Electronic Supplementary Information

Atomic Scale Surface Engineering of Micro- to Nano- Sized Pharmaceutical Particles for Drug Delivery Applications

Di Zhang, Michael J. Quayle, Gunilla Petersson, J. Ruud van Ommen, Staffan Folestad[†]

Dr. Di Zhang, Dr. Michael J. Quayle, Dr. Gunilla Petersson, Prof. Dr. Staffan Folestad

AstraZeneca R&D Gothenburg, Pepparedsleden 1, Mölndal, SE-431 83, Sweden

Prof. Dr. Ruud van Ommen,

Department of Chemical Engineering, Delft University of Technology, Van der Maasweg 9, 2629 HZ Delft, the Netherlands

†Email: staffan.folestad@astrazeneca.com

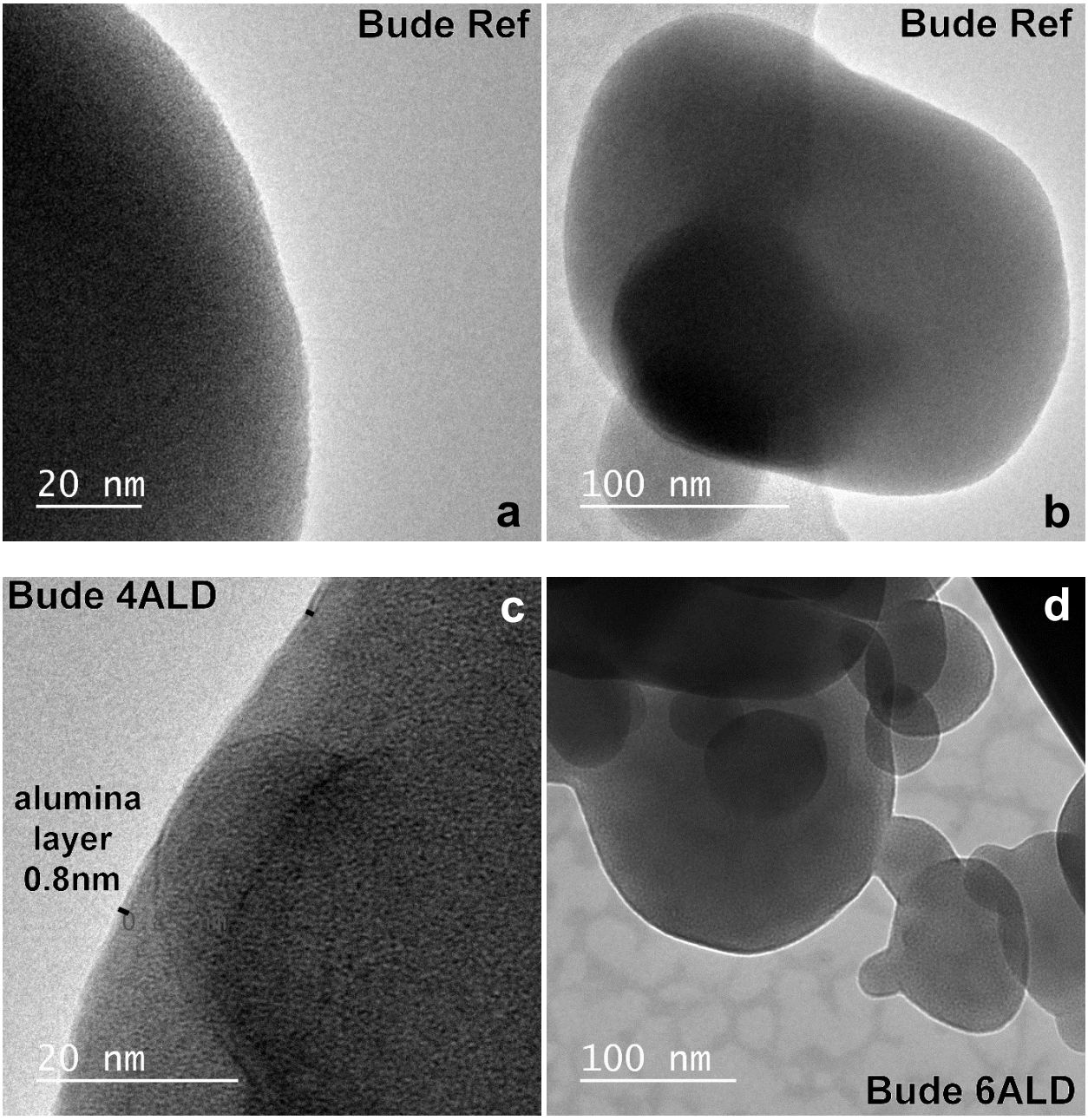

Figure S1. Transmission electron microscopy (TEM images) of the uncoated (a and b) and coated particles of budesonide after 4 (c) and 6 (d) ALD cycles. The white circle across the particles is not a layer, it is caused by reflection. As shown in the images, after 4 ALD cycles, a visible coating around 0.8 nm is indicated, which is very close to the thickness calculated based on the ICP analysis (0.7 nm). After 6 ALD cycles, the alumina layer (dark grey layer within the white reflection) was complete and conformal across all the particles, i.e. 2 nm, which is consistent with the ICP estimation.

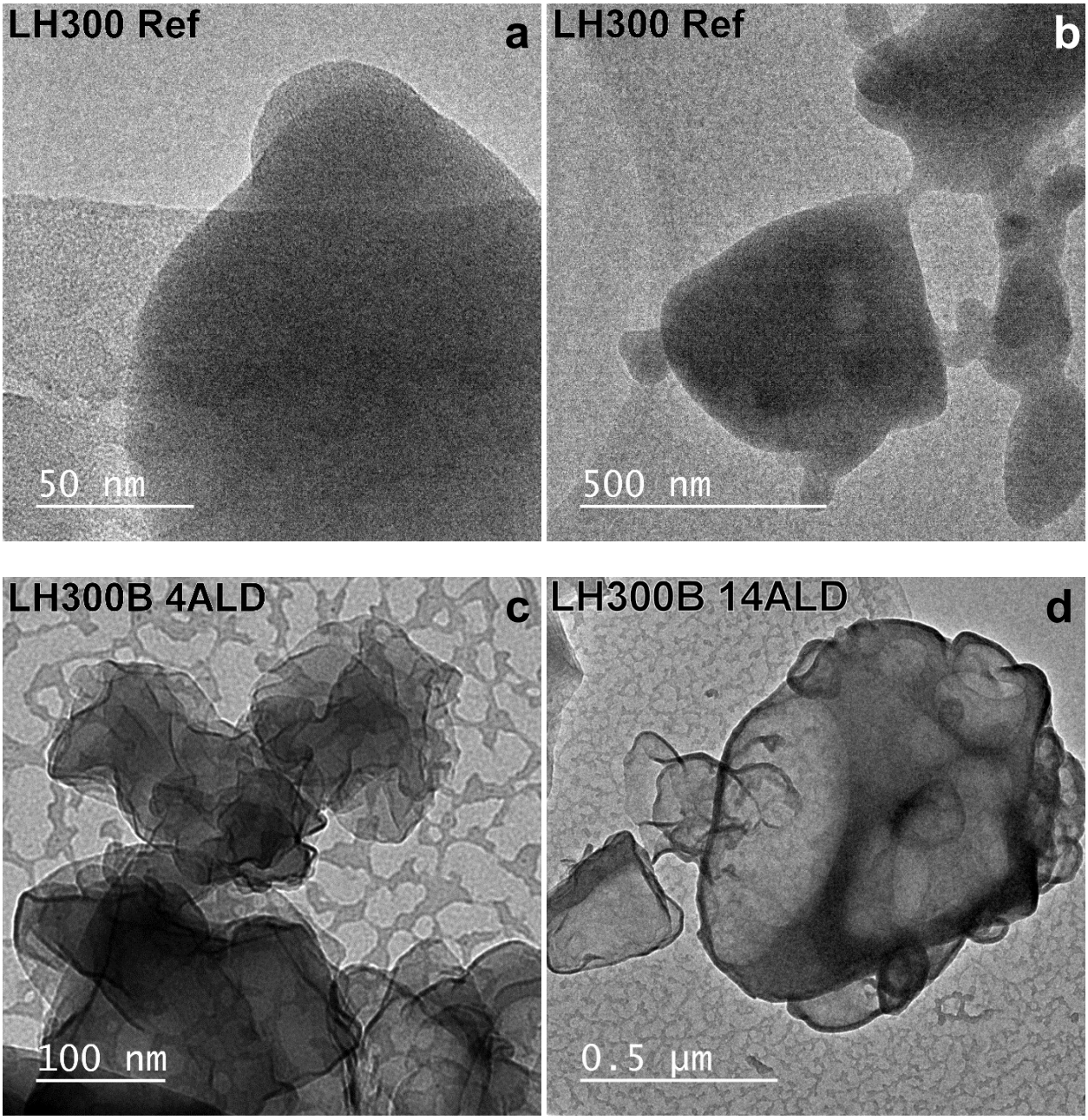

Figure S2. TEM images of the uncoated (a and b) and coated particles of lactose after 4 (c) and 14 (d) ALD cycles. The white circle across the particles is due to reflection. As shown in the figures, after 4 ALD cycles, a clear coating layer (dark grey layer) is already observed, and after 14 cycles the coating becomes thicker than that after 4 cycles.

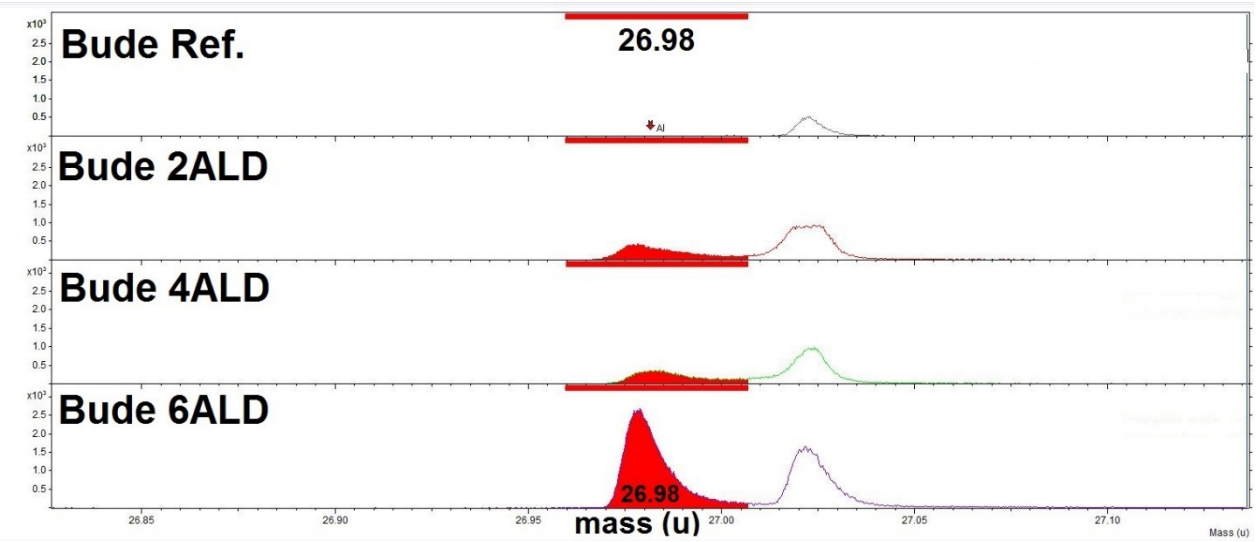

Figure S3. Time of flight secondary-ion mass spectrometry (TOF-SIMS) patterns of budesonide particles showing the peak area of aluminum as function of coating cycles.

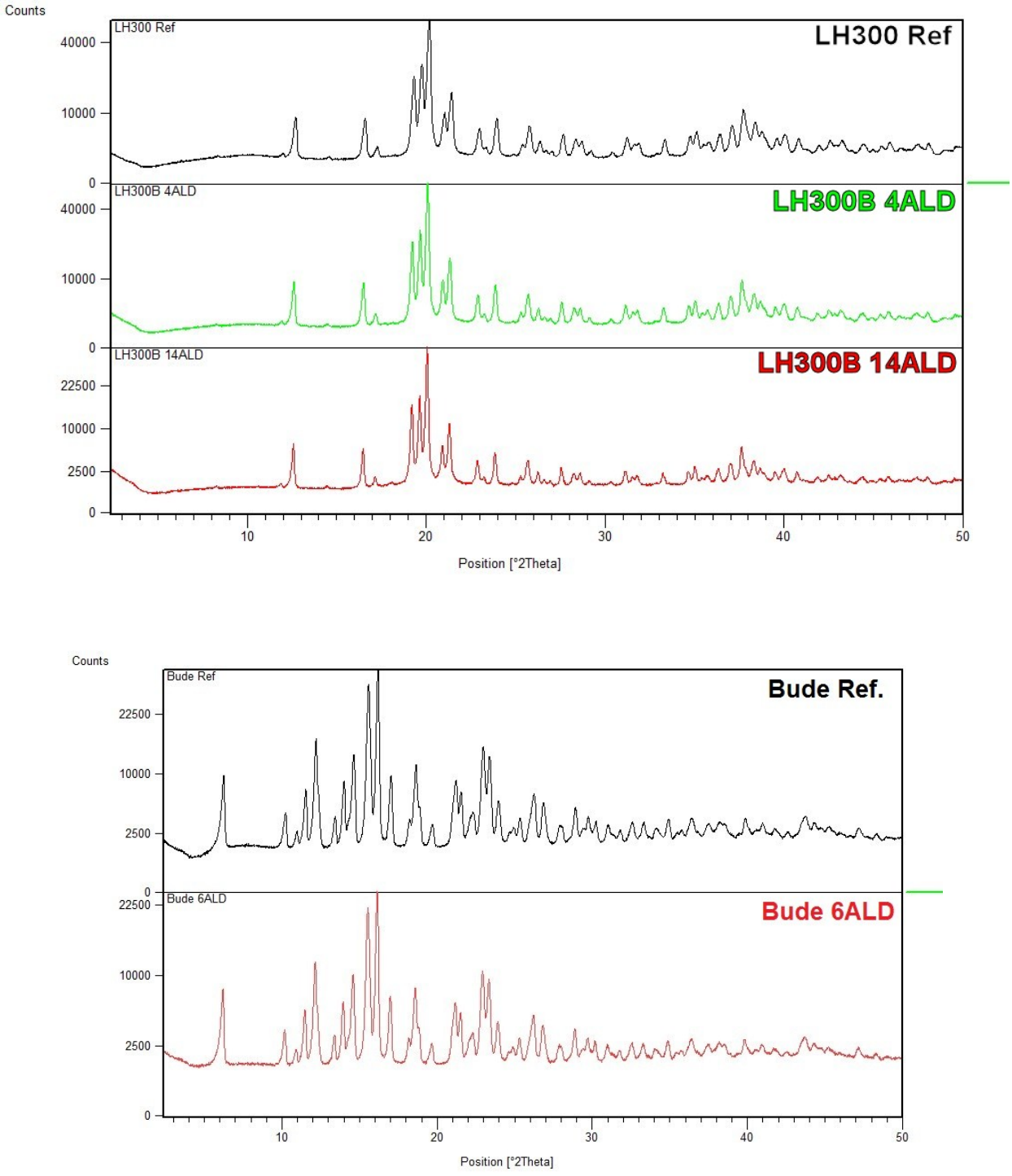

Figure S4. X-ray powder diffraction (XRPD) patterns of the particles of lactose LH300B and budesonide before and after ALD thin film deposition. The results show no major differences between the unmodified and surface modified samples.

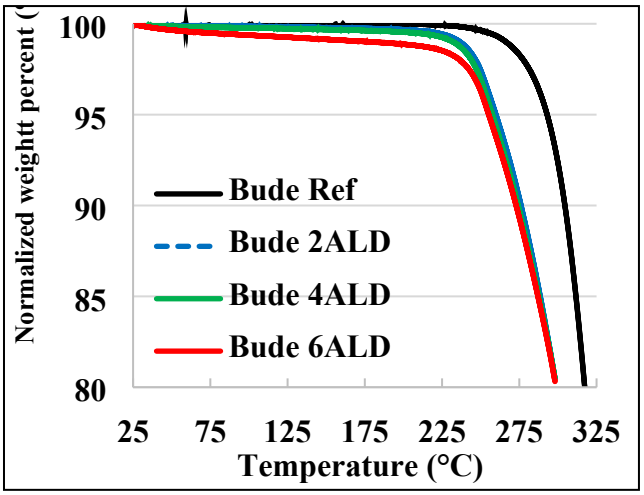

Figure S5. Thermogravimetric analysis (TGA) thermograms of the unmodified and modified budesonide samples at heating rate of 5°C per minute.

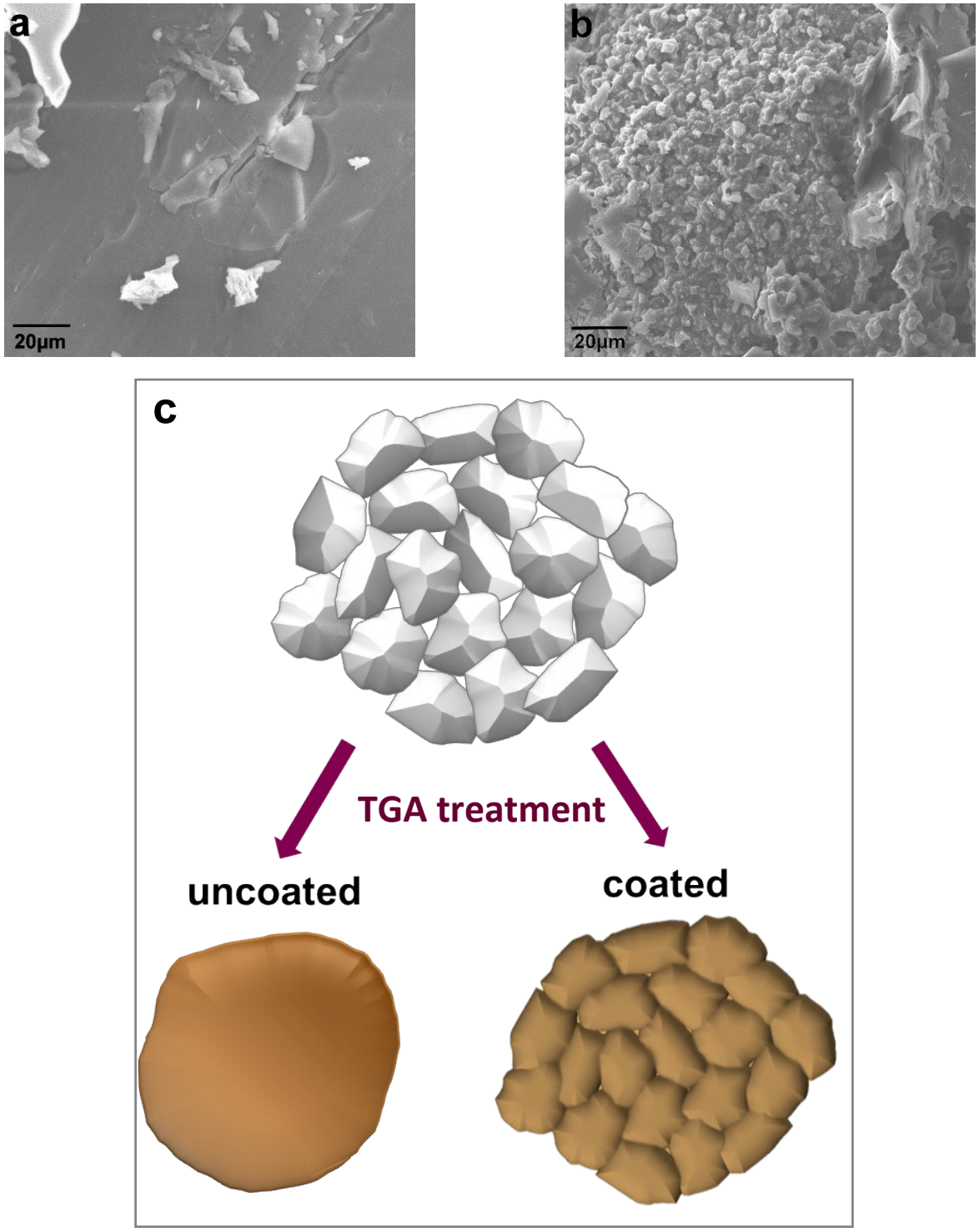

Figure S6. Scanning electron microscope (SEM) images for budesonide particles after TGA ended at 300°C: (a) Bude Ref; and (b) Bude 6ALD; and (c) schematic illustration showing the morphology of the particles after the TGA treatment: for the unmodified samples, the particles melt into a single mass; for the surface modified particles the particulate structure with different degree of sintering is indicated.

S7. Videos showing the difference in the dispersibility of the lactose particles in water for the 4ALD and 14ALD samples. The observed behaviour of the reference particles in water was very similar to that of the 4ALD sample. According to the focused beam reflectance measurements (FBRM) test, after 4 ALD cycles, the particles had similar dispersibility in solution as the unmodified sample, whereas the particles after 14 ALD cycles showed a dramatically improved dispersibility in solution. The videos confirm the observation by the FBRM (absolute EtOH as the media) when using water at room temperature with a rotation rate of 150 rpm.

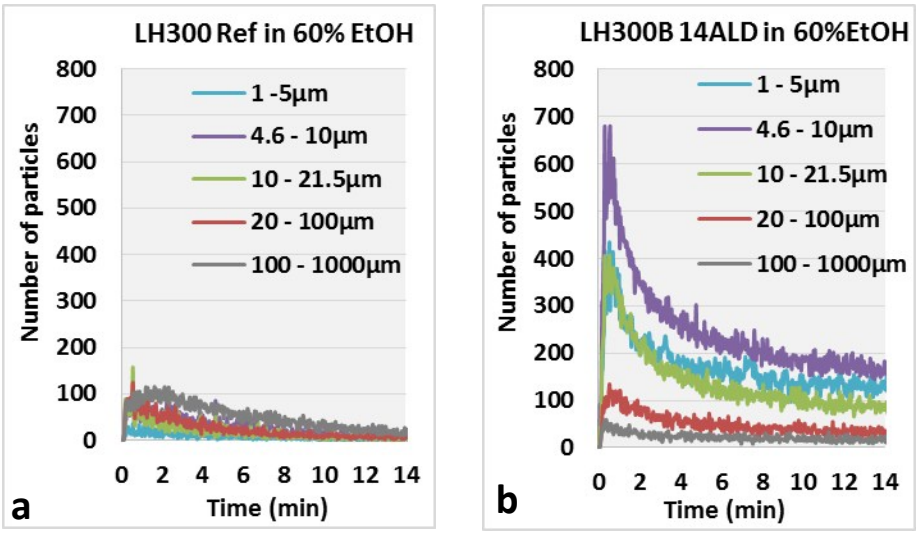

Figure S8. Particle size distribution during dissolution of lactose particles in 60% EtOH measured by FBRM for (a) LH300 Ref, and (b) LH300B 14ALD. The observation supports the results of the dissolution tests measured by UPLC. In contrast to the reference particles where the smallest particles immediately disappeared due to rapid dissolution, the 14 ALD cycles particles over the whole range (1 – 1000µm) remained present for some time during the same measurement period.

S9. *Materials:* semiconductor grade trimethylaluminum (TMA) was purchased from Akzo Nobel HPMO (Amersfoort, The Netherlands) in a 600 mL stainless steel bubbler (WW-600). Alpha-lactose monohydrate particles Lactohale® LH300 (d_{50} 3.53 μm) were donated by DFE pharma (Germany). The specific surface area (SSA) of the as-received particles was measured by Brunauer-Emmett-Teller (BET) N_2-sorption surface area analyzer (Micromeritics TriStar 3000 or TriStar 3020, United States). About 1 – 1.5 g particles were used for the BET surface area measurements. Prior to the measurement the particles were degassed for at least 3 hours at 25°C using SmartPrep or VacPrep (Micromeritics, United States). For each sample 2-4 parallel samples were carried out. The as-received particles were used as reference (Ref.) samples. Relevant data are given in Table 1.

S10. Experimental Section

Atomic layer deposition (ALD) on pharmaceutical particles: materials are described in the Supporting InformationS8. The assisted fluidized dry bed processing platform has been reported in detail in previous work.[1, 2] A general description is included here. Alumina films were deposited (as illustrated in Scheme 1) in a purpose-built fluidized bed reactor consisting of a glass column of 26 mm in diameter and 500 mm in length, placed on a single motor Paja PTL 40/40-24 vertical vibration table to assist the fluidization. The vibration table was operated at 35 Hz. and provided a vibration amplitude of 2 mm to the column. An infrared lamp placed parallel to the column, and a type-K thermocouple inserted in the column, were used to measure and control the bed temperature at 30 or 40°C. Two stainless-steel distributor plates with pore size of 37 mm placed at the bottom and top of the column, are used to obtain a homogeneous distribution of the gas inside the column and to prevent particles from leaving the reactor. TMA was kept at 30 °C during the coating experiments. The second precursor, demineralized water, was kept in a similar bubbler as for the TMA. Pressurized nitrogen grade 5.0 was provided to the column as the carrier gas; no pump was present after the column. The column was always kept at atmospheric pressure. During start-up of an experiment, nitrogen was used to drive away the air before starting the coating. The off-gas of the fluidized bed was led through a rack of five washing bubblers filled with Kaydol oil to remove possible traces of unreacted precursors and the products of the reactions. The precursor bubblers, the fluidized bed reactor and the washing bubblers were placed inside a nitrogen-blanketing cabinet as a TMA safety measure. The cabinet was operated at an O_2 concentration below 6%. The process was operated at 1 bar and 30 - 40°C (Table 1). At the beginning of each experiment, the powder was placed inside the column. Detailed experimental conditions are given in Table 1. To calculate the precursor dosing times, we estimated the total amount of active sites in the bed of particles. i.e., the dangling bonds such as hydroxyl groups. This amount was calculated with the measured BET

SSA and the mass of the substrate particles placed inside the column, and the surface concentration of the active groups. The maximum number of the TMA molecules that could attach to the surface of the substrate particles was estimated to be around 5 molecules per nm^2, according to the model given by Puurunen et al.[3] The details for the calculation were reported previously.[2] After dosing each precursor to the reactor, the system was pursed with N_2 to remove the excess precursors, establishing a feeding sequence of TMA–N_2–H_2O–N_2. To ensure a full saturation of all the powder inside the column, an excess dosing time was applied. For budesonide, the calculated dosing time was very short. The influence of the factors such as residence time (dead time) of the setup, sticking of precursors at the reactor wall, etc. would be large. Therefore, a much higher dosing time (15 times of the calculated ones) was used, as given in Table 1. For the process of lactose, dosing time of the precursors 4-5 times higher than the calculated ones was applied. The coating was performed for 2, 4, 6 and 14 ALD cycles depending on the sample (Table 1). At the end of each designed cycle, the reaction was stopped and around 25-30% powder was removed from the column for further characterization. The remaining powder was further coated by applying the same ALD sequence.

Characterization: TEM: the particles were suspended in ethanol and transferred to regular TEM grids (3.05 mm in diameter). TEM (JEOL JEM1400, Pleasanton, CA, USA) images were taken at several locations on the grids at a voltage of 120 kV and a current density of 50 pA/cm^2.

Elemental analysis was carried out using inductively coupled plasma optical emission spectroscopy (ICP-OES, PerkinElmer Optima 2100, PerkinElmer, Waltham, MA, USA). Before measurement, 8-15 mg particles were dissolved overnight in 10 ml acid mixture solutions of H_2O:HNO_3:HOAc in volume ratio of 6:2:2. After destruction, the samples were analyzed with ICP-OES to determine the mass fraction of aluminum in the samples. For each sample, 2-4 replicates were made.

The morphology of the particles was observed by SEM (FEI Quanta 200) at 15 keV under high vacuum mode. Before observation, the samples were coated with thin film of Au for 150 – 200 s using Cressington sputter coater (108 auto, Watford, United Kingdom). Elemental analysis for the chemical composition on the surface of some particles was carried out using Energy Dispersive X-ray (EDS) analyzer INCA Penta FETx3 (Oxford Instruments, Oxfordshire, United Kingdom), equipped with the SEM.

A TOF-SIMS[5] instrument (ION-TOF GmbH, Münster, Germany) equipped with a single-stage reflection analyzer and a bismuth liquid metal ion gun was used to analyses the elemental and molecular information from the outermost layer (typical 1-4 nm) of the surface of the particles. The analysis was conducted in high mass resolution mode with Bi_3^+ primary ions. The primary ion gun energy was 30 keV. TOF-SIMS analysis was performed on reference and ALD coated lactose particles for areas of 200 × 200 μm, at a resolution of 128 × 128 pixels, for 12 scans. The spectra were calibrated using the CH_3^+ and $C_2H_3^+$ fragment ions.

The particle size distributions of the particles were measured by laser diffraction Mastersizer 2000 (Malvern Instruments Ltd., Worcestershire, United Kingdom). For each sample. 2-4 parallel tests were carried out at a pressure of 3 bars.

The true density of the particles was measured by Gas Pycnometry (AccuPyc II 1340, Micromeritics Instrument, Norcross, GA, United States) in a 10 cm^3 cell. Two to four replicates were made for each sample. Structure characterization of the particles was made by XRPD (X'Pert PRO PANalytical Ltd., Nottingham, United Kingdom) through a 12 minutes fast scan program at 45 keV, 40 mA within 2θ 0 - 50°.

The thermal properties of the particles during heat treatment were observed by TGA (Q500, TA Instrument. New Castle, DE, United States) under N_2 atmosphere by ramping from 25°C to 250°C

or 300°C at 1, 5 and 20°C per minute. Around 5-10 mg particles were used for each test and 1 - 4 tests were run for each sample. SEM observations were made on some particles after heating to 250 or 300°C.

Dispersibility: the dispersibility of the lactose particles in suspension was monitored online by a FBRM probe (LASENTEC S400, Mettler Toledo, OH, USA) during mixing of 600±5 mg sample in 600 ml EtOH (99.5%) in a USP2 dissolution apparatus vial (DISTEK Premiere 5100, NJ, USA) with stirring rate of 150 rpm at room temperature. As a reference, uncoated lactose was tested also with the addition of 0.08% of sodium dodecyl sulfate (SDS) to the ethanol medium. Tests with the same conditions in 60% EtOH without SDS were also carried out in order to compare with the dissolution tests measured by HPLC.

Dissolution: the dissolution tests of the lactose particles were carried out in 80% EtOH in a 100 ml glass vial with stationary rotation of 190 rpm at room temperature (two replicates for each sample). 80% EtOH was used instead of water to dramatically slow down the dissolution rate of the lactose therefore allowing the observation in the initial dissolution stage, i.e. within the first 1-3 min. Prior to the dissolution tests, 50±0.5 mg of particles were pre-dispersed in 25ml of absolute EtOH with 0.08% SDS for 10 min in order to ensure a similar dispersive conditions for all the samples. 20 ml from the upper suspension was then taken for the dissolution test to make a sample concentration of 30±5 mg/ 100 ml. At each time point from 1 to 120 min (1, 3, 5, 7, 9, 12, 20, 30, 60 and 120 min), 1 ml of solution was taken and filtered using a 0.2 μm syringe filter (Millex®). The filtered solutions were analyzed by UPLC (ultra-performance liquid chromatography, Acquity™, Waters, MA, USA) with a charged aerosol detector (CAD, Dionex Coron Veo RS, Thermo Scientific, MA, USA). The dissolution tests for budesonide were carried out in sodium phosphate (NaP) buffer solutions (pH 6.8) with 0.08% SDS surfactant at 37°C and stirring rate 200 rpm via μDiss fiberoptic

system (Pion Inc., MA, USA), the signal was collected continuously (every 6 seconds in the initial 10 mins) by the UV spectroscopy. The used concentration was 0.5 mg of powder in 25 ml NaP solution. Three to six parallel measurements were taken for each sample. Both tests were carried out at a concentration that was at least 3 times lower than the measured solubility of the materials in the tested conditions.

References

1. D. Valdesueiro, P. Garcia-Triñanes, G. M. H. Meesters, M. T. Kreutzer, J. Gargiuli, T. W. Leadbeater, D. J. Parker, J. P. K. Seville and J. R. van Ommen, *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment*, 2016, **807**, 108-113.

2. D. Valdesueiro, M. G. Meesters, T. M. Kreutzer and R. J. van Ommen, *Materials*, 2015, **8**, 1249.

3. R. L. Puurunen, *Chemical Vapor Deposition*, 2003, **9**, 249-257.