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AN INSIGHT INTO THE PROCESS OF TABLET FORMATION OF MICROCRYSTALLINE CELLULOSE
Structural changes on a nanoscale level

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The present paper aims to show whether the shrinking of the microcrystalline cellulose (MCC) tablets can be derived from underlying processes and whether these processes can be visualized on a nanoscale level. Tableting of MCC was performed on an instrumented eccentric tableting machine to a maximum relative density ($\rho_{rel,max}$) of 0.90 of the tablets. The apparent density of the tablets was analyzed by helium pycnometry after tableting. The breaking surface of a MCC tablet was analyzed directly after tableting continuously by video in an environmental scanning electron microscope (ESEM) at constant humidity. Further the breaking surface was analyzed by transmission electron microscopy (TEM) after freeze fracturing. The results show that firstly apparent density by helium pycnometry increases after tableting and that secondly inside the tablet the fiber strength decreased while also the gaps between the fibers increased as was visualized by ESEM. Further the results by TEM indicate that the decrease in fiber strength is caused by a parallel orientation of the MCC microcrystals which is induced by a mechanical activation due to tableting. In conclusion the measured shrinking MCC tablets after tableting is caused by processes on a nanoscale level.

Keywords: *environmental scanning electron microscopy, microcrystalline cellulose, microcrystals, tableting, transmission electron microscopy*

Introduction

Microcrystalline cellulose (MCC) is one of the best compactible excipients used for tableting, e.g. [1, 2]. The produced tablets show already at low densification high crushing forces.

In 1964 MCC was introduced into the market [3]. It is produced by acid hydrolysis of the milled pulp and subsequent spray-drying of the resulting solution. Cellulose molecules with a level-off degree of polymerization of 150–300 DP result. MCC is partially crystalline (70%) and partially amorphous (30%) [4–6]. It consists of microcrystals and amorphous regions. Cellulose of different pulp and origin are used to produce materials of different density [7].

MCC shows predominantly plastic deformation, however at low densification parts of elastic deformation are detectable. Bonding results from hydrogen bridges and mechanical interlocking. The deformation behavior has been intensively studied, e.g. [8–13]. It was observed that the crystallinity of celluloses can change during tableting [14–16] and a change in conductivity is observed with incresasing density [17, 18]. It could be shown that inside the microcrystalline cellulose tablets a partial change from cellulose I to cellulose II induced by tableting takes place [19–21]. Moreover a higher amorphous amount of the remaining cellulose I in microcrystalline cellulose was found [19, 22]. Different manufacturers produce cellulose of different qualities and different deformation behavior, e.g. [9, 23, 24]. Different crystallinities of the materials might be responsible for these differences. Relative humidity (RH) as well influences bonding and deformation of MCC [13, 25, 26].

The glass transition temperatures (T_g) for the dried material were determined to be 132.7±4.1, 159.8±0.8 and 184.1±1.0°C [27]. This is different compared to pure cellulose, which possesses a T_g of 230°C [28, 29]. T_g is lowered by moisture (>22% RH) to values between 60 and 80°C [27], which is similar as for HPMC, for which at higher relative humidities a glass transition temperature of about 60°C was determined [30]. The amorphous parts in MCC can reversibly transgress the T_g during tableting as has been shown previously [31]. This reversible transgression of the T_g can contribute to the high compactibility of MCC. It can be assumed that MCC is for some time in the rubbery state during tableting, since higher temperatures are observed during tableting [31]. Thus a higher mobility of the molecules must be given.

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This higher mobility also seems to be responsible for a shrinking of MCC tablets directly after compression which was observed using different methods [32, 33]. For fibers a temperature interval of structural perfection between T_g and melting temperature has been described when the temperature of the fibers is increased during a DSC experiment. In this interval recrystallisation, perfection of structure and chain folding can take place [34]. Thus, the measured changes in elastic recovery indicate that the tablet elastically recovers during tableting and simultaneously a reorganization occurs which leads to shrinking. An expansion followed by shrinking is measured since both processes are superimposed [33].

The present paper aims now to show whether the shrinking of the MCC tablets can be derived from underlying processes and whether the observed polymorphic and pseudopolymorphic changes result in changes which can be visualized on a nanoscale level.

Experimental

Materials

The material used was microcrystalline cellulose (MCC, Avicel PH 101, Lot# 6911C, FMC Corp., Princeton, NJ, USA).

Methods

Test conditions

The experiments were performed at a relative humidity between 35 and 45% RH. Tableting was performed in a special climate 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.

Apparent density by helium pycnometry

The apparent density of the materials and tablets was determined by Helium pycnometry (Accupyc 1330, Micromeritics, Norcross, GA, USA) in triplicate. The equilibrated materials were analyzed in order to determine the apparent particle density of the materials containing some moisture [35].

Tableting

Tableting was performed on an instrumented eccentric tableting machine (EK0/DMS, No. 1.0083.92, Korsch GmbH, Berlin, Germany) with 11 mm diameter flat faced punches (Ritter GmbH, Hamburg, Germany). Equal volumes based on apparent particle density were tableted to a maximum relative density ($\rho_{rel,max}$) of the tablets (precision 0.001) of 0.90. The tablet height at maximum densification under load was held constant at 3 mm. Displacement of the punch faces was measured using an inductive transducer (W20 TK, Hottinger Baldwin Meßtechnik, Darmstadt, Germany) and corrected for elastic deformation of the punches. The depth of filling was held constant at 13 mm. The production rate was 10 tablets per minute. The powder mass for each tablet was manually weighed, filled in and the tablet was produced with an accuracy of ±0.001 at $\rho_{rel,max}$. No lubricant was used during tableting to avoid the influence of the lubricant on the microstructure of the tablets.

Environmental scanning electron microscopy

To analyze changes in the microstructure continuously a tablet was analyzed by environmental scanning electron microscopy (ESEM XL 30 FG, Philips, Kassel, Germany) at 40% RH and 2.9 torr for 12 h using video analysis. Accelerating voltage was 2 keV. The first and last image are shown. The images were also edited by Corel Photo Paint as black-white image.

Freeze fracturing and transmission electron microscopy

Tablets were frozen in a freeze fracturing apparatus (BAF 400, Balzers, Switzerland) at –210°C. The frozen tablets were broken inside the apparatus. The fractured surface was coated with a mixture of platinum and coal (2 nm). The platinum coating was stabilized with coal (20 nm). The replicas were detached using concentrated sulfuric acid. Afterwards, the replicas were analyzed by transmission electron microscopy (EM 300, Philips, Kassel, Germany).

Results and discussion

As described above, the shrinking of MCC tablets must be caused by a reorganization and structural perfection of the tableted material. To ensure this hypothesis it was tested whether changes of the apparent density measured by helium pycnometry occur. Density measurements after tableting showed that with storage time the apparent density of the tablets increased (0.064 g cm^{-1} (n=10). Thus the hypothesis of reorganization seems to be correct, however what is the reason?

To visualize the process in more detail, the breaking surface of a MCC tablet was analyzed directly after tableting continuously by video analysis in an environmental scanning electron microscope (ESEM) at constant humidity. Figure 1a_1 and a_2 show parts of the structure in the center of the breaking

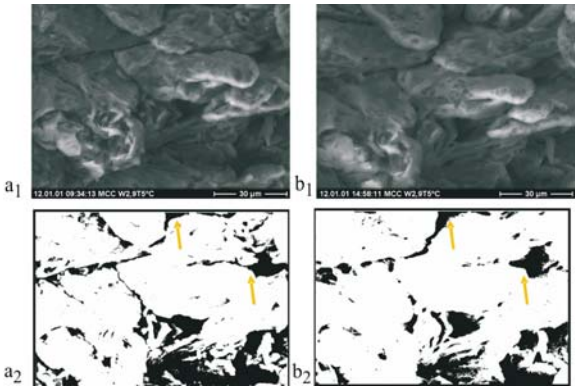

Fig. 1 1 – SEM and black-white image of the 2 – SEM of the same location at the breaking surface of a tablet of MCC at 40% RH (ESEM) a – half an hour and b – 12 h after tableting

surface shortly after tableting. Figure 1b_1 and b_2 show exactly the same spot 6 h later. The fiber strength decreased and also the gaps between the fibers increased (see arrows). The result proves that induced by tableting the fibers themselves and their arrangement changes which causes the overall increase in apparent density.

To visualize the fiber structure more precisely, the breaking surface of MCC tablets was analyzed by transmission electron microscopy (TEM) after freeze fracturing (Fig. 2). TEM is a frequently used method to analyze fibers [22, 36]. Figure 2a and b exhibit the inner fiber structure shortly after tableting and 24 h after tableting. At the given magnification (66000×) microcrystals of MCC become visible. These microcrystals are in disorder shortly after tableting, however 24 h after tableting stripes and a parallel orientation of the microcrystals can be observed. This indicates the reorganization process described by Jaffe *et al.* [34]. However in this case reorganization

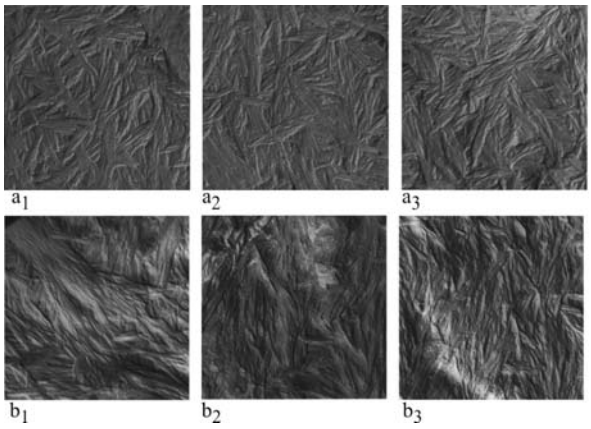

Fig. 2 TEMs of the replica of the breaking surface of a tablet of MCC after freeze fracturing a – 2 h and b – 24 h after tableting (magnification: 66000×)

is induced by tableting and not by heating-up the material.

A mechanical activation and a temperature increase during tableting might be responsible. Most probably reorganization occurs above T_g (60–80°C), since a higher mobility of the material is given. This hypothesis can be supported by the fact that the temperature on the surface of MCC tablets during ejection was significantly higher than for dicalcium phosphate dihydrate, lactose and starch [19].

Conclusions

Thus, in conclusion a mechanical activation occurred which caused changes in the fiber structure and lead to a shrinking of the tablets. This mechanical activation can contribute to bonding. The observed high crushing force of MCC tablets can be at least partially related to these processes.

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