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Production and characterization of aluminium oxide nanoshells on spray dried lactose

Joel Hellrup[a,1], Mårten Rooth[b], Anders Johansson[b], Denny Mahlin[a,*]

[a] Department of Pharmacy, Uppsala University, Uppsala, Sweden
[b] Nanexa AB, Virdings Allé 32B, SE-75240, Uppsala, Sweden

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ABSTRACT

Atomic layer deposition (ALD) enables deposition of dense nanometer thick metal oxide nanoshells on powder particles with precise thickness control. This leads to products with low weight fraction coating, also when depositing on nano- or micron sized powder particles. This study aimed at investigating the aluminium oxide nanoshell thickness required to prevent moisture sorption. The nanoshells were produced with ALD on spray-dried lactose, which is amorphous and extremely hygroscopic. The particles were studied with dynamic vapor sorption between 0 and 50% RH, light scattering, scanning electron microscopy, X-ray diffraction, differential scanning calorimetry, and polarized light microscopy. The ALD did not induce any recrystallization of the amorphous lactose. The dynamic vapor sorption indicated that the moisture sorption was almost completely inhibited by the nanoshell. Neat amorphous lactose rapidly recrystallized upon moisture exposure. However, only *ca.* 15% of the amorphous lactose particles recrystallized of a sample with 9% (by weight) aluminium oxide nanoshell at storage for six months upon 75% RH/40 °C, which indicate that the moisture sorption was completely inhibited in the majority of the particles. In conclusion, the aluminium oxide nanoshells prevented moisture sorption and dramatically improved the long term physical stability of amorphous lactose. This shows the potential of the ALD-technique to protect drug microparticles.

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1. Introduction

Atomic layer deposition (ALD) is a thin film deposition technique, usually performed at low pressure and elevated temperatures. Vaporized reactants called precursors are used to build a thin film on a substrate by alternating exposure of the precursors, in this study trimethyl aluminium (TMA) and water. The precursors only interact with each other on the surface where they form a thin film one layer at the time. The reaction is self-limiting, thus only one monolayer of each precursor can adsorb at the surface during each exposure. This behavior enables a perfect coverage of all accessible surfaces (George, 2010). A precursor exposure is referred to as a pulse in ALD. A pair of pulses are called a ALD-cycle. Beside precursor pulses, an ALD-cycle also contains purging pulses that are used to separate the precursor pulses. The thickness of the film growth is determined by the number of cycles. Thus, ALD enables control of the coating thickness at the atomic level simply by adjusting the number of deposition ALD-cycles used in the deposition of the coating (Miikkulainen et al., 2013). The ultrathin coating can be used to change the surface properties of the coated product without notable increasing its size (George, 2010; Longrie et al., 2014).

ALD can be used to deposit on a large variety of materials, including inorganic materials, organic materials, biological samples, and polymeric materials (George, 2010). The main application for ALD has so far been for semiconductor processing (George, 2010), but it has also been used in the production of catalyzers, batteries, and pigments (Miikkulainen et al., 2013).

ALD-coatings are typically applied to functionalize surfaces of silicon wafers, but there is also a number of reports on to ALD-coating of granular materials and particles (Beetstra et al., 2009; Hakim et al., 2005; King et al., 2007; Lakomaa et al., 1992; Longrie et al., 2014, 2012; McCormick et al., 2007; Raganati et al., 2015; Valverde Millán, 2013; van Ommen et al., 2015; Wank et al., 2004; Zhu et al., 2016). Potential applications for ALD on particles

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Abbreviations: ALD, atomic layer deposition; ΔC_p^{Tg}, magnitude of the step change in heat capacity at the glass transition temperature; DVS, dynamic vapor sorption; mDSC, modulated differential scanning calorimetry; RH, relative humidity; SEM, scanning electron microscopy; TMA, trimethylaluminium; XRD, X ray diffraction.

[*] Corresponding author at: Tel.: +46(0)18 471 4662; fax: + 46(0) 18 471 4223.
E-mail address: denny.mahlin@farmaci.uu.se (D. Mahlin).

[1] Present address: Nanexa AB, Virdings Allé 32B, SE-75240 Uppsala, Sweden.

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includes deposition of protective and insulating coatings to prevent particle oxidation or electrical conduction, and to modify optical or mechanical properties of the particles (George, 2010). Due to the extremely good surface coverage that ALD provides, it is possible to deposit materials that act as gas diffusion barriers. Pinhole free coatings are essential for such applications (Longrie et al., 2014).

Ideally when coating granular material, each primary particle will eventually be uniformly covered by a coating with an intended thickness. In powders consisting of cohesive particles, particle aggregation often happens which may significantly impair the formation of uniform coatings. There is a risk of ending up with coated particle aggregates. One way to prevent this from happening is by making all surfaces accessible for the precursor adsorption by intermittent re-dispersion of the particles during the processing (Carlsson et al., 2014). This re-dispersion can be accomplished by wet or dry techniques. The advantage with the dry techniques, for instance fluidized bed, is that it is possible to make the dispersion continuously in-process with the ALD (Wank et al., 2004). However, it is extremely challenging to accomplish a good dispersion by fluidization for particles smaller than 30 μm due to strong influence of cohesive forces (Geldart, 1972). For such powders, a wet dispersion off-line approach is favorable.

ALD on pharmaceutical relevant systems is previously almost unexplored (Lehtonen et al., 2012). Suggested applications for ALD within this field are, for instance, to control drug release, to mask badly tasting drugs (Hoppu et al., 2013), to improve powder flow of poorly flowing powders, or to increase physical and chemical stability of humidity sensitive drugs by depositing a gas diffusion barrier.

Sorption of water, both absorption and adsorption, strongly influence the properties of a solid material. Especially amorphous materials are prone to absorb moisture due to their low-density molecule arrangement, allowing penetration of water molecules into the material. It may cause degradation of the solid such as chemical degradation (Ahlneck and Zografi, 1990), relaxations (Surana et al., 2004), or recrystallization (Ahlneck and Zografi, 1990; Hellrup et al., 2015; Hellrup and Mahlin, 2011, 2017; Mullin, 2001; Sacchetti, 2014). Materials where water sorption may be an issue for product quality can be found in fields such as pharmaceuticals, cellulose-based materials and food products (Redman-Furey et al., 2013). The amount of water sorbed by a material when exposed to a specific relative humidity (RH) is a function of the inherent hygroscopicity of the material components, but also their mixing behavior. Chemical and physical interactions are of importance, but also the formation of absorption barriers, such as coatings and other confinement of hygroscopic domains within the material (Mwesigwa et al., 2008; Stubberud and Forbes, 1998).

Spray-dried amorphous lactose was utilized in this study as a model compound. Lactose is a hydrophilic low molecular compound (342.3 g/mol) and one of the most commonly used excipients in pharmaceutical drug delivery, food technology and flavoring (Lerk, 1993). Amorphous lactose is extremely hygroscopic. It may absorb more than 11 g H_20/100 g solid water before it rapidly recrystallizes (approximately above *ca.* 60% relative humidity (RH) (Hellrup, 2016)) due to the plasticizing effect of the water. Further, amorphous compounds are intrinsic physically unstable and overly intense processing may lead to recrystallization (Yang et al., 2014). The hygroscopicity of amorphous lactose provides means to monitor the integrity of the ALD-coating, i.e. if it is continuously solid and free from pin-holes, by the gravimetric method dynamic vapor sorption analysis (DVS). Furthermore, since hydrated amorphous lactose loose water during crystallization DVS can also be used to evaluate whether ALD can be applicable to sensitive materials such as amorphous drug compounds without inducing recrystallization.

In this paper we investigated aluminium oxide ALD-coatings—hereafter referred to as nanoshells—as gas diffusion barrier to increase the physical stability of micron-sized amorphous lactose particles. Aluminium oxide is nontoxic and pharmaceutically acceptable; its main use in pharmaceuticals is in tablet formulations for decoloring powders (Rowe et al., 2006).

The study aimed at investigating the possibility of coating an amorphous pharmaceutical relevant system, spray dried lactose, with the ALD technique without inducing recrystallization. The focus was at investigating the quality of the aluminium oxide nanoshell and the required nanoshell thickness to achieve a sufficient gas diffusion barrier for moisture, and in that way increase the physical stability of micron-sized amorphous lactose particles. Furthermore, by investigating the quality and the solubility of the aluminium oxide nanoshell, conclusions could be drawn on how nanoshells can be used for drug delivery with prolonged release.

2. Material and methods

2.1. Materials

Alpha-lactose monohydrate (Ph. Eur.), horse serum, heptane (HPLC grade), dioctyl sulfosuccinate sodium (98%), potassium phosphate dibasic trihydrate ($\geq$99%), and potassium phosphate monobasic ($\geq$99%) was purchased from Sigma-Aldrich (Buchs, Germany), trimethylaluminium (TMA, 98% purity) from ABCR (Karlsruhe, Germany), deionized water from Honeywell (Morris Planes, NJ), and hydrochloric acid (HCl, Laboratory grade) from Fischer scientific (Waltham, MA).

2.2. Sample preparation

The solution used for spray-drying was prepared by dissolving lactose in deionized water to a concentration of 15% (w/w) lactose. The solution was left stirring in room temperature over night to equilibrate with regard to spontaneous mutarotation. The lactose solution was spray-dried with a Büchi Mini Spray Dryer B-290 (Büchi, Flawil, Switzerland). A nozzle tip of 0.7 mm and nozzle screw cap of a diameter of 1.5 mm were used. The spray-dryer was operated in an open mode, whereby the drying gas was passed through a filter and a dehumidifier (B-296). A high-performance cyclone was used. During the spray drying, nozzle cleaning, volume flow, inlet temperature, spray air flow, and feed rate were set at level 2, 38 m^3/h, 150 °C, 473 l/h, and 4 ml/min respectively.

Aluminium oxide nanoshells were made with a Picosun R-series ALD processing tool (Picosun Oy, Finland) using the precursor combination TMA and deionized water. Depositions were made at a temperature of 50 °C with precursors temperatures at 18 °C and the pressure in the ALD-reactor was 10 hPa. Temperatures and pressure was maintained throughout all the depositions.

The ALD-cycles consisted of TMA-pulses, water-pulses, and in between them purging pulses using nitrogen gas. The growth of aluminium oxide is achieved according to the reaction below:

$$2Al(CH_3)_3 + 3H_2O \rightarrow Al_2O_3 + 6CH_4$$

The term ALD-set is, in this paper, referred to as a set of 50 or 100 ALD-cycles. Coatings were prepared using one to five ALD-sets. Between ALD-sets, the particles were agitated in heptane with 1% dioctyl sulfosuccinate sodium using ultra sonic equipment (Bandelin Sonopuls HD 3200 with BB6/EH6 cup horn indirect

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