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THE RELEVANCE OF GLASS TRANSITION TEMPERATURE FOR THE PROCESS OF TABLET FORMATION

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Abstract

The aim was to determine the relevance of the glass transition temperature (T_g) on the compressibility and compactibility of different excipients as celluloses, cellulose derivatives, lactoses, starch, maltodextrin and carrageenan. Their T_g was determined, they were tableted on an instrumented eccentric tableting machine and crushing force was analyzed. Using force, time and displacement tableting behavior was analyzed by 3D modeling. The parameters obtained, *d* (time plasticity), *e* (pressure plasticity) and ω (fast elastic decompression), show different deformation mechanisms for the materials in relation to their T_g. Further, if the T_g can be reversibly exceeded during tableting, crushing force is high, otherwise crushing force is lower.

Keywords: crushing force, 3D model, DSC, excipients, glass transition, tableting, temperature

Introduction

The "process of tablet formation" is a complex process which is the sum of "tableting inside the die" and the "final formation of the tablet after tableting". Inside the die the applied punch forces are responsible for the deformation and fracture of single particles as of particle collectives which deform in a continuous process. There is sliding, rearrangement and friction of the particles. Then the particles deform or break. Bonds are formed and the particle collectives are subjected to the same mechanisms [1, 2].

For the production of a tablet compressibility and compactibility are necessary [3, 4]. The materials have to be deformable and the deformation has to be consistent. Mainly plastic deformation is necessary which stays after compaction. Partially amorphous materials have shown to be easier compactible [5–7] since they have viscoelastic properties. It was postulated [8–10] that a good tableting materials exists when there is a balance between deformation by brittle fracture and plastic/viscoelastic deformation. Brittle fracture enhances the formation of new surfaces and thus enhances the formation of bondings. Other factors contributing to the formation of a compact are particle size and shape, crystallinity [11, 12], water content [13,14], mechanical interlocking [15] and entanglement of the fibers [16]. However, it is not the aim of this paper to study these factors, rather it shall be concentrated on the relevance of the glass transition temperature for the process of tablet formation.

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Tableting has thermal consequences: The applied pressure is partially transformed into heat and the rise of temperature could already be determined, either by calorimetric measurement [17, 18], by thermal sensors which are installed in the punches or inside the die [19–22], or by infrared measurement [23]. Beissenhirtz [24] measured the temperature rise indirectly by measuring conductivity which arose during tableting with conductive materials. Even partial melting of drugs during tableting could be analyzed [25] for materials whose melting temperature is as high as 94°C. A temperature rise of more than 50°C during tableting makes it possible to think of a reversible transgression of T_g.

However, in order to determine this influence it is necessary to determine the T_g for the material at the relative humidity for tableting and not for the dry material. Several methods are possible, namely differential scanning calorimetry (DSC), modulated temperature differential scanning calorimetry (MTDSC), dynamic mechanical analysis (DMA), thermomechanical analysis, and inverse gas chromatography [e.g. 26–30]. A well-established method is DSC and especially MTDSC for weak transitions.

In this paper, a special procedure to determine the T_g of equilibrated materials with a certain water content will be pointed out to determine T_g exactly. Taking into account that inside a tablet the temperature can be locally as high as 94°C, the aim of this paper is to determine which influence the thermal energy produced during tableting has on the compressibility and compactibility of different filler binders, and what the role of the glass transition temperature in this process is.

Materials

The materials used were microcrystalline cellulose (MCC, Avicel PH 101, Lot # 6911C, FMC Corp., Princeton, NJ, USA), two cellulose ethers, hydroxypropyl methylcellulose (HPMC, Metolose 90 SH 15.000, Lot # 506825, Shin Estu, Tokyo, Japan) and sodium carboxymethylcellulose (NaCMC 3000 cP, Lot # 16110, Serva Feinbiochemica, Heidelberg, Germany), cellulose acetate (CAC, CA 398-10, Lot # AC-632505, Eastman Chemical Company, Kingsport, TN, USA), two lactoses, crystalline and spray-dried lactose (Spherolac 100, Lot # S0046 and FlowLac 100, Lot # S0047, Meggle GmbH, Wasserburg, Germany), potato starch (Lot # 35439.008E5, Wasserfuhr GmbH, Bonn, Germany), maltodextrin, a starch hydrolysate (Glucidex 19, Lot # 9050-36-6, Roquettes Frères, Lestrem, France) and one carrageenan, a κ-carrageenan (Gelcarin GP-911 NF, Lot # ZC502, FMC Corp., Princeton, NJ, USA).

Methods

Test conditions

All experiments were performed at relative humidities between 35 and 45% RH. Tableting was performed in a special climate controlled room which was set to 23±1°C and 45±2% RH. At these conditions neither sorption nor desorption could influence the experiments. Before tableting the materials were equilibrated.

Water content

Sorption and desorption isotherms were determined. The material was equilibrated seven days at 32% RH and then they were transferred to the next higher RH for equilibration. The procedure was performed up to 90% RH and then desorption was measured the same way with always seven days for equilibration. Analysis was

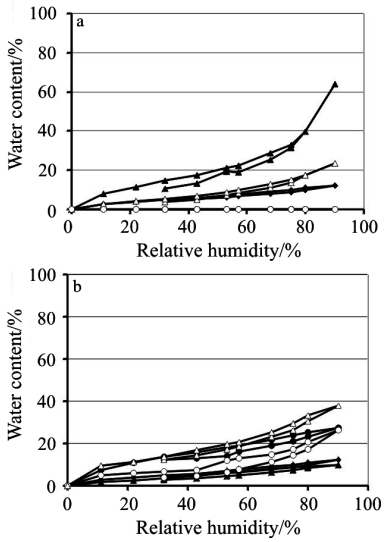

Fig. 1 Sorption and desorption isotherms of (a) ◆ – MCC, ○ – spray-dried lactose, ● – crystalline lactose, △ – HPMC and ▲ – NaCMC; (b) ◆ – MCC, ○ – maltodextrin, ● – potato starch, △ – κ-carrageenan and ▲ – CAC (SD not visible)

Table 1 Water content and glass transition temperature of different excipients after equilibration at ambient conditions as determined or/and given in literature

Material	Water content/%	T_g/°C determined	T_g/°C given in literature
MCC	4.99±0.09	60–80	60–80 [28]
HPMC	6.21±0.09	65.8±1.2	67 [39, 40]
NaCMC	10.38±0.07	54.2±1.1	54 [39, 40]
CAC	2.53±0.08	66.9±1.3	67 [44]
crystalline lactose	0.05±0.01	–	–
spray-dried lactose	0.38±0.02	75.0±4.5	75 [6, 38]
potato starch	13.65±0.02	–	<0 [41]
maltodextrin	6.48±0.08	70.9±0.9	–
κ-carrageenan	12.50±0.12	1.5±0.7	2 [16]

performed in triplicate. Fig. 1 gives the sorption and desorption isotherms of all excipients used.

The water content was determined by thermogravimetric analysis using TGA 209 (Netzsch Gerätebau GmbH, Selb, Germany) in triplicate. The results are given in Table 1. The powder was heated up to 150°C and water loss was determined. For materials which lose already crystal water at this temperature the water content was determined at 60°C for several hours.

Glass transition temperature

The T_g was determined using DSC 200 (Netzsch Gerätebau GmbH, Selb, Germany). Sample size varied in between 5 and 10 mg. Heating rate was 40 K min^{-1}. Only with a high heating rate weak transitions can be determined. For MCC a heating rate of 60 K min^{-1} was used [28]. The temperature interval for heating was chosen in a preliminary test. For a T_g higher than room temperature, it was set to 20 to 250°C, and for a T_g below room temperature the system was cooled down at least 20 K below the expected T_g. All determinations were performed for the materials equilibrated at ambient conditions which means between 35 and 45% RH. The materials were analyzed in hermetically closed pans. T_g was determined by calculating the temperature of the half step height during the first heating. During this heating in a closed pan an evaporation of moisture can be excluded, and the powder is at ambient conditions. To verify the results, additionally the maximum of the first derivative was determined.

True density

The true density (ρ_{true}) of all materials was determined by Helium pycnometry (Accupyc 1330, Micromeritics, Norcross, GA, USA). The equilibrated materials were analyzed in order to determine the true density of a material containing some moisture. The method is described by Picker [31].

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). Equal true volumes of the substances were tableted to five different maximum relative densities of the tablets, $\rho_{rel,\,max}$, ranging from 0.72 to 0.90 (±0.001). The maximum relative densities were chosen according to the expected deformability of the materials. The definition of $\rho_{rel,\,max}$ is as follows:

$$\rho_{rel,\,max} = \frac{\rho_{max}}{\rho_{true}} \tag{1}$$

with $\rho_{rel,\,max}$= maximum relative density, ρ_{max}= density at minimum height of the tablet under load and ρ_{true} – true density.

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. The depth of filling was held constant at 13 mm. The production rate was 10 tablets per min. The amount of material necessary for each tablet with a given $\rho_{rel,\,max}$ was calculated. The powder was manually filled into the die and one compaction cycle was performed. Ten single tablets were produced at each condition. 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.

The measured force, displacement, and time values were analyzed by 3D mathematical modeling using the 3D model [32, 33]. To the resulting data presented in a 3D parameter plot a twisted plane with the following equation was fitted:

$$z=\ln\left(\frac{1}{1-D_{rel}}\right)=(t-t_{max})(d+\omega p_{max}-p)+(ep)+(f+dt_{max}) \quad (2)$$

with D_{rel} = relative density, t = normalized time, p = pressure,

$$d=\frac{\delta\ln(1/(1-D_{rel}))}{\delta t},\ e=\frac{\delta\ln(1/(1-D_{rel}))}{\delta p},\ f=\ln\left(\frac{1}{1-D_0}\right) \quad (3)$$

where t_{max} = normalized time at maximum pressure, p_{max} = the maximum pressure, ω = twisting angle at t_{max} and D_0 = relative density at t=0.

From the fitting process the parameters d (time plasticity), e (pressure plasticity) and ω (twisting angle which indicates fast elastic decompression) were derived. For the calculated parameters resulting means (n=5) and standard deviations were calculated and the mean values were compared to each other by plotting these parameters for each tableting excipient in a 3D coordinate system. A 3D parameter plot was obtained which can be used for the description of the tableting properties. The mean standard deviation is 0.0112 for d, 0.0002 for e, and 0.003 for ω.

Tablet properties

Crushing force was determined with the crushing force tester (TBH 30, Erweka GmbH, Heusenstamm, Germany). Always five tablets were analyzed 10 days after tableting and means and standard deviations were calculated. Analysis was performed in the climate controlled room at the conditions given above.

Results and discussion

The glass transition temperature T_g of the tableting materials was determined as described above. Table 1 gives the results as determined in our laboratory and/or already determined in the literature. Most important for a determination is that the glass transition temperature is determined under controlled humidity conditions in a closed pan in order to analyze the material under the conditions as it is used during tableting. Table 1 shows that most of the excipients used for tableting possess a T_g which is in

between 60 and 80°C. Only starch and carrageenan have a T_g which is much lower. It is below room temperature. Does this result have a relevance for tablet formation?

Figure 2a shows the 3D parameter plot of MCC and different lactoses. The plot of MCC is compared to that of the lactoses flat. MCC is plastically deforming whereas lactoses deform mainly by brittle fracture [34–37]. Brittle fracture is expressed in the low *d*- and *e*-values and the decrease in ω-values. However the plot of spray-dried lactose is less flat than that of crystalline lactose. This means that in this case the brittle fracture is reduced and the deformation is more homogenous during tablet formation. Spray-dried lactose is partially amorphous as MCC. It has a T_g in the same temperature range (Table 1) [6, 38]. Assuming that this T_g can be reversibly exceeded the plots show this bond formation caused by thermal energy by less decrease of ω-values. This result can be further verified. The crushing force (Fig. 3a) of MCC is much higher than that of the lactoses and the crushing force of spray-dried lactose is higher than that of crystalline lactose. For MCC it is known that crystallinity changes during tableting [11, 12]. In combination with a reversible exceeding of T_g these changes can be responsible for the extraordinary high crushing force.

Figure 2b shows the 3D parameter plot of MCC and two cellulose ethers. HPMC exhibits higher *e*- and ω-values than MCC, NaCMC lower *e*- and ω-values. This is caused by the chemical structure since NaCMC possesses large substituents compared to MCC and HPMC [39]. Both materials are amorphous and possess a T_g which is at ambient conditions more than 20 K above room temperature (Table 1) [40]. Again it is imaginable that this T_g is reversibly exceeded during tableting when a certain degree of densification is reached. Thus the plot of NaCMC is flat and that of HPMC becomes more flat only at higher $\rho_{rel,\,max}$ since for HPMC the T_g is higher. However fast elastic decompression of NaCMC is too high in order to produce a stable tablet (Fig. 3a). The

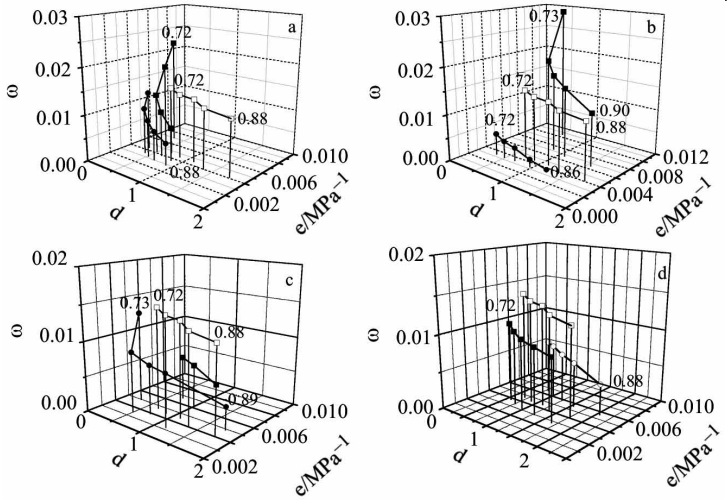

Fig. 2 3D parameter plots of (a) □ – MCC, ■ – crystalline lactose and ● – spray-dried lactose; (b) □ – MCC, ■ – HPMC and ● – NaCMC; (c) □ – MCC, ■ – potato starch and ● – maltodextrin; (d) □ – MCC, ○ – CAC and ■ – κ-carrageenan

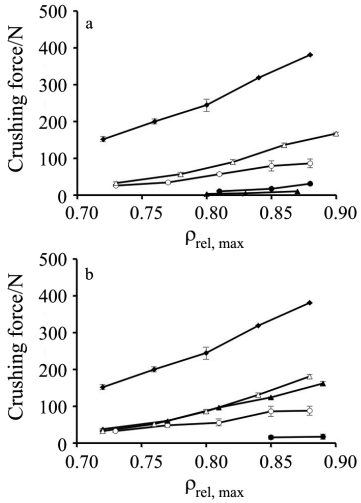

Fig. 3 Crushing force of tablets made of (a) ◆ – MCC, ○ – spray-dried lactose, ● – crystalline lactose, △ – HPMC and ▲ – NaCMC; (b) ◆ – MCC, ○ – maltodextrin, ● – potato starch, △ – κ-carrageenan and ▲ – CAC in dependence on maximum relative density

crushing force is low and cannot be determined at lower $\rho_{rel, max}$. For HPMC it is acceptable and in between that of MCC and spray-dried lactose. In this case there are no crystalline parts which stabilize the system, however the whole tablet body has undergone transformations at T_g.

Figure 2c gives the results of three dimensional modeling for starch and maltodextrin, a starch hydrolysate. Potato starch, a native starch was not able to be tableted at lower $\rho_{rel, max}$ (Fig. 3b). Contrary to crystalline lactose and NaCMC not even weak compacts resulted. The 3D parameter plot is steep and the material has low ω-values which means a lot of elasticity. Deformation behavior is not homogenous. This tableting behavior can be seen in combination with T_g. The T_g of the starch is below 0°C at these conditions (Table 1) [41]. That means the material is already in the rubbery state and it is in the rubbery state all the time during tableting. This causes elasticity and hinders the formation of a stable compact. Contrary to the starch, the strach hydrolysate maltodextrin exhibits a flat plot starting at lower $\rho_{rel, max}$. The tablets are much stronger and crushing force is higher. The material possesses very good compactibility in agreement with literature [42, 43]. This has again to be considered in relation to T_g which can be reversibly exceeded during tableting. The final compact is in the glassy state.

Figure 2d shows the 3D parameter plot of cellulose acetate and a carrageenan compared to MCC. Both materials exhibit lower ω-values than MCC, which is due to the substitution of the polymeric chains [16, 44]. Both plots are flat and the tablets made of both materials exhibit an acceptable crushing force (Fig. 3b). Carrageenan has a T_g about 0°, whereas that of cellulose acetate (Table 1) can be reversibly exceeded during tableting. The tablets formed from carrageenan are mainly hold together by entanglement of the fibers [16], those formed from cellulose acetate are

nearly 'fused' together [44] as it was already described. This difference becomes visible during the testing of crushing force. The tablets made of cellulose acetate really break, those made of carrageenan are hold together by the fibers until they are smashed. Thus, tablets made of cellulose acetate are formed by a reversible exceeding of T_g. However those formed by the carrageenans can only be stable because of the entanglement of the fibers. This fact is also responsible for the homogeneous deformation process shown in the 3D parameter plot.

Conclusions

The results show that a reversible exceeding of T_g can be responsible for the formation of a stable tablet with an acceptable crushing strength. The tablet is finally again in the glassy state. In cases when the excipient is already in the rubbery state before tableting other mechanisms are necessary for mechanical stabilization. This is the case for carrageenan. However, in the case of potato starch the formation of tablets is hindered.

In conclusion, it is desirable to look for tablet excipients with a T_g well above room temperature, e.g. between 60 and 80°C, in order to produce mechanically stable tablets.

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