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Improving Powder Characteristics by Surface Modification Using Atomic Layer Deposition

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Supporting Information

ABSTRACT: The particulate properties of a material after primary manufacturing have a large impact on the secondary manufacturing processes. Especially, powder characteristics leading to poor flowability are critical and need to be controlled at the late steps of primary operations. The surface properties of the primary particles are hereby one of the determining factors for the behavior of particulate systems. Materials with different particulate properties were coated using atomic layer deposition (ALD) to apply an ultrathin film of TiO_2 on the primary particles. The presence of TiO_2 coating was confirmed using X-ray photoelectron spectroscopy. Five TiO_2 ALD layers on the particle surface were enough to quadruple the flowability of a partially crystalline material and to triple the flowability of an amorphous material. The coating process did not change the solid form of the materials and did not affect other critical characteristics related to the functionality of the materials. Altogether, the ALD coating of powders provides new possibilities as a scalable and potentially continuously operating process that can solve problems related to powder flowability during handling of bulk powders.

KEYWORDS: *atomic layer deposition (ALD), materials science, surface chemistry, particle coating, powder properties*

1. INTRODUCTION

Powders can be considered as a separate state of matter, showing mechanical rigidity of a solid body, while also exhibiting flowability analogous to a liquid or a gas, depending on the processing environment. Fundamental understanding of the factors affecting powder behavior is one of the unsolved scientific challenges within the production of fine chemicals. This limited knowledge is dramatically affecting the commercial scale production of all fine chemicals. Challenges related to powder behavior are diverse and equally faced by every industry handling large amounts of powders (e.g., agricultural, cement, food, and pharmaceutical). Forces between the single particles of the material and between the particles and the surrounding material play a major role for understanding problems encountered during handling and processing of powders.[1−4] Both parameters are influenced by multiple factors, including size and shape of the individual particles,[5,6] particle surface chemistry,[7] and environmental conditions.[8] After primary manufacturing (synthesis and purification), large quantities of particulate materials are stored and finally transported to secondary manufacturing processing (e.g., pharmaceutical manufacturing of tablets). The ability of these materials to flow has a large impact on the processing. A poorly flowing powder can induce a forced stop in the production line, compromise the quality of the final product, and cause a large financial loss.[9,10] With the development toward end-to-end manufacturing,[11−14] control strategies are needed to ensure a more robust overall processing of particulate systems.

Different approaches for improving the powder flowability have been established. Increasing particle size by granulation is one way to not only improve the flowability but also decrease the risk of creating airborne fine particles during handling. Another common approach to improve the flowability of the particulate material is the addition of small quantities of flow enhancing materials.[15] Dry coating has shown promising results for improving the powder flowability. The key challenge when mixing flow improving materials to a powder is to achieve a homogeneous mixture and to retain properties required for downstream processing.[16−19] Instead of adding a flow enhancing material by mixing, there has also been an interest in coating the individual particles.[20,21] Coating of the particles should hereby ideally not affect other critical material attributes (e.g., solid form, water sorption potential) and as a consequence functionality of the final product. In order to retain the size and shape of the particles and other critical material attributes, an ultrathin coating would be desirable.

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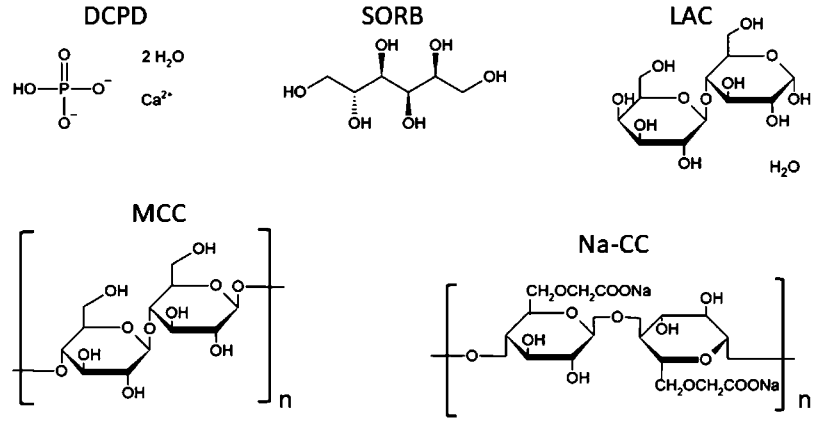
Scheme 1. Chemical Structure of the Used Materials



However, this can be extremely difficult to achieve with most techniques. An ideal solution would be to integrate this coating step into primary manufacturing processes in a continuous processing mode and by this means improve the logistics between primary and secondary processes.

Atomic layer deposition (ALD) is a surface-controlled, self-limiting, layer-by-layer coating technique, which deposits very thin films onto solid surfaces from the gaseous phase of the precursors.[22] The two most important advantages of ALD are excellent conformity and film thickness control at the atomic level. Traditionally, this method has been used on smooth surfaces such as electronics parts; however, there is a growing interest to coat porous substrates, such as catalyst particles.[22−25] Typical processing settings for the ALD coating of powder materials are a rotary reactor[26,27] and a fluidized bed reactor.[28] ALD has been further developed to handle powders on a commercial scale (tons/day) by implementation into a continuous setup.[29] Different coating materials are available for ALD,[23] for example, Al_2O_3, SiO_2, or TiO_2. This work used TiO_2 as a coating material because it has already been safely used in pharmaceutical products, for example, in tablet coating,[30,31] and is widely used in food and personal care products.[32] The main advantage of ALD is the chemical attachment of the coating material to the surface of each individual particle, which eliminates the risk for an inhomogeneous blend or demixing during downstream processing faced by a physical mixture.

The aim of this work was to investigate the effect of ALD on the particulate properties of diverse materials.

2. EXPERIMENTAL SECTION

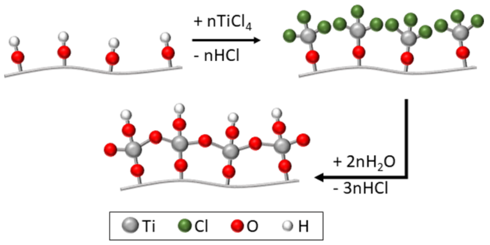
Croscarmellose-sodium (Na-CC/Primellose, DFE-Pharma, Goch Germany), microcrystalline cellulose (MCC/Vivapur 102, JRS Pharma, Rosenberg, Germany), α-lactose monohydrate (LAC/FlowLac 100SD, Meggle, Wasserburg, Germany), Sorbitol (SORB/Sigma-Aldrich, Steinheim, Germany), and dibasic calcium phosphate dihydrate (DCPD/Emcompress, JRS Pharma, Rosenberg, Germany) were used as model materials in this study (Scheme 1). All materials were coated with five TiO_2 ALD layers, and additionally SORB and Na-CC were coated with 20 TiO_2 ALD layers.

The visual appearance of the materials before and after the coating process was evaluated using a scanning electron microscope. Ti on the particle surface was detected using X-ray photoelectron spectroscopy (XPS). The effect of the coating on material properties such as solid form, vapor sorption behavior, and particle density was analyzed, and additionally, bulk behavior critical for downstream processing of the materials (powder flowability, triboelectrification, and behavior during compaction) was evaluated. Detailed descriptions of the used methods can be found in the Supporting Information.

3. RESULTS AND DISCUSSION

3.1. Coating of the Materials. Three crystalline powder materials, dibasic calcium phosphate dihydrate (DCPD), SORB, and LAC, one partially crystalline material (processed cellulose, "MCC"), and one amorphous material (chemically modified cellulose, sodium croscarmellose "Na-CC") were selected (Figure S1). All materials were coated with five TiO_2 ALD cycles. Additionally, Na-CC and SORB were coated with 20 TiO_2 ALD cycles. Each ALD coating cycle resulting in one ALD layer involved four main steps (summarized in Scheme 2): in the first step, the powder sample was exposed to $TiCl_4$ vapor. $TiCl_4$ reacts with the surface presenting hydroxyl groups, and hydrochloric acid (HCl) is formed. This process stops once all presented hydroxyl groups have reacted. In the second step, the reactor is purged with nitrogen to remove excess $TiCl_4$ and the reaction product HCl. In the third step, the powder sample was exposed to water vapor. The bound $-O-TiCl_3$ further reacts with the water to form TiO_2 and again HCl is formed.[33,34] In the fourth step, the reactor is purged with nitrogen to remove the excess of water and HCl. A more detailed description of this ALD cycle can be found in the literature.[20] The deposited layer thickness decreases with increasing temperature during coating. At an operational temperature of 100 °C, each deposited layer was expected to have a thickness of 2−3 Å, resulting in estimated coating thicknesses of 1.5 and 6 nm after 5 and 20 TiO_2 ALD cycles, respectively.[35]

Scheme 2. Simplified Representation of the ALD Process at a Particle Surface



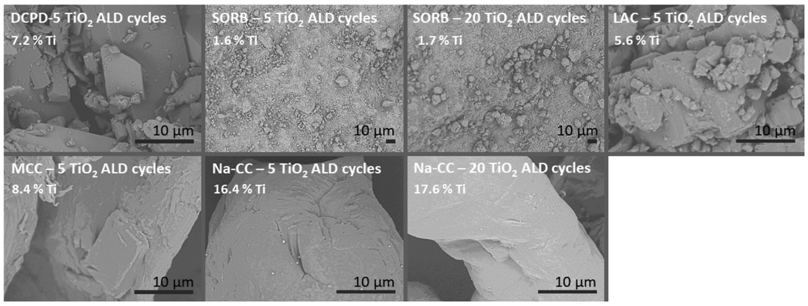


Figure 1. Scanning electron microscopy (SEM) images of the materials after ALD coating; the percentage shows the quantity of detected Ti (XPS measurements, mean, *n* = 3).

3.2. Coating Results. On the basis of a visual evaluation, the appearance of the surface of the individual particles did not change after ALD coating (Figures S2–S6). However, the presence of titanium (Ti) at the surface of the particles could be confirmed using XPS (Figure 1, Table S1). The X-ray photoelectron beam typically extracts electrons from the first 10 nm of the particle surface. XPS can be expected to detect elements from the particle under the TiO_2 coating, as the coating thickness is thinner than 10 nm even after 20 cycles. Furthermore, achieving a successful ALD coating requires $TiCl_4$ to react with the hydroxyl groups on the surface of the particles. Depending on the surface chemistry and the presence of hydroxyl groups on the particle surface, a noncontinuous coating can be formed with the ALD approach.[35,36] The XPS analysis indicated that the highest amounts of Ti could be detected on the surface of the partially crystalline MCC (8.4% Ti after 5 ALD layers) and amorphous NaCC (16.4 and 17.6% after 5 and 20 ALD layers, respectively) (Figure 1 and Table S1), followed by DCPD (7.2% Ti after 5 ALD layers), LAC (5.6% Ti after 5 ALD layers), and with the lowest detected Ti concentration SORB (1.6% and 1.7% Ti after 5 and 20 ALD layers, respectively). This suggests a more abundant TiO_2 coating or a higher presence of the surface presenting OH groups because of the random structure of amorphous materials. XPS binding energies for Ti ($2P_{1/2}$ and $2P_{3/2}$) are 463 and 457 eV, respectively, on all coated surfaces, indicating that Ti is strongly bound to the surface in the Ti(IV) or Ti(III) state. The similar results for Ti concentration on the surface of the particles coated with 5 and 20 ALD cycles could be explained by the dynamics of the coating process involving both thermal and mechanical stress to particles. This results in a potential inhomogeneous surface structure. Additional methods can be used to analyze the surface after coating in more detail. Atomic force microscopy (AFM) and AFM coupled with an infrared source[37] or inverse gas chromatography can be used for this purpose.[38] The covalent binding of $TiCl_4$ to the host materials can be a concern, especially when thinking about pharmaceutical active compounds. In previous work, it has been shown that with 50 Al_2O_3 or 50 TiO_2 ALD layers the dissolution behavior of acetaminophen was similar to the uncoated sample.[21] In a preclinical study with indomethacin coated with 115 Al_2O_3 ALD layers, it was shown that the dissolution could be delayed, allowing for an injectable depot formulation.[39] This potential change in dissolution can have a large impact and needs to be considered and investigated for ALD-coated materials. It should be noted that our goal was to affect the powder behavior but not the dissolution behavior. In general, the stability of the ALD-coated material needs to be considered, and both the safety and functionality after ALD processing need to be ensured.

3.3. Powder Flowability. The powder flowability of the coated and uncoated materials was measured and compared to the physical mixtures containing small quantities of particulate TiO_2. The particulate TiO_2 could enhance the flow of these materials by reducing the number of direct contact points between particles. This was observed for all materials (Figures 2 and S7). However, the improvement of flowability of the ALD-coated samples was remarkably higher compared to that of the physical mixtures, especially in the case of noncrystalline samples (MCC and Na-CC). Compared to the raw material, a 4 times higher flowability could be achieved for the ALD-coated MCC. For the amorphous Na-CC and the crystalline SORB, a 3 times higher flowability could be achieved after coating with five ALD layers of TiO_2. For the free flowing LAC and DCPD, the improvement in flowability after coating with five ALD cycles was relatively small but still statistically significant.

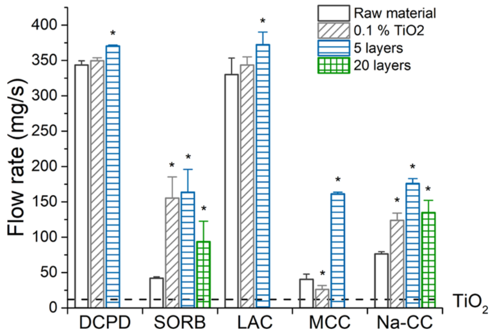


Figure 2. Powder flowability (*n* = 4; mean ± SD) of the raw materials (gray open bars), the physical mixtures containing 0.1% TiO_2 (light gray diagonally striped bars), and the samples coated with 5 (blue horizontally striped bars) and 20 (green checked bars) TiO_2 ALD cycles. * indicates significant difference between the sample and the raw material ($\alpha = 0.05$). The dashed line shows particulate TiO_2.

A reduction in the electrostatic charge generated by friction between the particles and the surrounding material can explain the improved powder flowability.[40] As TiO_2 itself generates only a relatively low charge against both steel and glass surfaces (Figure S8),[41] a reduction in the specific charge was expected for the ALD-coated materials. Against a steel surface (Figures 3A and S9), a significant reduction in generated charge could be observed for the SORB and Na-CC samples after coating with five TiO_2 ALD cycles. Uncoated DCPD generated minimal charge, and after ALD coating with TiO_2, the

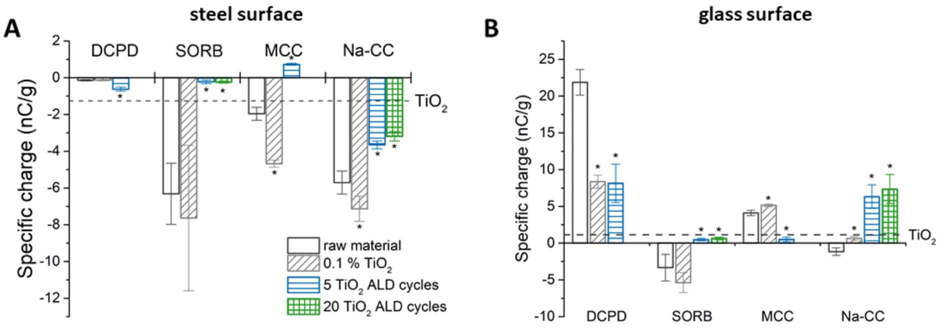


Figure 3. Electrostatic charging (n = 5; mean ± SD) against (A) steel and (B) of the raw materials (gray open bars), the physical mixtures containing 0.1% TiO_2 (light gray diagonally striped bars), and the samples coated with 5 (blue horizontally striped bars) and 20 (green checked bars) TiO_2 ALD cycles are shown. * indicates significant difference between the sample and the raw material (α = 0.05). The dashed line shows pure TiO_2.

generated charge approached that of the pure TiO_2. For MCC, the specific charge turned positive for the ALD-coated samples, but the absolute value of the specific charge decreased. Hence, less charge was generated because of the surface modification. This resulted in lower interparticle forces and an improved flowability. Similar behavior could be observed for the electrostatic charging against glass (Figures 3B and S10). Thus, the observed results for electrostatic charging supported the powder flowability results for these single component systems. LAC was excluded from the electrostatic charge measurement, as the LAC powder sample did not flow smoothly through the measurement tube and thereby could not build up a reproducible charge. Increasing the number of TiO_2 ALD cycles from 5 to 20 deteriorated powder flowability of NaCC and SORB, instead of further enhancing it. However, both still exhibited better flowability than the raw material (Figure 2). This indicates that five ALD coating cycles were sufficient to improve the powder behavior, which has also been reported for an active compound (acetaminophen) using the ALD technique.[21] In addition, the difference in specific charge generated by the materials coated with 5 and 20 TiO_2 ALD cycles was found to be relatively small, again indicating that a low number of ALD cycles was sufficient to improve the powder behavior.

3.4. Particulate Properties.

Changing the solid-state properties (e.g., crystallinity and polymorphic form) of a material can have a large impact on the functionality of a fine chemical product. It was therefore important to ensure that the coating process did not change the solid-state properties of the materials (Figure S1). The two crystalline hydrates (LAC and DCPD) did retain the water of crystallization, and no dehydration or indication of reduced crystallinity could be detected. Furthermore, no increase in crystallinity of the amorphous (Na-CC) or the partially crystalline (MCC) material was observed. Another concern when coating particles is that a particle coating can potentially alter the pore structure of the particle. The particle density was therefore analyzed using helium pycnometry, and no effect of the ALD on the particle density of the materials could be detected (Table S2). It should be noted that helium pycnometry has limitations when measuring the density of water-containing samples.[42,43] The lack of difference in measured particles density indicated that ALD coating did not affect the solid form and dehydration behavior of the tested samples, which all contained water to some degree.

One of the critical material attributes of MCC and Na-CC is the ability to absorb water, resulting in a swelling of the particles, which can be utilized to facilitate the disintegration of pharmaceutical products (e.g., tablets).[44,45] Because of their amorphous (in the case of MCC, partially crystalline) nature, relatively large amounts of water can be absorbed by these materials. It was therefore important that the ALD process did not affect this material property. During the vapor sorption analysis, it was observed that the extent of water sorption of the material did not show a difference between the uncoated and the coated samples (Figure S11). Additionally, the kinetics of water sorption are an important property. A slower water sorption means that the swelling property of MCC and NaCC would be delayed, which could potentially change the functionality of the final product. Isothermal microcalorimetry showed that the kinetics of water sorption did not change after the samples were ALD-coated (Figure S12). Crystalline materials usually have a lower potential to absorb water. Characteristic water−solid interactions for crystalline materials are water sorption to the particle surface and deliquescence, a phenomenon where the material starts forming an aqueous solution when exposed to surrounding air with adequate humidity.[46] The TiO_2 ALD coating did not show an effect on the water−solid interactions for SORB, LAC, and DCPD, and the deliquescence point of SORB was not affected by the coating with 5 and 20 TiO_2 ALD cycles (Figure S11). This is of importance because lowering of the deliquescence point would increase the risk of powder caking during storage. The water−solid interactions were not affected after ALD coating with low number of layers. In a previous work, coating of amorphous lactose with a higher number of ALD layers using Al_2O_3 as a coating material formed a protective shell around the particles that prevented water sorption and protected the material against recrystallization.[47] In several previously published papers, a higher number of ALD cycles has been used with a goal of either affecting the drug release from particles or protecting the material from environmental conditions.[39,47] An alternative strategy would be to utilize already generally accepted materials such as modified polymers for achieving the desired functionality (e.g., controlled drug release or moisture protection) and use only few ALD coating layers on top of the polymer coating layer for achieving the improved particulate behavior.

3.5. Tableting.

As in many other industrial sectors, the pharmaceutical industry relies on the handling of powders on a daily basis. The most common dosage form of medicines on the market is the tablet. During tablet production, powder has to flow into a tablet machine, where pressure is applied and the powder is compacted to form a solid body. The success of the production is mainly dependent on two parameters: the powder flowability, which has to be high enough to fill the tablet machine with the same volume of powder for each tablet, and the ability of the material to form a compact with sufficient strength to withstand further handling (i.e., coating and packaging) (Figures S13 and S14). Modifying the surface of the individual particles with TiO_2 ALD coating did decrease the tensile strength of the compacts made from MCC and LAC, but these compacts were still strong enough for downstream processing. This decrease in the tensile strength could be associated with a decrease of solid fraction of the coated samples. Na-CC showed an increase in tensile strength after being coated with five TiO_2 ALD cycles. The solid fraction did not differ between the ALD-coated and uncoated samples. However, an increase in the weight could be observed with the Na-CC coated with five layers (data not shown) because an improved flowability led to better initial packing of the powder in the tablet die and, hence, a larger mass within a constant fill volume. No difference was observed in the strength of the compacts made from SORB and DCPD. As an overall conclusion, the benefits from improved flowability of materials outweigh the slight decrease in tabletability, an effect that can be offset by slightly increasing the compaction pressure.

For tablet production, the basic unit operations have remained unchanged for over a century; however, there has been an increasing interest to modernize pharmaceutical production systems via implementation of continuous manufacturing principles and merging primary (synthesis) and secondary (powder handling) processes.[11,48,49] This end-to-end manufacturing approach would decrease the manufacturing time, increase the throughput, and allow reduction of the footprint of production equipment.[11] Another direction in the pharmaceutical manufacturing is the increasing use of smaller flow geometries for synthesis and particle production. Parallel use of micro reactors for the manufacturing of nanoparticles has been shown to be an efficient and promising production approach.[50,51] Interfacing the ALD coating process into continuously operating[52] and potentially microfluidic production geometry would provide an innovative way of combining primary and secondary manufacturing of pharmaceuticals. Coating particles to improve the flowability right after synthesis circumvents the common problems in storage and transportation, ensuring a smoother downstream processing (e.g., mixing and tablet production).

4. CONCLUSIONS

This study showed that ALD coating of materials with varying solid form composition was successful and could improve the processability of commonly used pharmaceutical materials. It was observed that the coating of both crystalline and amorphous materials with only five ALD layers improved the powder flowability by reducing the electrostatic charge generated at particle−particle and particle−container contacts, without noticeably compromising the critical material attributes, such as density, water−solid interactions, solid-state composition, and the compaction behavior. It is important to note that the performance of ALD-coated materials was improved without the need to mix additional additives. As a surface modification method for porous materials capable of reducing the number of components and mixing step in production, ALD coating has the potential to facilitate safer and more cost-efficient processing of particulate materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00247.

Characterization of solid form, SEM images, XPS, true density, powder flowability, electrostatic measurements, vapor sorption, and tableting (PDF)

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Author Contributions

J.R. directed the project. The experimental work was carried out by C.H., N.S.J., J.B., T.O.K. M.M. performed the electrostatic measurements. A.Ø.M., M.-L.K., P.H., S.M.G., C.C.S., and J.R. supported in planning the project. C.H. and J.R. wrote the paper. All authors discussed the results, commented on the paper, and have given approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): Tommi O. Kriinen, Marja-Leena Kriinen and Pekka Hoppu are employed at NovaldMedical Ltd Oy.

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