

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

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19 **ABSTRACT**

20 We introduce atomic layer deposition (ALD) as a novel method for the ultrathin coating
21 (nanolayering) of minitables. The effects of ALD coating on the tablet characteristics and taste
22 masking were investigated and compared with the established coating method. Minitables
23 containing bitter tasting denatonium benzoate were coated by ALD using three different TiO₂
24 nanolayer thicknesses (number of deposition cycles). The established coating of minitables was
25 performed in a laboratory-scale fluidized-bed apparatus using four concentration levels of
26 aqueous Eudragit[®] E coating polymer. The coated minitables were studied with respect to the
27 surface morphology, taste masking capacity, *in vitro* disintegration and dissolution, mechanical
28 properties, and uniformity of content. The ALD thin coating resulted in minimal increase in the
29 dimensions and weight of minitables in comparison to original tablet cores. Surprisingly, ALD
30 coating with TiO₂ nanolayers decreased the mechanical strength, and accelerated the *in vitro*
31 disintegration of minitables. Unlike previous studies, the studied levels of TiO₂ nanolayers on
32 tablets were also inadequate for effective taste masking. In summary, ALD permits a simple and
33 rapid method for the ultrathin coating (nanolayering) of minitables, and provides nanoscale-
34 range TiO₂ coatings on porous minitables. More research, however, is needed to clarify its
35 potential in tablet taste masking applications.

36 **KEYWORDS**

37 Atomic layer deposition, thin film coating, TiO₂, minitab, taste masking, polymer film coating

38 **ABBREVIATIONS**

39 ALD Atomic layer deposition

- 40 MCC Microcrystalline cellulose
- 41 HPC Hydroxypropyl cellulose
- 42 SPB Sodium phosphate buffer
- 43 ACN Acetonitrile
- 44 HPLC High performance liquid chromatography
- 45 RT Room temperature
- 46 RH Relative humidity
- 47 RSD Relative standard deviation
- 48 SEM Scanning electron microscope
- 49 SEM-EDS Scanning electron microscope with energy dispersive spectroscopy

50 **1. INTRODUCTION**

51 For tablets, polymer film coating is still the most widely used and efficient taste masking
52 technique in the pharmaceutical industry (Ayenew et al., 2009; Joshi and Petereit, 2013; Sohi et
53 al., 2004). In addition to taste masking purposes, polymer film coating of tablets offers a variety
54 of practical advantages that contribute to their therapeutic effect, as well as ensure patient
55 compliance and tablet product stability throughout their shelf life (Bruce et al., 2011; Felton,
56 2007; Joshi and Petereit, 2013; Pearnchob et al., 2003; Siepmann et al., 2013). With polymer
57 film coating, however, sufficient taste masking and drug release control demand relatively thick
58 polymer films, and consequently, the application of large amounts of polymers (Joshi and

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

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

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

91 ALD nanoscale films are formed (grown through deposition) utilizing self-limiting chemical
92 reactions between gaseous precursors chemisorbed on a solid substrate surface. For example,
93 when depositing metal oxide films, compounds of zinc, aluminum or titanium can be used as the
94 metal precursors and water as the oxygen precursor. In many cases, the ALD growth starts by
95 chemisorption of the metal precursor molecules on the hydroxyl groups of the surface. Tablets
96 should allow the initiation of the nanolayering process of ALD, as they are commonly composed
97 of multiple organic excipients containing free hydroxyl groups. In tablets, the number of surface
98 hydroxyl groups required for attachment of molecules can even be created with the small amount
99 of surface moisture readily existing on tablet surfaces and pores. Moreover, from a possible
100 tablet coating point of view, the chemical components like zinc, aluminum and titanium oxides
101 applied by ALD are all established pharmaceutical excipients, and thus their compatibility and
102 safety profiles are well known. Also, compared to the conventional polymer film coating, ALD
103 process is very different. The established polymer coating, performed by a fluidized-bed
104 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

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

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

138 **2. MATERIALS AND METHODS**

139 *2.1 Materials*

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

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

150 film forming and taste masking polymer in film coating of minitables. Lutrol[®] F127 (poloxamer
151 407, BASF, Germany) (10% m/m, on dry polymer) and dibutyl sebacate (Fluka Chemie AG,
152 Germany) (15% m/m, on dry polymer) were used as the dispersing agent and plasticizer,
153 respectively. Magnesium stearate, Ph.Eur. (donated by Orion Pharma, Finland) was used as an
154 antitacking agent (35% m/m, on dry polymer). Distilled water was used as a dispersion medium
155 for film coating.

156 ALD TiO₂ films were grown from titanium tetrachloride (TiCl₄) (Sigma-Aldrich, USA) and
157 deionized water. TiO₂ was chosen over zinc and aluminium oxides due to its common use as a
158 coloring agent in pharmaceutical coating formulations. The TiO₂ was considered beneficial also
159 for taste masking purpose due to its hydrophobic (water insoluble) nature.

160 Distilled water was used as a test medium for tablet disintegration *in vitro*. The *in vitro*
161 dissolution tests were performed using sodium phosphate buffer (SPB) pH 7.6 (US
162 Pharmacopoeia) as a testing medium. The SPB was composed of sodium hydroxide (VWR
163 International S.A.S., France), KH₂PO₄ (Riedel-de Haën, Germany) and distilled water. The
164 uniformity of content test of minitables was also performed with SPB (pH 7.6).

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

169 ***2.2 Design of experiments***

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

172 selected based on the results of preliminary experiments on ALD. For the polymer coating of
173 minitables, the design of experiments involved four different polymer coating concentrations of
174 2, 4, 6 and 8 mg/cm². The levels were selected based on the existing knowledge on the minimum
175 coating thickness of Eudragit® E (1-2 mg/cm²) effective enough for taste masking (Evonik,
176 2009).

177 ***2.3 Preparation of granules and minitables***

178 Wet granulations of powder mixtures (400 g) were performed in a Diosna high-shear granulator
179 (Dierks&Söhne GmbH, Germany) using distilled water as a granulating liquid. The mixing
180 speeds for impeller and chopper were 600 rpm and 1500 rpm, respectively. The water spraying
181 rate of 140 g/min was used. MCC, calcium hydrogen phosphate dihydrate, HPC and
182 crospovidone were first dry mixed for two minutes. Then, the aqueous solution of denatonium
183 benzoate was pipetted onto the surface of mixed dry powder bed, and subsequently distilled
184 water was sprayed while continuously mixing a powder blend. When the total amount of water
185 (0.45 g/g) was added, granulation was stopped without any kneading phase. The total amount of
186 water was empirically determined based on the preliminary granulation experiments.

187 Wet granules were wet-sieved (Quadro Comil, Quadro Engineering, Canada) and tray-dried at
188 40°C for 2 hours, and subsequently at room temperature (RT) for overnight. Prior to tablet
189 compression, the dried masses were sieved (Quadro Comil) with a mesh size of 800 µm.
190 Lubricant (sodium stearyl fumarate) was added and mixed with the granules (Turbula, Willy A.
191 Bachofen AG, Switzerland) for 5 minutes. The masses intended for minitab compression were
192 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

215 batch size was 100 g. The atomizing air pressure was 1.1 bar and the inlet air volume (air flow
216 rate) 12.5 l/s. All coatings were performed in an ambient inlet air RH of $22 \pm 0.4\%$ measured
217 with a Vaisala HUMICAP[®] HMT100 humidity and temperature probe (Vaisala Oyj, Finland).
218 Before each coating experiment, the coating chamber (made of glass) was preheated with an inlet
219 air flow rate of 12.5 l/s, inlet air temperature of 40-50°C, and outlet air temperature of
220 approximately 40°C. The main parameters for nozzle diameter, atomizing air pressure, inlet air
221 volume, inlet air temperature and spraying rate describing the actual coating process are given in
222 **Table 1**. The end-point of a spraying phase was determined as the point where the theoretical
223 polymer amount of 2, 4, 6 and 8 mg/cm² was achieved. The end-point of a drying phase was
224 reached when the difference in RH between the inlet and outlet air was constant. Coated
225 minitablets were further tray-dried and cured at 40°C for 24 hours.

226 *2.5 ALD coating of minitablets*

227 The ALD was performed in a laboratory-scale flow type ALD reactor (Beneq TFS 200, Finland).
228 Uncoated minitablets were placed on the bottom of the reactor plate and pretreated in the reactor
229 at 65°C and at the pressure of 2 mbar for 24 hours prior to deposition to remove the moisture
230 from the tablets. The thin nanolayers of TiO₂ were grown on minitablets from TiCl₄ and water at
231 65°C. Nitrogen (N₂) was used as a carrier and purging gas. The TiCl₄ and water were evaporated
232 from the sources at 20°C. The cycle consisted of a 300 ms TiCl₄ pulse, 20 s N₂ purge, 300 ms
233 water pulse and 30 s N₂ purge. The number of ALD cycles was 100, 300 and 500 corresponding
234 to approximately 10, 30 and 50 nm film thicknesses measured from the silicon reference sample
235 processed in the same runs. Using the approximate coating film thickness (10, 30 and 50 nm) and
236 the density of TiO₂ (4.23 g/cm³), the amount of TiO₂ coating was 0.0042 mg/cm², 0.0127
237 mg/cm² and 0.0212 mg/cm² 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 TiO₂ 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

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

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

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

273 ***2.7 HPLC assays***

274 For the uniformity of content and dissolution tests, the samples were analyzed using an Agilent
275 1100 series HPLC system (Agilent Technologies, USA) equipped with an UV-Vis detector. The
276 reverse-phase column Zorbax Eclipse Plus C18 (100x4.6 mm, 3.5 μ m) (Agilent Technologies,
277 USA) was utilized in the analyses.

278 The flow rate of eluent mixture of ammonium acetate (10 mM, pH 4.5):ACN was 1 ml/min.
279 Denatonium benzoate was detected at wavelength 210 nm at 25°C. For uniformity of content
280 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 minitables), and 60:40 and 2.4 min
282 (for the uncoated and the TiO₂ coated minitables). For dissolution testing of uncoated and both
283 polymer and TiO₂ coated minitables, 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 minitables*

293 **Table 2** shows the weight, active ingredient content, disintegration time, breaking force and
294 height of uncoated and coated tablets. For TiO₂ coated minitables, 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 minitables. As expected, similarly to tablet height, no changes in the
298 weight of TiO₂ coated minitables 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/cm² (Table 2). In comparison to uncoated tablets, film coated

302 tablets exhibited also an increase in the tablet height and weight, particularly with polymer
303 amounts of 4, 6 and 8 mg/cm² (tablet height) and with polymer amounts of 2, 6 and 8 mg/cm²
304 (tablet weight). The difference between uncoated and polymer coated tablets seemed gradual and
305 in accordance with increased polymer amount. The increase in tablet height with coating of
306 polymer amounts of 2 and 4 mg/cm² was lower than with polymer amounts 6 and 8 mg/cm². The
307 highest increase in tablet height and weight was observed with polymer amount of 8 mg/cm².
308 Tablet height remained relatively unchanged with polymer amount of 2 mg/cm² when compared
309 to uncoated tablets. However, the average weight of minitables with coating of 2 mg/cm²
310 decreased in comparison to uncoated minitables.

311 ***3.2 Minitablet hardness***

312 The TiO₂ coating significantly (p<0.05) decreased the breaking force (hardness) of minitables in
313 comparison to uncoated minitables (Table 2). No difference in the breaking force of minitables
314 between different TiO₂ thicknesses (100, 300 and 500 cycles) was revealed.

315 Surprisingly, the breaking force of polymer film coated tablets was also lower than that of
316 uncoated minitables. No changes in the breaking force were seen between the minitables coated
317 with polymer concentration of 2 and 4 mg/cm², and between the minitables coated with polymer
318 concentration of 6 and 8 mg/cm².

319 ***3.3 Disintegration in vitro***

320 The disintegration times of uncoated, TiO₂ coated, and polymer film coated minitables are
321 presented in Table 2. Surprisingly, the disintegration time of TiO₂ coated minitables was clearly
322 shorter (p<0.05) than that obtained with uncoated minitables. No clear differences in the
323 disintegration times between ALD coated tablets (100, 300 and 500 cycles) were revealed as the

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

326 Surprisingly, the disintegration time of minitables coated with polymer concentrations of 2 and
327 4 mg/cm² was shorter in comparison to that of uncoated minitables. However, minitables
328 coated with polymer concentration of 4 mg/cm² disintegrated more slowly than minitables
329 coated with 2 mg/cm² polymer concentration. In addition, the disintegration time of minitables
330 coated with polymer concentration of 6 mg/cm² was shorter than that of minitables coated with
331 higher amount (8mg/cm²) of polymer, but compared with uncoated tablets, the difference with
332 polymer amount of 6 mg/cm² was not statistically significant. As expected, the disintegration of
333 minitables containing polymer concentration of 8 mg/cm² was slower than that of uncoated or
334 other polymer coated tablets of the study. In addition, the minitables coated with higher polymer
335 concentration of 8 mg/cm² exhibited a clear lag-time prior to disintegration which was not
336 observed with the TiO₂ coated minitables.

337 *3.4 Dissolution in vitro*

338 The dissolution profiles of uncoated, ALD coated (TiO₂) and polymer film coated minitables are
339 shown in **Fig. 2**. With both uncoated and ALD coated minitables (100, 300 and 500 cycles), the
340 lag-time for denatonium benzoate release was very short (less than 45 seconds). With polymer
341 film coated minitables, denatonium benzoate release was detected at 45 s (2, 4 and 6 mg/cm²)
342 and at 1 min 15 s (8 mg/cm²).

343 At 45 seconds, the highest amount of released denatonium benzoate was detected for minitables
344 containing 2 mg/cm² and 4 mg/cm² of coating polymer, while no difference in the released
345 amount of denatonium benzoate was revealed between uncoated and polymer film coated (6

346 mg/cm²) minitabets. The polymer film coating of minitabets (2, 4 and 6 mg/cm²) increased the
347 release rate of denatonium benzoate compared to that obtained with uncoated minitabets.
348 However, when the highest amount of coating polymer (8 mg/cm²) was used, the minitabets
349 exhibited a clear delay in the release rate of denatonium benzoate.

350 TiO₂ ALD coating on minitabets 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 TiO₂ coated minitabets. Application of 100 and 300 cycles in the TiO₂ ALD coating of
353 minitabets exhibited only a slight delay in the release rate of denatonium benzoate compared to
354 that obtained with uncoated minitabets.

355 **3.5 SEM and EDS**

356 The SEM images defining the internal structure and surface morphology of uncoated and coated
357 minitabets are shown in **Fig. 3**. The SEM-EDS linescans of TiO₂ ALD coated minitabets (500
358 cycles) are presented in **Fig. 4** (intact minitabets) and **Fig. 5** (the cross-section of the minitabets).
359 The surface of uncoated minitabets (Fig. 3A) was relatively smooth with dark and white areas,
360 and application of TiO₂ ALD coating had virtually no effect on the surface morphology of
361 minitabets (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/cm² in Fig. 3E) revealed rough eroded holes on an uneven
363 tablet surface. Smoother and more even minitabets surfaces were obtained with higher coating
364 polymer concentrations (4 mg/cm² in Fig. 3F, 6 mg/cm² in Fig. 3G, and 8 mg/cm² in Fig. 3H).

365 The SEM-EDS linescan of the TiO₂ ALD coated tablet surface revealed the presence of titanium
366 and chlorine on the surface of minitabets (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

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

373 **4. DISCUSSION**

374 *4.1 Effect of coating method on the properties of minitab*

375 It is well known that the tablet cores in a conventional fluidized-bed polymer coating process are
376 exposed to a long-term attrition (friction) and collisions resulting in the erosion (even breakage)
377 of tablets during processing. However, the ALD thin coating of tablets with TiO₂ in flow type
378 ALD reactor is a much more gentle procedure as the tablets are stationary during coating and
379 thus, are not susceptible to kinetical attrition or collisions similar in fluidized-bed. Thus, no
380 statistically significant differences between uncoated and ALD-coated tablets were revealed for
381 tablet integrity, weight, dimensions, or active drug content.

382 Surprisingly, however, the breaking force (hardness) and disintegration time of minitab
383 decreased after ALD coating. This was confusing, especially as in the literature, the ALD coated
384 3-layer tablets have been reported to comply with the specifications for hardness and
385 disintegration time of such dosage forms (Lehtonen et al., 2013). Thus, by contrast to a decrease
386 in the minitab strength and disintegration, a delay was our more likely expectation,
387 particularly as in theory, the chosen minitab formulation was thought to support the formation
388 of even, pinhole-free and moisture protective TiO₂ ALD nanolayers. Moreover, in the present
389 study, the experimental composition of minitab 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 minitables 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

413 substrate surface. This could indicate the formation of a completely new chemical component
414 with characteristics totally different from those of the original substance. Also, the variation in
415 the configuration and the level of the hydroxyl-grouped surfaces may complicate the film growth
416 (Ritala et al., 1993). It is evident that areas with uneven and variable level of hydroxyl groups
417 lead to uneven TiO₂ layers. Furthermore, the amphoteric chemical behavior of TiO₂ surface due
418 to differently orientated and bonded hydroxyl groups on the TiO₂ surface (Parfitt, 1976) can lead
419 to additional reactions other than with TiCl₄. Low deposition temperatures used in the TiO₂ ALD
420 thin coating can also induce the formation of chemical impurities (residual ions), such as
421 chlorine in ALD thin films originating from TiCl₄ precursor ligands (Ritala et al., 1993; Jögi et
422 al., 2006), and may therefore change the film properties. In addition, at this growth temperature
423 ALD TiO₂ thin films are in fact amorphous and may thus have increased intensity for moisture
424 related interactions.

425 The success of TiO₂ ALD coating is therefore very much dependent on the tablet core
426 composition, structure and properties. With the present minitables, phenomena occurring on the
427 heterogeneous tablet surface are hence strongly emphasized. Lehtonen and co-workers (2013)
428 investigated the ALD thin coatings applied to the tablets composed of three-layered
429 pharmaceutical solids containing layers of probiotics and vitamin C. Pharmaceutical tablets are
430 commonly compressed from heterogeneous mixtures. Due to such complex compositions, the
431 coatings applied to the outer surface of tablet cores are exposed to multiple different
432 components, which all have characteristic porosity and interaction capabilities, e.g. with
433 moisture or chemicals. Consequently, the formation of even and pinhole-free TiO₂ ALD
434 nanolayers is greatly affected by the chemical composition of the tablet surface (especially, the
435 excipients rich on hydroxyl groups play a key role), and most likely also by surface moisture. In

436 other words, the formation and growth of TiO₂ thin films is fostered by the surfaces exhibiting
437 very high hydroxyl group density. In addition, the pore density, size and tortuosity of excipients
438 can play a crucial role affecting TiO₂ ALD thin films. Depending on the physicochemical
439 characteristics, the active outer surface area of tablet excipients can be very different due to
440 interaction with moisture. Consequently, deep voids or complex pore structures can result in
441 inadequate TiO₂ ALD nanolayer formation and growth. Moreover, the formation of intact TiO₂
442 ALD coating in tablet pores is most likely to be fostered by the presence of high hydroxyl group
443 density. With the present minitablets, it is evident that excipients and/or denatonium benzoate
444 interact with titanium to different extent and mechanism, thus affecting the formation of
445 nanolayers. Therefore, the reason for the unexpected decrease in the hardness and disintegration
446 time of coated minitablets is most likely the heterogeneity and physicochemical diversity of
447 chemical components in the tablet surface.

448 ALD thin coating has a number of advantages compared to a traditional fluidized-bed film
449 coating method. The TiO₂ ALD nanolayering is a gentle procedure in a flow type reactor without
450 any actual collision related impact on tablets. On the contrary, the traditional fluidized-bed
451 coating requires adequate mechanical strength of tablet cores, and appropriate and well-designed
452 tablet compositions. In a fluidized-bed coating process, tablet breakage takes place readily due to
453 a long-term collision and abrasion during fluidization, and due to the elevated temperature and
454 humidity conditions during polymer dispersion spraying and drying. Moreover, particles
455 detached from tablet cores can disturb the formation of even polymer coating and lead to a great
456 variation in an active ingredient content, disintegration and dissolution of tablets. It is also well-
457 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.

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

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

526 The *in vitro* dissolution results of TiO₂ ALD coated minitables were in accordance with the *in*
527 *vitro* disintegration times of the respective nanolayered minitables (Fig. 2). The early
528 denatonium benzoate release from both uncoated and TiO₂ ALD coated minitables was
529 observed at 45 s. This suggests that the coating thickness of the present ALD nanolayered
530 minitables (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 TiO₂ 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 TiO₂ 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 TiO₂ coated minitables
537 was observed, this regarding minitables 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 TiO₂ ALD layered minitables compared to uncoated minitables.

540 We found that the minitables coated with a polymer amount of 8 mg/cm² are evidently
541 applicable for the bitter taste masking of denatonium benzoate. The present fluidized-bed coated
542 minitables 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 minitables 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

547 especially applicable in case of moisture sensitive tablet formulations since tablet cores are not
548 exposed to high humidity conditions similar to those in fluidized-bed coating. Consequently,
549 ALD nanolayering should not affect the physicochemical and pharmaceutical properties of
550 tablets. Our results suggest also that the adequate taste masking efficacy of minitables could be
551 achieved by increasing the number of coating cycles in the TiO₂ ALD nanolayering, as the
552 release of bitter tasting denatonium benzoate was, though only slightly, delayed from minitables
553 coated with 500 coating cycles. Attention should also be put onto the time required for the
554 precursor pulse, as the unexpected dissolution of TiO₂ coated minitables could be also explained
555 by the pulse of 300 ms being possibly inadequate for precursors to penetrate into the tablet pores.
556 In addition, the coating materials other than TiO₂ or the multilayer ALD coatings could also open
557 new alternatives to single ALD thin coatings for taste masking applications. For example, Al₂O₃
558 ALD thin coated tablets have been shown to exhibit faster drug release in water in comparison to
559 TiO₂ ALD coated tablets (Lehtonen et al., 2013). The use of an ALD coating system (reactor)
560 other than the flow type one could also provide improvements in taste masking efficiency.
561 Carlsson and co-workers (2016) reported the existence of holes in the ALD coated nanoparticles
562 due to the contact points with other nanoparticles during deposition. In theory, this could be also
563 possible with the present TiO₂ ALD thin-coated minitables, since the exposure of stationary
564 tablet(s) to ALD could lead to disruptions in thin coatings due to the direct contact of the tablet
565 lower surface with an ALD tray. The probability for the formation of uncoated contact points in
566 minitables, however, is minimal, since the tablets are slightly vibrating in the semifluid state
567 during the flow of ALD coating. Therefore, the major reason for the defects of TiO₂ ALD thin
568 coating (and obviously for a limited taste masking efficacy of minitables) is the heterogeneous
569 structure of the tablet surface. It is evident that the surface moisture is adequate for ALD and for

570 the formation of even TiO₂ nanolayers, but the affinity of some tablet excipients varies a lot and
571 this can prevent the formation of homogeneous and continuous TiO₂ nanolayers.

572 *4.3 Surface morphology and content analysis*

573 The surface properties of fluidized-bed film coated minitables were dependent on the amount of
574 coating polymer used. The minitables coated with the lowest polymer amount of 2 mg/cm²
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/cm² 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/cm²) to a few hundred micrometers (8 mg/cm²). Such great
579 variation in coating thicknesses (and intactness) explains also the changes in physical and
580 pharmaceutical properties of minitables coated with different amounts of polymer.

581 Since SEM did not permit the nanometer-scale analysis of the ALD nanolayered minitables, 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 minitables. 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 minitables. In accordance
587 to the theory on hermetic ALD layers on porous minitables, the SEM-EDS results suggested that
588 the TiO₂ 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 TiO₂ precursors seem to diffuse into the voids
591 and pores of minitables with the estimated diffusion length of approximately 100-200 μm. This

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

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

610 The SEM-EDS morphological and elemental analysis revealed that the surface of uncoated
611 minitables is porous and heterogeneous due to the multiple excipients used for formulating the
612 tablet cores. The surface of uncoated minitables (cores) was covered with the grey-white and
613 dark areas (spots), which were still clearly visible in TiO_2 ALD coated tablets. The bright areas
614 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.

637 The ALD thin coating is a rapid process since no spraying and drying steps are needed.
638 However, the unexpected changes in the TiO₂ ALD coated minitablet mechanical properties seen
639 as an accelerated tablet disintegration rate and decreased tablet hardness may challenge its
640 feasibility in the coating of heterogeneous substrates composed of substances with different
641 chemical characteristics and reaction ability, until a thorough understanding on possible
642 phenomena taking place on tablet surface and within used diverse and physicochemically
643 variable excipients during ALD process is established. Therefore, the major challenges of ALD
644 thin coating are related to the sufficient taste masking capacity and interactions of
645 coating/layering material (TiO₂) with the excipients used in the tablet core. More research is
646 needed to clarify the potential of ALD in tablet coating applications. For example, coating
647 materials other than TiO₂, the effects of the number of coating cycles and the length of the
648 precursor pulses on the taste masking are suggested for further study.

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712

713 Captions to illustrations:

714 **Fig. 1.** The theoretical formation of TiO₂ nanolayers via the chemical reaction between water and
715 TiCl₄ in atomic layer deposition (ALD) thin-coating process. In ALD involving metal oxides, a
716 cycle of surface saturation takes place through two reaction steps performed commonly in
717 vacuum at controlled temperature. During step one (the first half cycle) the metal precursor such
718 as TiCl₄ vapor, pulsed to the coating chamber, is allowed to react with the free hydroxyl groups
719 on the substrate surface. The chemical pulse therefore saturates the surface with Ti containing
720 groups through molecular bonds. During step two (the second half cycle) the molecularly bonded
721 structures on the substrate surface react with the oxygen precursor (water vapor) and form the
722 first nanolayer of TiO₂. Between the steps, a purge of inert gas (N₂) is applied to the chamber to
723 remove the possible excess of precursor and reaction by-products. The film thickness is
724 controlled by repeating the number of reaction cycles to reach the desired coating.

725 **Fig. 2.** Dissolution profiles of uncoated minitables, TiO₂ ALD (100, 300 and 500 cycles) thin-
726 coated and fluidized-bed polymer film coated (2, 4, 6 and 8 mg/cm² of polymer) minitables
727 (n=4). The dissolution curves describe the cumulative release of denatonium benzoate from
728 minitables.

729 **Fig. 3.** Scanning electron microscopy (SEM) images on uncoated minitab (Fig. 3A), TiO₂
730 ALD thin-coated minitables (100, 300 and 500 cycles; Fig. 3B-D, respectively) and fluidized-
731 bed polymer film coated minitables (2, 4, 6 and 8 mg/cm²; Fig. 3E-H, respectively).

732 **Fig. 4.** Scanning electron microscopy-energy dispersive spectroscopy (SEM-EDS) image on the
733 intact TiO₂ ALD thin-coated minitab (500 cycles). Arrows indicate the presence of titanium on
734 the ALD thin-coated minitab surface followed by signals on calcium and phosphorous.

735 **Fig. 5.** SEM-EDS image on the cross-section of TiO₂ ALD thin-coated minitab (500 cycles).

736 **Table 1.** Used parameters for minitabulet 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

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738 **Table 2.** Results of the tests performed on both uncoated, and for TiO₂ and EPO coated
 739 minitables 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

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