Atomic Layer Deposition – A Novel Method for the Ultrathin Coating of Minitablets

Jaana Hautala[a,*], Tommi Kääriäinen[b,c,d], Pekka Hoppu[c], Marianna Kemell[d], Jyrki Heinämäki[e], David Cameron[f], Steven George[b], Anne Mari Juppo[a]

[a] Industrial Pharmacy, Faculty of Pharmacy, University of Helsinki, P.O. Box 56 (Viikinkaari 5E, Biocenter 2), FI-00014 University of Helsinki, Finland

[b] Department of Chemistry and Biochemistry, Faculty of Chemistry and Biochemistry, University of Colorado Boulder, 596 UCB, Boulder, CO 80309, USA

[c] NovaldMedical Ltd Oy, Telkäntie 5, FI-82500 Kitee, Finland

[d] Department of Chemistry, Faculty of Science, University of Helsinki, P.O. Box 55 (A. I. Virtasen aukio 1), FI-00014 University of Helsinki, Finland

[e] Institute of Pharmacy, Faculty of Medicine, University of Tartu, Nooruse 1, EE-50411 Tartu, Estonia

[f] Ceplant, Masaryk University, Kotlářská 267/2, CZ-61137 Brno, Czech Republic

*Corresponding author at: Formulation and Industrial Pharmacy, Department of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, P.O. Box 56 (Viikinkaari 5E, Biocenter 2), FI-00014 University of Helsinki, Finland. Tel.: +358 2941 59627. E-mail address: jaana.hautala@helsinki.fi

ABSTRACT

We introduce atomic layer deposition (ALD) as a novel method for the ultrathin coating (nanolayering) of minitablets. The effects of ALD coating on the tablet characteristics and taste masking were investigated and compared with the established coating method. Minitablets containing bitter tasting denatonium benzoate were coated by ALD using three different TiO_2 nanolayer thicknesses (number of deposition cycles). The established coating of minitablets was performed in a laboratory-scale fluidized-bed apparatus using four concentration levels of aqueous Eudragit® E coating polymer. The coated minitablets were studied with respect to the surface morphology, taste masking capacity, *in vitro* disintegration and dissolution, mechanical properties, and uniformity of content. The ALD thin coating resulted in minimal increase in the dimensions and weight of minitablets in comparison to original tablet cores. Surprisingly, ALD coating with TiO_2 nanolayers decreased the mechanical strength, and accelerated the *in vitro* disintegration of minitablets. Unlike previous studies, the studied levels of TiO_2 nanolayers on tablets were also inadequate for effective taste masking. In summary, ALD permits a simple and rapid method for the ultrathin coating (nanolayering) of minitablets, and provides nanoscale-range TiO_2 coatings on porous minitablets. More research, however, is needed to clarify its potential in tablet taste masking applications.

KEYWORDS

Atomic layer deposition, thin film coating, TiO_2, minitablet, taste masking, polymer film coating

ABBREVIATIONS

ALD Atomic layer deposition

MCC Microcrystalline cellulose

HPC Hydroxypropyl cellulose

SPB Sodium phosphate buffer

ACN Acetonitrile

HPLC High performance liquid chromatography

RT Room temperature

RH Relative humidity

RSD Relative standard deviation

SEM Scanning electron microscope

SEM-EDS Scanning electron microscope with energy dispersive spectroscopy

1. INTRODUCTION

For tablets, polymer film coating is still the most widely used and efficient taste masking technique in the pharmaceutical industry (Ayenew et al., 2009; Joshi and Petereit, 2013; Sohi et al., 2004). In addition to taste masking purposes, polymer film coating of tablets offers a variety of practical advantages that contribute to their therapeutic effect, as well as ensure patient compliance and tablet product stability throughout their shelf life (Bruce et al., 2011; Felton, 2007; Joshi and Petereit, 2013; Pearnchob et al., 2003; Siepmann et al., 2013). With polymer film coating, however, sufficient taste masking and drug release control demand relatively thick polymer films, and consequently, the application of large amounts of polymers (Joshi and

Petereit, 2013). The conventional film coating methods are associated also with laborious, expensive and technical expertise demanding material selection and process development, a lot is required also from coated tablet core and coating formulation design (Joshi and Petereit, 2013). Thus, the pharmaceutical industry is continually searching for new effective and inexpensive coating approaches for tablet taste masking and palatability improvement.

Atomic layer deposition (ALD) is a surface controlled, self-limiting layer-by-layer proceeding coating method for depositing ultra-thin, high quality and conformal thin films, these even on high aspect ratio structures (George, 2010). ALD is commonly used in microelectronics and nanotechnology applications, in functions, where miniaturization of structures requires the control of film thickness at atomic level (George, 2010; Puurunen, 2005). Consequently, the important features of ALD regard surface protection, modification, and functionalization, these in a number of applications benefiting from the characteristics of ALD (George, 2010). In pharmaceuticals, the moisture protective element of ALD coating has been already utilized for nano- and micro-sized drug particles (Carlsson et al., 2016). The ALD technique has been successfully applied also in the design of larger-sized, single particles intended for pharmaceutical powder applications (Hoppu et al., 2015). Here, the present situation is more than inspiring, since the thin film technology combined with material science could lead to new pharmaceutical manufacture and formulation options for fabricating the protective coatings on single drug particles. Bringing such approach to life science markets to serve the evolving needs of drug development, formulation engineering and manufacturing processes could hold great promises on homogeneous drug particles, the creation of new and tailor-made solid dosage forms, improvements in handling moisture sensitive and electrically charged single drug particles, and a decrease in the number of excipients and manufacturing process steps. In

addition to pure drug substances and single particles, ALD coatings could be also applicable for larger, more complex shaped, porous and heterogeneous substrates, such as tablets. The approach seems attractive, as ALD coatings are not only continuous, ultra-thin, dense, and smooth, but also most importantly pinhole-free, very conformal to the substrate, and provide good diffusion barriers with low gas and moisture permeability (George, 2010). In addition, the thin ALD coatings can reach and fill the surface of even the deepest and narrowest voids and pores (Ritala and Leskelä, 2002). Therefore, from the pharmaceutical product design and industry point of view, ALD would provide a very exciting technology not only for drug particle design but also as a potential method for tablet coating purposes.

ALD nanoscale films are formed (grown through deposition) utilizing self-limiting chemical reactions between gaseous precursors chemisorbed on a solid substrate surface. For example, when depositing metal oxide films, compounds of zinc, aluminum or titanium can be used as the metal precursors and water as the oxygen precursor. In many cases, the ALD growth starts by chemisorption of the metal precursor molecules on the hydroxyl groups of the surface. Tablets should allow the initiation of the nanolayering process of ALD, as they are commonly composed of multiple organic excipients containing free hydroxyl groups. In tablets, the number of surface hydroxyl groups required for attachment of molecules can even be created with the small amount of surface moisture readily existing on tablet surfaces and pores. Moreover, from a possible tablet coating point of view, the chemical components like zinc, aluminum and titanium oxides applied by ALD are all established pharmaceutical excipients, and thus their compatibility and safety profiles are well known. Also, compared to the conventional polymer film coating, ALD process is very different. The established polymer coating, performed by a fluidized-bed technique, sets high demands for tablet core strength, and consequently, for tablet formulation

105 design. During polymer coating in a fluidized-bed, tablets are exposed to frequent collisions,
106 high friction, increased moisture and high temperature. Consequently, tablet cores with limited
107 hardness and mechanical strength are eroded and broken down, especially in the beginning of the
108 coating process until the uniform film coating is formed through concomitant moisture
109 evaporation and polymer particle coalescence (Lehmann, 1997; Mehta, 1997). Thin coating by
110 ALD does not involve such limitations. In flow type ALD reactor, tablet cores are stationary, and
111 are coated during separate surface saturation (deposition) cycles involving chemical interactions
112 (**Fig. 1**). In theory, in ALD involving metal oxides, a cycle of surface saturation takes place
113 through two reaction steps performed commonly in vacuum at controlled temperature. During
114 step one (the first half cycle) the metal precursor such as $TiCl_4$ vapor, pulsed to the coating
115 chamber, is allowed to react with the free hydroxyl groups on the substrate surface. Therefore, in
116 theory, the chemical pulse saturates the surface with Ti containing groups through molecular
117 bonds. During step two (the second half cycle) the molecularly bonded structures on the
118 substrate surface react with the oxygen precursor (water vapor) and form the first nanolayer of
119 TiO_2. Between these steps, a purge of inert gas (N_2) is applied in order to remove any excess of
120 precursor and the reaction by-products. The thickness of the films can be controlled by repeating
121 the number of reaction cycles to reach the desired coating thickness. Moreover, compared to the
122 established polymer coating, the ALD process can be completely pre-programmed, and it does
123 not involve high labor or coating raw material related costs.

124 To date, no well-documented or established study to evaluate the feasibility of ALD for thin
125 coating of tablets has been performed. Lehtonen and co-workers (2013) have evaluated ALD on
126 simple and single material layered tablets, but as pharmaceutical solids traditionally are
127 heterogeneous and complex substrates, a need for a more thorough study on the applicability of

ALD on tablets is evident. Moreover, taste and odor masking capacity of ALD has been studied only on fish oil containing soft gel capsules (Lehtonen et al., 2013). Therefore, we are also completely lacking of information on the applicability and capacity of such ALD ultrathin coatings to improve palatability and taste masking associated with tablets.

Here, we therefore introduce our study describing ALD on minitablets composed of multiple excipients and a bitter tasting model drug. We investigated ALD as a novel technique for thin coating of minitablets, and for masking the bitter taste of model substance of denatonium benzoate. Special attention was paid to the effects of the ALD nanolayering process on the minitablet properties and taste masking efficacy. An established bottom-spray fluidized-bed coating (with a Wurster column set-up) was used as a reference coating technique.

2. MATERIALS AND METHODS

2.1 Materials

Granules were prepared using denatonium benzoate (Sigma-Aldrich, China) as a model substance of a bitter tasting active drug ingredient (0.04% m/m). Microcrystalline cellulose (MCC) (Avicel® PH-102, FMC Corporation, Ireland) (63% m/m) and calcium hydrogen phosphate dihydrate (Emcompress®, Albright & Wilson, Australia) (30% m/m) were used as fillers, and hydroxypropyl cellulose (HPC) (Klucel® JXF, Aqualon France SA, France) (3% m/m) and crospovidone (Kollidon® CL-F, BASF Corporation, Germany) (4% m/m) as a binder and disintegrant, respectively. Sodium stearyl fumarate (Pruv®, JRS Pharma, Spain) (1% m/m) was added as a lubricant before tableting.

The synthetic copolymer based on butyl methacrylate, (2-dimethylaminoethyl) methacrylate and methyl methacrylate (1:2:1) (Eudragit® E PO, Evonik Industries AG, Germany) was used as a

film forming and taste masking polymer in film coating of minitablets. Lutrol® F127 (poloxamer 407, BASF, Germany) (10% m/m, on dry polymer) and dibutyl sebacate (Fluka Chemie AG, Germany) (15% m/m, on dry polymer) were used as the dispersing agent and plasticizer, respectively. Magnesium stearate, Ph.Eur. (donated by Orion Pharma, Finland) was used as an antitacking agent (35% m/m, on dry polymer). Distilled water was used as a dispersion medium for film coating.

ALD TiO_2 films were grown from titanium tetrachloride ($TiCl_4$) (Sigma-Aldrich, USA) and deionized water. TiO_2 was chosen over zinc and aluminium oxides due to its common use as a coloring agent in pharmaceutical coating formulations. The TiO_2 was considered beneficial also for taste masking purpose due to its hydrophobic (water insoluble) nature.

Distilled water was used as a test medium for tablet disintegration *in vitro*. The *in vitro* dissolution tests were performed using sodium phosphate buffer (SPB) pH 7.6 (US Pharmacopoeia) as a testing medium. The SPB was composed of sodium hydroxide (VWR International S.A.S., France), KH_2PO_4 (Riedel-de Haën, Germany) and distilled water. The uniformity of content test of minitablets was also performed with SPB (pH 7.6).

Acetonitrile (ACN) (Sigma-Aldrich Chemie GmbH, Germany) and aqueous 10mM ammonium acetate pH 4.5 (Sigma-Aldrich Chemie GmbH, Germany) were used as eluents for high performance liquid chromatography (HPLC) analyses conducted for the dissolution and uniformity of content tests.

2.2 Design of experiments

Three different number of coating cycles (100, 300 and 500 cycles) resulting different coating thicknesses were used for the ALD thin coating of minitablets. The numbers of cycles were

selected based on the results of preliminary experiments on ALD. For the polymer coating of minitablets, the design of experiments involved four different polymer coating concentrations of 2, 4, 6 and 8 mg/cm^2. The levels were selected based on the existing knowledge on the minimum coating thickness of Eudragit® E (1-2 mg/cm^2) effective enough for taste masking (Evonik, 2009).

2.3 Preparation of granules and minitablets

Wet granulations of powder mixtures (400 g) were performed in a Diosna high-shear granulator (Dierks&Söhne GmbH, Germany) using distilled water as a granulating liquid. The mixing speeds for impeller and chopper were 600 rpm and 1500 rpm, respectively. The water spraying rate of 140 g/min was used. MCC, calcium hydrogen phosphate dihydrate, HPC and crospovidone were first dry mixed for two minutes. Then, the aqueous solution of denatoniun benzoate was pipetted onto the surface of mixed dry powder bed, and subsequently distilled water was sprayed while continuously mixing a powder blend. When the total amount of water (0.45 g/g) was added, granulation was stopped without any kneading phase. The total amount of water was empirically determined based on the preliminary granulation experiments.

Wet granules were wet-sieved (Quadro Comil, Quadro Engineering, Canada) and tray-dried at 40°C for 2 hours, and subsequently at room temperature (RT) for overnight. Prior to tablet compression, the dried masses were sieved (Quadro Comil) with a mesh size of 800 μm. Lubricant (sodium stearyl fumarate) was added and mixed with the granules (Turbula, Willy A. Bachofen AG, Switzerland) for 5 minutes. The masses intended for minitablet compression were allowed to equilibrate at RT/60%RH (relative humidity) for at least 12 hours before tableting.

193 The granulated masses were tableted at RT/50%RH with a rotary tablet press (Ronchi, Officine
194 Meccaniche F.lli Ronchi, Italy) and single tip punches of 3 mm in diameter to receive round and
195 biconvex minitablets with a target weight of 25 mg and denatonium benzoate strength of 10 µg.
196 Tablets were produced in three separate batches. The average upper and lower punch
197 compression forces (and relative standard deviations, RSD) for the batches I-III were as follows:
198 Batch I 1.8 kN (10.3%) / 0.7 kN (27.1%); Batch II 2.0 kN (11.9%) / 1.8 kN (13.8%); and Batch
199 III 1.7 kN (10.6%) / 1.5 kN (11.6%).

200 ***2.4 Polymer film coating of minitablets***

201 The aqueous polymer coating dispersions were prepared by adding emulsifier and plasticizer into
202 a small portion of distilled water and mixing with a magnetic stirrer. Next, the film-forming
203 polymer was progressively added into the aforementioned solution and mixed with a magnetic
204 stirrer for 30 minutes. Magnesium stearate was then homogenously suspended in the remaining
205 portion of water for 30 minutes with a high-shear mixer (Ultra-Turrax, IKA, Germany). The
206 magnesium stearate suspension was added to the polymer dispersion, and the mixture was
207 rapidly homogenized with a high-shear mixer. Finally, the coating suspension was passed
208 through a 500-µm sieve. The final coating dispersions were continuously mixed for overnight
209 with a magnetic stirrer prior to film coating process.

210 Polymer coating of minitablets was performed in a laboratory-scale fluidized-bed apparatus
211 (Aeromatic AG, Switzerland) equipped with bottom spray-installed Wurster set-up. The height
212 of the Wurster column was 7.0 cm. The nozzle was a Schlick 970/7-1 pneumatic external mixing
213 two-fluid nozzle (Düsen-Schlick GmbH, Germany). The coating processor with instrumentation
214 was connected to a PC and operated via InTouch –software (Wonderware, USA). The coating

batch size was 100 g. The atomizing air pressure was 1.1 bar and the inlet air volume (air flow rate) 12.5 l/s. All coatings were performed in an ambient inlet air RH of 22 ± 0.4% measured with a Vaisala HUMICAP® HMT100 humidity and temperature probe (Vaisala Oyj, Finland). Before each coating experiment, the coating chamber (made of glass) was preheated with an inlet air flow rate of 12.5 l/s, inlet air temperature of 40-50°C, and outlet air temperature of approximately 40°C. The main parameters for nozzle diameter, atomizing air pressure, inlet air volume, inlet air temperature and spraying rate describing the actual coating process are given in **Table 1**. The end-point of a spraying phase was determined as the point where the theoretical polymer amount of 2, 4, 6 and 8 mg/cm^2 was achieved. The end-point of a drying phase was reached when the difference in RH between the inlet and outlet air was constant. Coated minitablets were further tray-dried and cured at 40°C for 24 hours.

2.5 ALD coating of minitablets

The ALD was performed in a laboratory-scale flow type ALD reactor (Beneq TFS 200, Finland). Uncoated minitablets were placed on the bottom of the reactor plate and pretreated in the reactor at 65°C and at the pressure of 2 mbar for 24 hours prior to deposition to remove the moisture from the tablets. The thin nanolayers of TiO_2 were grown on minitablets from $TiCl_4$ and water at 65°C. Nitrogen (N_2) was used as a carrier and purging gas. The $TiCl_4$ and water were evaporated from the sources at 20°C. The cycle consisted of a 300 ms $TiCl_4$ pulse, 20 s N_2 purge, 300 ms water pulse and 30 s N_2 purge. The number of ALD cycles was 100, 300 and 500 corresponding to approximately 10, 30 and 50 nm film thicknesses measured from the silicon reference sample processed in the same runs. Using the approximate coating film thickness (10, 30 and 50 nm) and the density of TiO_2 (4.23 g/cm^3), the amount of TiO_2 coating was 0.0042 mg/cm^2, 0.0127 mg/cm^2 and 0.0212 mg/cm^2 corresponding to respective ALD cycles of 100, 300 and 500. After

238 the coating, the minitablets were collected from the coating chamber and were stored in carefully
239 closed glass vials at RT prior to further analyses.

240 ***2.6 Characterization of minitablets***

241 The surface morphology of uncoated and coated minitablets containing denatonium benzoate
242 was studied using a scanning electron microscope (SEM) (FEI Quanta FEG250, FEI Inc., USA)
243 at the Electron Microscope Unit, Institute of Biotechnology, Helsinki, Finland. Dry platinum-
244 coated samples were scanned using a voltage of 10 kV. The surface morphology and surface
245 content analysis for uncoated and TiO_2 coated minitablets (500 cycles) were further determined
246 by field emission scanning electron microscope with energy dispersive spectroscopy (SEM-EDS)
247 (Hitachi S-4800 equipped with Oxford INCA 350) at the Department of Chemistry, Helsinki,
248 Finland. The measurements were performed using the voltage of 20 kV. Minitablet samples were
249 coated with carbon prior to the measurements.

250 The height of minitablets was measured with a Sony digital micrometer (Sony Digital Indicator
251 U30-F, Sony, Japan) (n=10). The uniformity of mass and uniformity of content tests were
252 performed according to Ph. Eur. (the tests described in the chapters 2.9.5 and 2.9.6, respectively).

253 The dissolution of denatonium benzoate minitablets was determined using a modified Ph.Eur.
254 (2.9.3) basket method and apparatus A (Erweka DT6, Erweka GmbH, Germany) (n=4). The
255 dissolution medium was 40 ml of SPB (pH 7.6) at 37 - 38°C. The basket rotation speed was 50
256 rpm. The samples were collected manually at time periods of 0 and 15 s, and then, after every 30
257 seconds until the end-point of 6 minutes 15 s. The dissolution sample size for denatonium
258 benzoate containing minitablets was 250 µl. Prior to HPLC analysis, the samples were

centrifuged (13,200 rpm/5 min) and pipetted into HPLC sampling vials. HPLC analyses were performed within 24 hours after dissolution testing.

The disintegration tests of uncoated and coated minitablets were performed using a Sotax DT3 tablet disintegration apparatus (Sotax AG, Switzerland). The method was slightly modified for small minitablets from the standard Ph.Eur. tablet disintegration method (2.9.1): the bottom of each testing cylinder was covered with a stainless steel mesh (with an average mesh size 0.2 mm) to prevent a small tablet dropping down to the bottom of a test glass beaker.

The tablet breaking force (tablet hardness) was determined using a Schleuniger-2E tablet hardness tester (Dr. K. Schleuniger & Co., Switzerland) with a slight modification compared to the Ph.Eur. method (2.9.8). Instead of determining the load required to crush a tablet diametrically (when placing tablets diametrically onto their flat side between the jaws), tablets were placed diametrically on their edge (belt) between the jaws. This was due to the occasional non-detectability of the load needed to crush the minitablet placed diametrically onto their flat side.

2.7 HPLC assays

For the uniformity of content and dissolution tests, the samples were analyzed using an Agilent 1100 series HPLC system (Agilent Technologies, USA) equipped with an UV-Vis detector. The reverse-phase column Zorbax Eclipse Plus C18 (100x4.6 mm, 3.5 μm) (Agilent Technologies, USA) was utilized in the analyses.

The flow rate of eluent mixture of ammonium acetate (10 mM, pH 4.5):ACN was 1 ml/min. Denatonium benzoate was detected at wavelength 210 nm at 25°C. For uniformity of content test, the corresponding ratio of the eluents and the retention time of denatonium benzoate was

281 55:45 and 1.8 min (for the uncoated and the polymer coated minitablets), and 60:40 and 2.4 min
282 (for the uncoated and the TiO_2 coated minitablets). For dissolution testing of uncoated and both
283 polymer and TiO_2 coated minitablets, the ratio of the eluents was 60:40, and the retention time of
284 denatonium benzoate was 2.4 min.

285 ***2.8 Statistical method of calculation***

286 The Student´s t-test (two-tailed distribution, two-sample unequal variance) was used for the
287 calculation of statistical differences between uncoated and coated tablets, these in the results of
288 tablet dissolution, uniformity of tablet mass and denatonium benzoate content, tablet
289 disintegration rate, breaking force and height. Difference between uncoated and coated tablets
290 was considered statistically significant with $p<0.05$.

291 **3. RESULTS**

292 ***3.1 Content and dimensions of minitablets***

293 **Table 2** shows the weight, active ingredient content, disintegration time, breaking force and
294 height of uncoated and coated tablets. For TiO_2 coated minitablets, no statistically significant
295 ($p<0.05$) change in the tablet height between uncoated tablets and different coatings of 100, 300
296 or 500 cycles was revealed, though the average tablet height of uncoated tablets was slightly
297 higher than that of coated minitablets. As expected, similarly to tablet height, no changes in the
298 weight of TiO_2 coated minitablets or denatonium benzoate content were revealed.

299 Compared to uncoated tablets, a slight decrease in the denatonium benzoate content was
300 observed in polymer film coated tablets, the difference being statistically significant with
301 polymer amounts of 6 and 8 mg/cm^2 (Table 2). In comparison to uncoated tablets, film coated

tablets exhibited also an increase in the tablet height and weight, particularly with polymer amounts of 4, 6 and 8 mg/cm^2 (tablet height) and with polymer amounts of 2, 6 and 8 mg/cm^2 (tablet weight). The difference between uncoated and polymer coated tablets seemed gradual and in accordance with increased polymer amount. The increase in tablet height with coating of polymer amounts of 2 and 4 mg/cm^2 was lower than with polymer amounts 6 and 8 mg/cm^2. The highest increase in tablet height and weight was observed with polymer amount of 8 mg/cm^2. Tablet height remained relatively unchanged with polymer amount of 2 mg/cm^2 when compared to uncoated tablets. However, the average weight of minitablets with coating of 2 mg/cm^2 decreased in comparison to uncoated minitablets.

3.2 Minitablet hardness

The TiO_2 coating significantly ($p<0.05$) decreased the breaking force (hardness) of minitablets in comparison to uncoated minitablets (Table 2). No difference in the breaking force of minitablets between different TiO_2 thicknesses (100, 300 and 500 cycles) was revealed.

Surprisingly, the breaking force of polymer film coated tablets was also lower than that of uncoated minitablets. No changes in the breaking force were seen between the minitablets coated with polymer concentration of 2 and 4 mg/cm^2, and between the minitablets coated with polymer concentration of 6 and 8 mg/cm^2.

3.3 Disintegration in vitro

The disintegration times of uncoated, TiO_2 coated, and polymer film coated minitablets are presented in Table 2. Surprisingly, the disintegration time of TiO_2 coated minitablets was clearly shorter ($p<0.05$) than that obtained with uncoated minitablets. No clear differences in the disintegration times between ALD coated tablets (100, 300 and 500 cycles) were revealed as the

disintegration tendency described by the average disintegration time was only slightly decreasing over coating cycles.

Surprisingly, the disintegration time of minitablets coated with polymer concentrations of 2 and 4 mg/cm^2 was shorter in comparison to that of uncoated minitablets. However, minitablets coated with polymer concentration of 4 mg/cm^2 disintegrated more slowly than minitablets coated with 2 mg/cm^2 polymer concentration. In addition, the disintegration time of minitablets coated with polymer concentration of 6 mg/cm^2 was shorter than that of minitablets coated with higher amount (8mg/cm^2) of polymer, but compared with uncoated tablets, the difference with polymer amount of 6 mg/cm^2 was not statistically significant. As expected, the disintegration of minitablets containing polymer concentration of 8 mg/cm^2 was slower than that of uncoated or other polymer coated tablets of the study. In addition, the minitablets coated with higher polymer concentration of 8 mg/cm^2 exhibited a clear lag-time prior to disintegration which was not observed with the TiO_2 coated minitablets.

3.4 Dissolution in vitro

The dissolution profiles of uncoated, ALD coated (TiO_2) and polymer film coated minitablets are shown in **Fig. 2**. With both uncoated and ALD coated minitablets (100, 300 and 500 cycles), the lag-time for denatonium benzoate release was very short (less than 45 seconds). With polymer film coated minitablets, denatonium benzoate release was detected at 45 s (2, 4 and 6 mg/cm^2) and at 1 min 15 s (8 mg/cm^2).

At 45 seconds, the highest amount of released denatonium benzoate was detected for minitablets containing 2 mg/cm^2 and 4 mg/cm^2 of coating polymer, while no difference in the released amount of denatonium benzoate was revealed between uncoated and polymer film coated (6

346 mg/cm^2) minitablets. The polymer film coating of minitablets (2, 4 and 6 mg/cm^2) increased the
347 release rate of denatonium benzoate compared to that obtained with uncoated minitablets.
348 However, when the highest amount of coating polymer (8 mg/cm^2) was used, the minitablets
349 exhibited a clear delay in the release rate of denatonium benzoate.

350 TiO_2 ALD coating on minitablets had only a small effect on the release rate and profile of
351 denatonium benzoate. The slowest release of denatonium benzoate was revealed for 500 cycles
352 ALD TiO_2 coated minitablets. Application of 100 and 300 cycles in the TiO_2 ALD coating of
353 minitablets exhibited only a slight delay in the release rate of denatonium benzoate compared to
354 that obtained with uncoated minitablets.

355 ***3.5 SEM and EDS***

356 The SEM images defining the internal structure and surface morphology of uncoated and coated
357 minitablets are shown in **Fig. 3**. The SEM-EDS linescans of TiO_2 ALD coated minitablets (500
358 cycles) are presented in **Fig. 4** (intact minitablet) and **Fig. 5** (the cross-section of the minitablet).
359 The surface of uncoated minitablet (Fig. 3A) was relatively smooth with dark and white areas,
360 and application of TiO_2 ALD coating had virtually no effect on the surface morphology of
361 minitablets (100 cycles in Fig. 3B, 300 cycles in Fig. 3C, and 500 cycles in Fig. 3D). The surface
362 of polymer film coated tablet (2 mg/cm^2 in Fig. 3E) revealed rough eroded holes on an uneven
363 tablet surface. Smoother and more even minitablet surfaces were obtained with higher coating
364 polymer concentrations (4 mg/cm^2 in Fig. 3F, 6 mg/cm^2 in Fig. 3G, and 8 mg/cm^2 in Fig. 3H).

365 The SEM-EDS linescan of the TiO_2 ALD coated tablet surface revealed the presence of titanium
366 and chlorine on the surface of minitablets (Fig. 4). Moreover, the intensity of the titanium signal
367 seemed to be in accordance with the intensities of elements of calcium and phosphorous (arrows

in Fig. 4 for titanium). With the cut ALD coated minitablet, the intensity of the titanium signal was verified to be exceptionally high on the minitablet surface but decreased rapidly when moving towards the minitablet core (Fig. 5). The penetration of Ti into the structure of the tablet was reaching an approximate depth of 0.2 mm. No titanium was present at the surface of uncoated minitablet (data not shown).

4. DISCUSSION

4.1 Effect of coating method on the properties of minitablets

It is well known that the tablet cores in a conventional fluidized-bed polymer coating process are exposed to a long-term attrition (friction) and collisions resulting in the erosion (even breakage) of tablets during processing. However, the ALD thin coating of tablets with TiO_2 in flow type ALD reactor is a much more gentle procedure as the tablets are stationary during coating and thus, are not susceptible to kinetical attrition or collisions similar in fluidized-bed. Thus, no statistically significant differences between uncoated and ALD-coated tablets were revealed for tablet integrity, weight, dimensions, or active drug content.

Surprisingly, however, the breaking force (hardness) and disintegration time of minitablets decreased after ALD coating. This was confusing, especially as in the literature, the ALD coated 3-layer tablets have been reported to comply with the specifications for hardness and disintegration time of such dosage forms (Lehtonen et al., 2013). Thus, by contrast to a decrease in the minitablet strength and disintegration, a delay was our more likely expectation, particularly as in theory, the chosen minitablet formulation was thought to support the formation of even, pinhole-free and moisture protective TiO_2 ALD nanolayers. Moreover, in the present study, the experimental composition of minitablet core was considered ideal for ALD thin

390 coating, since the presence of the free hydroxyl groups on the surface of MCC in addition to the
391 tablet surface moisture were expected to provide excellent binding sites for $TiCl_4$. This should
392 foster also the formation of homogeneous TiO_2 nanolayers on tablet surfaces, voids and crevices,
393 thus reducing the core ability to interact with its surroundings. Moreover, the low deposition
394 temperature of 65°C used in the present study was not harmful for the tablet core. In the
395 literature, TiO_2 ALD nanolayering of tablets using $TiCl_4$-water chemistry has been successfully
396 conducted at temperatures even lower than 65°C (Lehtonen et al., 2013). The decrease in
397 hardness and disintegration time of minitablets after ALD thin coating can be explained by the
398 fact that pharmaceutical tablets are heterogeneous and porous solid systems, unlike to the
399 substrates traditionally used in ALD thin coating. Moreover, the real ALD film growth
400 mechanism may not be as simple as the theory outlines.

401 A short interaction between moisture and heterogeneous tablet core components (such as the
402 disintegrant crospovidone or MCC) can cause the microerosion of tablets during an ALD thin
403 coating processing. It is evident that this also induces the creation of new pores, new open intact
404 tablet surfaces, and even new complicated pore networks to the tablet structure. Moreover, the
405 risk for microerosion can increase (especially at low temperatures) because of the liberation of
406 the reaction side product of hydrochloric acid gas, due to $TiCl_4$-water chemistry, adsorbing onto
407 the TiO_2 surface (Ritala et al., 1993). As microerosion enlarges, the active surface area of tablets
408 requiring coating also becomes larger. This means that during deposition the exposed new
409 surfaces and pore networks are not likely to be adequately covered by TiO_2 nanolayers, simply
410 due to insufficient amount of coating precursor. Thus, microerosion could reduce the layer
411 moisture protecting capability and accelerate the tablet disintegration rate, as well as decrease the
412 tablet hardness. Moreover, in theory, the TiO_2 is covalently bonded to the hydroxyl-covered

substrate surface. This could indicate the formation of a completely new chemical component with characteristics totally different from those of the original substance. Also, the variation in the configuration and the level of the hydroxyl-grouped surfaces may complicate the film growth (Ritala et al., 1993). It is evident that areas with uneven and variable level of hydroxyl groups lead to uneven TiO_2 layers. Furthermore, the amphoteric chemical behavior of TiO_2 surface due to differently orientated and bonded hydroxyl groups on the TiO_2 surface (Parfitt, 1976) can lead to additional reactions other than with $TiCl_4$. Low deposition temperatures used in the TiO_2 ALD thin coating can also induce the formation of chemical impurities (residual ions), such as chlorine in ALD thin films originating from $TiCl_4$ precursor ligands (Ritala et al., 1993; Jõgi et al., 2006), and may therefore change the film properties. In addition, at this growth temperature ALD TiO_2 thin films are in fact amorphous and may thus have increased intensity for moisture related interactions.

The success of TiO_2 ALD coating is therefore very much dependent on the tablet core composition, structure and properties. With the present minitablets, phenomena occurring on the heterogeneous tablet surface are hence strongly emphasized. Lehtonen and co-workers (2013) investigated the ALD thin coatings applied to the tablets composed of three-layered pharmaceutical solids containing layers of probiotics and vitamin C. Pharmaceutical tablets are commonly compressed from heterogeneous mixtures. Due to such complex compositions, the coatings applied to the outer surface of tablet cores are exposed to multiple different components, which all have characteristic porosity and interaction capabilities, e.g. with moisture or chemicals. Consequently, the formation of even and pinhole-free TiO_2 ALD nanolayers is greatly affected by the chemical composition of the tablet surface (especially, the excipients rich on hydroxyl groups play a key role), and most likely also by surface moisture. In

other words, the formation and growth of TiO_2 thin films is fostered by the surfaces exhibiting very high hydroxyl group density. In addition, the pore density, size and tortuosity of excipients can play a crucial role affecting TiO_2 ALD thin films. Depending on the physicochemical characteristics, the active outer surface area of tablet excipients can be very different due to interaction with moisture. Consequently, deep voids or complex pore structures can result in inadequate TiO_2 ALD nanolayer formation and growth. Moreover, the formation of intact TiO_2 ALD coating in tablet pores is most likely to be fostered by the presence of high hydroxyl group density. With the present minitablets, it is evident that excipients and/or denatonium benzoate interact with titanium to different extent and mechanism, thus affecting the formation of nanolayers. Therefore, the reason for the unexpected decrease in the hardness and disintegration time of coated minitablets is most likely the heterogeneity and physicochemical diversity of chemical components in the tablet surface.

ALD thin coating has a number of advantages compared to a traditional fluidized-bed film coating method. The TiO_2 ALD nanolayering is a gentle procedure in a flow type reactor without any actual collision related impact on tablets. On the contrary, the traditional fluidized-bed coating requires adequate mechanical strength of tablet cores, and appropriate and well-designed tablet compositions. In a fluidized-bed coating process, tablet breakage takes place readily due to a long-term collision and abrasion during fluidization, and due to the elevated temperature and humidity conditions during polymer dispersion spraying and drying. Moreover, particles detached from tablet cores can disturb the formation of even polymer coating and lead to a great variation in an active ingredient content, disintegration and dissolution of tablets. It is also well-known that traditional polymer film coating can lead to a significant increase in tablet weights

458 and delay in disintegration times, especially if thick polymer coatings involving high amounts of
459 polymer are used.

460 In our study, fluidized-bed polymer film-coated tablets exhibited a clear decrease in hardness
461 (breaking force), tablet weight and denatonium benzoate content compared to the corresponding
462 uncoated tablets, all mostly related to tablet erosion and breakage during film coating process.
463 The possibility for tablet breakage was expected to be avoided with the inclusion of MCC as a
464 main component in the tablet core formulation. MCC deforms plastically under compression and
465 maximizes the area of inter-particle hydrogen bonding, thus increasing tablet mechanical
466 strength and hardness (Bolhuis and Lerk, 1973). Consequently, no friability test was performed
467 for the MCC containing minitablet cores, and also because the tablet friction during the strong
468 fluidization in the actual fluidized-bed apparatus was considered to provide a more accurate
469 result for tablet friability. MCC can also entrap and hold significant amounts of moisture inside
470 its structure (Zografi and Kontny, 1986), thus making it an excipient of choice for the moisture-
471 sensitive ingredients in tablets. Its moisture related interactions during processing and drying are
472 also well-documented (Luukkonen, 2001; Luukkonen et al., 2001; Kleinebudde, 1994).

473 In fluidized-bed coating, several process-related conditions (e.g. high humidity, agitation and
474 elevated temperatures during spraying and drying) can affect the final polymer film coated
475 tablets. Using aqueous polymer coating dispersions, the process-induced changes (interactions)
476 are naturally more evident if the tablet cores are composed of amorphous and/or moisture
477 sensitive excipients, e.g. binders (HPC) or disintegrants (crospovidone) (Joshi and Petereit,
478 2013). These changes are also greatly dependent on the duration (time) of a fluidized-bed
479 process. In our study, the most significant process-induced changes were resulted by the decrease
480 of the hardness of minitablets.

We found that the minitablet cores used in the fluidized-bed polymer coating experiments did not completely withstand the process conditions (agitation, high humidity and elevated temperature). This was obviously partly due to the interaction of MCC with moisture, thus leading to a notable decrease in the mechanical strength (hardness) of tablets. This finding is also in good agreement with that reported in the literature (Westermarck et al., 1999). Moreover, the moisture-induced softening and erosion of tablet cores are most likely fostered with the presence of moisture-sensitive HPC and crospovidone in the tablet formulation. The deteriorating influence of moisture and agitation continues until the uniform and intact film coating is formed around tablets. Deterioration of polymer film-coated tablets can continue even after a coating process, if moisture is entrapped inside the tablet core and polymer film.

To avoid tablet deterioration related problems with moisture-sensitive tablet formulations, spraying of polymer dispersion in fluidized-bed coating could be started with a small amount of dispersion followed by an immediate drying phase. This kind of spraying protocol is expected to enhance the initial film formation, thus protecting tablet cores from future moisture interactions. In the fluidized-bed film coating of minitablets, it is also important to control and optimize the spraying properties of dispersion such as droplet size in order to avoid over-wetting and subsequent softening of tablet cores. Compared to large-sized tablets, adequate coating of minitablets containing swellable excipients in particular requires higher amounts of coating polymer due to the larger outer surface area of such minitablets (Mehta, 1997). This is even more important with taste masking film coatings where the applicability and efficacy of coating is dependent of film thickness and intactness. One option to overcome the challenge associated with the larger outer surface area of minitablets is to prolong contact time of tablet cores with the

503 coating polymer dispersion, e.g. by modifying a Wurster column set-up or by increasing a
504 coating process time. However, such changes will impact also the other coating parameters.

505 ***4.2 Taste masking efficacy of minitablets***

506 Sensing the taste requires the initial interaction of the tablet with moisture (saliva), and
507 subsequent tablet disintegration and dissolution of tastant in the oral cavity. The sensory
508 information from the tongue is then instantly transmitted via neural pathways to the brain to be
509 interpreted as taste perception (Thombre, 2004). The requirement of saliva solubility makes the
510 taste a chemical sense. Normally, the physiological pH of human saliva is neutral varying from
511 pH 6 to pH 7.5 (Tenovuo, 1995). The diet can greatly affect the pH of saliva. Therefore, the
512 typical pH of saliva in herbivores and omnivores is more alkaline than the saliva pH of
513 carnivores.

514 For the evaluation of minitablet dissolution and bitter taste masking efficacy *in* vitro, we used an
515 aqueous buffer solution pH 7.6 representing the average pH for the saliva. The expected
516 residence time of tablets in the mouth was also taken into account in a study protocol. In our
517 study, a mouth residence time longer than 45 seconds without detected bitter tasting denatonium
518 benzoate was required for effective minitablet taste masking, as on average, the time period of a
519 solid dosage form to remain in the mouth is relatively short ranging from a few seconds to 30-60
520 seconds (Joshi and Petereit, 2013). In this study, the modified disintegration and dissolution tests
521 of minitablets *in vitro* were used to indirectly show the taste masking efficacy of the coated
522 tablets. With better mimicking of the soft tissue function and conditions in the mouth and
523 gastrointestinal system, the more gently proceeding tablet dissolution test with results on

524 detected denatonium benzoate release were emphasized when used as a tool for the rapid taste
525 masking efficacy evaluation purposes of the coated minitablets of the study.

526 The *in vitro* dissolution results of TiO_2 ALD coated minitablets were in accordance with the *in*
527 *vitro* disintegration times of the respective nanolayered minitablets (Fig. 2). The early
528 denatonium benzoate release from both uncoated and TiO_2 ALD coated minitablets was
529 observed at 45 s. This suggests that the coating thickness of the present ALD nanolayered
530 minitablets (i.e., the coating cycles of 100, 300 and 500) is not sufficient for the effective taste
531 masking. The present finding is rather surprising since the multiple TiO_2 nanolayers were
532 expected to act as effective barriers to prevent water and oxygen penetration, and thus delay the
533 onset of denatonium benzoate release, and moreover, as Lehtonen and co-workers (2013)
534 reported about the delay in the onset of drug release of TiO_2 ALD layered vitamin C tablets as
535 well as the taste and smell masking of ALD coated fish oil soft gelatin capsules. In our study,
536 only negligible delay in the dissolution of denatonium benzoate from TiO_2 coated minitablets
537 was observed, this regarding minitablets coated with 500 coating cycles. Furthermore, no
538 statistical significant difference ($p>0.05$) was found between the early-stage dissolution (within
539 45 s – 1 min 15 s) of TiO_2 ALD layered minitablets compared to uncoated minitablets.

540 We found that the minitablets coated with a polymer amount of 8 mg/cm^2 are evidently
541 applicable for the bitter taste masking of denatonium benzoate. The present fluidized-bed coated
542 minitablets exhibited the most extensive delay in the onset of disintegration and dissolution *in*
543 *vitro* (Fig. 2 and Table 2). However, it should be emphasized that the dissolution and mechanical
544 properties (softening) of these polymer film coated minitablets are greatly dependent on the
545 fluidized-bed coating conditions. The ALD thin coating method has some advantages over
546 fluidized-bed coating conditions. The ALD nanolayering is a simple and rapid method, and

especially applicable in case of moisture sensitive tablet formulations since tablet cores are not exposed to high humidity conditions similar to those in fluidized-bed coating. Consequently, ALD nanolayering should not affect the physicochemical and pharmaceutical properties of tablets. Our results suggest also that the adequate taste masking efficacy of minitablets could be achieved by increasing the number of coating cycles in the TiO_2 ALD nanolayering, as the release of bitter tasting denatonium benzoate was, though only slightly, delayed from minitablets coated with 500 coating cycles. Attention should also be put onto the time required for the precursor pulse, as the unexpected dissolution of TiO_2 coated minitablets could be also explained by the pulse of 300 ms being possibly inadequate for precursors to penetrate into the tablet pores. In addition, the coating materials other than TiO_2 or the multilayer ALD coatings could also open new alternatives to single ALD thin coatings for taste masking applications. For example, Al_2O_3 ALD thin coated tablets have been shown to exhibit faster drug release in water in comparison to TiO_2 ALD coated tablets (Lehtonen et al., 2013). The use of an ALD coating system (reactor) other than the flow type one could also provide improvements in taste masking efficiency. Carlsson and co-workers (2016) reported the existence of holes in the ALD coated nanoparticles due to the contact points with other nanoparticles during deposition. In theory, this could be also possible with the present TiO_2 ALD thin-coated minitablets, since the exposure of stationary tablet(s) to ALD could lead to disruptions in thin coatings due to the direct contact of the tablet lower surface with an ALD tray. The probability for the formation of uncoated contact points in minitablets, however, is minimal, since the tablets are slightly vibrating in the semifluid state during the flow of ALD coating. Therefore, the major reason for the defects of TiO_2 ALD thin coating (and obviously for a limited taste masking efficacy of minitablets) is the heterogeneous structure of the tablet surface. It is evident that the surface moisture is adequate for ALD and for

570 the formation of even TiO_2 nanolayers, but the affinity of some tablet excipients varies a lot and
571 this can prevent the formation of homogeneous and continuous TiO_2 nanolayers.

572 ***4.3 Surface morphology and content analysis***

573 The surface properties of fluidized-bed film coated minitablets were dependent on the amount of
574 coating polymer used. The minitablets coated with the lowest polymer amount of 2 mg/cm^2
575 exhibited a large variation in film coating appearance (quality) due to erosion and tablet breakage
576 (Fig. 3E). The tablets coated with the highest polymer amount of 8 mg/cm^2 had an intact and
577 smooth surface (Fig. 3H). The actual coating thickness of polymer coated tablets ranged from
578 some tenths of micrometers (2 mg/cm^2) to a few hundred micrometers (8 mg/cm^2). Such great
579 variation in coating thicknesses (and intactness) explains also the changes in physical and
580 pharmaceutical properties of minitablets coated with different amounts of polymer.

581 Since SEM did not permit the nanometer-scale analysis of the ALD nanolayered minitablets, the
582 surface of an uncoated and a TiO2 coated (500 cycles) minitablet was analyzed also with SEM-
583 EDS. This analysis (elemental mapping) was primarily carried out to explain the accelerated
584 disintegration and dissolution behavior of ALD thin-coated minitablets. The presence of Ti
585 signal on the porous ALD coated minitablet surface can be considered as an important
586 verification on the successful nanolayer formation onto the surface of minitablets. In accordance
587 to the theory on hermetic ALD layers on porous minitablets, the SEM-EDS results suggested that
588 the TiO_2 layer was integral and indeed entirely covering the various areas over the linescan on
589 the minitablet surface leaving no disrupted areas in the coating. Moreover, in agreement with our
590 theory of ALD thin coating on porous tablets, the TiO_2 precursors seem to diffuse into the voids
591 and pores of minitablets with the estimated diffusion length of approximately 100-200 μm. This

finding supports the view that the ALD thin coating of minitablets can be successfully performed. The major limitation of the presented coated substrates, however, was that they did not permit us to analyze the interface between the minitablet core and nanolayer, and thus to determine the actual thickness of titanium coating. Lehtonen and co-workers (2013) used SEM to measure a nanometer scale Al_2O_3 (10 nm) + TiO_2 (10 nm) layer thickness of fish oil containing soft gel gelatin capsules. In our study, however, the analysis of the interface of tablet core and nanolayers, and coating thickness are much more challenging due to the porous structure of tablet surface compared to that of soft gelatin capsule. Nevertheless, this issue could be overcome by the verification of integral titanium layer on minitablets combined with the known theoretical nanocoating thickness.

In addition to titanium, traces of chlorine were also present on TiO_2 ALD coated minitablet surface. This is obviously due to a porous substrate and low ALD coating temperature of 65°C which is known to leave residuals of incompletely reacted $TiCl_4$ on surfaces (Ritala et al., 1993). The residuals present could be minimized by increasing the ALD coating temperature up to and even over 200°C (Ritala et al., 1993). Many active pharmaceutical substances and excipients, however, are thermally sensitive, which limits the use of very high handling temperatures during ALD thin coating. Further studies will be needed on the formation and role of precursor residuals (including safety and toxicity) in ALD nanolayers.

The SEM-EDS morphological and elemental analysis revealed that the surface of uncoated minitablets is porous and heterogeneous due to the multiple excipients used for formulating the tablet cores. The surface of uncoated minitablets (cores) was covered with the grey-white and dark areas (spots), which were still clearly visible in TiO2 ALD coated tablets. The bright areas revealed a more intense signal for phosphorous and calcium over dark areas. The presence of

615 phosphorous and calcium refers to the calcium hydrogen phosphate dihydrate used as an
616 excipient in the minitablet composition. Surprisingly, the behavior of phosphorous and calcium
617 seemed to be followed by an increase in the manifestation for titanium. The difference in
618 titanium intensity between white and dark areas was found to be notable and in contrast to other
619 surface elements. The intensity of titanium was clearly the highest in the white surface areas
620 together with phosphorous and calcium.

621 The present finding is considered as significant. The high intensity of titanium signals indicates
622 that certain pharmaceutical excipients (such as in our study calcium hydrogen phosphate
623 dihydrate) can be coated (nanolayered) with TiO_2 more easily than others. The differences in the
624 intensity of titanium signals can also indicate the uneven formation of nanolayers on the
625 heterogeneous surface of minitablets, thus resulting in the limited moisture protection and
626 changes of the performance of ALD coated minitablets. However, the formation of uneven
627 nanolayers, can be argued since titanium was also detected in the surface pores of the minitablet
628 cores, and may therefore not be seen there at the equal levels found in the calcium and
629 phosphorous rich surfaces. Further studies will be needed on using TiO_2 nanolayers with both
630 active pharmaceutical substances and excipients.

631 **5. CONCLUSIONS**

632 ALD provides a simple and rapid method for the ultrathin coating (nanolayering) of minitablets.
633 It is evident that the level of agitation and collision forces between tablets in ALD are minor
634 compared to polymer coating in a fluidized-bed, not to mention that the method is relatively
635 simple compared to the conventional and challenging polymer film coating process. The ALD
636 thin coating method has both advantages and limitations over traditional film coating methods.

The ALD thin coating is a rapid process since no spraying and drying steps are needed. However, the unexpected changes in the TiO_2 ALD coated minitablet mechanical properties seen as an accelerated tablet disintegration rate and decreased tablet hardness may challenge its feasibility in the coating of heterogeneous substrates composed of substances with different chemical characteristics and reaction ability, until a thorough understanding on possible phenomena taking place on tablet surface and within used diverse and physicochemically variable excipients during ALD process is established. Therefore, the major challenges of ALD thin coating are related to the sufficient taste masking capacity and interactions of coating/layering material (TiO_2) with the excipients used in the tablet core. More research is needed to clarify the potential of ALD in tablet coating applications. For example, coating materials other than TiO_2, the effects of the number of coating cycles and the length of the precursor pulses on the taste masking are suggested for further study.

ACKNOWLEDGEMENTS

The authors would like to thank Research Technician Mervi Lindman from the Electron Microscopy Unit of University of Helsinki for all her expertise in SEM imaging of minitablets.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

655 **REFERENCES**

656 Ayenew, Z., Puri, V., Kumar, L., Bansal, A.K., 2009. Trends in pharmaceutical taste masking
657 technologies: A patent review. Recent Pat. Drug Deliv. Formul. 3, 26-39.

658 Bolhuis, G.K., Lerk, C.H., 1973. Comparative evaluation of excipients foe direct compression, I.
659 Pharm. Weekbl. 108, 469-481.

660 Bruce, H.F., Sheskey, P.J., Garcia-Todd, P., Felton, L.A., 2011. Novel low-molecular-weight
661 hypromellose polymeric films for aqueous film coating applications. Drug Dev. Ind. Pharm. 37,
662 1439-1445.

663 Carlsson, J-O., Johansson, A., Rooth, M., 2016. A solid nanoparticle with inorganic coating. U.S.
664 Patent 0081945 A1.

665 Evonik Industries. Eudragit® Application Guidelines, 11th Ed. 2009.

666 Felton, L.A., 2007. Characterization of coating systems. AAPS PharmSciTech 8, 112.

667 George, S., 2010. Atomic layer deposition: an overview. Chem. Rev. 110, 111-131.

668 Hoppu, P., Kaariainen, T., Kaariainen, M-L., Turunen, A., 2015. Method for coating
669 pharmaceutical substrates. U.S. Patent 0250731 A1.

670 Joshi, S., Petereit, H-U., 2013. Film coatings for taste masking and moisture protection. Int. J.
671 Pharm. 457, 395-406.

672 Jõgi, I., Aarik, J., Laan, M., Lu, J., Kukli, K., Käämbre, H., Sajavaara, T., Uustare, T., 2006.
673 Effect of preparation conditions on properties of atomic layer deposited TiO_2 films in Mo-TiO_2-
674 Al stacks. Thin Solid Films 510, 39-47.

675 Kleinebudde, P., 1994. Shrinking and swelling properties of pellets containing microcrystalline
676 cellulose and low substituted hydroxypropylcellulose: I. Shrinking properties. Int. J. Pharm. 109,
677 209-219.

678 Lehmann. K., 1997. Chemistry and application properties of polymethacrylate coating systems,
679 in: McGinity, J., (Ed.), Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, 2nd Ed.
680 Marcel-Dekker, Inc., New York, USA, pp. 101-176.

681 Lehtonen, L., Bley, H., Van Der Heyden, L., 2013. Coated solid pharmaceutical preparation.
682 U.S. Patent 0337056 A1.

683 Luukkonen, P., 2001. Rheological properties and the state of water of microcrystalline cellulose
684 and silicified microcrystalline cellulose wet masses. PhD Thesis, University of Helsinki, Finland.

685 Luukkonen, P., Maloney, T., Rantanen, J., Paulapuro, H., Yliruusi, J., 2001. Microcrystalline
686 cellulose-water interaction – a novel approach using thermoporosimetry. Pharm. Res. 18, 1562-
687 1569.

688 Mehta, A., 1997. Processing and equipment considerations for aqueous coatings, in: McGinity,
689 J., (Ed.), Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, 2nd Ed. Marcel-
690 Dekker, Inc., New York, USA, pp. 287-326.

691 Parfitt, G.D., 1976. The surface of titanium dioxide. Progr. Surf. Membrane Sci. 11, 181-226.

692 Pearnchop, N., Siepmann, J., Bodmeier, R., 2003. Pharmaceutical applications of shellac:
693 moisture-protective and taste-masking coatings and extended-release matrix tablets. Drug Dev.
694 Ind. Pharm. 29, 925-938.

695 Puurunen, R., 2005. Surface chemistry of atomic layer deposition: A case study for the
696 trimethylaluminum/water process. J. Appl. Phys. 97, 121301-121352.

697 Ritala, M., Leskelä, M., 2002. Atomic layer deposition, in: Nalwa, H.S. (Ed.), Handbook of Thin
698 Film Materials, Volume I: Deposition and Processing of Thin Films. Academic Press, San
699 Diego, USA, pp. 103-159.

700 Ritala, M., Leskelä, M., Nykänen, E., Soininen, P., Niinistö, L., 1993. Growth of titanium
701 dioxide thin films by atomic layer epitaxy. Thin Solid Films 225, 288-295.

702 Siepmann, J., Bodmeier, R., McGinity, J., 2013. Progress in film coating. Int. J. Pharm. 457, 361.

703 Sohi, H., Sultana, Y., Khar, R.K., 2004. Taste masking technologies in oral pharmaceuticals:
704 Recent developments and approaches. Drug Dev. Ind. Pharm. 30, 429-448.

705 Tenovuo, J., 1995. Sylki diagnostisena nesteenä. Duodecim. 111, 1355-1359.

706 Thombre, A.G., 2004. Oral delivery of medications to companion animals: palatability
707 considerations. Adv. Drug Deliv. Rev. 56, 1399-1413.

708 Westermarck, S., Juppo, A.M., Kervinen, L., Yliruusi, J., 1999. Microcrystalline cellulose and its
709 microstructure in pharmaceutical processing. Eur. J. Pharm. Biopharm. 48, 199-206.

710 Zografi, G., Kontny, M.J., 1986. The interactions of water with cellulose- and starch-derived
711 pharmaceutical excipients. Pharm. Res. 3, 187-194.

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Captions to illustrations:

Fig. 1. The theoretical formation of TiO_2 nanolayers via the chemical reaction between water and $TiCl_4$ in atomic layer deposition (ALD) thin-coating process. In ALD involving metal oxides, a cycle of surface saturation takes place through two reaction steps performed commonly in vacuum at controlled temperature. During step one (the first half cycle) the metal precursor such as $TiCl_4$ vapor, pulsed to the coating chamber, is allowed to react with the free hydroxyl groups on the substrate surface. The chemical pulse therefore saturates the surface with Ti containing groups through molecular bonds. During step two (the second half cycle) the molecularly bonded structures on the substrate surface react with the oxygen precursor (water vapor) and form the first nanolayer of TiO_2. Between the steps, a purge of inert gas (N_2) is applied to the chamber to remove the possible excess of precursor and reaction by-products. The film thickness is controlled by repeating the number of reaction cycles to reach the desired coating.

Fig. 2. Dissolution profiles of uncoated minitablets, TiO_2 ALD (100, 300 and 500 cycles) thin-coated and fluidized-bed polymer film coated (2, 4, 6 and 8 mg/cm^2 of polymer) minitablets (n=4). The dissolution curves describe the cumulative release of denatonium benzoate from minitablets.

Fig. 3. Scanning electron microscopy (SEM) images on uncoated minitablet (Fig. 3A), TIO_2 ALD thin-coated minitablets (100, 300 and 500 cycles; Fig. 3B-D, respectively) and fluidized-bed polymer film coated minitablets (2, 4, 6 and 8 mg/cm^2; Fig. 3E-H, respectively).

Fig. 4. Scanning electron microscopy-energy dispersive spectroscopy (SEM-EDS) image on the intact TiO_2 ALD thin-coated minitablet (500 cycles). Arrows indicate the presence of titanium on the ALD thin-coated minitablet surface followed by signals on calcium and phosphorous.

Fig. 5. SEM-EDS image on the cross-section of TiO_2 ALD thin-coated minitablet (500 cycles).

736 **Table 1.** Used parameters for minitablet polymer coating.

Parameter	**Value**
Nozzle diameter	0.5 mm
Atomizing air pressure	1.1 bar
Inlet air volume	12.5 l/s
Inlet air temperature	40-50°C
Spraying rate	2.2 g/min

737

738 **Table 2.** Results of the tests performed on both uncoated, and for TiO_2 and EPO coated
739 minitablets of the study. Statistically significant ($p<0.05$) difference between uncoated and
740 coated tablet is marked in bold.

Tablet	Uniformity of mass Average ± SD (mg)	Uniformity of content Average ± SD (mg)	Disintegration rate Average ± SD (s)	Tablet breaking force Average ± SD (N)	Tablet height Average ± SD (mm)
Batch I Uncoated	23.0 ± 0.4	8.6 ± 0.4	48 ± 3	50 ± 4	2.42 ± 0.02
TiO_2 coated, 100 cycles	22.7 ± 0.3	8.3 ± 0.4	**23 ± 2**	**45 ± 2**	2.41 ± 0.03
TiO_2 coated, 300 cycles	22.8 ± 0.4	8.5 ± 0.2	**20 ± 6**	**43 ± 3**	2.40 ± 0.02
TiO_2 coated, 500 cycles	22.7 ± 0.4	8.7 ± 0.3	**19 ± 5**	**44 ± 4**	2.39 ± 0.02
Batch II Uncoated	24.5 ± 0.5	10.0 ± 0.8	44 ± 8	61 ± 7	2.46 ± 0.05
EPO coated, 2 mg/cm^2	**23.9 ± 0.5**	9.8 ± 0.9	**16 ± 2**	**44 ± 3**	2.46 ± 0.02
EPO coated, 4 mg/cm^2	24.8 ± 0.6	9.6 ± 0.6	**25 ± 3**	**44 ± 4**	**2.51 ± 0.04**

Batch III Uncoated	23.3 ± 0.5	10.0 ± 0.6	31 ± 3	51 ± 3	2.40 ± 0.03
EPO coated, 6 mg/cm^2	**24.4 ± 0.6**	**9.3 ± 0.4**	29 ± 4	**37 ± 2**	**2.49 ± 0.03**
EPO coated, 8 mg/cm^2	**25.5 ± 0.6**	9.6 ± 0.8	50 ± 3	**41 ± 3**	**2.54 ± 0.02**

741