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Research paper

Compaction mechanism and tablet strength of unlubricated and lubricated (silicified) microcrystalline cellulose

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Abstract

This paper describes the differences in compaction properties between microcrystalline cellulose (MCC) and microcrystalline cellulose co-processed with colloidal silicon dioxide (SMCC). The different compaction parameters are not only compared for the pure materials, but also for the lubricated powders with magnesium stearate. Neither magnesium stearate, nor colloidal silicon dioxide, facilitates extensively the densification of (silicified) microcrystalline cellulose during compaction. The difference in tablet relaxation of MCC and SMCC indicates a small negative effect of colloidal silicon dioxide on the interparticle bonding strength of unlubricated MCC. However, for lubricated MCC a larger increase in tablet relaxation at a high compression speed was found than for lubricated SMCC tablets. Accordingly, the decrease in tablet strength was larger for the MCC tablets than for the SMCC tablets when lubrication was applied. The examination of the tablet strengths of tablets compressed from physical mixtures of MCC with increasing concentrations of colloidal silicon dioxide proved the slightly negative influence of silicon dioxide on the tablet strength of unlubricated MCC tablets and the positive effect of colloidal silicon dioxide addition on the tensile strength of lubricated MCC tablets. Co-processing of MCC with colloidal silicon dioxide showed no extra contribution on the tablet strength of lubricated tablets above the physical mixtures. The interactions between the different materials were further supported by the interaction parameters based on partial solubility parameters.
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Keywords: Microcrystalline cellulose; Silicified microcrystalline cellulose; Colloidal silicon dioxide; Direct compression; Lubricant

1. Introduction

Silicified microcrystalline cellulose (SMCC) was introduced in 1996 [1–3], initially produced by Penwest Pharmaceuticals Co. as Prosolv SMCC® and is recently marketed under the same trademark by J. Rettenmaier and Sohne [4]. It is produced by co-processing 98% microcrystalline cellulose with 2% colloidal silicon dioxide (colloidal silica). The excipient is available in two particle grades: SMCC 50 and SMCC 90 with particle size distributions equivalent to the two most commonly known grades of MCC, $D_{50} = 50$ and 90 μm, respectively. The flow rate of SMCC 90 was found to be equivalent to that of Avicel PH-200 ($D_{50} = 180$ μm) and higher than that of Emcocel® 90M [5]. Accordingly, SMCC shows also greater bulk densities than regular MCC, which can be explained by the improved flowability and packing properties [6]. Studies using helium pycnometry, laser light scattering particle size analysis, Fourier-transform infrared spectroscopy, gas-adsorption, X-ray powder diffraction, solid state-NMR, calorimetry, water vapour sorption and Raman spectroscopy have detected that silicification appears to have no distinctive effect on the primary chemical and polymorphic characteristics of MCC [5,7,8]. However, the specific surface area of SMCC was found to be about 5 times higher compared to MCC, whereas the pore volume size distributions calculated from nitrogen adsorption isotherms showed that the total pore volume was greater for SMCC [6]. These effects were attributed to the very large specific surface area of colloidal silicon dioxide. The pore size distribution characteristics of the powders determined by mercury porosimetry were very similar for SMCC 90 and MCC 90 [8]. This suggests that bulk

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modification of MCC does not occur during silicification. Based on scanning electron microscopy studies together with electron microprobe analysis it was stated that silicon dioxide is primarily located at the surface of the SMCC particles, while certain amounts of silicon dioxide were detected in the internal regions of some particles [9]. The colloidal silicon dioxide particles present at the surfaces of the SMCC particles are shown to be uniformly distributed [10]. These observations suggest that the presence of silicon dioxide at the surface is primarily responsible for the improvements in functionality, whether by providing surface modifications or by modifying particle interactions.

In an earlier published study dealing with mechanical properties of unlubricated compacts of MCC and SMCC, it has been found that at relatively slow compression rate compacts with comparable relative densities were obtained, which suggests that the two materials exhibit comparable compaction behaviour [11]. In direct compaction, SMCC is 10–40% more compactable than regular MCC [1–3]. Not only tensile strength, but also stiffness and energy of failure were greater for compacts prepared from SMCC than for compacts prepared from MCC [11].

The goal of this paper is to elucidate the effect of co-processing colloidal silicon dioxide with MCC on different compaction parameters and tablet strength. Alterations in tablet strength of MCC and SMCC by addition of magnesium stearate are compared with those of physical mixtures containing colloidal silicon dioxide and MCC.

2. Materials and methods

The materials used were microcrystalline cellulose (Emcocel® 90M), silicified microcrystalline cellulose (Prosolv SMCC® 90), both from Penwest Pharmaceuticals (Reigate, UK), magnesium stearate Ph.Eur. (Centrachemie, Etten-Leur, The Netherlands) and colloidal silicon dioxide (Aerosil® 200, Degussa, Frankfurt a.M., Germany). Before use, MCC and SMCC were conditioned at 20 °C and 60% relative humidity (RH) for at least a period of a week. The true densities of MCC and SMCC measured by helium pycnometry were 1.549 and 1.559 g cm^{-3}, respectively.

The preparation of the physical mixtures of MCC with colloidal silicon dioxide was performed with a Turbula mixer model 2P (W.A. Bachofen, Basle, Switzerland) at 90 rev min^{-1} for a period of 15 min. For the production of tablets containing magnesium stearate ('lubricated tablets'), mixing of MCC, SMCC or the physical mixtures with magnesium stearate was also performed with the Turbula mixer at 90 rev min^{-1}, but now only for 5 min.

Compaction of 500 mg powder into flat-faced tablets with a diameter of 13 mm was carried out on a compaction simulator (ESH, Brierley Hill, UK) at 20 °C and 60% RH. The upper punch displacement profiles were sine waves with different amplitudes in order to vary the maximum compression pressures. The average compression rates were 3 and 300 mm s^{-1} reflecting slow and high compaction speeds, respectively. The lower punch was stationary during compression. The ejection time was always 10 s. To secure equal frictions between die wall and powder bed for compacts, the die was always prelubricated with magnesium stearate with a brush before each compression. Yield pressures and tap densities were calculated according to Heckel [12].

Tablets were stored for at least 14 h in a controlled climate chamber (Heraeus, Hanau, Germany) at 20 °C and 60% RH. Tablet dimensions were measured with an electronic micrometer (Miutoyo, Tokyo, Japan) and weights were determined on an analytical balance (Mettler-Toledo, Greifensee, Switzerland). Tablet porosity was calculated from tablet dimensions and tablet weight. Crushing strengths of the tablets were measured using a Schleuniger 6D strength tester (Dr Schleuniger Productronic, Soloturn, Switzerland). Tensile strength was calculated according to Fell and Newton [13]. Subsequently, the tensile strength of 20 or more compacts with different porosities was related to the porosity and fitted by the Ryskewitch–Duckworth equation [14]. Using this fit, the tensile strengths at different porosities were obtained.

3. Results and discussion

3.1. Densification of MCC and SMCC powders

The densification behaviours of MCC and SMCC powders can be represented by the porosity under pressure. Fig. 1 shows the porosity under pressure as a function of the compaction load for unlubricated and lubricated MCC and SMCC powders. The porosities under pressure of the lubricated materials were similar to those of the unlubricated materials. This means that the presence of magnesium stearate has no significant influence on the consolidation of (silicified) microcrystalline cellulose. This observation is consistent with previous work on MCC and sorbitol [15].

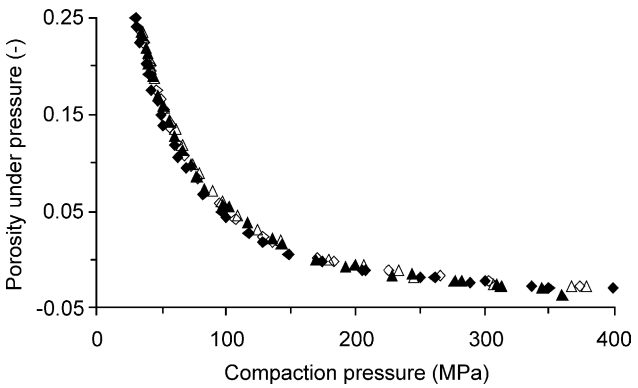

Fig. 1. Porosity under pressure of unlubricated (open symbols) and lubricated (closed symbols) tablets compressed from MCC (△) and SMCC (◇). Compression speed is 3 mm s^{-1}.

Table 1
Yield pressure and tap density obtained from Heckel plots of MCC and SMCC at compression speeds of 3 and 300 mm s^{-1}

	Yield pressure (MPa)		Tap density (g cm^{-3})	
	3 mm/s	300 mm/s	3 mm/s	300 mm/s
MCC	42.0	51.7	0.536	0.503
SMCC	40.3	50.7	0.564	0.518

Commonly derived parameters to reflect powder densification and particle deformation are the yield pressure and tap density. Table 1 gives the yield pressures and tap densities for unlubricated MCC and SMCC powders. The small difference in yield pressure shows that the particle deformation of the SMCC particles is hardly affected by the presence of co-processed colloidal silicon dioxide. This observation is confirmed by the tap densities at both compaction speeds (Table 1). Colloidal silicon dioxide minimally enhances the particle rearrangement at the initial stage of the powder bed densification. Nevertheless, no discriminating differences were found between the densification behaviours of MCC and SMCC powders, resulting in minor differences in porosities under pressure (Fig. 1).

3.2. Tablet relaxation

In this study tablet relaxation is depicted as porosity expansion, which is defined as the difference between the porosity under pressure and the final tablet porosity. The measured porosity expansions are given in Table 2. The table shows that there is a small difference in porosity expansion between unlubricated MCC and SMCC tablets. Tablet relaxation is normally considered as a fine balance between stored elastic energy as driving force for expansion and particle bonding as counteracting force [16]. Stored energy is mostly controlled by the yield pressure of the material. Since the yield pressures of both materials were found to be comparable (Table 1) and intraparticle silicon dioxide does not change the chemical and physical properties of MCC [8], the stored elastic energy is considered to be similar for both materials. Therefore, it can be deduced from the slightly higher tablet relaxations of unlubricated SMCC compacts in comparison to those of the MCC tablets (Table 2) that surface located colloidal silicon dioxide has more negative than positive effect on interparticle bonding.

Table 2
Tablet relaxation, given as porosity expansion, of unlubricated and lubricated tablets compressed from MCC and SMCC at compression speeds of 3 and 300 mm s^{-1}

	Unlubricated tablets (%)	Lubricated tablets (%)	Change in tablet relaxation (%)
3 mm/s			
MCC	6.4	7.3	0.9
SMCC	6.6	7.5	0.9
300 mm/s			
MCC	7.0	8.4	1.5
SMCC	7.5	8.4	0.9

In previous work, it was demonstrated that the larger tablet relaxation of lubricated MCC tablets, as compared with unlubricated MCC tablets, can be ascribed to a reduction of interparticle bonding by the presence of a lubricant film upon the MCC particles [15]. Because a strong interparticle bonding counteracts tablet relaxation [16,17], tablets produced from materials with low interparticle attraction tend to suffer from more relaxation than tablets made from materials where interparticle attractions are large [18,19]. Realizing that magnesium stearate negatively affects interparticle bonding, it was expected that the relaxation of lubricated tablets is higher than that of unlubricated tablets. Table 2 shows indeed increased tablet relaxations for all lubricated tablets. Remarkable is the higher increase found for lubricated MCC tablets at a high compaction speed. In contrast, the change in tablet relaxation of SMCC tablets by an increased tablet speed was hardly affected by the presence of 0.5% magnesium stearate. This implies that the negative effect of the lubricant on the interparticle bonding of SMCC particles is smaller compared to MCC particles. It must be mentioned that this phenomenon was not observed for tablets compacted at a low compression speed. As the only difference between SMCC and MCC is the presence of colloidal silicon dioxide, the difference in interparticle bonding points to an interaction between magnesium stearate and colloidal silicon dioxide. Although the densification of the (un)lubricated MCC and SMCC powders were comparable, after ejection and relaxation of the tablets, SMCC tablets contained marginally higher tablet porosities than the MCC tablets at equal compaction pressures.

3.3. Tablet strength of tablets compressed from MCC, SMCC and physical mixtures

Fig. 2a and b show the tensile strength of MCC and SMCC compacts, both unlubricated and lubricated with 0.5% magnesium stearate. The average compression speeds were 3 (Fig. 2a) and 300 mm s^{-1} (Fig. 2b), respectively. The tensile strengths of the unlubricated MCC and SMCC compacts are comparable in both figures. Only at higher compaction pressures, the tensile strength of unlubricated SMCC tablets is a little higher than that of unlubricated MCC. At compaction pressures higher than 150 MPa, the apparent porosity under pressure reaches values below 0%. This indicates intraparticle changes combined with material density increase under compaction pressure. These processes are obviously to some extent altered by colloidal silicon dioxide.

For the lubricated filler-binders, much larger differences can be observed. Although the presence of magnesium stearate decreases the tensile strength of tablets compressed from both materials, the effect is much larger for MCC

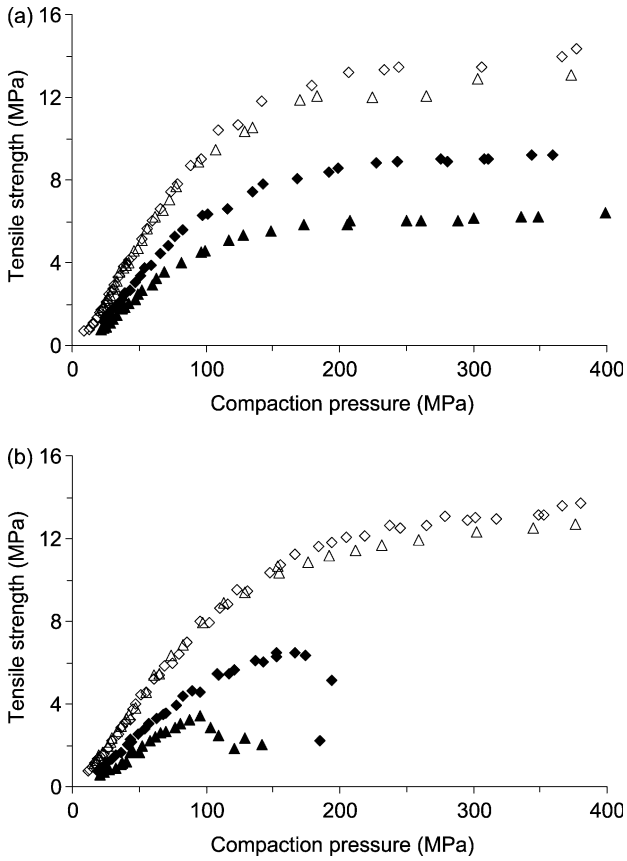

Fig. 2. (a) Tensile strength of unlubricated (open symbols) and lubricated (closed symbols) tablets compressed from MCC (△) and SMCC (◇). Compression speed is 3 mm s^{-1}. (b) Tensile strength of unlubricated (open symbols) and lubricated (closed symbols) tablets compressed from MCC (△) and SMCC (◇). Compression speed is 300 mm s^{-1}.

tablets than for SMCC tablets. Capping of tablets is observed at a higher compaction speed (Fig. 2b). Since the higher tensile strength of SMCC tablets in comparison with MCC tablets cannot be explained by a high increase in tablet porosity (Section 3.2), it confirms the conclusion of Edge et al. [11] that the strength enhancement by silicification of MCC tablets may be a consequence of interfacial interaction rather than modification of bulk MCC properties. In order to elucidate the effect of both colloidal silicon dioxide and magnesium stearate and their possible interactions on the binding properties of MCC, the tensile strength of tablets compressed from different physical mixtures of MCC and colloidal silicon dioxide, with and without magnesium stearate was compared with that of (un)lubricated MCC and SMCC.

Fig. 3 depicts the tensile strength of unlubricated tablets compressed from physical mixtures of MCC and different percentages colloidal silicon dioxide. The three different tablet porosities (10, 20 and 30%) reflect high, medium and low densificated tablets, respectively. A small addition of silicon dioxide (0.2–0.4%) to MCC powder enhances the tablet strength, especially for high densificated tablets. However, it can be generally stated that increasing amounts

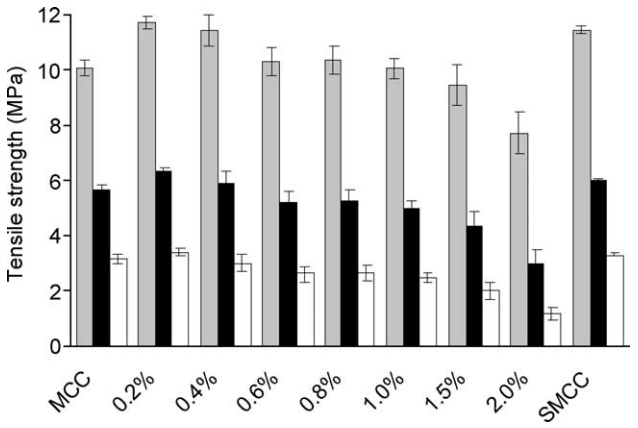

Fig. 3. Tensile strength of unlubricated tablets compressed from MCC, physical mixtures of MCC with different concentrations colloidal silicon dioxide and SMCC at 10% (grey bars), 20% (black bars) and 30% (white bars) porosity. (Standard deviations are indicated by error bars).

of colloidal silicon dioxide decrease the tablet strength, most probably by lowering the interparticle bonding strength between MCC particles. The difference in tensile strength between the physical mixture containing 2% colloidal silicon dioxide and its co-processed equivalent (SMCC) is the combined result of (1) a lower concentration of colloidal silicon dioxide at the particle surface of SMCC [9] and (2) its uniform distribution in case of SMCC in opposite of earlier reported inhomogeneity of the physical mixtures [10].

Fig. 4 shows the tensile strength as a function of the concentration of colloidal silicon dioxide of tablets compressed from physical blends of MCC, different percentages colloidal silicon dioxide and 0.5% magnesium stearate at three different porosities. This figure clearly shows that at all concentrations colloidal silicon dioxide used increase the tensile strength of lubricated MCC tablets. The tensile strength of the tablets containing MCC, 0.5% magnesium stearate and colloidal silicon dioxide concentrations between 0.4 and 1.0% were even better than those

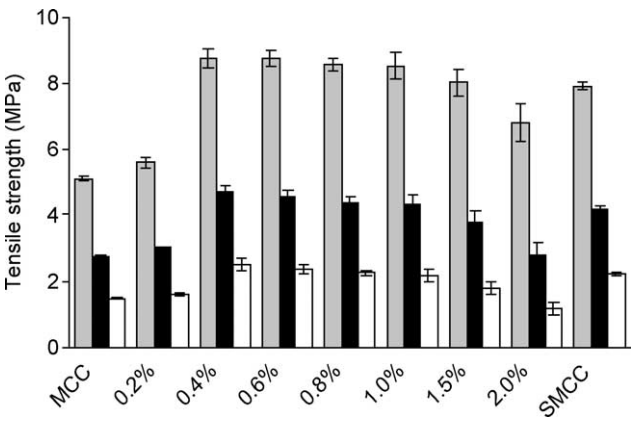

Fig. 4. Tensile strength of lubricated tablets compressed from MCC, physical mixtures of MCC with different concentrations colloidal silica and SMCC at 10% (grey bars), 20% (black bars) and 30% (white bars) porosity. (Standard deviations are indicated by error bars).

compressed of lubricated SMCC. This is in contradiction to the claim that co-processing of colloidal silicon dioxide with microcrystalline cellulose is essential for the enhanced compactibility [5]. Figs. 3 and 4 combined show that the same results of (un)lubricated SMCC can be obtained by physical mixing of MCC with 0.4–0.6% colloidal silicon dioxide. It can be concluded that only 20–30%, which is mostly surface located, of the original 2% colloidal silicon dioxide in SMCC is effectively used.

The effect of colloidal silicon dioxide on the compactibility of lubricated MCC particles can be elucidated by an interaction between magnesium stearate and colloidal silicon dioxide. In previous work, it was found that simultaneous mixing of filler-binder particles with magnesium stearate and colloidal silicon dioxide can significantly suppress the negative effect of the lubricant on the bonding properties [20]. A larger effect was obtained when the host particles were blended prior to the addition of magnesium stearate, like in the case of SMCC. The interaction between magnesium stearate and colloidal silicon dioxide has been elucidated by the measurement of contact angles, electron microprobe analysis (EDAX) and dissolution measurements [21]. The interaction between magnesium stearate and colloidal silicon dioxide was explained by a competitive inhibition of magnesium stearate molecular layers at the adhesion sites, which are occupied by colloidal silicon dioxide particles [22].

A theoretical understanding of the different particle interactions and observed phenomena was provided by Rowe [23,24] based on partial solubility parameters. He calculated the adhesive and cohesive interactions between MCC, colloidal silicon dioxide and magnesium stearate. He showed that the cohesive strength of interaction of colloidal silicon dioxide (311.5 MPa) was lower than that of MCC (386.1 MPa) in a binary powder mixture. This explains that increasing concentrations of colloidal silicon at the outer surfaces of MCC particles will eventually obstruct MCC–MCC bonding and lower the tablet strength (Fig. 3). In a ternary mixture with magnesium stearate, Rowe demonstrated that there is a greater interaction between MCC and colloidal silicon dioxide (306.9 MPa) than between magnesium stearate and MCC (121.0 MPa), although both interactions are greater than the cohesive interaction within the lubricant itself (82.8 MPa) [24]. With the understanding that colloidal silicon dioxide and magnesium stearate are both smaller in size than microcrystalline cellulose, it can be predicted that the MCC particles will preferentially be coated by colloidal silicon dioxide. The majority of magnesium stearate will be enrobed by colloidal silicon dioxide [22]. Although the model is something crude and oversimplified, the theoretical considerations are consistent with the previously described protecting effect of colloidal silicon dioxide with respect to lubricant sensitivity.

In conclusion, SMCC can be considered as a premix of colloidal silicon dioxide and MCC, although as an effect of co-processing, the colloidal silicon dioxide is fixed into and upon the MCC particles. As a result, only 20–30% of the 2% colloidal silicon dioxide in SMCC is working effectively in relation to the negative effect of magnesium stearate as lubricant on tablet strength. Although higher tablet strengths were found for lubricated physical binary mixtures in comparison to lubricated SMCC, silicon dioxide fixation at MCC surfaces is very efficient in powder formulations. Since MCC is often the filler-binder in powder formulations with the main function to secure sufficient tablet strength, silicon dioxide will prevent magnesium stearate to occupy the MCC surfaces.

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