glass test tubes in the climate controlled room with a temperature of 21±1°C and 45±2% RH.

Tablet properties

Crushing force was determined with the crushing force tester (TBH 30, Erweka GmbH, Heusenstamm Germany). Five tablets were analyzed 10 days after tableting and means and standard deviations were calculated.

## Results and discussion

Figures 2 and 3 show the temperature pattern measured with both the infrared thermoviewer and the infrared sensor. Both these systems allow contact-less and fast analysis of temperature. One problem is that measurement can only be performed after ejection at the surface of the tablet. This implies that the temperatures actually reached inside the tablet can be assumed to be much higher than those which are measured. However the order of temperature increase should be similar if the materials are compared at the same conditions.

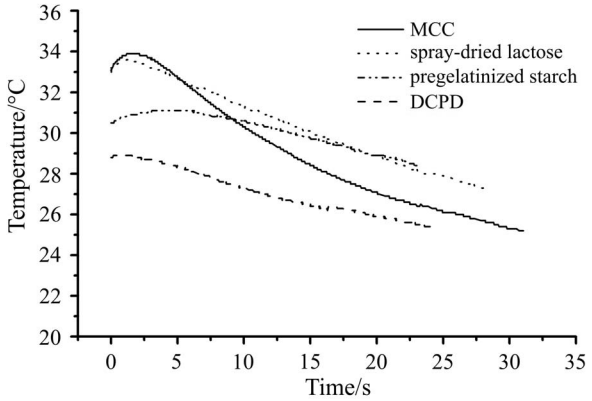


**Fig. 2** Surface temperature pattern of the tablets measured with the infrared thermoviewer starting at ejection from the die

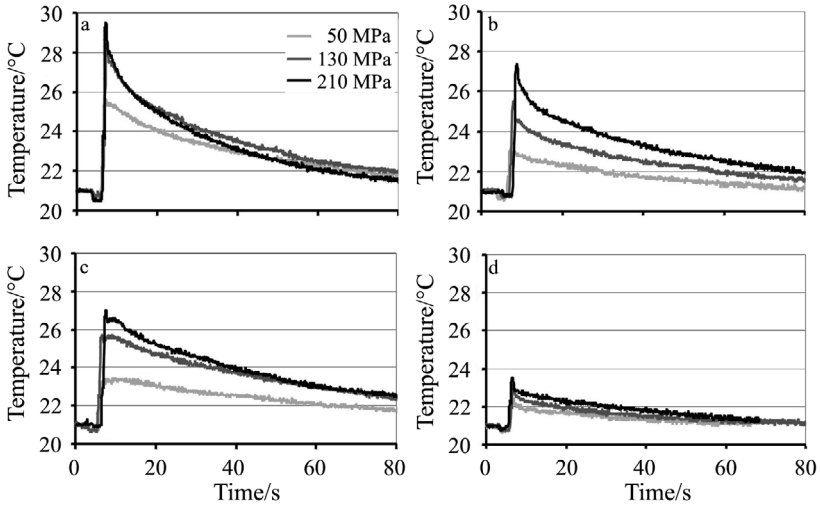


**Fig. 3** Surface temperature pattern of the tablets produced at different compaction pressures measured with the infrared sensor starting at ejection from the die for a – MCC, b – spray-dried lactose, c – pregelatinized starch, and d – DCPD

Figure 2 shows the highest increase in temperature for MCC. The maximum temperature measured was 34°C. The cooling down process was fast. For spray-dried lactose almost the same surface temperature was reached, however the cooling down process was slower. Pregelatinized starch showed a flatter temperature pattern and the maximum temperature was only 31°C. The lowest temperature was obtained for DCPD with 28.9°C. Thus the order of temperature increase (TI) is:

TI (MCC) >TI (spray-dried lactose) >TI (pregelatinized starch) >TI (DCPD)

Standard deviation in temperature was measured for MCC examplarily to be 0.3°C.

Figure 3 shows the temperature patterns measured with the infrared sensor. Generally, the measured increase in temperature was lower than with the infrared thermoviewer. Obviously, the infrared sensor is less sensitive to temperature development. In this case, a more extensive analysis at different compression pressures was possible. Three different temperature patterns are exhibited for the different excipients. A general trend is that with increasing compression pressure the temperature increase is higher.

For MCC (Fig. 3a) the temperature difference between different compression pressures decreases with increasing upper punch pressure. Highest maximum temperatures were measured and as with the infrared thermoviewer temperature decrease was fast.

Spray-dried lactose (Fig. 3b) showed the second highest increase in temperature. For spray-dried lactose tablets nearly the same temperature differences were found between tablets produced at different compression pressures. The cooling down process was relatively fast.

Pregelatinized starch (Fig. 3c) showed a medium increase in temperature. Lower temperature differences between tablets with different compression pressures were detected than for spray-dried lactose. As measured with the infrared sensor the temperature pattern was quite flat and the cooling down process was slower than for MCC or spray-dried lactose.

With DCPD (Fig. 3d) intact tablets could only be produced at 50 and 130 MPa. Higher compression pressures led to capping of these tablets produced without magnesium stearate. For DCPD the lowest temperature increase (1–2°C) of all materials was found at all compression pressures. The temperature pattern is very flat.

In conclusion, the results with the infrared sensor show the following ranking order of temperature increase (TI):

TI (MCC)>TI (spray-dried lactose)>TI (pregelatinized starch)>TI (DCPD)

This is the same order as measured with the infrared thermoviewer. This result is supported by Fig. 4. Summarizing, Fig. 4 shows the maximum temperatures at different compaction conditions both for the analysis with the infrared thermoviewer and for the analysis with the infrared sensor.

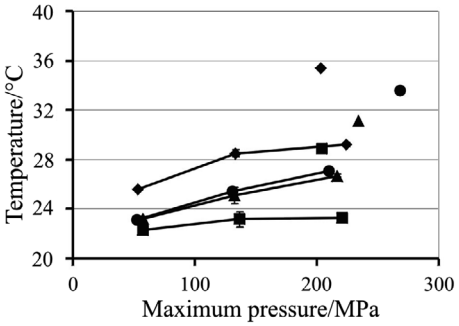


**Fig. 4** Maximum temperatures measured with the infrared sensor (line) or with the infrared thermoviewer (without line) at different compaction pressures for ◆ – MCC, ● – spray-dried lactose, ▲ – pregelatinized starch and ■ – DCPD

For tablets of all four excipients crushing forces were determined. Figure 5 exhibits the results of tablets produced at four different compression pressures. The highest crushing forces (CF) were found for MCC followed by spray-dried lactose and pregelatinized starch, and the lowest crushing force was obtained for DCPD:

CF (MCC) > CF (spray-dried lactose) > CF (pregelatinized starch) > CF (DCPD)

This is the same ranking order as obtained for the increase in temperature. Obviously, the increase in temperature influences the crushing force of the tablets.

In order to evaluate whether the temperature increase causes structural changes in the materials, which might be responsible for the increase in crushing force, tablets were analyzed by FT-Raman spectroscopy (Fig. 6). Details of the FT-Raman spectra which are of interest in this respect are exhibited.

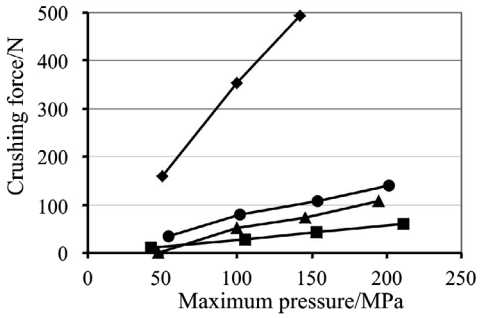


**Fig. 5** Crushing force of the tablets at different compaction pressures for ◆ – MCC, ● – spray-dried lactose, ▲ – pregelatinized starch and ■ – DCPD (standard deviation smaller than symbols)

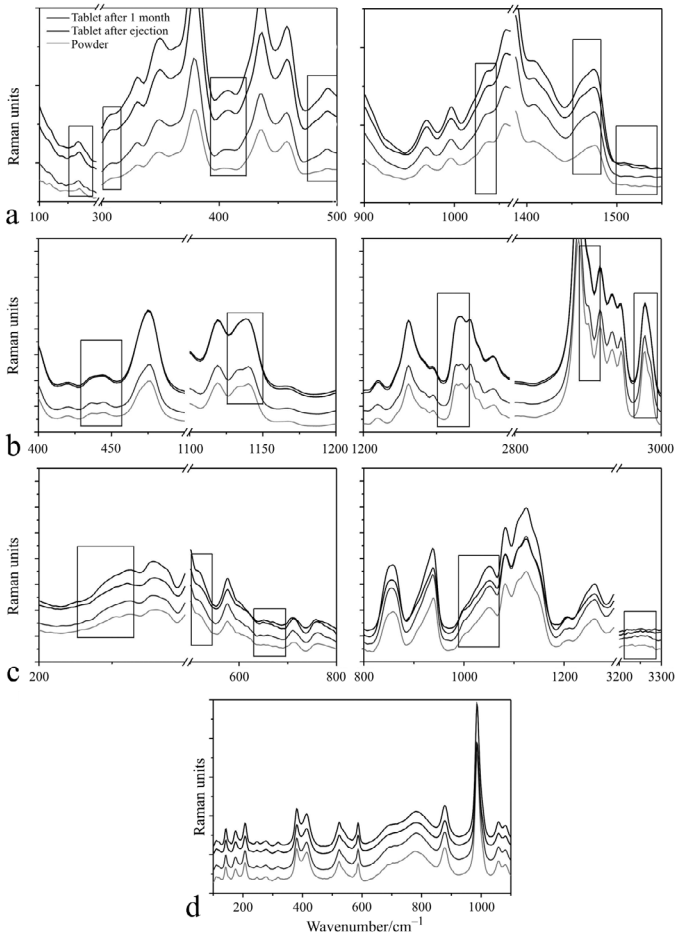


**Fig. 6** Details of Raman spectra of powder and tablets at different storage times for a – MCC, b – spray-dried lactose, c – pregelatinized starch and d – DCPD

The spectra were analyzed for differences between the powder, the tablets directly after ejection, and the tablets after 1 month of storage.

For MCC (Fig. 6a) mainly an increase in band height is visible at the wavenumbers 300–340, 390–420, and 1020–1050 $cm^{-1}$. At wavenumber 1450–1480 and 1500–1530 $cm^{-1}$ bands seem to develop. The difference between powder and tablets becomes more clear with increasing storage time. Thus tableting induces a process which continued during storage. The powder samples did not show this change.

The changes observed are similar to those which were observed when cellulose I changed to cellulose II as reported by Schenzel and Fischer [20]. Moreover the change at wavenumber 1450–1480 $cm^{-1}$ indicates a higher amorphous amount of the remaining cellulose I in microcrystalline cellulose [21]. In conclusion, a partial change from cellulose I to cellulose II takes place induced by tableting [22].

For spray-dried lactose (Fig. 6b) the spectra of powder and tablets also exhibit differences and at some wavenumbers two bands of the powder reduce to one band of the tablets after 1 month of storage. This is the case at wavenumber 440, 1140, 1330, and 2980 $cm^{-1}$. At wavenumber 2900 $cm^{-1}$ one band vanishes.

The spectra of pregelatinized starch (Fig. 6c) show only slight differences for the powder and the tablets. For this excipient band intensity increases at wavenumber 290, 510, 650–680 and 1040–1080 $cm^{-1}$. At wavenumber 3250 one band vanishes.

In both cases, it seems that tableting induced a process continued during storage, since the powder samples did not show any changes after one month of storage. For spray-dried lactose as well as for pregelatinized starch, a reason for the spectral changes is not yet known. However, changes in food quality have also been reported for these materials [23].

At last, for DCPD (Fig. 6d) no differences could be detected between the spectra of powder and tablets. The bands stayed the same.

Summarizing, the intensity of changes (IC) in the spectra can be ranked as follows:

$$IC\ (MCC) = IC\ (\text{spray-dried lactose}) > IC\ (\text{pregelatinized starch}) > IC\ (DCPD)$$

This ranking is almost the same as found for the temperature increase induced by tableting and the crushing force of the tablets produced with the different excipients.

Even when in all cases the observed changes are slight the authors suppose that these changes in material structure can contribute to the final tablet properties. They are assumed to be due to a reversible exceeding of the glass transition temperature [2] since for MCC and spray-dried lactose glass transition temperatures between 60 and 80°C were found. For pregelatinized starch, which has a quite low glass transition temperature, less changes in the FT-Raman spectra were found than for MCC or spray-dried lactose, and at last, for DCPD no changes could be detected. The assumption of a reversible exceeding of the glass transition temperature [2] is strengthened by the fact that the ranking of the glass transition temperature goes parallel with the increase of temperature measured at the surface of the tablet directly after ejection.

## Conclusions

For all analyzed excipients, MCC, spray-dried lactose, pregelatinized starch, and DCPD, a temperature increase induced by tableting could be measured with the infrared thermoviewer as well as with the infrared sensor. The ranking order of this increase was the same using both methods. The same ranking order could also be found for the crushing force of the resulting tablets, and changes in the FT-Raman spectra could be detected to a higher extent for the materials producing tablets with a higher crushing force and a higher temperature increase. In conclusion, the temperature increase during tableting contributes to slight changes in material structure. This temperature increase and the material changes induced are factors which determine the crushing force of the tablets and thus other resulting tablet properties, e.g. robustness and stability. Tablet quality is influenced.

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