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Tricalcium citrate – a new brittle tableting excipient for direct compression and dry granulation with enormous hardness yield

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ABSTRACT

Objectives: Tricalcium citrate (TCC) was characterized as a tableting excipient for direct compression (DC) and dry granulation (DG).

Significance: Brittle materials usually lead to tablets of inferior mechanical strength compared to plastic deforming materials. A brittle material exhibiting a high tabletability with the ability to retain that behavior during recompression would represent a valuable alternative to the commonly used microcrystalline cellulose.

Methods: Tablets of TCC and other common fillers were directly compressed for the purpose of compression analysis including Heckel analysis, speed dependency, and lubricant sensitivity. DG by roller compaction of TCC was first simulated via briquetting and experiments were subsequently repeated on a roller compactor.

Results: TCC appears as an excellent flowing powder of large agglomerates consisting of lower micron to submicron platelets. Despite the brittle deformation mechanism identified in the Heckel analysis, TCC demonstrated a very high mechanical strength up to 11 MPa in conjunction with an astonishingly low solid fraction of 0.85 at a compression pressure of 400 MPa. This was seen along with hardly any speed and lubricant sensitivity. Nevertheless, disintegration time was very short. TCC tablets suffered only a little from the re-compression: a slight loss in tensile strength of 1–2 MPa was observed for granules produced via roller compaction.

Conclusions: TCC was found to be suitable for DC as a predominantly brittle deforming filler, nevertheless demonstrating an enormous hardness yield while being independent of lubrication and tableting speed. TCC furthermore retained enough bonding capacity after DG to maintain this pronounced tabletability.

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KEYWORDS
Tricalcium citrate; material characterization; direct compression; dry granulation; compression analysis; roller compaction; tabletability

Introduction

Tricalcium citrate (TCC) is already widely used as a calcium source in pharmaceuticals and nutrition supplements. It is suitable for a variety of applications and is a subject of a U.S. Pharmacopeial Convention (USP) monograph [1]. Coincidentally, it was found that TCC positively affects the tableting process, besides being an excellent calcium source.

Tablets are still the most commonly used oral dosage form. Their cost-effective manufacturing, the generally favorable storage stability, the convenience in packaging, and the easy administration turn tablets into a popular dosage form for both manufacturer and patient [2,3].

Direct compression (DC) is a simple method of tableting powder mixtures without a previous granulation step developed in the 1960's. Pharmaceutical industries increasingly tend to select a DC process [4,5]. Beside saving time, energy, and costs, DC places great demands on the powder mixture: excipients need to show good compressibility, excellent flow properties to ensure uniform die filling, and high intake capacity for poorly compressible active pharmaceutical ingredients (APIs) [6–9].

Dry granulation (DG) can be used if particle size enlargement is necessary to improve flow properties, to prevent segregation of excipients that differ greatly in particle size, or to lower the dust content in the mixture. In contrast to wet granulation, roller compaction and subsequent slugging are suitable for heat and moisture-sensitive compounds [8,10,11]. However, DG results in tablets of inferior tensile strength (TS) compared to DC [12]. This work-hardening effect can be explained as the bonding capacity of the excipients already being partially consumed in the first compression step during granulation [13].

Tableting excipients are usually classified according to their bonding mechanism during tableting into plastic and brittle materials. The market offers a huge variety of materials, especially for DC fillers. Microcrystalline cellulose (MCC) is probably the most frequently used DC excipient exhibiting mostly plastic deformation [14]. The particles deform like play dough under compression: increasing the intermolecular bonding forces, mainly the van der Waals interaction, by reducing the interspace between the particles results in forming a common surface by deformation [15]. In brittle deforming materials like dicalcium phosphate (DCP) or alpha-lactose monohydrate, intermolecular bonding forces are established by brittle fragmentation. As these particles are not able to change their particle shape by plastic deformation, larger particles need to be broken down into smaller particles. Those small particles are subsequently shifted into place to maximize the

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common interface at minimized interspace [15], similar to building a wall without mortar.

The energy that is needed for forming a compact is generally higher for brittle materials as it is easy to imagine that the steps of brittle fragmentation and reorientation need more energy compared to plastic flow [16,17]. However, if agglomerates consisting of lower micron range particles of a brittle material are agglomerated, only energy for reorientation is needed during the tableting process [18,19]. This phenomenon still needs more compression energy compared to plastic flow but otherwise shows similar compression behavior as plastic material [16]. Fujicalin (functionalized dicalcium phosphate anhydrous, FDCP) and Omyapharm FCC (functionalized calcium carbonate, FCC) are two excipients with some similarities to such a structure and behavior [20–22].

One of the main advantages of brittle materials is their independence of tableting speed and lubrication [23–28]. A composition containing a brittle material is less prone to problems during scale up, like capping and lamination as well as TS failure due to magnesium stearate issues. However, brittle materials usually lead to tablets of inferior mechanical strength compared to plastic deformable ones like MCC.

A brittle material exhibiting a high tabletability (TS dependent on compression pressure, CP) with the ability to keep that behavior during recompression (DG by roller compaction) similarly to FDCP and FCC would represent a valuable alternative to the commonly used MCC.

The purpose of this study was the characterization of TCC regarding its use as a DC tableting excipient including compression analysis and comparison with other common fillers as well as the evaluation of TCC as an excipient for DG.

Materials and methods

Materials

TCC TB (tricalcium citrate tetrahydrate, TCC) and tricalcium citrate anhydrate (TCCah) were obtained from Jungbunzlauer Ladenburg GmbH (Ladenburg, Germany). The white, odorless powder is poorly soluble in water (1 g/l), slightly acidic (pH 5.7; 2.5% suspension) and is approved as food additive E333.

A-Tab (DCP anhydrous) was donated by Innophos (Cranbury, New Jersey, USA), Avicel PH 101 (MCC) by FMC (Philadelphia, Pennsylvania, USA), Flowlac 100 (alpha-lactose monohydrate, spray-dried) by Meggle Group (Wasserburg, Germany) and Lycatab C (maize starch, pregelatinized) by Roquette (Lestrem, France). Magnesium stearate (MgSt; Ligamed MF-2-V, Peter Greven, Bad Münstereifel, Germany) was used as an external and internal lubricant.

Prior to investigations, the materials were stored at least for two weeks under production conditions.

Methods

Direct compression

Pure excipients were initially compressed on a fully instrumented single punch tablet press (StylOne Classic 105 ML, Medelpharm, Beynost, France/Romaco Kilian, Cologne, Germany) equipped with a set of four external incremental displacement transducers (Magnescale Co., Kanagawa, Japan; upper punch: DK812R5, lower punch: DK25PR5). Eight millimeter round, flat face tooling, external lubrication with MgSt before compression, and manual die filling were used for the purpose of compression analysis.

Testing TCC's suitability for DC, excipients were compressed on a fully instrumented single punch tablet press/compression simulator (StylOne Evolution, Medelpharm, Beynost, France) using 9 mm round concave tooling ($r = 15$ mm) with automatic die filling using internal lubrication with MgSt. The compression simulator was miming the compression profile of a Fette 1200 at low compression speed.

Speed dependent behavior was tested on a 24-station rotary tablet press (Fette 102i, Fette Compacting, Schwarzenbek, Germany). The machine was equipped with 9 mm round concave tooling ($r = 15$ mm) running at various machine speeds. Internal MgSt lubrication and automatic die filling by the fillomatic were chosen for production resembling conditions. In some experiments, pre-compression (PC) was applied before main compression to investigate the effect on tablet TS and variability.

Table 1. Process parameters DG on gerteis macro-pactor; roller width 10 cm.

Process parameter	Setting
Compaction force	1, 2, 4, 6, 8, and 12 kN/cm
Gap	2.0 mm
Roll speed	5.0 rpm
Granulator angle [cw/ccw]	250°/200°
Granulator speed [cw/ccw]	100/80 rpm

Dry granulation

DG of TCC was first simulated via briquetting, enabling the use of only a very small amount of excipient [29]. Tablets of various TS were compressed in single punch mode on the Fette 102i rotary tablet press using 10 mm round flat tooling. Tablet thickness was kept constant over all CPs miming a constant gap during roller compaction. Tablets were subsequently milled into granules on a Gerteis hand mill (prototype, Gerteis Maschinen + Processengineering AG, Jona, Switzerland) equipped with a square-wire sieve of aperture 1.25 mm and a distance block of 1.25 mm. The principle of the hand mill equals the sieve granulator attached to standard Gerteis roller compactors [29].

DG experiments were repeated on a roller compactor (Macro-Pactor GMP Polygran 250/100/3, Gerteis Maschinen + Processengineering AG, Jona, Switzerland) using a hardware setup of 10 cm width power-grip rolls, a pocket granulator and a square-wire sieve (aperture 1.25 mm) with a rotor sieve distance of 1.25 mm. Roller compaction was performed at the settings shown in Table 1. In order to maintain an average gap of 2.0 mm, feeding and tamping auger speed had to be adjusted manually to the different compaction forces as gap control was inactive.

Blending

For compression analysis of the pure excipients on the single punch press StylOne Classic, no previous blending was needed due to external lubrication before compression. Internally lubricated excipients were blended with 0.5% of MgSt or in case of DCP 1.0% of MgSt. Blends were prepared using a Turbula mixer (Type T2A, Willy A. Bachofen AG Maschinenfabrik, Muttenz, Switzerland) at 70 rpm for 30 s for DC experiments on the single punch press StylOne Evolution and DG simulation on the rotary tablet press. For DG on the roller compactor, blending was performed in a gyro wheel blender (RRM 100/1.4541, J. Engelmann AG, Ludwigshafen, Germany) at 30 rpm for 2 min.

Analysis

Particle size distribution of TCC was determined five times using a Sympatec HELOS KF laser diffraction system equipped with a

Table 2. Determination of the tablet parameters breaking force F (N), thickness t (mm), diameter d (mm), and mass m (mg) for DC, and DG using an analytical balance (AB), micrometre gauge (MG; mitutoyo absolute ID-C125B, kawasaki, Japan), erweka breaking force tester TBH 30 (TBH; erweka GmbH, heusenstamm, Germany) or erweka multicheck (multi).

Experiment	Sample size	F (N)	t (mm)	d (mm)	m (mg)
StylOne Classic					
Compression analysis	5	TBH	MG	MG	AB
StylOne Evolution					
DC	15	Multi	Multi	Multi	Multi
Fette					
DC	20	Multi	Multi	Multi	Multi
DG simulation via briquetting	5	Multi	MG	MG	Multi
DG via roller compaction	50	Multi	Multi	Multi	Multi

Rhodos disperser (Sympatec GmbH, Clausthal-Zellerfeld, Germany). Samples were measured as dry dispersions at a pressure of 1 bar with a 500 mm lens. Granules obtained from DG were investigated via sieve analysis according to Ph. Eur. 2.9.38 on a Retsch AS200 digit sieve tower (Retsch GmbH, Haan, Germany).

Powder flow properties were evaluated in triplicate as bulk and tapped density (TD) in line with Ph. Eur. 2.9.34 using an Erweka SVM 22 (Erweka GmbH, Heusenstamm, Germany). Hausner ratio and Carr index were calculated accordingly.

Dynamic vapor sorption (DVS) was used to determine water activity of TCCah. The equilibrium moisture content was measured at ten humidity levels from 0% to 98% relative humidity using a DVS 1 (Surface Measurements Systems, London, UK) with an incubator temperature of 25 °C and equilibration convergence criteria of 0.002%·min^{-1}.

Scanning Electron Microscopy (SEM) was used to assess the surface morphology of TCC powder and tablets. Samples were coated with gold in a Polaron SC7640 Sputter Coater (Quorum Technologies Ltd., Laughton, UK) and examined under a Hitachi S-2460 N (Hitachi High-Technologies Corp., Tokyo, Japan).

Tablet testing

Tablets were measured 24 h after compression for breaking force F (N), thickness t (mm), diameter d (mm), and mass m (mg) as listed in Table 2. *Tablet TS* σ (N mm^{-2}) was calculated for all samples produced on StylOne Evolution and Fette 102i [30]:

$$\sigma = \frac{2F}{\pi dt} \tag{1}$$

The axial *elastic recovery* was calculated as the relative difference between tablet height at maximum density and out-of-die tablet height 24 h after ejection [31]. *Friability* was determined conforming to Ph. Eur. 2.9.7 using an Erweka TA3R friability tester (Erweka GmbH, Heusenstamm, Germany) and *disintegration* was performed according to Ph. Eur. 2.9.1 test A, however, using only three tablets due to small sample size. Disintegration time was automatically detected by the tester (Erweka ZT72, Erweka GmbH, Heusenstamm, Germany).

Compression analysis

Relative density for directly compressed tablets was determined by measuring the tablet thickness in-die during compression using the displacement data of the external transducers for tablets produced on the StylOne Classic. Prior to evaluation, displacement measurements were corrected for the first-degree punch deformation, which was determined from a punch to punch loading up to 500 MPa. Solid fraction (SF) was calculated from in-die apparent density ρ_a and true density ρ_t [32]:

$$SF = \frac{\rho_a}{\rho_t} = \frac{m}{V\rho_t} = \frac{4m}{\pi d^2 t \rho_t} \tag{2}$$

SF for tablets produced on StylOne Evolution and Fette 102i was calculated from out-of-die data according to Equation (2), using the volume of a concave tablet, however:

$$V = 2\left(\frac{\pi h^2}{3}(3r - h)\right) + R^2\pi(t - 2h) \tag{3}$$

where h is the cup height, calculated from the punch curvature radius r, and the tablet radius R using Pythagoras' theorem:

$$h = r - \sqrt{r^2 - R^2} \tag{4}$$

True density was measured using a helium pycnometer (AccuPyc 1330, Micromeritics Instrument Corp., Norcross, Georgia, USA). CP was calculated from applied compression force and cross-sectional area of the punch. Identifying the predominant deformation behavior, the Heckel equation [33] was fitted to the in-die measured data:

$$\ln\left(\frac{1}{1 - SF}\right) = kP + A \tag{5}$$

where slope k and intercept A are fitting constants and P is the applied CP. Determining the optimal position for this fit, a linear regression on the basis of the least squares method was conducted. Applied CP data was corrected prior to fit by iteration and non-linear approximation enabling a correct weighting for logarithmic display. Mean yield pressure P_Y was derived as reciprocal of slope k.

Data processing

WINDOX 3.4 software (Sympatec GmbH, Clausthal-Zellerfeld, Germany) was used for Frauenhofer evaluation of laser diffraction measurements. Data acquisition of external displacement transducers was performed with a data acquisition software (DAQ4SPP, Mathias Hucke Software-Entwicklung, Solingen, Germany). Heckel equation was fitted to the Heckel plots using a software especially developed for the purpose of Heckel analyses (Mathias Hucke Software-Entwicklung, Solingen, Germany). All other mathematical operations and curve fittings were conducted via Origin Pro 8 G (Origin Lab, Northampton, Massachusetts, USA).

Results

Powder properties

In SEM images, TCC appears as a powder of almost spherical shaped large agglomerates with a mean particle size of 135 µm (Figures 1(A) and 2) consisting of platelets in the lower micron and submicron range (Figure 1(B)).

The determined density values of TCC are 0.63 g cm^{-3} for initial bulk density (BD) and 0.70 g cm^{-3} for final TD resulting in a Hausner ratio of 1.11 and a Carr index of 10.0; the true density ρ_t of TCC is 1.9550 ± 0.0081 g cm^{-3}. The mean particle size of the anhydrate (TCCah) is 130 µm. Density values of TCCah are 0.59 g cm^{-3} for BD and 0.66 g cm^{-3} for TD resulting in a Hausner ratio of 1.12 and a Carr index of 10.8; the true density ρ_t of TCCah is 2.0809 ± 0.0007 g cm^{-3}.

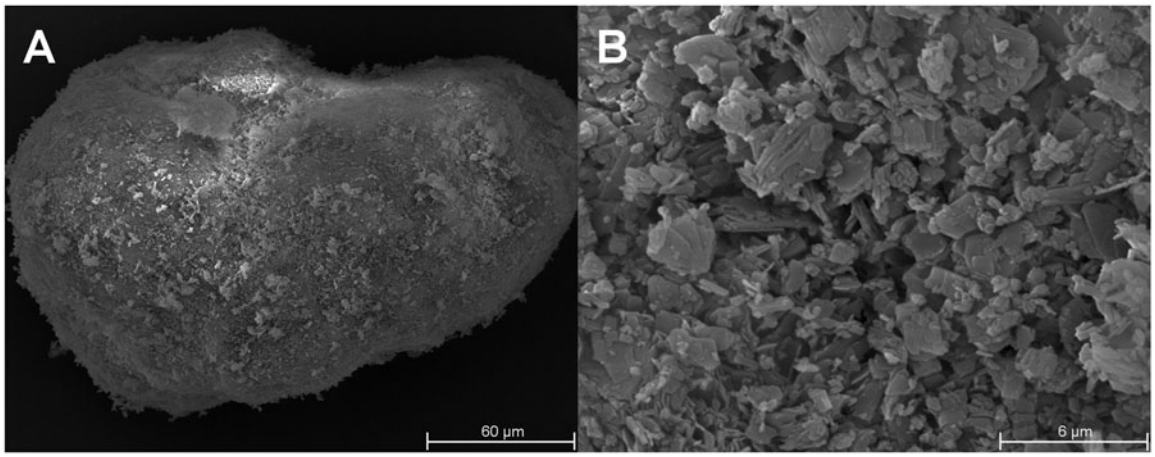

Figure 1. SEM images of tricalcium citrate powder showing large agglomerates (A) consisting of lower micron and submicron platelets (B).

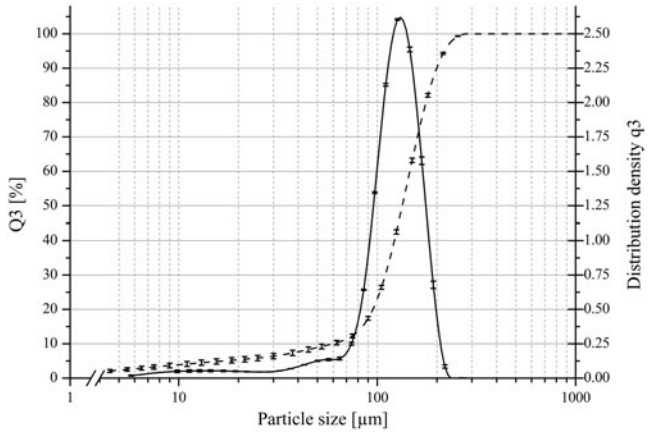

Figure 2. Particle size distribution of tricalcium citrate powder determined by laser diffraction exhibiting a mean particle size of 135 µm.

TCC as an excipient for DC

Figure 3 shows SEM images of TCC tablets compressed on the Fette 102i at 250 MPa. The single agglomerates are still visible on the overall smooth tablet surface (A and B) due to differences in density. The tablet cross-section images (C and D) reveal the shifting into place of the small TCC platelets resulting in a maximized common surface and therefore very strong van der Waals attraction forces.

Friability for directly compressed TCC tablets produced at 50–400 MPa on the Fette 102i ranged from 0.6% (50 MPa) to 0.1% (150–400 MPa). Accordingly, even tablets produced at very low CP fulfill the criterion of the European Pharmacopoeia, which considers a maximum friability of 1% as suitable for most of the products.

Disintegration time of TCC tablets containing 0.5% of MgSt as an internal lubricant was below 3 min for TS values up to 8 MPa, independently whether PC was applied or not. Only higher mechanical strength resulted in an increase in disintegration time up to 20 min (see Figure 12).

To assess the *compression behavior* of TCC, tablets were compressed on the single punch press StylOne Evolution as well as on the rotary tablet press Fette 102i. A comparative evaluation with other common fillers was carried out. Three relationships among CP, SF, and TS are commonly described [34–36]. *Tabletability,* depicted in Figures 4 and 5, expresses the ability of a powder to be transformed into a tablet of specified strength under a certain CP. *Compressibility,* illustrated in Figure 7, is defined as the ability of a powder to decrease in volume under applied pressure, reaching a theoretical maximum SF value of 1 for a tablet without porosity. *Compactability,* shown in Figure 8, describes the ability of a powder to produce tablets of specified strength under densification. Tabletability is considered the most interesting and relevant one [35,37], although the other two likewise are critical to understanding the compression process [36].

In the *tabletability* plot (Figure 4), TCC demonstrated next to overall very high mechanical strength almost linearly increasing TS with increasing CP. In comparison with other commonly used tableting excipients, TCC resulted in tablets of highest TS of fillers showing predominantly brittle fracture: far superior to anhydrous DCP (A-Tab) and spray-dried alpha-lactose monohydrate (Flowlac 100). Only fine quality MCC (Avicel PH101) could exceed the mechanical strength values of TCC.

To evaluate *time-dependency*, namely whether the TS of TCC is affected by compression speed, the experiment conducted on the single punch tablet press StylOne Evolution was repeated on the rotary tablet press Fette 102i at low, medium, and high compression speed (see Figure 5). Despite the increasing linear machine speed, tablets produced with the Fette 102i not only demonstrated identical TS values as tablets compressed on the StylOne but also remained almost linearly increasing.

Remarkably, the internal lubricant also did not reduce the mechanical strength of the TCC compacts compared to externally lubricated ones. Additionally, comparison of compression with and without an applied PC did neither result in changed TS values nor in reduced variability (Data not shown).

Directly compressible DCP (A-Tab) showed similar compression behavior like TCC, particularly with respect to speed-dependency and influence of PC, however at less than half of the TS values of TCC. Furthermore, DCP could hardly be processed at a 1.0% level of MgSt-lubrication, while TCC was smoothly running with 0.5% MgSt lubrication on the rotary tablet press Fette 102i.

Since DG is especially suitable for moisture sensitive compounds [8,10,11], also *anhydrous tricalcium citrate* (TCCah) was evaluated in terms of water sorption and desorption properties as well as tabletability. Above 75% relative humidity, TCCah started to sorb water up to 20% of the anhydrous weight of TCCah and retained this water down to a relative humidity of 20% (see Figure 6). As illustrated in Figure 5, tabletability of TCCah was comparable to TCC (tetrahydrate) showing no influence of tableting speed or PC. Even if TS values are linearly lower by about 30% compared to TCC, TCCah nevertheless still results in tablets of superior

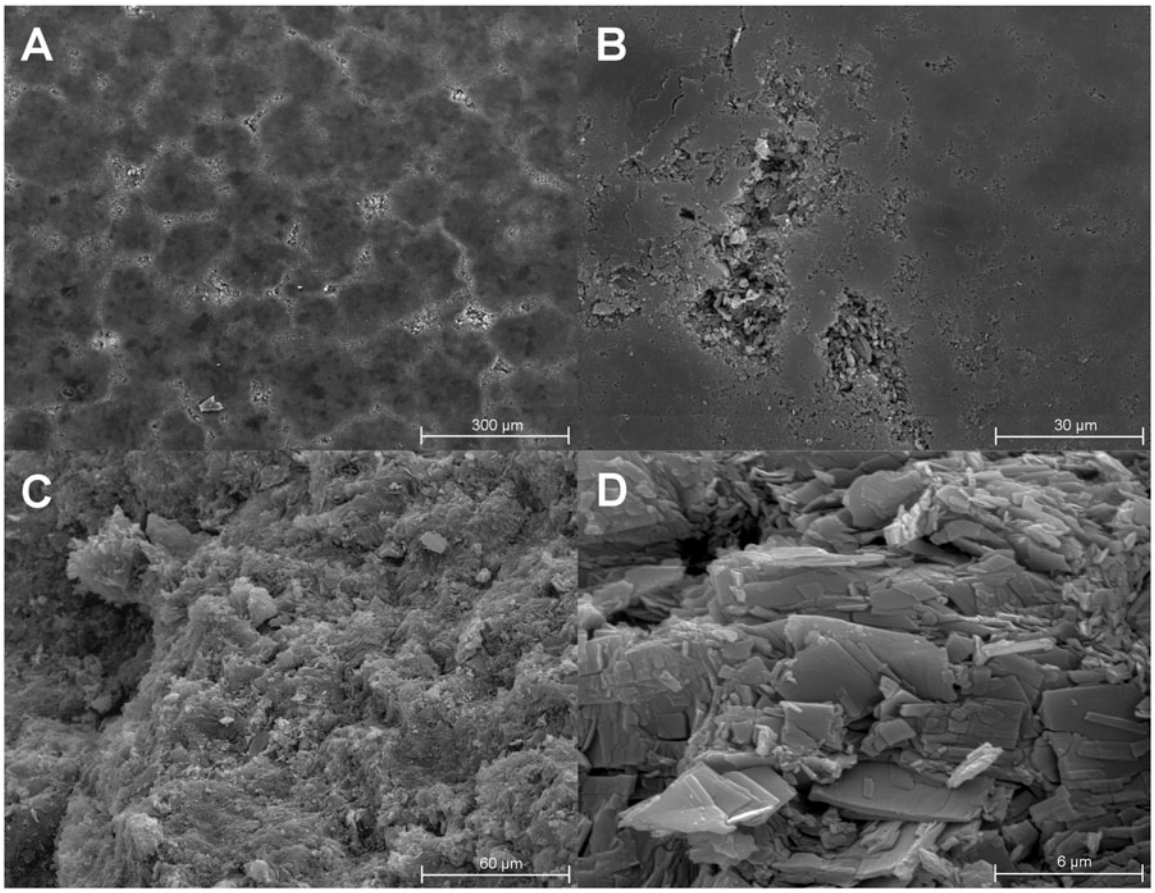

Figure 3. SEM images of tricalcium citrate tablets compressed at 250 MPa on a Fette 102i: tablet surface (A, B) and tablet cross-section (C, D).

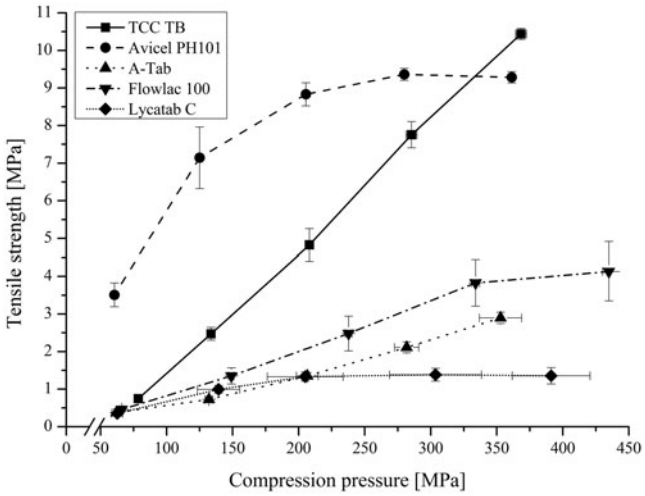

Figure 4. Tabletability profile of tricalcium citrate in comparison with various tableting excipients (fillers) using internal lubrication with MgSt. Tablets were compressed on a single punch press (StylOne Evolution) miming a Fette 1200 at low speed (17 rpm).

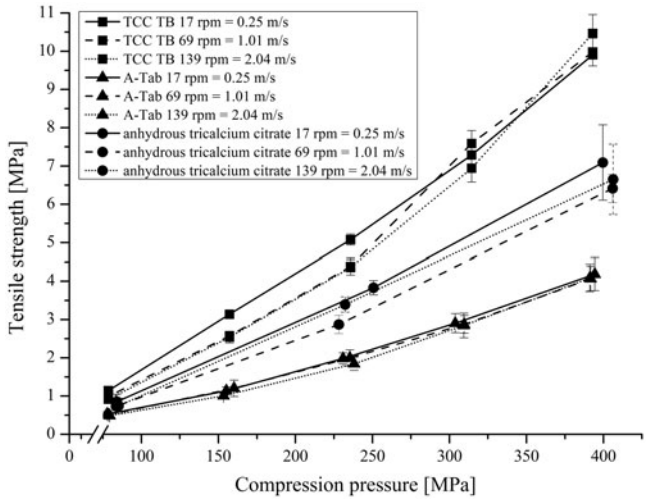

Figure 5. Tabletability profiles of TCC TB and anhydrous tricalcium citrate with 0.5% MgSt as well as A-Tab with 1.0% MgSt as internal lubricant compressed on a rotary tablet press (Fette 102i) at various tableting speeds with PC.

mechanical strength in comparison with DCP, spray-dried lactose and pregelatinized starch (Figure 4).

The *compressibility* plot (Figure 7) reveals an astonishing low SF for TCC, which is not even reaching a value of 0.80 at a CP of 250 MPa despite the enormous TS between 5 and 6 MPa, as can be seen from the *compactability* plot (Figure 8). MCC was the only excipient, which led to higher TS at similar CP, nevertheless representing already SF values above 0.90 at the same load. DCP clearly showed inferior behavior in the applied range of CP exhibiting a TS of 3 MPa at an SF distinctly lower than TCC, however.

The *Heckel equation* [see Equation (4)] is often used to mathematically describe the compression behavior of pharmaceutical powders, assuming first-order kinetics for powder densification [33]. The linear region of the Heckel plots, presented in Figure 9 for tablets compressed on the StylOne Classic at 250 MPa, claimed to describe the plastic deformation of the compact whereas the

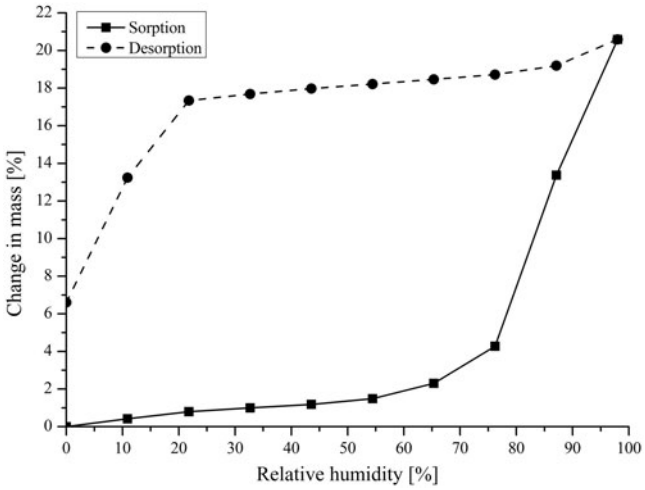

Figure 6. Water sorption and desorption isotherm of anhydrous tricalcium citrate determined by DVS at 25 °C.

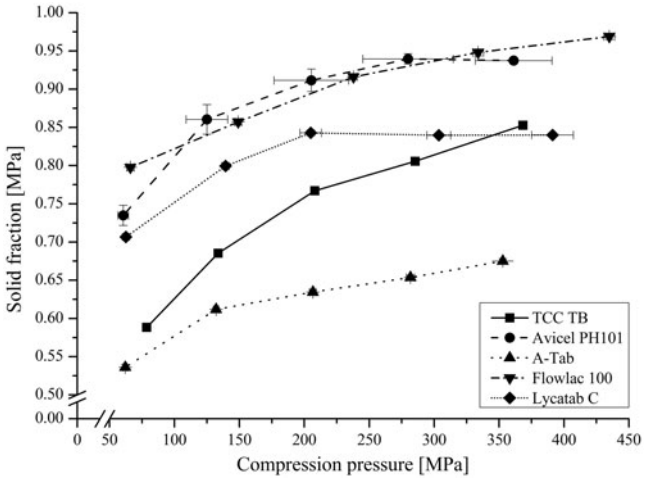

Figure 7. Compressibility profile of tricalcium citrate in comparison with various tableting excipients (fillers) using internal lubrication with MgSt. Tablets were compressed on a single punch press (StylOne Evolution) miming a Fette 1200 at low speed (17 rpm).

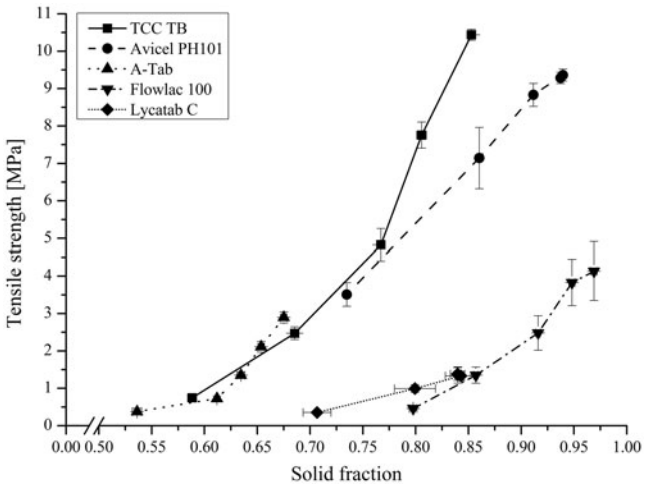

Figure 8. Compactability profile of tricalcium citrate in comparison with various tableting excipients (fillers) using internal lubrication with MgSt. Tablets were compressed on a single punch press (StylOne Evolution) miming a Fette 1200 at low speed (17 rpm).

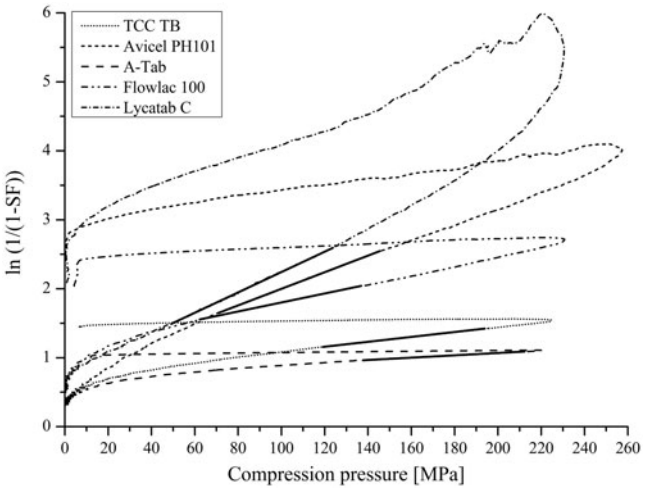

Figure 9. Heckel plots of tricalcium citrate and various tablet fillers compressed on a single punch press (StylOne Classic) at 250 MPa. The part of the plot used for calculation of the yield pressure is depicted as a full line.

curved region is supposed to represent reorientation or fragmentation prior to plastic flow.

The derived parameters are displayed in Table 3. The mean yield pressure P_Y is considered to correlate with the start of plastic flow [38]. The intercept A indicates the SF at which bonding would occur in case of no reorientation or fragmentation. TCC appears similarly to DCP, both exhibiting an SF at intercept A comparable to the plastic ones. However, TCC showed a medium mean yield pressure: clearly higher than MCC but also distinct lower than DCP. Elastic recovery ranged from 22% for the viscoelastically deforming pregelatinized starch to 4% for the predominantly brittle deforming materials like DCP. TCC showed medium to low elasticity.

TCC as an excipient for DG

To *mimic a roller compaction process via briquettin*g, tablets of various TS were produced at low to very low compression speed (as roller compaction is not a fast process in terms of compression) and pressure levels between 30 and 100 MPa (see Table 4) and were subsequently milled into granules.

Forming TCC dry granules via briquetting resulted in particle sizes, which display a substantial fraction of fines in the same range as the original TCC powder (46–200 µm) independently of mechanical strength of the tablets used for briquetting (see Figure 10). Despite increasing coarse particle fractions (>400 µm) with increasing TS of the tablets, which were crushed into granules, the flowability of all dry granules decreased compared to the original powder: Hausner ratio/Carr index for granules ranged from 1.17 to 1.19/14.3 to 16.2 whereas it was 1.11/10.0 for the powder.

TCC tablets suffered only a little from the re-compression out of granules (hardly any work hardening). Figure 11 quantifies the loss in TS: a loss of 1–2 MPa can be determined at meaningful process parameters (TS of tablets for briquetting ~1 MPa and re-CP 150–250 MPa).

Congruent to the independence of compression speed during tableting, the speed of compression during the manufacturing process of the granules also had no influence on the tablets TS (data not shown). As seen for all tablets compressed out of TCC, mechanical strength was independent of the applied machine speed within the re-compression cycle as well (data not shown).

Despite the high mechanical strength of the tablets, the disintegration time (Figure 12) was very short, although, the tablets did

Table 3. Compression analysis parameters of tricalcium citrate and various tablet fillers compressed on a single punch press (StylOne) at 250 MPa.

Excipient	True density (g cm^{-3})	Mean yield pressure P_Y (MPa)	Intercept A	SF corresponding to A	Elastic recovery (%)
TCC TB	1.9550 ± 0.0081	279.5 ± 4.6	0.73 ± 0.01	0.52 ± 0.00	5.29 ± 0.19
Avicel PH101	1.5880 ± 0.0037	85.4 ± 1.9	0.83 ± 0.03	0.56 ± 0.01	7.94 ± 0.67
A-Tab	2.8765 ± 0.0053	576.8 ± 11.2	0.73 ± 0.00	0.52 ± 0.00	5.50 ± 0.07
Flowlac 100	1.5343 ± 0.0005	151.6 ± 3.2	1.13 ± 0.02	0.68 ± 0.01	3.74 ± 0.15
Lycatab C	1.5163 ± 0.0005	66.5 ± 2.1	0.73 ± 0.05	0.52 ± 0.02	21.28 ± 0.47

Table 4. Characteristics of tricalcium citrate tablets used for briquetting as a surrogate for DG, compressed on a rotary tablet press (fette 102i) at low to very low compression speed ([1]17 rpm = 0.25 m/s; [2]5 rpm = 0.07 m/s).

CP used to achieve target TS	TS (MPa)	Tablet volume (mm^3)	SF	Porosity (%)
32 MPa[1]/TS 0.5 MPa	0.596 ± 0.047	238.19 ± 0.73	0.524 ± 0.006	47.6 ± 0.6
60 MPa[1]/TS 1.0 MPa	1.164 ± 0.026	243.45 ± 0.28	0.579 ± 0.002	42.1 ± 0.2
83 MPa[1]/TS 1.5 MPa	1.738 ± 0.099	246.66 ± 0.11	0.612 ± 0.002	38.8 ± 0.2
97 MPa[1]/TS 2.0 MPa	2.195 ± 0.121	248.17 ± 0.34	0.634 ± 0.004	36.6 ± 0.4
62 MPa[2]/TS 1.0 MPa	1.386 ± 0.076	243.64 ± 0.16	0.589 ± 0.003	41.1 ± 0.3

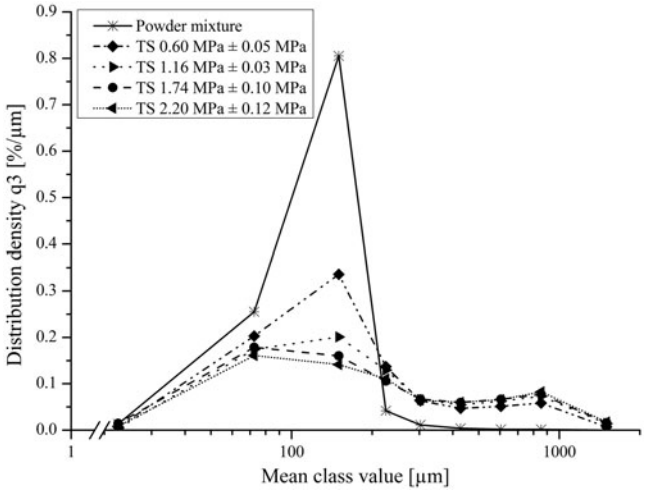

Figure 10. Particle size distribution of tricalcium citrate 99.5% and MgSt 0.5% powder mixture and granules thereof dependent on the TS of the tablets (see Table 4) for simulation of DG.

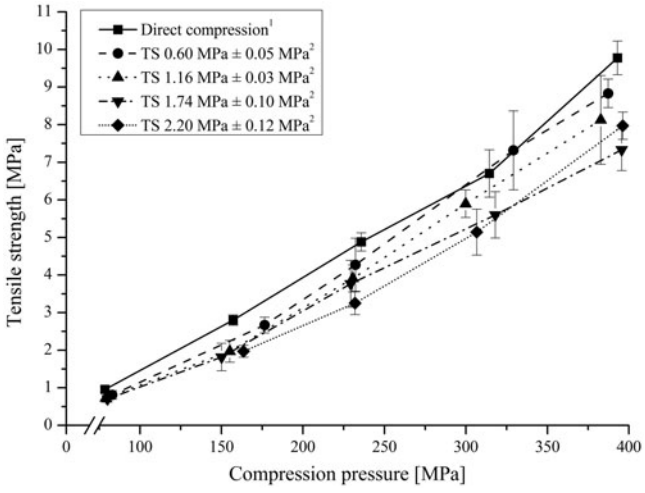

Figure 11. Tabletability profile of tricalcium citrate 99.5% with MgSt 0.5% made of a physical mixture or dry granules of various TS (see Table 4), compressed on a rotary tablet press (Fette 102i) at high tableting speed ([1]139 rpm =2.04 m/s; [2]87 rpm =1.28 m/s).

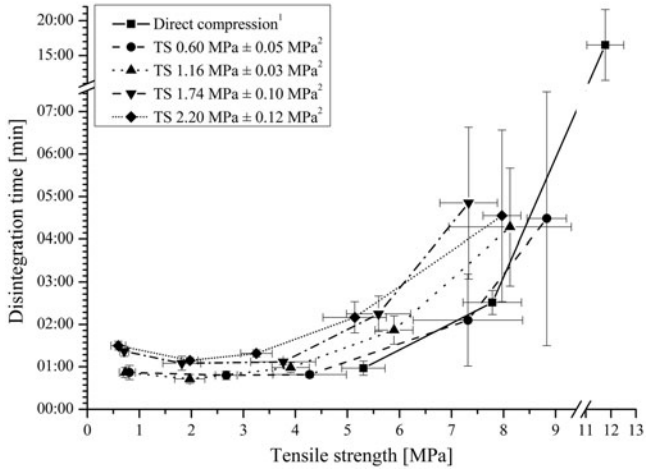

Figure 12. Disintegration time of tricalcium citrate 99.5% with MgSt 0.5% made of a physical mixture or dry granules of various TS (see Table 4), compressed on a rotary tablet press (Fette 102i) at high tableting speed ([1]139 rpm =2.04 m/s; [2] 87 rpm =1.28 m/s).

not contain any disintegrant. However, granules of higher TS (1.5 and 2.0 MPa) led in general to slightly increased disintegration time at TS exceeding 4 MPa. Nevertheless, the disintegration time was below 5 min independent on granules TS, while up to TS values of 4 MPa a rapid disintegration below 2 min was observed. Interestingly, the very pronounced disintegration time of directly compressed TCC tablets exceeding 8 MPa in TS was considerably lower for the re-compressed material.

After achieving these promising results via briquetting, *roller compaction* was performed at increasing specific compaction forces from 1 kN/cm up to a maximum specific compaction force of 12 kN/cm. At none of the applied compaction forces, draw-in problems occurred. Observed gap width variations were at slightly higher levels compared to other free-flowing materials with the relative standard deviation varying from 8.0% for 1 kN/cm to 15.8% for 12 kN/cm [39]. Intact intermediate ribbons could be produced at compaction forces of 2 kN/cm and above while the intermediate ribbon at 1 kN/cm showed almost no integrity. Due to the following comminution step, a reduction in average particle size is expected for very low compaction forces.

Forming dry granules via roller compaction resulted in similar particle size distributions as simulation via briquetting for

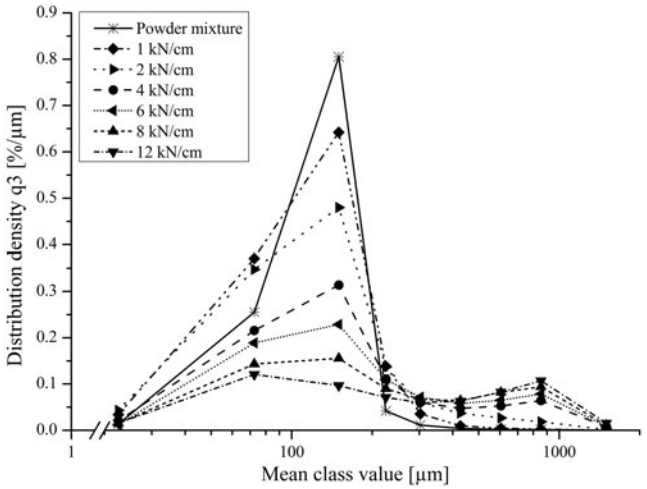

Figure 13. Particle size distribution of tricalcium citrate 99.5% and MgSt 0.5% powder mixture and dry granules thereof produced on a roller compactor (MacroPactor).

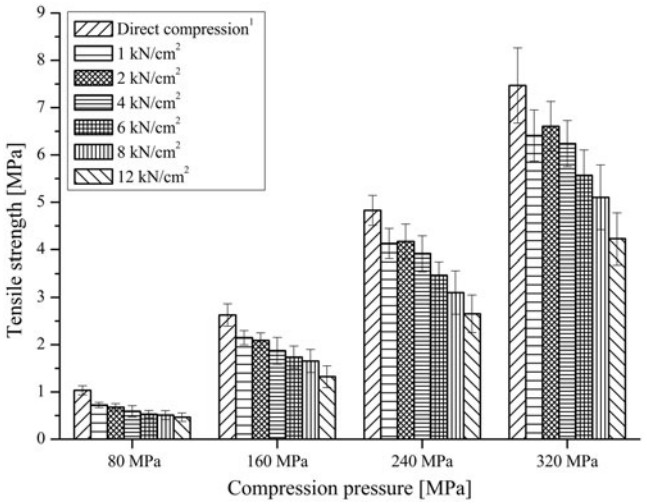

Figure 14. Tabletability of tricalcium citrate 99.5% with MgSt 0.5% made of a physical mixture or dry granules from roller compaction (see Table 4), compressed on a rotary tablet press (Fette 102i) at high tableting speed ([1]139 rpm =2.04 m/s; [2]87 rpm =1.28 m/s).

meaningful process parameters of 4–8 kN/cm, depicted in Figure 13. The expected reduction in particle size was observed for 1 and 2 kN/cm.

Since tabletability plots of DG via roller compaction were comparable to the ones via briquetting and DC in terms of speed-independency, Figure 14 again exemplifies only the tabletability for re-compression of roller compaction granules at high tableting machine speed as a worst case. As seen already for the granules formed via briquetting, a slight loss in TS of 1–2 MPa was observed for granules produced via roller compaction as well.

Discussion

Powder properties

Flow properties are of great importance in formulation development. The powder morphology examined by SEM already indicates the good flowability of TCC: This excipient consists of larger agglomerates of lower micron to submicron particle size range platelets. Conclusions on flow properties can be drawn from TD and BD, and the derived Hausner ratio [40] and Carr index [41]. According to Ph. Eur. 2.9.36, values below 1.12 for Hausner ratio and below 11 for Carr index are related to excellent flowability confirming the assumption of flowability advantages for TCC: With a Hausner ratio of 1.11 and a Carr index of 10.0 TCC exhibits slightly better flowability compared to FDCP that features a Hausner ratio of 1.17 and a Carr index of 15.1 [42].

Powder densities of excipients intended for DC should match approximately with the density of the API since differences are usually causing segregation issues during blending and tableting [6,7,43]. True densities of most organic-based excipients such as MCC, lactose, or starch as well as many APIs range between 1.3 and 1.6 g cm^{-3}, while mineral containing excipients like DCP display higher densities. The true density of TCC is with 2 g cm^{-3} much lower than the one of DCP (3 g cm^{-3}) and thus much closer to organic-based excipients and APIs. A reduced segregation tendency of TCC over DCP, e.g. Fujicalin, is hence expected.

TCC as an excipient for DC

First of all, the most important evaluation criterion for a developer to judge a filler is its ability to form strong compacts which, on the other hand, will also disintegrate easily. Secondly, good fillers preferably show limited viscoelastic properties, i.e. are not speed-dependent, meaning bonding of the particles is mostly independent of applied speed and dwell time during the compression cycle.

Compression behavior

TCC demonstrated favorable compression behavior despite the fact that the tablets were compressed with MgSt as an internal lubricant, implying that a possible interference of bonding by the lubricant is already reflected in the results. Furthermore, no lubrication sensitivity was observed and a comparison showed no difference between internally and externally lubricated tablets. Since it is known that lubricants have practically no effect on the binding properties of brittle materials [7,44], this is the first indication of a predominantly brittle deformation behavior of TCC.

These findings were also reflected in the Heckel plots (Figure 9). Although the limitations of the Heckel function have been critically evaluated [18,45,46], the equation was found to be practical for obtaining data concerning the compression behavior of powders [47]. Brittle materials as DCP and alpha-lactose monohydrate displayed pronounced reorientation followed by a linear phase at relatively high pressure levels which is less steep compared to plastically or viscoelastically deforming fillers as MCC or pregelatinized starch. Spray-dried lactose is less brittle than DCP due to the increase of the amorphous fraction during spray drying, which is exhibiting rather plastic flow [48]. TCC proves to compress via brittle fragmentation similarly as DCP, nevertheless with 280 MPa featuring a mean yield pressure below half of the value of DCP that is also lower compared to FDCP with around 450 MPa [21] and FCC with around 350 MPa [22].

The remarkable high mechanical strength of tablets made of TCC already achieved reasonable TS values at low CPs of 100–200 MPa (good tabletability, Figure 4). Reaching both a maximum TS around 4 MPa, DCP and alpha-lactose monohydrate showed inferior tabletability. However, DCP is achieving this mechanical strength at distinctly lower SF (low compressibility, Figure 7). In contrast to TCC, this low SF nevertheless is not linked with a high mechanical strength meaning that DCP likely establishes

weaker particle interaction compared to TCC. Plastically deforming MCC, which is commonly used as filler in tablets and as an excipient for DG, achieved higher TS values compared to TCC, but the bonding capacity is already exhausted at a medium CP of about 250 MPa. Similarly, the viscoelastic behaving pregelatinized starch is approaching its maximum SF already at 200 MPa. Further compression of MCC and pregelatinized starch would result in an increased elastic deformation, which has been associated with issues during tableting and downstream processing like capping and lamination [24–26]. On the contrary, TCC retains an enormous bonding capacity, which leads to a tremendous TS of 11 MPa for a SF of only 0.85 at 400 MPa. Although further compression of TCC beyond 400 MPa might still be possible, pressures in such a high range are usually not applied during tableting. At the same time, TCC shows moderate to low elastic recovery, similar to other brittle fillers.

Interestingly, the TS of TCC is exceptionally high even though the SF is low (very high compactability, Figure 8). The higher the SF of a tablet becomes, the closer the particles approximate each other, resulting in increased interactions via dispersive interaction forces (i.e. van der Waals forces). TCC seems to establish stronger bonds compared to other brittle fillers like DCP or alpha-lactose monohydrate, facilitating a high mechanical strength at a low SF. This behavior has also been observed for other functionalized materials, namely FDCP [20,21] and FCC [22].

Since it is not easily possible to categorize these functionalized materials, there is a need to further elaborate on the deformation mechanism. Schlack et al. presumed the high specific surface area to be the main effect contributing to the strong cohesion of FDCP [21]. For spherical FCC, Stirnimann et al. assumed initial good packaging under low CP with the formation of interlocking structures of lamellae, followed by fragmentation under higher CP resulting in new contact surfaces for bonding [22]. SEM images could confirm the predominantly brittle fracture mechanism of TCC (Figure 3): First of all, the large secondary agglomerates consisting of lower micron to submicron primary platelets fracture during the tableting process. However, the primary particles remain intact. Secondly, since the single secondary particles are still visible on the surface of the compacts, it can be assumed that the fragmentation process mainly takes places after the rearrangement process [49]. The orientation of the small platelets and the shifting into place explains the high interaction forces in between the particles resulting in very strong compacts. The smaller a brittle particle becomes, the higher the fracture strength increases until further breaking becomes impossible [16]. According to Kendall, this calculated size limit to crushing is around 1 μm for calcium carbonate [16]. A similar size limit can be assumed for TCC as well. The smaller the primary particles are, the less probably they fracture and the more likely they are shifted into place. This leads to stronger compacts, similar to plastic materials. Nevertheless, the small particles still change the position, thereby creating new surfaces. These new surfaces explain the brittle behavior during tableting concerning speed and lubricant sensitivity. The question arises, if the described phenomenon of the functionalized excipients can be included in the definition of brittle behavior. In the opinion of the authors, it is questionable to refer to this rather brittle tableting performance as plastic behavior. Since the collective of primary particles as a whole with the shifting into place rather deforms via flow, the deformation behavior of functionalized excipients like TCC, FDCP, and FCC therefore converges rather to a term like 'pseudo plastic' excipients.

Apart from tableting features, the low SF of TCC might be advantageous for incorporating poorly compressible compounds and furthermore could act as a 'compressibility buffer' in case the material is compressed two times as during roller compaction (DG) and subsequent tableting. In contrast, MCC as one of the standard excipients for DG establishes new bonds via plastic flow. This is limited by the effect known as work hardening [11]: Most of the bonding capacity is exhausted during establishing the granule bonds, subsequently resulting in lacking of bonding capacity remaining for the tablets. Especially if MCC is compressed at high specific compaction force during DG, the resulting tablets will be weak in strength [11,13]. In contrast, TCC displayed a completely different behavior as discussed in the DG section below.

Influence of compression speed

Time-dependency of pharmaceutical materials has been recognized to be related to the consolidation mechanism by many researchers [18,23,25,27,36,50]. Plastic deformation is generally believed to be strain rate dependent due to stress relaxation after compression. It has been shown already that the mechanical strength of plastically deforming fillers decreases at increased machine speed [49]. In contrast, brittle fragmentation is expected to be relatively insensitive to compression speed since fragmentation is rapidly achieved. If a material is not affected by increased punch velocity, it will less likely cause problems during scale up to faster tableting machines.

TCC demonstrated no relevant influence of tableting speed. The tabletability profile remained almost the same even if the linear speed during tableting was increased eightfold from 17 rpm (equal to 0.25 m s^{-1}) to 139 rpm (equal to 2.04 m s^{-1}). Additionally, it should be mentioned that results for the simulation of a Fette 102 i compression profile on the compression simulator StylOne properly matched with results obtained on the actual rotary tablet press later. The same behavior can also be seen for DCP but the latter one required much higher concentrations of MgSt for being processed at far lower mechanical strength of the tablets. Hence, TCC is not expected to cause speed-dependent issues during scale-up.

Anhydrous TCC

In general, TCCah showed similar behavior as TCC (tetrahydrate): comparable powder properties and linearly increasing tabletability along with no influence of tableting speed or PC and no lubrication sensitivity. Mechanical strength of the compacts was reduced compared to TCC, however still resulting in tablets exceeding a TS of 1.5 MPa for CPs above 150 MPa (Figure 5). Furthermore, TCCah exhibited some drying ability in DVS measurements (Figure 6). Compared to FDCP that adsorbed up to 7% of water [21], TCCah demonstrated a threefold higher water sorption and additionally retained this water down to a relative humidity of 20% in contrast to FDCP. TCCah might hence be an excellent choice for moisture sensitive APIs which are supposed to be processed via DG.

TCC as an excipient for DG

The DG process consists of agglomerating various powder materials by compaction and subsequent milling to granules. The material will be compressed two times as the dry granules will further be processed into tablets. MCC, the standard excipient for DG via roller compaction, has limited bonding capacity as already shown above. Therefore, the granulation process needs to be conducted carefully not to exhaust the bonding capacity for establishing the granules [11,12]. Otherwise, not enough bonding capacity would remain for forming tablets of sufficient mechanical strength.

TCC demonstrated excellent behavior during the DG experiments similar to the one of FDCP [51]. To begin with, briquetting of TCC tablets could successfully mimic the roller compaction process by using constant tablet thickness and a hand mill, which equals the sieve granulator of standard Gerteis roller compactors. Roller compaction subsequently confirmed the suitability of TCC as an excipient for DG. Dry granules produced on a roller compactor exhibited similar particle size distributions compared to briquetting. However, an expected increase in the fraction of fines for very low specific compaction forces (1–2 kN/cm) was observed. The loose attraction of particles in these fragile ribbons results in a reduced particle size after the granulation step, which is in principle a milling step after the compaction into ribbons.

Besides, the flowability of the dry granules decreased as opposite to the aim of DG. An explanation might be the broadened particle size distribution and possibly a change in shape. Further investigations including shape analysis will be necessary to confirm this hypothesis. However, the difference in Hausner ratio/Carr index of 1.11/10.0 for the powder to around 1.18/16 for the granules is of little practical relevance.

Furthermore, re-compression of the granules to tablets resulted in only little reduction of the compactability. Although a distinct reduction in TS by about 50% after intensive DG with 12 kN/cm was observed, the slight loss in TS of 1–2 MPa during the re-compression cycle at meaningful process parameters (DG with 4–8 kN/cm, CP 150–250 MPa) seems to be negligible since TCC features overall very high mechanical strength: Tablets still led to TS values of around 1.5–3.5 MPa.

Being congruent with the DC experiments, the non-dependency on the compression speed is also reflected in the production of the tablets for further briquetting as well as in the re-compression cycle.

Disintegration time for TCC tablets was very short, although the tablets did not contain any disintegrant as it is needed for FDCP [20] or FCC [52]. The prolonged disintegration time at higher TS values could be reduced by including disintegrant into the composition. However, tablets produced at meaningful process parameters disintegrated rapidly enough to meet the criteria of the European Pharmacopeia (<15 min for uncoated tablets).

In conclusion, TCC demonstrated favorable properties for both DC and DG. Its independence of tableting speed is an important advantage of TCC as a predominantly brittle deforming material. In combination with its excellent flowability, tabletability, and compactability, TCC will unlikely cause problems during scale up to faster tableting machines. Furthermore, TCC features the ability to maintain the pronounced tabletability during re-compression. Bonding capacity is not exhausted during the DG process: no pronounced work hardening effect was observed at meaningful process parameters. In contrast to MCC, TCC retains enough bonding capacity for forming tablets of sufficient mechanical strength in subsequent tableting. However, this needs to be confirmed using API containing mixtures. Overall, tricalcium citrate can be used as a brittle, rather 'pseudo plastic,' filler for DC with MCC-like hardness yield and furthermore represents an attractive alternative to commonly used excipients for DG.

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Disclosure statement

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