Supporting Information

Improving powder characteristic by surface modification using atomic layer deposition (ALD)

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1 SAMPLE PREPARATION

All materials were coated with five ALD layers of TiO₂. Additionally, Na-CC and SORB were coated with 20 ALD layers. Titanium tetrachloride (TiCl4, Sigma-Aldrich, 98 %, St. Louis, MO, USA) and deionized water were used as precursors for ALD coating. For the physical mixtures particulate titanium – dioxide (TiO2/ Fusgaard, Copenhagen, Denmark) was used. The physical mixtures were mixed for 5 min at 32 rpm using a Turbula mixer (Type T2F, System Schatz, Willy A. Bachhofen AG, Maschinenfabrik, Switzerland). Prior to testing, all samples were conditioned at 43 % relative humidity (ambient temperature) for 48 h using a saturated salt solution (potassium carbonate, VWR chemicals, Søborg, Denmark). Sodium chloride (Sigma Aldrich, Steinheim, Germany) was used to create an elevated relative humidity condition in isothermal microcalorimetry. As a lubricant for preparing compacts, Mg-Stearate (Sigma Aldrich, Copenhagen, Denmark) was used, and mixed with the materials for 30 s at 32 rpm (Turbula mixer as described before).

2 COATING WITH ATOMIC LAYER DEPOSITION (ALD)

Atomic layer deposition was used for conformal nanometer scale coating on pharmaceutical particles. The atomic layer deposition method was performed in a rotary type particle ALD reactor, where particles are mechanically agitated during static ALD reactant exposures (described in ¹). The static ALD reactant exposures are achieved by evacuating the rotary reactor from the pump line during the exposure. The ALD films were grown at temperatures around 100 °C using an alternate static exposures of titanium tetrachloride and deionized water in a gaseous phase. As a by-product of the coating process, HCl was created, leaving a film of TiO2 on the particle surface ². For each cycle, corresponding to one atomic layer on the particles, the following process was performed; 1) exposure to TiCl₄ at a vapour pressure of 1-2 Torr, 2) hold for metal precursor time, 3) pump out excess metal precursor, 4) dose N₂ for purging the reactor, 5) pump out N₂, 6) expose H₂O at 1-2 Torr, 7) hold for reaction time, 8) pump out excess H₂O and HCl, 9) dose N₂ for purging the reactor, 10) pump out N₂.

3 ANALYTICAL METHODS

3.1 Scanning electron microscopy (SEM)

Pictures of the uncoated and coated samples were taken using a scanning electron microscope (TM3030 Tabletop Microscope HITACHI, Tokyo, Japan). The samples were prepared on carbon sticky stubs and were gold

coated (Cressington sputter coater 108 auto, Cressington Scientific Instruments, Watford, UK) prior to the analysis. A voltage of 5 kV was used to take the images.

3.2 X-ray powder diffraction (XRPD)

X-ray powder diffraction measurements were performed using an X'Pert PANalytical PRO X-ray diffractometer (PANalytical, Almelo, the Netherlands). The following settings were used: CuKa radiation = 1.54187Å; acceleration voltage = 45kV; current= 40 mA; reflectance mode = 5°-35° 2Θ; scan rate = 0,067° 2Θ/s; step size = 0,001°.

3.3 X-ray Photoelectron Spectroscopy (XPS).

A PHI Versa Probe III XPS System (ULVAC-PHI) with a monochromated Al K_{α} X-ray source (1486.6 eV) was used to perform the X-ray photoelectron spectroscopy measurements. The base pressure was set to 5.0 x 10⁻⁸ Pa. During data collection, the pressure was set to 1.0 x 10⁻⁶ Pa. For measurement, the samples were mounted on a stainless steel holder, using a piece of carbon sticking tape. Charge neutralization was used. The X-ray spot size was 0.2 x 0.2 mm² with a powder of 50 W under 15 kV. 280 eV pass energy was used to collect the survey spectra with a 1.0 eV/step. The penetration depth of this method ranges between 1-10 nm. For each sample, three independent points were measured and at each point 10 spectra were recorded. The Multipak software provided with the XPS system was used to calculate the atomic percentages from the survey spectrum.

3.4 Dynamic vapour sorption (DVS)

The vapour sorption profiles of the different materials were analysed using a VTI-SA⁺ (TA-Instruments, New Jersey, US). Approximately 10 mg of sample were used for one measurement. Prior to the measurement, the samples were dried at 0 % RH and 60°C for 180 min or until weight equilibrium (< 0.0010 wt% change within 5 min) was established. The measurement was then performed at 25°C. For MCC, Na-CC, CaHPO4 and TiO₂ the relative humidity was ramped up to 90 % in 10 % steps and an additional step at 95 % was added. Maximum equilibrium time was set to 180 min. The next step was started when weight equilibrium was established. For lactose the humidity was increased up to 90 % in 10 % steps and then up to 98 % in 2 % steps. Additionally, weight gain at 99 % relative humidity was measured. To capture the deliquescence point of sorbitol, the relative humidity was increased to 60 % in 10 % steps and afterwards in 3 % steps to 81 % and down to 72 % in 3 % steps. For both, lactose and sorbitol, the maximum equilibrium time was set to 90 min.

3.5 Isothermal microcalorimetry.

The kinetic events during water sorption of Na-CC and MCC were recorded using a Thermal Activity Monitor (TAM III), equipped with a six-channel microcalorimeter (both: TA instruments, Waters LLC, New Castle, Delaware, US). The samples were dried at 80 °C prior to the measurement for 2 h, and were kept in dry conditions before testing. 500 ± 10 mg were weighed into 5 mL sample vials and an insert, containing a saturated salt solution (sodium chloride/ 75 % RH) was added before sealing. Prior to the measurement, a baseline was recorded for 30 min. Afterwards the samples were lowered into equilibrium position to adjust to 25°C for 15 before lowered into measurement position. In measurement position, the first 45 min of data recording were discarded and the data collected afterwards were used.

3.6 Helium Pycnometry.

The true density of the samples was analysed using a helium pycnometer (Accu Pyc, micromeritics, Aachen, Germany). A 10 mL sample holder was used for analysis. Each sample was purged 10 times and then measured 10 times. For the raw material, three independent samples were analysed. Due to the limited amount of coated material, each coated material was only measured once.

3.7 Powder Flowability.

A FlowPro (SAY group, Helsinki, Finland), using the flow through an orifice technique, was used to analyse the flowability of the samples. The sample holder, containing approx. 5 ml of sample is tapped against the top of the instrument with a frequency of 1/s. A balance below the sample holder, recorded the amount of powder released per second. The last 15 % of the released weight were not taken into the calculation of the flow rate, which was calculated as the slope of a linear regression of weight released per second. Prior to measurement, the samples were conditioned in a humidity controlled environment (desiccator with Potassium -carbonate – approx. 43 % RH at ambient temperature)

3.8 Electrostatic behaviour.

Electrostatic charging of the powder samples was measured by sliding powder sample through a glass or steel pipe with an inner diameter of 25 mm and a length of 500 mm at an angle of 55° into a Faraday's cup. The mass of the used powder is known and thereby the amount of charge per unit mass can be calculated. Humidity of the room was kept between 30-40 %. For each sample 10 independent measurements were performed. The last five measurement points were used to calculate a mean and a standard deviation.

3.9 Tablet compaction.

Tablets were prepared, using an HB10 compaction simulator (Huxley Bertram Engineering Limited, Cambridge, UK) using a 10 mm flat faced punch and a die filling height of 8 mm. The tablets were compacted using both punches at three different compaction pressures (100, 182 and 157 MPa) with a speed of 2 mm/s and a dwell time of 50 ms. After 24h, the mass of the tablet (balance: Mettler AJ150, Mettler Toledo, Columbus, Ohio, USA), the height (stage 7007 and digimatic indicator, Type IDF-130; both Mitutoyo Deutschland GmbH, Neuss, Germany), the diameter and the crushing strength were determined (Pharmatron Tablet Tester 8M, Dr. Schleuniger Pharmatron 2013, SOTAX AG, Aesch, Switzerland). To avoid the material sticking to the punch, 0.5 % (wt) of Magnesium Stearate was added.

The strength of the tablet was calculated as,

$$\sigma = \frac{2F}{(10^6 * \pi * D * T)} ,$$
 (S1)

using the breaking force of the tablet (F in N), the tablet diameter (D in m) and the tablet thickness (T in m). The tensile strength calculated from Eqn. S1 (in MPa), can then be used as an indicator for the tablet strength.

The solid fraction (SF) to describe the compactibility of the materials was calculated as,

$$SF = \rho_{tablet} / \rho_{true}$$
, (S2)

using the tablet density (ρ_{tablet}) calculated from the tablet weight and the tablet dimensions after relaxation and the true density (ρ_{true}) measured with helium pycnometry. Eqn. S2 then gives a dimensionless value, describing the solid fraction of the tablet.

4 SOLID FORM CHARCTERISATION



Figure S1: X-ray powder diffraction patterns of DCPD, SORB, LAC, MCC, Na-CC and TiO₂; solid line: uncoated sample; dashed line: sample coated with five TiO₂ ALD cycles; dotted line: sample coated with 20 TiO₂ ALD cycles

5 SCANNING ELECTRON MICROSCOPY IMAGES

5.1 DCPD



Figure S2: Scanning electron microscope pictures of DCPD before (A) and after coating with five TiO_2 ALD cycles (B) in 500x magnification (1) and 5000x magnification (2) 5.2 LAC



Figure S3: Scanning electron microscope pictures of LAC before (A) and after coating with five TiO_2 ALD cycles (B) in 500x magnification (1) and 5000x magnification (2)

5.3 SORB



Figure S4: Scanning electron microscope pictures of SORB before (A), after coating with five TiO_2 ALD cycles (B) and with 20 TiO_2 ALD cycles (C) in 180x magnification (1) and 1000x magnification (2)

5.4 MCC



Figure S5: Scanning electron microscope pictures of MCC before (A) and after coating with five TiO_2 ALD cycles (B) in 500x magnification (1) and 5000x magnification (2)



5.5 Na-CC

Figure S6: Scanning electron microscope pictures of SORB before (A), after coating with five TiO_2 ALD cycles (B) and with 20 TiO_2 ALD cycles (C) 500x magnification (1) and 5000x magnification (2)

6 X-RAY PHOTOELECTRON SPECTROSCOPY

	DCPD SO		RB	LAC	МСС	Na-CC	
# of TiO ₂ ALD cycles	5	5	20	5	5	5	20
% Ti	7.2 ± 0.2	1.6 ± 0.8	1.7 ± 1.5	5.6 ± 0.5	8.4 ± 0.9	16.4 ± 1.2	17.6 ± 0.9

Table S1: % Ti detected on the particle surfaces with X-ray photoelectron spectroscopy (mean ± SD, n=3)

7 FLOWABILITY



Figure S7: Summary of powder flowability data of DCPD, LAC, SORB, MCC and Na-CC. The raw materials (open bars; grey), the physical mixtures containing 0.1 % (right faced diagonal stripes; light grey), 0.5% (left faced diagonal stripes; light grey) and 1 % (diagonal checked; light grey) of TiO₂ and the samples coated with five (horizontal stripes; blue) and 20 (checked; green) TiO₂ ALD cycles are shown. The* is indicating significant different behavior compared to the raw material (α =0.05; mean ± SD, n=5)

8 ELECTROSTATIC CHARGING



Figure S8: electrostatic charge measurements of TiO₂ against: closed diamond: glass and open diamond: steel

8.1 Electrostatic charge against stainless steel



Figure S9: Individual measurements of electrostatic charge build against steel for coated and uncoated samples of DCPD, SORB MCC and Na-CC, black squares: raw material, grey diamonds: physical mixture containing 0.1 % TiO₂, blue circle: material coated with five TiO₂ ALD cycles, green triangle: material coated with 20 TiO₂ ALD

cycles

8.2 Electrostatic charge against glass



Figure S10: Individual measurements of electrostatic charge build against glass for coated and uncoated samples of DCPD, SORB MCC and Na-CC, black squares: raw material, grey diamonds: physical mixture containing 0.1 % TiO₂, blue circle: material coated with five TiO₂ ALD cycles, green triangle: material coated with 20 TiO₂ ALD cycles

9 WATER SORPTION



Figure S11: Water sorption profiles for uncoated and ALD-coated DCPD, LAC, MCC , NaCC and TiO2, and deliquescence behavior of SORB. Black squares: uncoated materials, blue circle: sample coated with five TiO₂ ALD cycles; green diamonds: sample coated with 20 TiO₂ ALD cycles

10 ISOTHERMAL MICROCALORIMETRY



Figure S12: microcalorimetric output of water sorption of Na-CC and MCC (uncoated and ALD-coated) at exposure to 75 % relative humidity at 25°C. Grey straight line: uncoated sample, blue dashed line: sample coated five TiO₂ ALD cycles; blue dotted line: sample coated with 20 TiO₂ ALD cycles

11 True density

Table S2: True density of the ALD - coated and not coated materials, analyzed by helium pycnometry. For eachsample 10 measurements were performed. The raw materials were analyzed with three independent samples

		true density (g/cm ³)
DCPD	raw material	2.323 ± 0.007
	5 TiO ₂ ALD cycles	2.387 ± 0.003
	raw material	1.481 ± 0.003
SORB	5 TiO ₂ ALD cycles	1.485 ± 0.002
	20 TiO ₂ ALD cycles	1.479 ± 0.0003
	raw material	1.541 ± 0.003
2.0	5 TiO ₂ ALD cycles	1.547 ± 0.002
мсс	raw material	1.587 ± 0.002
mee	5 TiO ₂ ALD cycles	1.600 ± 0.001
	raw material	1.566 ± 0.001
Na-CC	5 TiO ₂ ALD cycles	1.570 ± 0.001
	20 TiO ₂ ALD cycles	1.578 ± 0.001

and the coated samples with one sample (mean ± SD)

12 Behavior under compaction



12.1 Tabletability



12.2 Compactibility



Figure S14: Tensile strength over solid fraction of DCPD, SORB, LAC, MCC and Na-CC for the raw material (closed square; grey), physical mixtures containing 0.1 % (open squares; light grey), 0.5 % (open circle; light grey), 1 % (open triangle; light grey) TiO₂ and the sample coated five TiO₂ ALD cycles (half-open diamond; blue) and 20 TiO₂ ALD cycles (half-open triangle; green) of TiO₂ (mean ± SD; n=4)

13 References

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