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Influence of Compacted Hydrophobic and Hydrophilic Colloidal Silicon Dioxide on Tableting Properties of Pharmaceutical Excipients

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ABSTRACT The effect of noncompacted and compacted hydrophilic as well as hydrophobic colloidal silicon dioxide (CSD) on tableting properties of three different pharmaceutical excipients used for direct compression, namely, Avicel® PH 101, Starch 1500®, and Tablettose® 80, was investigated. Binary powder mixtures containing 0.5% CSD and 99.5% excipient were compressed on an instrumented single-punch tablet press, and the radial tensile strength/compaction load profiles were examined. The Ryshkewitch-Duckworth relationship shows that the influence of CSD on tablet strength was dependent on the hydrophobic and hydrophilic nature of the CSD and on the compaction characteristics of the excipients. Tablets from each excipient with and without CSDs were subjected to different levels of relative humidity at 20°C for 7 days. The sorption isotherms and the radial tensile strengths of the tablets after the storage period showed that neither hydrophilic nor hydrophobic CSD influenced the tablet properties of Avicel® PH 101, Starch 1500®, and Tablettose® 80. Moreover, ternary powder mixtures containing magnesium stearate as a third component were compressed in order to study the influence of CSD on the deleterious effect of magnesium stearate on the interparticle bonding. The radial tensile strength/compaction load profiles and the residual and ejection forces of tablets made from ternary mixtures showed that CSD eliminated the negative effect of magnesium stearate on interparticle bonding while maintaining the lubrication action, in a manner that was affected by its hydrophobicity/hydrophilicity and by the particle deformation properties of the excipient upon compression.

KEYWORDS Colloidal silicon dioxide, Excipient, Tableting, Moisture study, Lubrication, Magnesium stearate

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INTRODUCTION

Glidants used in tablet formulations include talc, colloidal silicon dioxide (CSD), calcium phosphates, and to a certain extent various metal stearates (Ritschel & Bauer-Brandl, 2002). AEROSIL® 200 Pharma (Degussa AG, Düsseldorf, Germany) is a CSD that is widely used to improve flowability (AEROSIL®, 2001). This conventional CSD has low bulk and tapped densities requiring considerable storage space. Furthermore, it is relatively complex to process, producing dust if not handled properly. Therefore, special mechanical processes were developed to create a compacted type of CSD in order to improve its handling. Compacted products have been recently introduced as AEROSIL® 200 VV Pharma (AEROSIL®, 2002), which is hydrophilic and especially designed for the pharmaceutical industry, and AEROSIL® R 972 V (AEROSIL®, 2003), which is hydrophobic, as a result of substitution of dimethyl silyl groups on the silica surface.

In a previous study, the glidant properties of compacted hydrophilic and hydrophobic CSD were compared to a noncompacted type (Jonat et al., 2004a). The flowability studies using angle of repose and dynamic conveyor belt methods have shown differences between the CSD types when mixed with microcrystalline cellulose (Avicel® PH 101) or pregelatinized starch (Starch 1500®). Besides their handling advantages, the compacted CSDs were superior to the noncompacted with respect to their powder flow enhancing properties. Furthermore, the hydrophobic CSD types were more effective compared to the hydrophilic types under gentle mixing conditions. The better flow characteristic was due to a higher degree and uniformity of coverage of the hydrophobic CSD on the excipient's surface, which led to a higher adhesion force reduction between the particles (Jonat et al., 2004b). For α-lactose-monohydrate (Tablettose® 80), there was only a limited improvement in the flowability, but there was no difference between the various CSD types. This was due to the agglomerated structure of Tablettose® 80, where CSD settles to a bigger extent in the cavities of the agglomerates.

On the basis of these results, the aim of this study is to investigate the influence of different hydrophobic and hydrophilic CSD types on the tableting properties of Avicel® PH 101, Starch 1500®, and Tablettose® 80. The study is based on binary mixtures to show the influence of CSD on tablet properties. Moreover, ternary mixtures containing magnesium stearate as a third component were evaluated in order to study the influence of CSD on the deleterious effect of magnesium stearate on interparticle bonding and tablet strength.

MATERIALS AND METHODS

Materials

One hydrophilic and noncompacted CSD (AEROSIL® 200 Pharma henceforth referred to as AEROSIL® 200), two hydrophilic and compacted CSDs (AEROSIL® 200 VV Pharma henceforth referred to as AEROSIL® 200 VV and AEROSIL® 130 V), and two hydrophobic and compacted CSDs (AEROSIL® R

TABLE 1 Physicochemical Properties of Hydrophilic and Hydrophobic Colloidal Silicon Dioxide (CSD) Types Used in the Study

	AEROSIL® 200	AEROSIL® 200 VV	AEROSIL® 130 V	AEROSIL® R 972 V	AEROSIL® R 974 V
Average primary particle size (nm)[a]	12	12	16	16	12
BET surface area (m^2/g)[b]	206	201	138	111	176
Bulk density (g/cm^3)[b]	0.050	0.119	0.104	0.094	0.089
Tapped density (g/cm^3)[b]	0.054	0.134	0.118	0.115	0.105
Silanol group density (nm^{-2})[a]	Approx. 2	Approx. 2	Approx. 2	Approx. 0.75	Approx. 0.75
Behavior towards water	Hydrophilic	Hydrophilic	Hydrophilic	Hydrophobic	Hydrophobic

[a] Typical values.
[b] Batch record, ex-plant.

972 V and AEROSIL® R 974 V) were used as received from Degussa AG (Düsseldorf, Germany). The physicochemical properties of the various CSD types are listed in Table 1 (AEROSIL®, 2003).

AEROSIL® 130 and AEROSIL® 200 are the starting materials for the synthesis of AEROSIL® R 972 and AEROSIL® R 974, respectively. For all compacted types, compaction takes place after chemical treatment.

Three excipients used as filler/binders for direct compression of tablets, namely, microcrystalline cellulose (Avicel® PH 101, FMC Biopolymer, Cork, Ireland), pregelatinized starch (Starch 1500®, Colorcon, Kent, England), and agglomerated α-lactose-monohydrate (Tablettose® 80, Meggle GmbH, Wasserburg, Germany), were selected according to their different structures, flow properties, and compression behavior. Magnesium stearate and oleic acid were supplied by Bärlocher GmbH (Munich, Germany) and Merck KGaA (Darmstadt, Germany), respectively.

Sodium hydroxide, potassium acetate, magnesium chloride, potassium carbonate, sodium nitrite, sodium chloride, and potassium chloride (Merck KGaA, Darmstadt, Germany) were of analytical grade and used as saturated salt solutions in water sorption experiments.

Blending

Based on preliminary investigations, the CSD concentration was set to 0.5% w/w. CSD was prescreened through a 315-μm sieve onto a portion of the excipient. The residual portion of excipient was added and mixed by hand. The mixture was sieved through an 800-μm sieve before and after 10 min mixing in a free-fall mixer (Turbula T2C, W. A. Bachofen, Basel, Switzerland) using a 2-L vessel. The maximum filling degree and the rotational speed were set at 75% and 42 rpm, respectively.

To investigate the effect of CSD on the film formation of a lubricant, 0.5% magnesium stearate was sieved through a 315-μm sieve onto the previously described mixture, and mixing was continued for another 5 min in the same free-fall mixer.

Characterization of Test Materials and Mixtures

Bulk (poured) and tapped density were measured according to the European Pharmacopeia 5th Edition using a 250-mL graduated cylinder and a settling apparatus (model STAV 2003, J. Engelsmann AG, Ludwigshafen, Germany) (European Pharmacopoeia, 2005a).

The true density was determined using a Beckman air comparison pycnometer (Model 930, Beckman Instruments, Fullerton, CA) at room temperature. The true densities of Avicel® PH 101, Starch 1500®, and Tablettose® 80 were 1.535, 1.445, and 1.47 g/cm^3, respectively.

The specific surface area was determined by nitrogen gas adsorption at a temperature of 77 K according to the European Pharmacopeia 5th Edition (European Pharmacopoeia, 2005b). Samples were first prepared by drying overnight at 105°C, followed by degassing for 1 hour at 200°C in vacuo before performing the analysis using the volumetric method (Model ASAP 2400, Micromeritics, Norcross, GA). Six data points were recorded for $0.05 < p/p_0 < 0.22$.

Tablet Preparation

Tablets were compressed on an instrumented single-punch tablet press Korsch EK II (Korsch Pressen, Berlin, Germany) using 10-mm round flat tooling. The compaction pressure range was 25–150 MPa, 100–200 MPa, and 100–250 MPa for Avicel® PH 101, Starch 1500®, and Tablettose® 80 mixtures, respectively. For Tablettose® 80, the die and the punches were prelubricated using pure oleic acid on Q-tips. After compression of nine tablets, tablet no. 10 was recorded. This procedure was repeated 10 times to produce 10 tablets for further investigations. The tablet weight was adjusted to approximately 400 mg for Avicel® PH 101, and 450 mg for Starch 1500® and Tablettose® 80. Compaction pressure was measured by a full Wheatstone bridge circuit of strain gauges [Type 6/120 LY 11, Hottinger Baldwin Messtechnik (HBM), Darmstadt, Germany] at the upper punch holder and by a piezo-electric load washer (Type 9041, Kistler, Winterthur, Switzerland) mounted directly below the lower punch. The upper punch displacement was measured using a digital incremental displacement transducer MT 2571 (Heidenhain, Traunreut, Germany). Data were acquired using the MGC Plus system including an ML 10 B voltage amplifier (HBM) and Catman software (HBM). Details of the instrumentation and calibration of the machine are given by Dressler et al. (2001).

Tablet Parameters

The tablets were immediately weighed after compression (AE 200 balance, Mettler Toledo GmbH, Giessen, Germany). The thickness (0.01-mm micrometer, Mitutoyo Messgeraete GmbH, Neuss, Germany), the diameter (TBH-30 tester, Erweka GmbH, Heusenstamm, Germany), and the crushing force (TBH-30 tester) of 10 tablets were measured 24 hours after tableting. The radial tensile strength (S) was calculated from the thickness (H), diameter (D), and crushing force (F_c) using the equation (Frocht, 1945):

$$S = 2F_c/\pi DH$$

The porosity of the tablets was calculated from the thickness (H) out of die, diameter (D) and weight (m) of the tablets, and the true density of the material. A Ryshkewitch-Duckworth relation between the radial tensile strength and the porosity was determined for every blend according to equation (Duckworth, 1953):

$$\ln(S/S_0) = -k * \epsilon$$

where S is the radial tensile strength, S_0 the radial tensile strength at zero porosity, ϵ the porosity of the tablet, and k a constant, referred to as the bonding capacity, which indicates the effect of a change in porosity on the radial tensile strength. Using the Ryshkewitch-Duckworth relation, the radial tensile strength was calculated for every mixture at 20% porosity for Avicel® PH 101 and Starch 1500® and at 10% porosity for Tablettose® 80.

The elastic recovery (ER) was measured during the decompression phase according to equation:

$$[ER] = ((h_{400N} - h_{min}) * 100)/h_{min}$$

where h_{400N} is tablet height at a 400-N tablet-upper punch contact and h_{min} the minimal tablet height. Details of the measurement are given by Dressler (2002).

Moisture Studies

Pyrex desiccators containing appropriate saturated salt solutions in distilled water were prepared to create chambers with different levels of relative humidity. All desiccators were kept at 20±0.5°C to maintain the desired relative humidity level. Saturated salt solutions of sodium hydroxide, potassium acetate, magnesium chloride, potassium carbonate, sodium nitrite, sodium chloride, and potassium chloride were used to create a relative humidity at 20°C of 7%, 20%, 33%, 44%, 65%, 75%, and 85%, respectively.

Tablets from each excipient without CSD or containing 0.5% AEROSIL® 200 VV or AEROSIL® R 972 V were compressed at 100 MPa for Avicel® PH 101 and at 200 MPa for Starch 1500® and Tablettose® 80. Ten tablets from each group were placed in the seven desiccators, which were equilibrated at 20°C, for 7 days in a dry oven (T5050, Heraeus Holding GmbH, Hanau, Germany). The weight, thickness, and radial tensile strength of the tablets were accurately measured after 7 days. The changes were calculated and expressed as percentages.

RESULTS AND DISCUSSION

Tablet Strength

Avicel® PH 101

Tablets compressed without CSD produced the highest values of radial tensile strength (Fig. 1a). The strong binding properties were due to the plastic deformation and the rough surface texture of microcrystalline cellulose (Gustafsson et al., 2003; Nyström et al., 1993). Addition of 0.5% CSD reduced the radial tensile strength of the Avicel® PH 101 tablets. The small CSD particles act as spacers between the Avicel® PH 101 particles, reducing the interparticle attraction forces between them. These results are in agreement with the adhesion force measurements performed on powder mixtures of a previous study, where the force increased in the following order: hydrophobic CSD/Avicel® PH 101<hydrophilic CSD/Avicel® PH 101<Avicel® PH 101/Avicel® PH 101 (Jonat et al., 2004b). The adhesive interaction between Avicel® PH 101 and CSD was lower compared to the cohesive attraction forces between Avicel® PH 101 particles. Therefore, tablets prepared with Avicel® PH 101/CSD mixtures will be slightly weakened by the presence of CSD. The hydrophobic CSD led to a stronger decrease in tablet strength, due to the lower density of silanol groups (Table 1). The better distribution of the hydrophobic CSD on the Avicel® PH 101 surface, decreasing the contact area between two Avicel® PH 101 particles, was also responsible for the reduction of tablet strength (Duckworth, 1953).

Previous studies (van der Voort Maarschalk et al., 1996; van Veen et al., 2000; Zuurman et al., 1999)

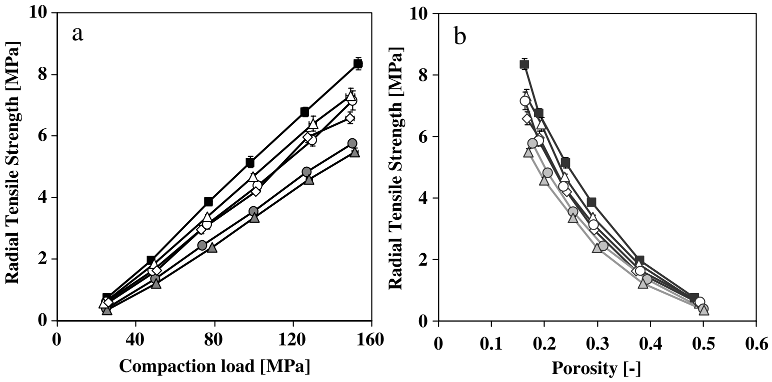

FIGURE 1 Radial Tensile Strength vs. Compaction Load (a) and Radial Tensile Strength as a Function of Tablet Porosity (b) of Tablets Compressed from Avicel® PH 101, Containing 0.5% AEROSIL® 200 VV (△), 0.5% AEROSIL 200 (◇), 0.5% AEROSIL® 130 V (○), 0.5% AEROSIL® R 972 V (●), 0.5% AEROSIL® R 974 V (▲) and Without CSD (■). Error Bars Represent the 95% Confidence Interval of Ten Measurements.

have demonstrated that the interaction between particles in a tablet can be derived from the relationship between radial tensile strength and porosity. Figure 1b shows the radial tensile strength/porosity profiles for Avicel® PH 101/CSD mixtures and indicates that addition of CSD modified the radial tensile strength/porosity profiles. At the same porosity, tablets compressed with Avicel® PH 101 and CSD showed lower radial tensile strength values compared to Avicel® PH 101 tablets, indicating a decrease in the bonding capacity of the material. The fitting parameters and the calculated radial tensile strength values are depicted in Table 2. The radial tensile strength values at 20% porosity confirmed that hydrophobic CSD (4.54–5.01 MPa) led to a higher reduction of the interparticle bonding compared to hydrophilic CSD (5.43–5.97 MPa).

However, tablets compressed at a pressure exceeding 50 and 75 MPa for hydrophilic and for hydrophobic CSD, respectively, displayed acceptable radial tensile strength values, and the friability of the tablets was lower than 1%. An increase of the compaction load, when tableting Avicel® PH 101 with CSD, led to tablets displaying the same

TABLE 2 Fitting Parameters (k, S_0, and Coefficient of Correlation) from the Ryshkewitch-Duckworth Relation and Calculated Radial Tensile Strength (RTS) Values at 20% Porosity for Avicel® PH 101 and Starch 1500® and at 10% Porosity for Tablettose® 80

	Fitting parameters			
	k	S_0	R^2	RTS [MPa]
Avicel® PH 101 (MCC)	6.47	23.64	0.990	6.48
MCC+AEROSIL® 130 V	6.70	21.26	0.988	5.57
MCC+AEROSIL® 200	6.68	20.70	0.991	5.43
MCC+AEROSIL® 200 VV	6.50	21.90	0.987	5.97
MCC+AEROSIL® R 972 V	6.74	19.34	0.993	5.01
MCC+AEROSIL® R 974 V	6.73	17.45	0.992	4.94
Starch 1500® (ST)	9.45	5.80	0.946	0.88
ST+AEROSIL® 130 V	11.85	13.83	0.991	1.30
ST+AEROSIL® 200	11.99	15.63	0.976	1.42
ST+AEROSIL® 200 VV	11.02	12.48	0.979	1.38
ST+AEROSIL® R 972 V	13.56	6.43	0.850	/
ST+AEROSIL® R 974 V	4.06	0.54	0.155	/
Tablettose® 80 (TAB)	14.96	10.01	0.923	2.24
TAB+AEROSIL® 130 V	14.13	6.05	0.943	1.47
TAB+AEROSIL® 200	13.31	5.74	0.957	1.50
TAB+AEROSIL® 200 VV	12.46	5.37	0.958	1.52
TAB+AEROSIL® R 972 V	13.75	5.81	0.970	1.46
TAB+AEROSIL® R 974 V	12.42	4.72	0.952	1.34

Note: /=not fitted due to low R^2 of <0.9.

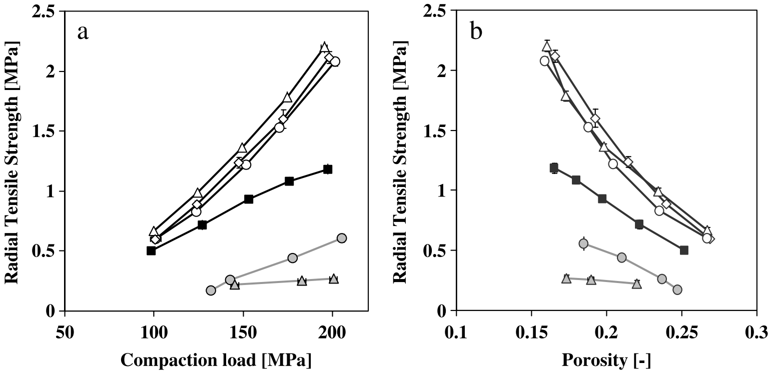

FIGURE 2 Radial Tensile Strength vs. Compaction Load (a) and Radial Tensile Strength as a Function of Tablet Porosity (b) of Tablets Compressed from Starch 1500® Mixtures (Keys as in Fig. 1). Error Bars Represent the 95% Confidence Interval of Ten Measurements.

properties as pure Avicel® PH 101 tablets. Therefore, considering the flowability enhancement induced by CSD (Jonat et al., 2004a), improving the powder flow into the hopper and the die of the tablet press, the use of hydrophilic and hydrophobic CSD facilitates the tableting of Avicel® PH 101.

Starch 1500®

The radial tensile strength of Starch 1500® tablets (Fig. 2a) was lower compared to Avicel® PH 101, because the plastic deformation was too slow to produce strong interparticle bonding during compression (Mattsson & Nyström, 2001). Furthermore, a large proportion of the total deformation of Starch 1500® was elastic during compaction at high strain rates (Bolhuis & Chowhan, 1996; Rees & Rue, 1978). The radial tensile strength of Starch 1500® increased when mixed with 0.5% hydrophilic CSD and decreased when mixed with 0.5% hydrophobic CSD.

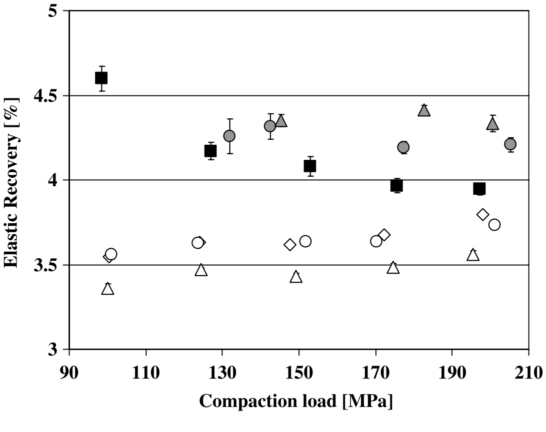

FIGURE 3 Elastic Recovery of Tablets Compressed from Starch 1500® Mixtures (Keys as in Fig. 1). Error Bars Represent the 95% Confidence Interval of Ten Measurements.

As the surface coverage of hydrophobic CSD on Starch 1500® was high (Meyer & Zimmermann, 2004), reducing the surface contact between two Starch 1500® particles and the adhesive interaction between Starch 1500® and CSD was much less compared to the cohesive attraction between Starch 1500® particles (Meyer & Zimmermann, 2004), the radial tensile strength of the tablets was dramatically weakened. Therefore, tablets could only be compressed at a compaction pressure greater than 125 MPa and 150 MPa for AEROSIL® R 972 V and AEROSIL® R 974 V, respectively. The radial tensile strength/porosity profile of hydrophobic CSD did not fit the Ryskewitch-Duckworth relation, probably because of the very low radial tensile strength values (Table 2). Nevertheless, it can be seen that the relationship between the radial tensile strength and the porosity changed dramatically, especially for AEROSIL® R 974 V and that the bonding capacity of Starch 1500® was decreased (Fig. 2b). The decreased tensile strength with hydrophobic CSD can be related to a larger elastic recovery of the tablets (Fig. 3).

Tablets compressed with hydrophilic CSD and Starch 1500® showed an increase in the radial tensile strength (Fig. 2a) and a decrease in elastic recovery (Fig. 3). The calculated radial tensile strength at 20% porosity indicated that hydrophilic CSD increased the bonding capacity of Starch 1500® (Table 2). The increased radial tensile strength may be attributed to the reduced destruction of interparticle bonding due to elastic recovery.

Tablettose® 80

Tablets compressed with CSD and Tablettose® 80 showed only a slight decrease in radial tensile strength

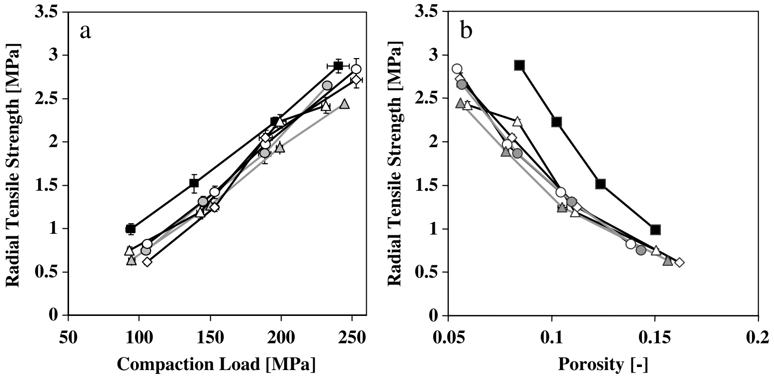

FIGURE 4 Radial Tensile Strength vs. Compaction Load (a) and Radial Tensile Strength as a Function of Tablet Porosity (b) of Tablets Compressed from Tablettose® 80 Mixtures (Keys as in Fig. 1). Error Bars Represent the 95% Confidence Interval of Ten Measurements.

(Fig. 4a). This can be explained first by the porous structure of the material and second by the brittle nature of α-lactose-monohydrate, which fragmented during compression and produced new surfaces, free of CSD and available for bonding. Consequently, attraction forces between Tablettose® 80 and CSD and between CSD particles were much lower compared to those between Tablettose® 80 particles, leading to a small decrease in the radial tensile strength and no difference between hydrophobic and hydrophilic materials. Figure 4b shows that the addition of CSD modified the radial tensile strength/porosity profiles. The decrease in radial tensile strength at the same porosity confirmed the reduced bonding capacity of the material. Furthermore, the same radial tensile strength values were calculated for CSD/Tablettose® 80 tablets at 10% porosity (Table 2), indicating no difference between hydrophobic and hydrophilic CSD.

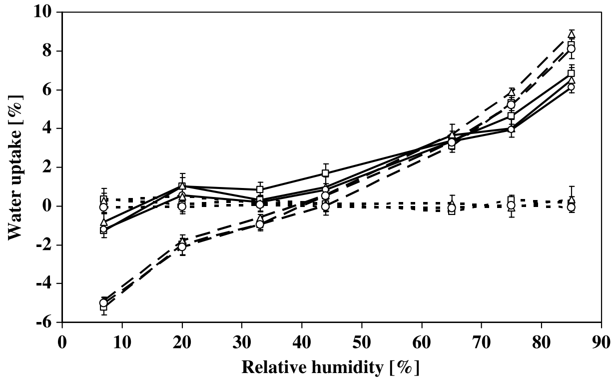

FIGURE 5 Moisture Sorption of Tablets Compressed from Avicel® PH 101 (– – – – –), Starch 1500 (—— ——), and Tablettose® 80 (- - - -), Containing 0.5% AEROSIL® 200 VV (△), 0.5% AEROSIL® R 972 V (○), and Without CSD (□), after 7 Days Storage at Various Levels of Relative Humidity and 20°C. Error Bars Represent the 95% Confidence Interval of Ten Measurements.

Moisture Studies

One of the characteristics of hydrophobic CSD powder is its low and relatively constant water uptake at all humidity levels, while hydrophilic CSD powder adsorbs more water with increasing relative humidity (AEROSIL®, 2003). Tablets containing 0.5% hydrophilic or hydrophobic CSD were compressed at ambient relative humidity (35–45% r.h.) and temperature (20–25°C) in order to evaluate the influence of the nature of CSD on the moisture sorption and the radial tensile strength of tablets after 7 days storage at various levels of relative humidity and 20°C. The study includes tablets compressed from Avicel® PH 101, Starch 1500®, and Tablettose® 80, containing 0.5% AEROSIL® 200 VV, 0.5% AEROSIL® R 972 V, and without CSD. Even though the water uptake behavior of hydrophobic and hydrophilic CSD powders differs greatly, the moisture sorption (Fig. 5) and the radial tensile strength (results not shown) of the tablets during storage was not affected by the addition of CSD. The moisture sorption was characteristic for each excipient. The radial tensile strength and moisture sorption were independent of the presence of either CSD or the type of CSD used.

Magnesium Stearate and Colloidal Silicone Dioxide Grade Interaction During Tableting

The addition of 0.5% magnesium stearate to pure Avicel® PH 101, Starch 1500®, or Tablettose® 80 reduced the radial tensile strength of all tablets (Fig. 6). As shown in Table 3, the addition of magnesium stearate reduced the residual and ejection forces for

Avicel® PH 101 and Starch 1500®. A comparison for Tablettose® 80 was not possible because the die was prelubricated with oleic acid in order to successfully compress pure Tablettose® 80. Magnesium stearate forms a lubricant film around the excipient particles during the mixing process (Vromans & Lerk, 1988), and this film interferes with the bonding properties of the excipient particles by acting as a physical barrier. The decrease in radial tensile strength can be explained by the formation of weaker bonds between lubricant/lubricant particles rather than strong excipient/excipient bonds. The formation of a lubricant film during mixing can be influenced by numerous factors including a third component, such as CSD (Bolhuis & Hölzer, 1996). Lerk et al. (1977) showed that AEROSIL® 200 can significantly suppress the negative effect of the lubricant on the binding properties. A greater effect was found when the host particles were first mixed with CSD and subsequently for a short time with magnesium stearate. Therefore, a chronological mixing step was chosen to investigate the effect of compacted hydrophilic and hydrophobic CSD on film formation of magnesium stearate. The results obtained were then compared with the more commonly used AEROSIL® 200.

CSD eliminated the deleterious effect of magnesium stearate on interparticle bonding and maintained the lubricating action, by destroying or reducing the continuity of the film developed, in a manner affected by its hydrophilicity/hydrophobicity and by the particle deformation of the excipient upon compression. A theoretical understanding of the different particle/particle interactions was provided by Rowe (1988) by calculating the adhesive and cohesive interactions between microcrystalline cellulose, magnesium stearate, and CSD. On the basis of the results,

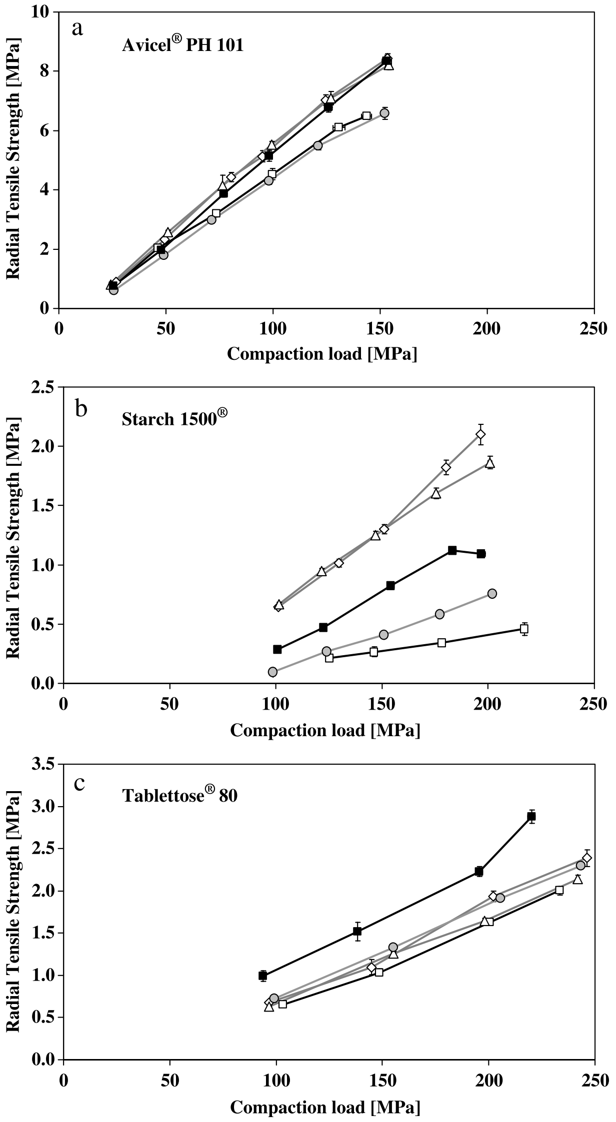

FIGURE 6 Radial Tensile Strength of Tablets Compressed from Avicel® PH 101 (a), Starch 1500® (b), and Tablettose® 80 (c), Containing 0.5% Magnesium Stearate (□), 0.5% Magnesium Stearate, and 0.5% CSD [AEROSIL® 200 VV (△), AEROSIL® 200 (◇), AEROSIL® R 972 V (●)] and No Additives (■). Error Bars Represent the 95% Confidence Interval of Ten Measurements.

TABLE 3 Residual and Ejection Forces of Tablets Compressed at 100 MPa for Avicel® PH 101 and at 200 MPa for Starch 1500® and Tablettose® 80 (n=10, Mean and Standard Deviation)

	Avicel® PH 101		Starch 1500®		Tablettose® 80	
	Residual force [kN]	Ejection force [kN]	Residual force [kN]	Ejection force [kN]	Residual force [kN]	Ejection force [kN]
No additives	0.662±0.011	1.121±0.013	0.561±0.022	0.674±0.018	0.287±0.097[a]	0.673±0.193[a]
Magnesium stearate (MS)	0.062±0.007	0.164±0.008	0.107±0.016	0.186±0.016	0.247±0.024	0.679±0.021
MS+AEROSIL® 200	0.060±0.003	0.164±0.008	0.129±0.009	0.214±0.011	0.348±0.039	0.690±0.040
MS+AEROSIL® 200 VV	0.053±0.006	0.160±0.005	0.130±0.020	0.218±0.021	0.451±0.016	0.741±0.024
MS+AEROSIL® R 972 V	0.084±0.006	0.182±0.007	0.202±0.022	0.278±0.025	0.483±0.032	0.799±0.028

[a] Prelubrication with oleic acid.

microcrystalline cellulose would be preferentially coated by CSD and the majority of magnesium stearate will be coated by CSD. The predictions are consistent with the results reported by Staniforth & Ahmed (1987), who additionally explained that the positive influence of CSD on tablet strength of microcrystalline cellulose, without adversely increasing the ejection force, was due to the ability of CSD to enrobe magnesium stearate in a protective coat, which was broken down under the high shear forces existing close to the wall. Particularly, elimination of deleterious effect and maintenance of lubricating action was observed with all the CSD grades for the plastically deforming Avicel® PH 101, but not with hydrophobic AEROSIL® R 972 V for the elastically deforming Starch 1500®. For the case of fragmenting Tabletose® 80, the interaction between CSD and magnesium stearate was limited by the creation of new surfaces of Tablettose® 80, free of lubricant and glidant, during fragmentation.

CONCLUSIONS

The results of the investigation on the influence of noncompacted and compacted hydrophilic as well as hydrophobic colloidal silicon dioxide on the tableting properties of Avicel® PH 101, Starch 1500®, and Tablettose® 80 can be summarized as follows:

1. The influence of CSD on tablet strength is dependent on its hydrophobic and hydrophilic nature and on the compaction characteristics of the excipients. The differences can be explained by the Ryshkewitch-Duckworth relationship. For Avicel® PH 101, hydrophilic CSD slightly reduces the radial tensile strength of the tablets (−10%), whereas the hydrophobic type leads to a larger reduction (−30%). For Starch 1500®, hydrophilic CSD increases the tablet strength while hydrophobic CSD leads to a strong decrease. Tablets compressed from CSD and Tablettose® 80 show a slight decrease in the radial tensile strength and no differences between CSD types.
2. None of the CSD types used show an influence on the tablet properties of Avicel® PH 101, Starch 1500®, and Tablettose® 80 after 7 days storage at various relative humidities.
3. Under the mixing conditions chosen, the deleterious effect of magnesium stearate on the bonding properties of excipient particles can be reduced, while still retaining its lubricating properties, in a manner that is affected by the nature of the CSD and by the compaction properties of the excipient under pressure.
4. AEROSIL® 200 VV and AEROSIL® 200 behave identically as far as tablet strength, moisture sorption, and magnesium stearate film formation are concerned, indicating that the densification process of CSD has no effect on tablet properties.

As hydrophilic compacted CSD types are easier to handle and show better flow enhancement and identical tableting properties compared to their noncompacted counterparts, they are more efficient excipients. The hydrophobic CSD types show better flow enhancing properties, but they dramatically reduce the tablet strength of poor binding materials like Starch 1500®. Nevertheless, they present an alternative to hydrophilic types for plastically deforming materials like Avicel® PH 101 and for fragmenting excipients like Tablettose® 80.

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