



<b>Title</b>	Determination of parameters for successful spray coating of silicon microneedle arrays
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36 **Abstract**

37

38 Coated microneedle patches have demonstrated potential for effective, minimally invasive,  
39 drug and vaccine delivery. To facilitate cost-effective, industrial-scale production of coated  
40 microneedle patches, a continuous coating method which utilises conventional  
41 pharmaceutical processes is an attractive prospect. Here, the potential of spray-coating silicon  
42 microneedle patches using a conventional film-coating process was evaluated and the key  
43 process parameters which impact on coating coalescence and weight were identified by  
44 employing a fractional factorial design to coat flat silicon patches. Processing parameters  
45 analysed included concentration of coating material, liquid input rate, duration of spraying,  
46 atomisation air pressure, gun-to-surface distance and air cap setting. Two film-coating  
47 materials were investigated; hydroxypropylmethylcellulose (HPMC) and  
48 carboxymethylcellulose (CMC). HPMC readily formed a film-coat on silicon when suitable  
49 spray coating parameter settings were determined. CMC films required the inclusion of a  
50 surfactant (1% w/w Tween 80) to facilitate coalescence of the sprayed droplets on the silicon  
51 surface. Spray coating parameters identified by experimental design, successfully coated 280  
52  $\mu\text{m}$  silicon microneedle arrays, producing an intact film-coat, which follows the contours of  
53 the microneedle array without occlusion of the microneedle shape. This study demonstrates a  
54 novel method of coating microneedle arrays with biocompatible polymers using a  
55 conventional film-coating process. It is the first study to indicate the thickness and roughness  
56 of coatings applied to microneedle arrays. The study also highlights the importance of  
57 identifying suitable processing parameters when film coating substrates of micron  
58 dimensions. The ability of a fractional factorial design to identify these critical parameters is  
59 also demonstrated. The polymer coatings applied in this study can potentially be drug loaded  
60 for intradermal drug and vaccine delivery.

61

62 **Keywords:** microneedle, spray coat, silicon, hydroxypropylmethylcellulose,  
63 carboxymethylcellulose.

64

65

66

67 ***Introduction***

68  
69 Microneedle-assisted drug delivery has the potential to overcome many of the disadvantages  
70 associated with traditional injection using a hypodermic needle. An alternative to invasive  
71 and painful hypodermic injections, an ideal microneedle product would deliver the required  
72 drug dose reproducibly, increase the pharmacokinetic profile and drug safety, decrease the  
73 level of expertise required for administration and decrease the risks associated with sharps  
74 waste disposal. Microneedle application can be used to enhance the delivery of drug-loaded  
75 solutions applied to the skin (Prausnitz, 2004). Drug-coated microneedle arrays have the  
76 advantage of producing a single unit delivery system, incorporating the drug and delivery  
77 device (microneedle array) in a single dosage form. Techniques currently described for drug-  
78 coating microneedle arrays include dip-coating (Ameri et al., 2009; Gill and Prausnitz, 2007;  
79 Kim et al., 2010; Zhu et al., 2009), coating using a roller drum (Ameri et al., 2009), gas-jet  
80 dry coating (Chen et al., 2009), coating using aerosolisation (Cormier et al., 2004; Dalton,  
81 2007; Sathyan, 2005) and coating by immersion (Maa, 2005; Matriano et al., 2002). Scale up  
82 of the these microneedle coating processes poses a number of challenges relating to factors  
83 such as efficiency of drug loading, regulatory compliance and automation. The objective of  
84 this study was to investigate whether a conventional spray coating process, similar to that  
85 used for film-coating tablets, could be employed to apply polymer films to microneedle  
86 arrays. To our knowledge this conventional spray coating approach to applying polymeric  
87 coatings to microneedle arrays has not previously been investigated.

88  
89 Within the pharmaceutical industry spray coating is widely used to coat tablets and particles  
90 with coatings of the millimetre thicknesses (Behzadi, 2008). Microneedle dimensions  
91 (ranging from approximately 60 to 700 $\mu$ m in height), necessitate a coating thickness in the  
92 micron range which would not occlude the needles or inhibit skin penetration, thus

93 suggesting that common spraying techniques would not be sufficiently sensitive to coat  
94 microneedles. Ideally, a film-coat applied to microneedles for insertion into the skin should  
95 be composed of approved biocompatible materials. HPMC coating material, while not an  
96 approved biocompatible material, was chosen initially to prove the concept that a  
97 conventional spray coating approach could apply a polymeric coating to a microneedle array.  
98 HPMC was selected because it is considered to be a polymer with good film forming  
99 properties and is a widely used film-coating agent (Aulton and Twitchell, 1995; Aulton et al.,  
100 1986; Twitchell, 1990). After demonstrating the capability to film-coat microneedle arrays  
101 using HPMC, an approved biocompatible film-forming agent, carboxymethylcellulose  
102 sodium salt (CMC) was selected (Rowe, 2003).

103

104 Spraying a film-coat on to microneedle arrays requires the deposition of fine droplets (< 280  
105  $\mu\text{m}$ ) on to the microneedle array and spreading and coalescence of the droplets after  
106 deposition to form an intact film-coat. The spray coating process can be divided into three  
107 steps, 1) generation of fine droplets (atomisation) and 2) impingement on the surface  
108 (deposition) and 3) coalescence of droplets on the substrate (coalescence). The droplet size  
109 generated by atomisation of the coating solution is dependent on nozzle design,  
110 physicochemical properties of the coating solution (surface tension, viscosity and density)  
111 and processing parameters such as the air-to-liquid mass ratio (Aulton and Twitchell, 1995;  
112 Missaghi and Fassihi, 2004; Mueller and Kleinebudde, 2007). Two-substance nozzles, of the  
113 type used in this investigation, can produce fine droplets with droplets diameters less than 50  
114  $\mu\text{m}$  (Mueller and Kleinebudde, 2007). Spray velocity and spray density influence the  
115 deposition of droplets on a surface. The spray velocity is influenced by the atomisation air  
116 pressure, gun-to-surface distance and air cap setting. Increasing the air cap setting increases  
117 the air flow rate as it exits the nozzle. Higher atomisation air pressure, higher air cap setting

118 and lower gun-to-surface distances increase spray velocity. While high spray velocities have  
119 been reported to facilitate spreading of droplets upon impingement on the surface (Twitchell,  
120 1990), too high a velocity can result in droplets being blown off the surface by the stream of  
121 atomising air. The air cap setting also controls the spray angle of the cone of liquid droplets  
122 exiting the nozzle. Increasing the air cap setting increases the spray angle, while reducing it  
123 decreases it. The more acute the spray angle, the smaller the surface area coated by the spray  
124 and the greater the spray density. The coalescence of solution droplets after deposition is  
125 influenced by the composition of the substrate, the physicochemical properties of coating  
126 solution and the droplet size deposited.

127

128 In our investigation, a design of experiments approach was utilised to identify the  
129 combination of process parameters suitable for spraying film-coating silicon substrates. To  
130 facilitate efficient analysis of film formation, which is complicated for three dimensional  
131 surfaces such as microneedle arrays, we initially coated flat silicon patches and then validated  
132 findings using silicon microneedle arrays. We hypothesised that the key factors that would  
133 influence the process were concentration of coating material, liquid input rate, duration of  
134 spraying, atomisation air pressure, gun-to-surface distance and air cap setting. Due to the  
135 number of factors identified for investigation (6 factors), a Taguchi method of fractional  
136 factorial experimental design was selected to identify suitable parameter settings. The  
137 Taguchi method of experimental design is considered to be both more efficient and easier to  
138 interpret than a full factorial design when investigating this large number of factors (Roy,  
139 1990).

140

141 Our study demonstrates that an intact film-coating, of micron thickness, can be applied to  
142 silicon substrates using a conventional spray coating process. A fractional factorial



143 experimental design efficiently identified a suitable combination of process parameters for  
144 applying polymer coatings to flat silicon patches. Based on the findings of the fractional  
145 factorial experimental design, intact, uniform film-coatings of HPMC and CMC were applied  
146 to silicon microneedle arrays.

147

## 148 ***Materials and methods***

### 149 *Materials*

150 Hydropropylmethylcellulose (HPMC) (Methocel® E5 Premium LV, Colorcon, UK) or  
151 carboxymethylcellulose sodium salt (CMC) ultra low viscosity (Fluka, Finland) were the  
152 coating agents of choice. Polyethylene glycol sorbitan monooleate (Tween 80®) was sourced  
153 from Sigma-Aldrich, (USA). Flat silicon patches (2 x 2 cm<sup>2</sup>) and wet-etched silicon  
154 microneedle arrays (1 cm<sup>2</sup>) were provided by the Tyndall National Institute, Ireland. Silicon  
155 microneedles were fabricated using a wet-etch fabrication method which has been previously  
156 described (Wilke et al., 2006). Water-based coating formulations were used throughout this  
157 study.

158

### 159 *Characterisation of the coating solutions*

160 Surface tension was quantified using a Kruss GMBH Tensiometer K6, (Germany). Kinematic  
161 viscosity was measured using a Vibro Viscometer SV-10, (Japan). Contact angle  
162 measurements were obtained using a Dataphysics Contact Angle System OCA, (Germany).  
163 Surface tension and viscosity measurements were conducted at 20°C.

164

### 165 *Spray coating process*

166 A Düsen-Schlick nozzle 970 S8 two substance nozzle, (Germany) with a 0.5mm nozzle  
167 diameter was used to produce an atomised spray. The nozzle was connected to a compressed

168 air source and coating solution (Figure 1). The flat silicon patches or silicon microneedle  
169 arrays were fixed to an adjustable stage using double sided tape during the spray coating  
170 process. In the HPMC study, a Masterflex® peristaltic pump, (USA), was used to control the  
171 rate of liquid input and in the CMC study an Aladdin AL-2000 syringe driver, World  
172 Precision Instruments, (USA), was used. After coating application, coatings were allowed to  
173 dry at room temperature for 12 hours before analysis.

174

#### 175 *Identification of suitable processing parameters*

176 HPMC film-coating was investigated in the HPMC study and CMC film-coating was  
177 investigated in the CMC study. Both experimental designs consisted of a six factor, two level,  
178 fractional factorial design applied to a L<sub>8</sub> orthogonal array to define the experimental  
179 conditions, as described in **Table 1** and **2**. Each set of experiments was carried out in  
180 triplicate. Two way analysis of variance (ANOVA) was used to assess the impact of the  
181 various processing parameters on the coating weight response factor. The average  
182 experimental response for each factor at each level was calculated. These values indicate the  
183 relative impact of using a high or low level of each factor on the coating weight. The  
184 statistical significance of each factor at each level was determined by calculating the sum of  
185 squares using all individual data points. From the sum of squares data, variance (mean  
186 square) values for each factor and the variance due to the error term were then calculated.  
187 From these values, the F statistic, the ratio of variance due to the effect of a factor and  
188 variance due to the error term, was determined. The F factor measures the significance of the  
189 factor under investigation with respect to variance of all the factors included in the error term  
190 (Roy, 1990).

191

#### 192 *Assessment of film-coating coalescence and weight*

193 Film-coated silicon patches were visually assessed by light microscopy using an Olympus  
194 BX51 optical microscope and magnification of 10x. Coating thickness and roughness was  
195 assessed using a Zygo NewView 5022 white-light interferometer for selected coated patches.  
196 Film-coated silicon patches were sputter coated with gold (Au) for 20 seconds prior to  
197 analysis by Zygo-white light interferometry. To determine thickness and roughness using this  
198 technique a portion of the coating from the silicon patch surface was removed to obtain a  
199 baseline measurement. From the baseline a visual representation of the coating was created.  
200 Film thickness and roughness were measured through a central point on the coated wafer.  
201 The surface roughness of the coating was determined using the arithmetic surface roughness  
202 ( $R_a$ ) value.  $R_a$  is based on the distance of the coating from a central reference point over a  
203 measured distance. Coating weight was determined using a Sartorius RC210D 5 place  
204 balance for coating runs in the HPMC study and a Mettler Toledo MX5 6 place electronic  
205 weighing balance in the CMC study. Coated microneedles were imaged by scanning electron  
206 microscopy using a JSM 5510 SEM. Coated microneedles were sputter coated with Au for 20  
207 seconds prior to SEM analysis.

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218 **Results**

219 ***Characterisation of coating solutions***

220 It is hypothesised that properties of the substrate to be coated and the physicochemical  
221 properties of the coating solution would affect the formation of an intact film. In advance of  
222 coating trials a number of relevant physicochemical properties were determined. All HPMC  
223 and CMC coating solutions used in this study were aqueous based. The contact angle of water  
224 on flat silicon patches was determined to be  $32.5^\circ \pm 2.0^\circ$  at ambient temperature. A surface  
225 is considered hydrophilic when the contact angle of water on its surface is  $< 90^\circ$ . The contact  
226 angle measured suggests that silicon is a hydrophilic material and will be wetted by aqueous  
227 based formulations employed in this investigation, thereby facilitating coating of the silicon  
228 substrates investigated. The surface tension of HPMC and CMC coating solutions employed  
229 are detailed in **Table 4**. HPMC exhibited surfactant properties and these values correlated  
230 well with those previously described (Twitchell, 1990). The surface tension of 1 %w/v CMC  
231 coating solutions, were significantly higher than those determined for the 5 %w/v CMC and  
232 both HPMC coating solutions ( $p \leq 0.01$ ). As increased surface tension can adversely affect  
233 coating coalescence, a surfactant Tween 80 was incorporated as a formulation variable within  
234 the CMC study. The addition of 1 % w/v Tween 80 to CMC solutions reduced surface  
235 tension to values comparable to the HPMC solutions. The viscosity of HPMC and CMC  
236 coating solutions employed are also detailed in **Table 4**. There was a disproportionate  
237 increase in the viscosity of HPMC solutions with increase in concentration. This increase in  
238 viscosity is thought to be the result of an increased resistance to flow due to the large  
239 hydrodynamic volume of the randomly coiled polymer chains and their associated hydrogen-  
240 bonded water molecules (Clasen and Kulicke, 2001). The viscosity of CMC solutions also  
241 increased disproportionately with increased concentration. The addition of 1% w/v Tween 80  
242 altered the viscosity marginally. The surface tension and viscosity of HPMC solutions

243 employed are similar to those of HPMC solutions which were previously reported to form  
244 film-coats (Aulton and Twitchell, 1995). While the surface tension of CMC solutions  
245 investigated were higher than the HPMC solution which may adversely affect film-coat  
246 coalescence, the addition of Tween 80 reduced the surface tension into a range similar to that  
247 of the HPMC solutions.

248

#### 249 *Assessment of HPMC film-coat coalescence and weight*

250 The effect of six parameters (HPMC concentration, liquid input rate, duration of spraying,  
251 atomisation air pressure, gun-to-surface distance and air cap setting) on HPMC film-coat  
252 coalescence on silicon patches was assessed in a fractional factorial design. Processing  
253 parameters for the eight runs performed in this design of experiments are detailed in **Table 3**.  
254 Visual inspection of the film-coating produced for each run by light microscopy indicated  
255 clear variability between the eight coating runs performed. Observation of replicate samples  
256 for each run suggests inter-batch consistency with respect to the coating appearance. Visually  
257 film-coating appearance was divided into three categories; (1) intact coalesced coating which  
258 was blemish and bubble free, (2) coating with blemishes and bubbles present and (3) coating  
259 that failed to coalesce on the silicon surface. The best quality film-coat was produced by the  
260 processing parameters in Run 5 (**Figure 2a**). The coating was complete to the silicon patch  
261 edges. Analysis using the zygo white light interferometer determined a film thickness of 3 - 4  
262  $\mu\text{m}$  and a Ra (roughness) value of 0.16  $\mu\text{m}$ , which confirms the smooth nature of the film  
263 formed. A typical blemished film-coat was produced by the processing parameters in Run 4.  
264 Light microscope images of coated samples from Run 4 highlight regions of uniform blemish  
265 free film and regions of film with air bubbles and blemishes in the coating (**Figure 2b**). This  
266 coating process resulted in a coat of variable thickness (12-35  $\mu\text{m}$ ) and relatively high Ra  
267 value of 0.74  $\mu\text{m}$ . Coalescence of the droplets on the surface was incomplete with areas

268 remaining uncoated. Light microscope images of film-coated substrates from Run 6 show  
269 examples of coatings where droplets failed to coalesce on the surface (**Figure 2c**). Despite  
270 lack of coalescence, the coating was consistent and covers the entire wafer surface. Zygo  
271 white light analysis confirms an Ra value of 0.73  $\mu\text{m}$  indicating a coating of variable  
272 thickness and a coating thickness of 5  $\mu\text{m}$ .

273

274 The effect of processing variables on HPMC film-coat weight was also assessed in the  
275 HPMC coating study. **Table 5** shows the average film-coat weight for each run. **Figure 3**  
276 shows a plot of mean coating weight for the low and high levels of each parameter compared  
277 to the global average coating weight. All parameters investigated, with the exception of liquid  
278 input rate, significantly influenced coating weight ( $p < 0.05$ ). Increased spray time had a  
279 positive effect on coating weight which was expected due to the increased mass of material  
280 deposited. Increased atomisation air pressure also increased the coating weight. Increasing  
281 gun-to-surface distance or decreasing air cap setting had a negative effect on coating. The use  
282 of higher HPMC concentrations failed to increase the coating weight as would be expected.  
283 The high viscosity of the 12% w/v HPMC solution may have resulted in irregular flow of the  
284 coating solution through the nozzle, resulting in blockages, irregular coating and therefore a  
285 lower than expected coating weight.

286

287 The HPMC coating study efficiently highlighted the effect of processing parameters on the  
288 coalescence, thickness, roughness and weight of HPMC film-coating applied to a flat silicon  
289 substrate. This information was then used to identify a set of suitable processing parameters  
290 to apply a HPMC film-coat to silicon microneedle arrays.

291

292 *Spray coating microneedles with HPMC*

293 We next determined if the critical parameters identified in the HPMC coating study translated  
294 to coating silicon microneedles. We hypothesised that suitable parameters for coating silicon  
295 microneedles would be low HPMC concentration (5% w/v), low spray time (30 secs), low  
296 liquid input (3.1 mls/min), high air pressure (1 bar), high air cap setting (3) and low gun-to-  
297 surface distance (5 cm). **Figure 4a** shows a single silicon microneedle and silicon  
298 microneedle array film-coated with HPMC using the selected processing parameters. The  
299 coating formed was intact, followed the contours of the microneedle array and does not  
300 occlude the microneedle shape. Therefore the coating achieved confirms that using a Taguchi  
301 fractional factorial design to identify suitable parameters to apply a film-coat on to a flat  
302 silicon patch, the processing parameters identified could be translated to successfully coat  
303 silicon microneedle arrays.

304

#### 305 *Assessment of CMC film-coat coalescence and weight*

306 The well characterized film-coating material employed in the first study, HPMC, was  
307 replaced with the biocompatible film-forming polymer CMC in the second study. Building on  
308 the knowledge regarding film-coating silicon surfaces acquired with HPMC coating material,  
309 in the second study the influence of six processing variables on coating coalescence and  
310 weight was investigated using a second fractional factorial design. The processing parameters  
311 investigated were CMC concentration, addition of surfactant (1% w/v Tween 80),  
312 atomisation air pressure, gun-to-surface distance and air cap setting. The total volume of  
313 solution sprayed was constant for all runs and the duration of spraying was dependent on the  
314 liquid input rate. Processing parameters for the eight runs performed in this design of  
315 experiments are detailed in **Table 2**. Visual inspection of the dried film-coating produced for  
316 each run by light microscopy indicated variability between the eight coating runs performed.  
317 When compared to the initial HPMC coating study, there was a marked difference in the

318 nature of the film-coating variability between the CMC runs which was attributed to the  
319 increased role of surface tension.

320

321 Coating solutions which did not include Tween 80 in the formulation (Runs 1, 3, 5, 7)  
322 typically displayed a combination of large uncoated areas in which some droplets had dried in  
323 isolation, small patches of coating where isolated droplets had coalesced and large areas in  
324 which droplets had coalesced well and formed an intact coat (**Figure 5a**). The edges of these  
325 coated areas were jagged, indicating that the coating retracted from the silicon surface on  
326 drying. The high surface tension of the coating solution promotes cohesion of the coating  
327 solution droplets and inhibits even spread of the droplets across the wafer surface. The  
328 reduction in the coating solution surface tension associated with the addition of 1% w/v  
329 Tween 80 (Runs 2, 4, 6, 8), resulted in a film-coat that coalesced well and coated the entire  
330 wafer patch (**Figure 5b and c**). However, there was notable variation observed in the texture  
331 of film-coatings formed from solutions of CMC containing Tween 80. For example, Run 6  
332 (**Figure 5c**) produced a smooth film-coating (average thickness of 2.1  $\mu\text{m}$  and average  $R_a$   
333 value of 0.8  $\mu\text{m}$ ), while Run 4 (**Figure 5b**) produced a textured coating (average thickness  
334 4.4 $\mu\text{m}$  and average  $R_a$  value of 1.4 $\mu\text{m}$ ). Of the eight runs, the processing parameters  
335 employed in Run 6 were deemed to be the most suitable for film-coating flat silicon patches  
336 with CMC.

337

338 The average film-coat weight for the eight runs varied from 0.1 to 4.6 mg (**Table 5**). **Figure 6**  
339 shows a plot of mean coating weight at the low and high levels of each parameter compared  
340 to the global average coating weight. All processing parameters, with the exception of liquid  
341 input rate and air cap setting, had a significant effect on coating weight ( $p < 0.05$ ). CMC  
342 concentration had the greatest positive effect which was expected due to the increased mass



343 of the material being sprayed. The presence of 1% w/v Tween 80 also had a positive effect  
344 on the coating weight. While the atomisation air pressure range (0.5 to 1 bar) investigated in  
345 the HPMC study had no effect on coating weight, the range investigated in the CMC study  
346 (0.5 to 1.75 bar) had a negative effect. The high level of atomisation air pressure investigated  
347 in the CMC study may have resulted in coating being blown away from the silicon surface  
348 prior to adhesion due to increased spray velocity at these pressures. Using the information  
349 gained from the CMC coating fractional factorial design, a set of revised processing  
350 parameters was identified for applying CMC film-coating to silicon microneedle arrays  
351 which are detailed below.

352

#### 353 *Spray coating microneedles with CMC*

354 Finally, it was determined whether the set of process parameters identified for coating flat  
355 silicon patches could be translated to coating silicon microneedles with CMC. An aqueous  
356 coating solution containing 3% w/v CMC with 1% w/v Tween 80 was selected. A low liquid  
357 input rate (1.5 ml/min), low air pressure (0.5 bar), an intermediate air cap setting (3) and  
358 gun-to-surface distance (6 cm) were selected. **Figure 4b** shows a single microneedle and a  
359 microneedle array coated using these parameters. The coating appears uniform and follows  
360 the contours of the microneedle array and its thickness does not occlude the microneedle  
361 shape. The intact, uniform film-coat achieved confirms that biocompatible polymers, such a  
362 CMC, can be film-coated onto silicon microneedle arrays using a conventional film-coating  
363 process. It also highlights the importance of selecting an appropriate set of processing  
364 parameters to achieve a film-coat of the desired quality.

365

366

367 **Discussion**

368 The results of this study demonstrate the capability of conventional film-coating processes,  
369 similar to those utilised to film-coat tablets, to apply a film-coat to microneedle arrays. Other  
370 researchers have published more novel approaches to apply coatings to microneedle  
371 substrates (Ameri et al., 2009; Chen et al., 2009; Cormier et al., 2004; Dalton, 2007; Gill and  
372 Prausnitz, 2007; Kim et al., 2010; Maa, 2005; Matriano et al., 2002; Sathyan, 2005; Zhu et  
373 al., 2009). To our knowledge this is the first report using a conventional film-coating  
374 approach to coat microneedle substrates. Additionally, this is the first report to give an  
375 indication of the thickness and roughness of coatings applied to microneedles. Employing  
376 conventional technology offers a number of advantages over more novel approaches. These  
377 include the relative low-cost and availability of cGMP compliant equipment and the vast pool  
378 of existing know-how regarding the technology and its scale-up from laboratory to industrial  
379 scale (Aulton and Twitchell, 1995; Mehta, 2008; Mueller and Kleinebudde, 2007; Muller and  
380 Kleinebudde, 2006).

381

382 As previously highlighted, the physicochemical properties of coating solutions (surface  
383 tension and viscosity) can influence atomised droplet size and film-coat coalescence. Both  
384 HPMC and CMC have surfactant properties in solution which would facilitate the production  
385 of small droplet sizes by atomisation. While the surface tension of CMC solutions was higher  
386 than that of the HPMC solutions, the addition of 1% Tween 80 reduced the surface tension to  
387 within a similar range. The viscosity of HPMC and CMC showed disproportional increases  
388 with increase in concentration. HPMC is reported to exhibit Newtonian behaviour at low  
389 concentrations and pseudoplastic rheological properties at higher concentrations (Aulton and  
390 Twitchell, 1995). During the atomisation process the coating solution is exposed to various  
391 rates of shear. While the viscosity of pseudoplastic solutions will decrease with increase in

392 shear the Newtonian solutions will not change rheologically during this process. The air-to-  
393 liquid mass ratio, which also influences droplet size, is related to two processing parameters  
394 both investigated in the HPMC and CMC studies; atomisation air pressure and liquid input  
395 rate. The higher the air to liquid mass ratio the smaller the droplet size, up to an air to liquid  
396 mass ratio of 4 (Aulton and Twitchell, 1995; Tobiska and Kleinebudde, 2003; Twitchell,  
397 1990). Highest air to liquid mass ratios were obtained in the HPMC and CMC studies for  
398 coating runs with high levels of atomisation air pressures and low levels of liquid input rates.

399

400 The coalescence of solution droplets after deposition depends on the physicochemical  
401 properties of the coating solution but also the composition of the substrate. Microneedles  
402 substrates coated in this investigation were fabricated from silicon using a wet etch process  
403 and thoroughly cleaned prior to coating. Silicon is a relatively hydrophilic material, as  
404 indicated by the 32.5° contact angle of water on its surface. A hydrophilic surface would  
405 facilitate the spread of HPMC and CMC aqueous based solutions after deposition. Low  
406 surface tension and low viscosity also facilitate droplet spread and coalescence once they are  
407 deposited on the substrate. The viscosity of coating solutions can increase during deposition  
408 due to evaporation. The gun-to-surface distance, air temperature and air to liquid ratio  
409 influence the extent of evaporation prior to deposition. After deposition the increased surface  
410 area of smaller droplets facilitates coalescence on the substrate surface.

411

412 As a wide range of processing parameters highlighted in the introduction can influence film-  
413 coat formation, the number of processing parameters identified for investigation in studies 1  
414 and 2 was relatively large (6 factors). A full factorial design of experiment would have  
415 required 64 individual runs for each study. The Taguchi method of experimental design  
416 enabled us to employ a fractional factorial design that reduces the number of runs to 8

417 individual runs per study. Fractional factorial experimental designs are efficient in the  
418 number of runs required to determine main effects. A drawback to fractional experimental  
419 designs is that they do not allow analysis by changing one factor at a time.

420

421 Coating coalescence was not evaluated quantitatively but qualitatively by visual observation  
422 under a light microscope. Examining film coalescence for individual runs of the fractional  
423 factorial design enabled the main processing parameters that facilitate or undermine film-coat  
424 coalescence to be identified. In the HPMC study, the most suitable set of parameters for film-  
425 coat formation were observed for Run 5. Examples of unsuitable parameters combinations  
426 were observed for Runs 4 and 6. Run 4 had regions of film with air bubbles and blemishes in  
427 the coating (**Figure 2b**). The air bubbles and blemishes in the coating can be explained by the  
428 decreased air-to-liquid mass ratio for Runs 4 (poor coalescence) compared to Run 5 (good  
429 coalescence). Lower air-to-liquid-mass ratios can result in increased droplet size and larger  
430 droplets exhibit reduced tendency for coalescence after deposition resulting in bubbles  
431 present in the coating. More information on parameters that influence coalescence can be  
432 gained by comparing Runs 6 (poor coalescence) and Run 5 (good coalescence). Light  
433 microscopy images of film-coated substrates from Run 6 confirm the failure of the droplets to  
434 coalesce on the surface (**Figure 2c**). The failure of droplets to coalesce could be attributed to  
435 the considerably higher viscosity of the 12% w/v HPMC solution spray coated in Run 6  
436 compared to the 5% w/v solution in run 5 (**Table 2**). High viscosity solutions have been  
437 reported to produce larger droplets, reducing evaporation and coalescence of the droplets  
438 (Twitchell, 1990).

439

440 The second study focused on substituting HPMC with a more biocompatible polymer (CMC)  
441 and allowed further refining of the processing parameters. Results highlight the role of

442 surface tension in film coating. The higher surface tension of CMC solutions employed  
443 without the addition of Tween 80 (**Table 4**) resulted in poor film coalescence (**Figure 5a**).  
444 Adjusting the surface tension to values similar to those of HPMC solutions improved film  
445 coalescence (**Figure 5b and c**). The surface texture of coalesced films varied between Runs.  
446 The smoothest films were obtained for Run 6;  $R_a$  value of 0.8  $\mu\text{m}$ . The film produced in Run  
447 4 had a more textured coating;  $R_a$  value of 1.4 $\mu\text{m}$ . The textured coating may have been  
448 caused by the acute spray angle at the lower air cap setting of 1 resulting in a higher spray  
449 density and drying effects due to the increased air flow focussed on the substrate surface.

450

451 The influence of processing parameters on a quantitative property coating weight is clearly  
452 illustrated in **Figures 3 and 6**. As expected the increase of the mass of solids atomised during  
453 the spray coating process when using longer spray time had a significantly positive impact on  
454 coating weight in the HPMC coating study. The lack of effect of liquid input rate on coating  
455 weight in the CMC coating study can be explained by the volume of coating liquid being kept  
456 constant for all runs. In this study that the mass of material deposited was controlled by the  
457 concentration of material in the coating solution, as observed in **Figure 6**. The inclusion of a  
458 surfactant to the coating solution in the CMC study had a positive effect on coating weight.  
459 The addition of 1% w/v Tween 80 would increase the material contents of the coating  
460 solutions and this resulted in an increase in the weight of solid material deposited.

461

462 The atomisation air pressure range investigated in the HPMC study had a positive effect on  
463 coating weight (1.0 bar), however the higher upper air pressure range investigated in the  
464 CMC study (1.75 bar) had a negative effect on coating weight. The use of higher atomisation  
465 air pressure, while beneficial for producing small droplet sizes which facilitate coating and  
466 spreading of droplets after deposition (Twitchell, 1990), should be controlled to minimise

467 loss of coating due to increased spray velocity, associated impingement force on the surface  
468 coated and material loss from the surface in the atomisation air stream after impingement.  
469 Increasing gun-to-surface distance from 5 to 10 cm had a negative effect on coating weight in  
470 the HPMC study, which can be attributed to a decrease in spray density on the silicon surface.  
471 In the CMC study this effect was reversed when the gun-to-surface distance was increased  
472 from 3 to 6 cm. The decrease in coating weight at smaller gun-to-surface distances can be  
473 explained by the increased impact of spray velocity at the lower distances in the CMC study,  
474 similar to that observed for the high atomisation air pressure. While increasing the air cap  
475 setting had a positive effect on coating weight in the HPMC study due to a wider spray angle  
476 and lower spray density, this effect was not observed in the CMC study with the air cap  
477 setting having no effect. The combination of processing parameters selected in the CMC  
478 study negated the effect of the air cap setting on coating weight.

479

480 Based on the finding in the HPMC study, a set of processing parameters were identified for  
481 coating microneedle arrays with HPMC. A coating solution with the low level of HPMC  
482 concentration (5% w/v) was selected to minimise the effects of solution viscosity observed in  
483 the HPMC study. Low liquid input (3.1 mls/min) and high air pressure (1 bar) were selected  
484 to obtain a high air-to liquid mass ratio and hence a small droplet size to achieve a thin intact  
485 film-coat and good coat coalescence. Although a low air cap setting and gun-to-surface  
486 distance maximised coating weight, a high air cap setting (3) and high gun-to-surface  
487 distance (10 cm) were selected reduce the impact of a high spray velocity on film-coat  
488 appearance and texture. The identified parameters successfully coated microneedles arrays  
489 with a HPMC coat and demonstrate the ability to transfer learnings from coating flat silicon  
490 patches to coating three-dimensional silicon microneedle arrays.

491 The set of processing parameters were revised following the CMC study and selected  
492 parameters for applying a CMC coat to silicon microneedle arrays included the addition of  
493 1% Tween 80 to a 3% w/v CMC concentration solution to facilitate film-coat coalescence.  
494 An intermediate air cap setting (3) was selected to focus the spray on the 1 cm<sup>2</sup> microneedle  
495 array. A high gun-to-surface distance (6 cm) and a low atomisation air pressure (0.5 bar)  
496 were chosen to minimise the effects of a high spray velocity on coating loss and texture. The  
497 atomisation air pressure chosen was coupled with a low liquid input rate (1.5 ml/min) to  
498 obtain an relatively high air-to-liquid mass ratio suitable to generate small droplets sizes to  
499 facilitate coalescence. The intact thin CMC film-coat obtained again validates the hypothesis  
500 that spray coating can be used to apply a polymer coating to microneedle arrays and that the  
501 findings obtained from coating flat silicon substrates can be translated to coating  
502 microneedles arrays.

503

## 504 **Conclusions**

505 This study demonstrates the ability of conventional film-coating processes to coat intact films  
506 of polymers on silicon microneedle arrays. The process understanding obtained in this study  
507 can be applied to other spray coated drug delivery systems, such as coated medical devices. It  
508 also is the first study to define the coating thickness and roughness that can be achieved. The  
509 HPMC and CMC coatings produced were intact, followed the contours of the microneedle  
510 shapes and did not occlude the microneedle tip. The study also highlights the influence of  
511 coating solution physicochemical properties and spray process parameters on film-coat  
512 formation and hence the importance of identifying a set of suitable processing parameters  
513 when film coating substrates of micron dimensions. The ability of fractional factorial design  
514 to identify the effect of critical parameters on film-coat coalescence and weight with a limited  
515 number of coating runs was also demonstrated. The scale up of this conventional spray

516 coating process it not expected to pose the same level of challenge relating to regulatory  
517 compliance and automation as may be posed by other novel microneedle coating  
518 technologies. Therefore we propose that spray coating is an attractive process for applying a  
519 polymer coat to microneedles and potentially could be exploited to apply drug and vaccine  
520 materials to microneedles for delivery intradermally.

521

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523

524

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530

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632 **Figure Legends**

633

634 **Figure 1.** Schematic diagram of spray coating apparatus.

635

636 **Figure 2.** Images of surface topography of HPMC spray coated flat silicon substrates  
637 prepared using parameters detailed in Table 1 (a) Run 5 (good coalescence), (b) Run 4 (poor  
638 coalescence) and (c) Run 6 (poor coalescence). Left hand side images were produced by zygo  
639 white-light interferometer and right hand side were images obtained by light microscopy  
640 (magnification x10).

641

642 **Figure 3.** A plot showing the average HPMC coating weight for each processing parameter  
643 setting relative to the global average HPMC coating weight (indicated by the grey horizontal  
644 line). Solid line indicates the effect is not statistically significant ( $p > 0.05$ ). Broken line  
645 indicates the effect is statistically significant ( $p < 0.05$ ).

646

647 **Figure 4.** Scanning electron microscopy images of a film coated single silicon microneedle  
648 and a film coated silicon microneedle array. A) shows a HPMC film-coat and B) shows a  
649 CMC film-coat.

650

651 **Figure 5.** Images of surface topography of CMC spray coated flat silicon substrates prepared  
652 using parameters detailed in Table 2 (a) Run 3 (poor coalescence), (b) Run 4 (rough textured  
653 coating) and (c) Run 6 (good coalescence). Left hand side images were produced by zygo  
654 white-light interferometer and right hand side were images obtained by light microscopy  
655 (magnification x10).

656

657 **Figure 6.** A plot showing the average CMC coating weight for each processing parameter  
658 setting relative to the global average CMC coating weight (indicated by the grey horizontal  
659 line). Solid line indicates the effect is not statistically significant ( $p > 0.05$ ). Broken line  
660 indicates the effect is statistically significant ( $p < 0.05$ ).

661

662

**Table 1.** The parameter values selected for the L8 orthogonal array used to develop spray coating of silicon with HPMC.

No.	Atomisation air pressure (bars)	Liquid input (mls/min)	Gun-to- surface distance (cms)	Conc. HPMC (% w/v )	Spray time (secs)	Air cap setting
<b>1</b>	0.5	3.1	5	5	30	1
<b>2</b>	0.5	3.1	5	12	90	3
<b>3</b>	0.5	4.5	10	5	30	3
<b>4</b>	0.5	4.5	10	12	90	1
<b>5</b>	1.0	3.1	10	5	90	1
<b>6</b>	1.0	3.1	10	12	30	3
<b>7</b>	1.0	4.5	5	5	90	3
<b>8</b>	1.0	4.5	5	12	30	1

*\*Overall liquid input varies from 1.33-13.5mls as described per run*

**Table 2.** The parameter values selected for the L8 orthogonal array used to develop spray coating of silicon with CMC.

No.	Conc. CMC (% w/v)	Liquid input (mls/min)	Gun-to-surface distance (cms)	Tween ( % w/v)	Atomisation air pressure (bars)	Air cap setting
1	1	1.5	3	0	0.5	1
2	1	1.5	3	1	1.75	5
3	1	9	6	0	0.5	5
4	1	9	6	1	1.75	1
5	5	1.5	6	0	1.75	1
6	5	1.5	6	1	0.5	5
7	5	9	3	0	1.75	5
8	5	9	3	1	0.5	1

*\*Total volume sprayed was 0.8mls throughout this study*

**Table 3.** Process parameter settings used in the HPMC and CMC studies.

	The HPMC study		The CMC study	
	Variable 1 (low)	Variable 2 (high)	Variable 1 (low)	Variable 2 (high)
Concentration HPMC (% w/v)	5	12	n/a	n/a
Concentration CMC (% w/v)	n/a	n/a	1	5
Concentration Tween 80 (% w/v)	n/a	n/a	0	1
Liquid input (ml/min)	3.1	4.5	1.5	9.0
Spray time (sec)	30	90	n/a	n/a
Atomisation Air Pressure (bar)	0.5	1.0	0.5	1.75
Gun-to-surface distance (cm)	5	10	3	6
Air cap setting	1	3	1	5

*n/a indicates not applicable*

**Table 4.** Average surface tension and viscosity measurements of coating solutions n=3, figures in brackets indicate the standard deviation.

	<b>Surface tension (mN.m)</b>	<b>Viscosity (mPa.sec)</b>
<b>The HPMC study</b>		
<b>5% w/v</b>	44.7 (0.93)	9.5 (0.03)
<b>12% w/v</b>	46.1 (1.23)	345 (10.54)
<b>The CMC study</b>		
<b>1% w/v</b>	55.0 (1.58)	3.9 (0.10)
<b>1% w/v + 1% Tween 80</b>	42.0 (0.92)	3.3 (0.02)
<b>5% w/v</b>	48.7 (1.49)	48.2 (0.71)
<b>5% w/v + 1% Tween 80</b>	45.7 (0.51)	52.7 (0.70)

**Table 5.** Average coating weight determined for each run in the HPMC and CMC studies (n=3), standard deviation shown in brackets.

	HPMC study	CMC study
Run no.	Coating Weight (µg)	Coating Weight (µg)
1	4 (1.7)	103 (80.0)
2	12 (5.0)	216 (8.7)
3	3 (1.0)	465 (54.7)
4	12 (2.6)	460 (66.6)
5	6 (1.5)	1908 (197.8)
6	1 (1.4)	4609 (332.1)
7	5 (0.6)	1684 (308.0)
8	16 (1.0)	3870 (661.5)



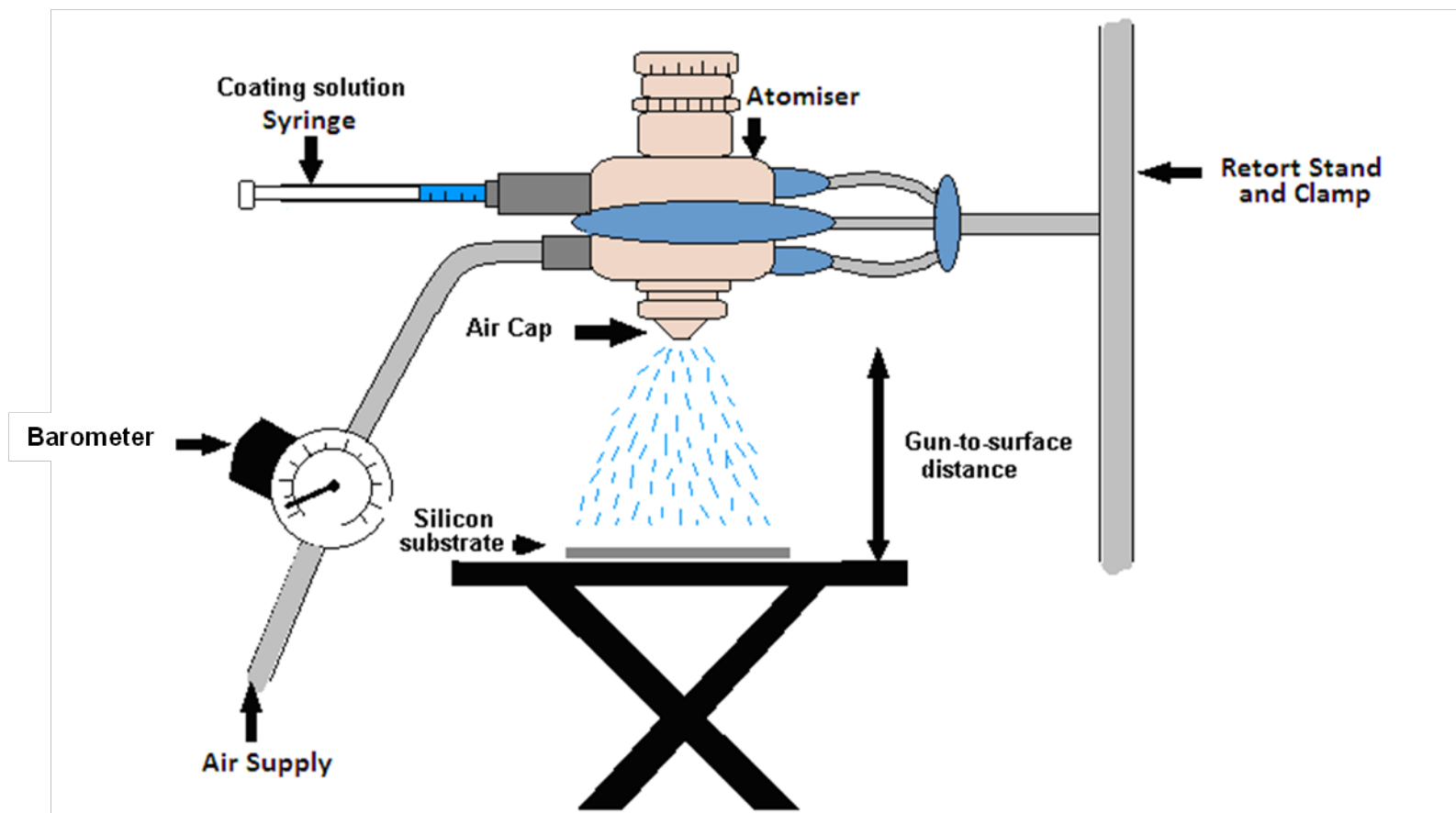


Figure 1

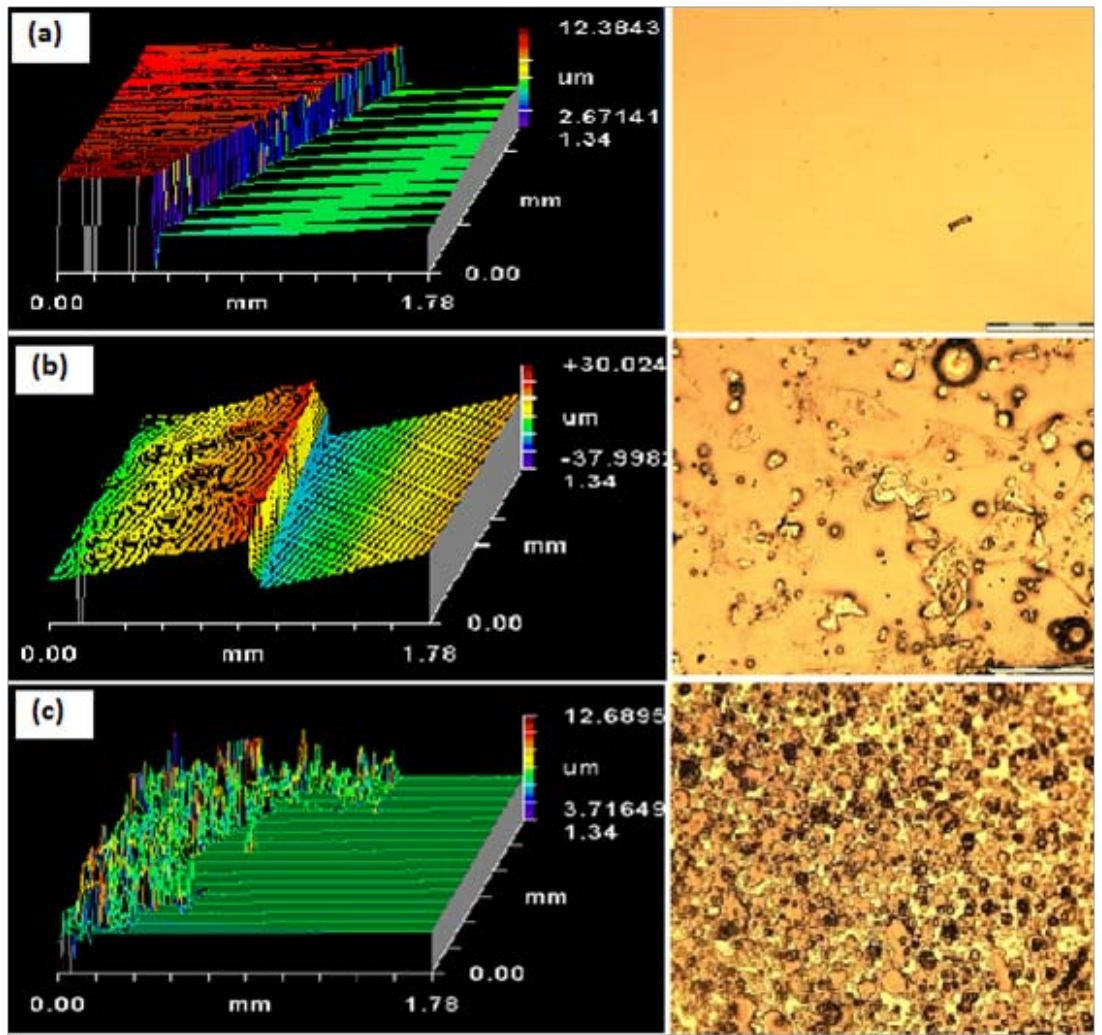


Figure 2.

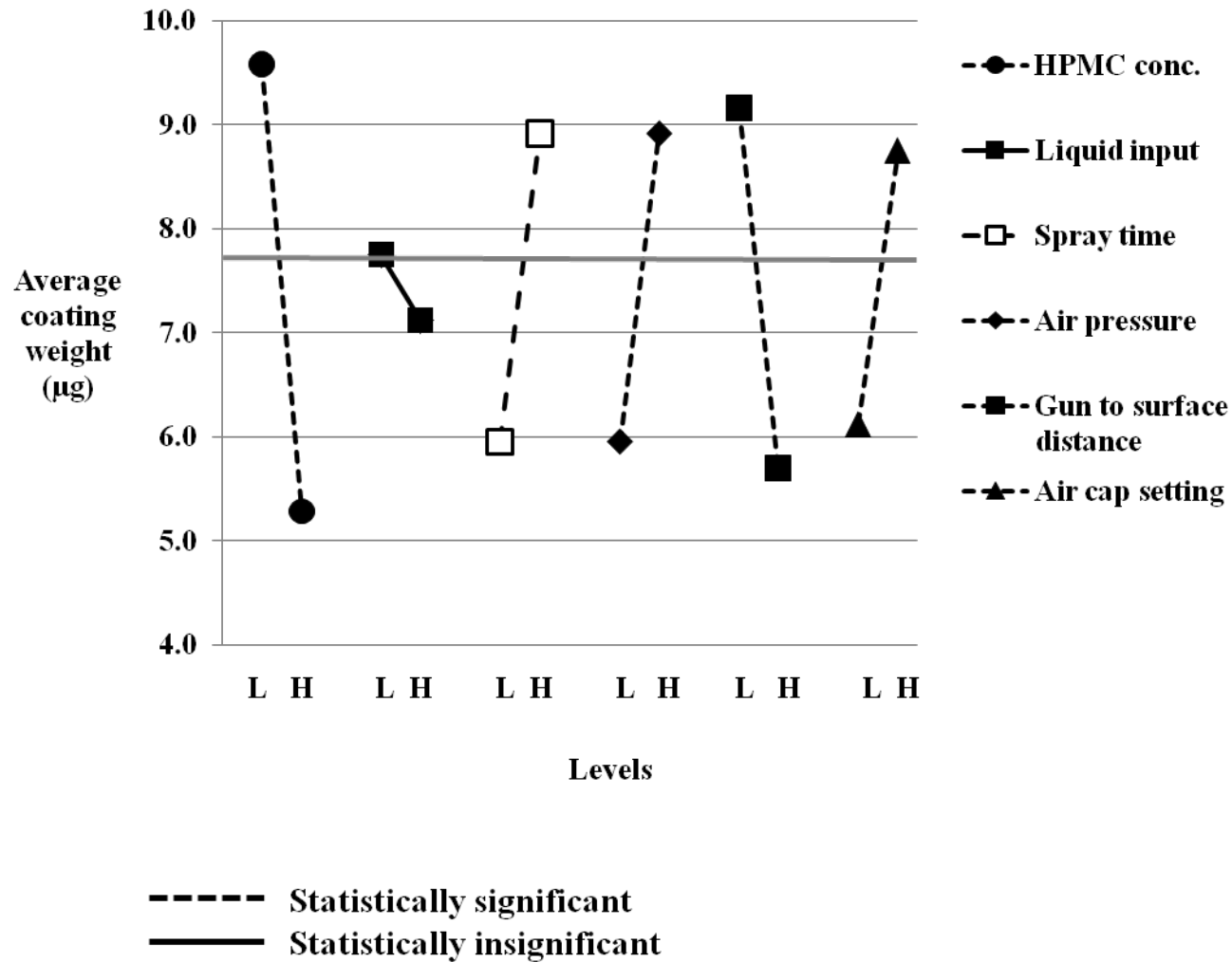
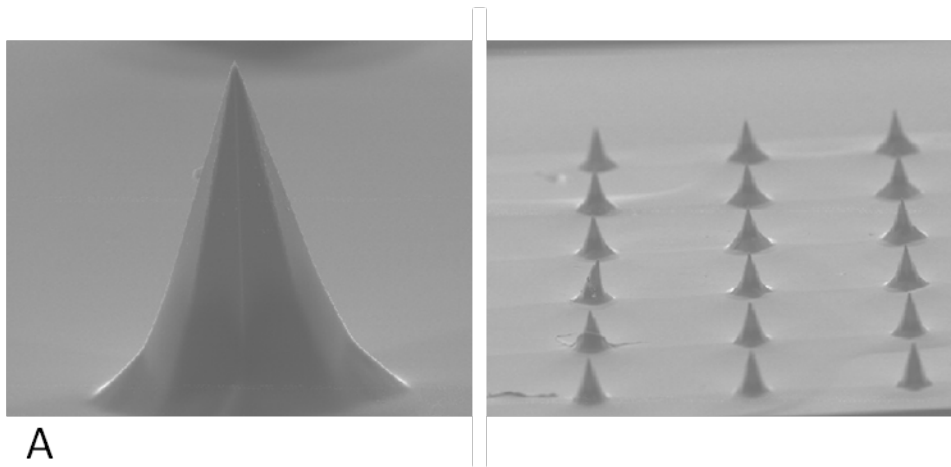
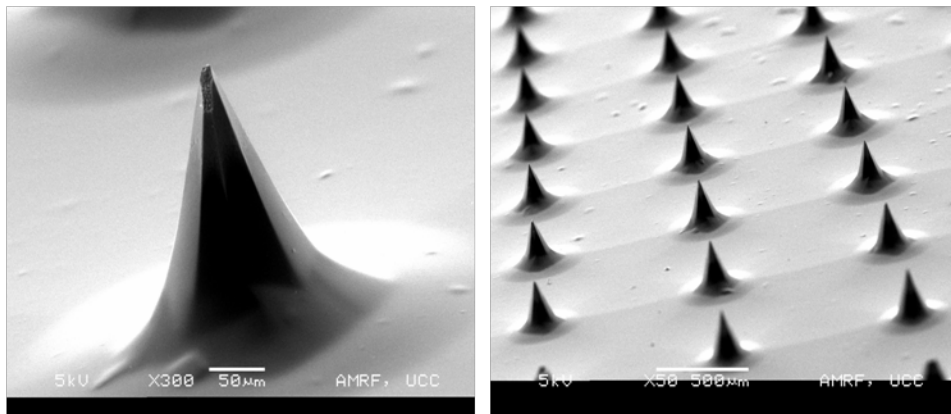


Figure 3.



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**Figure 4.**

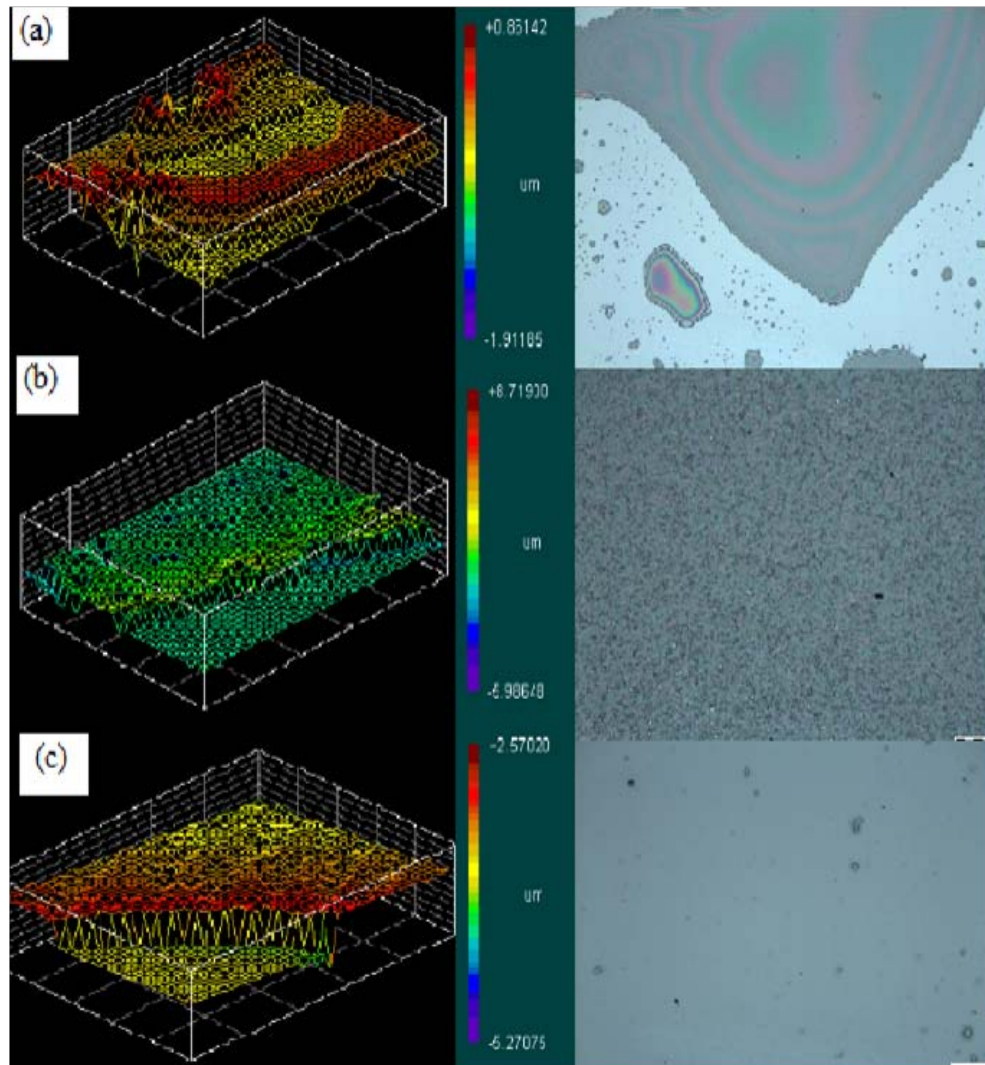


Figure 5

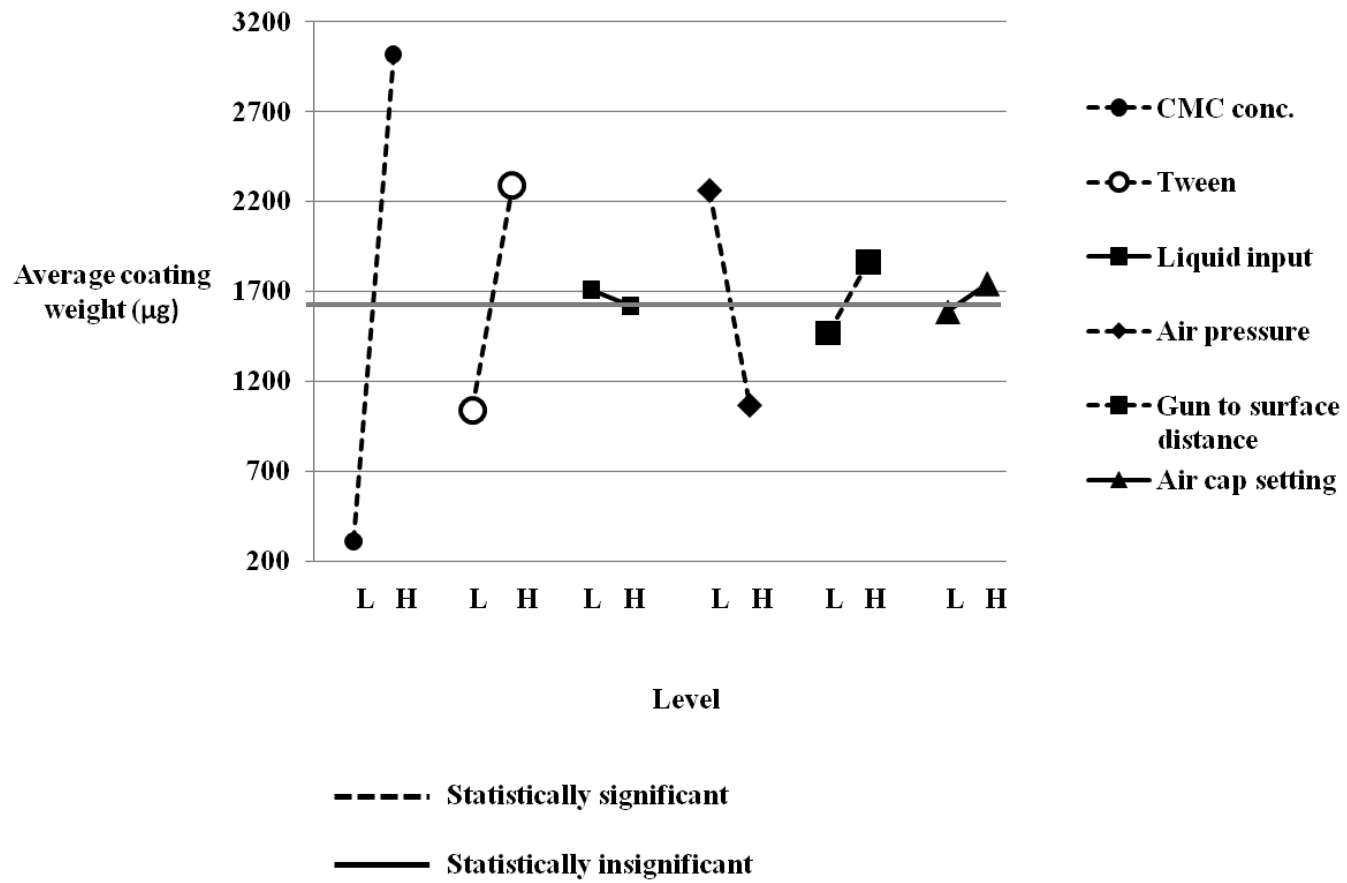


Figure 6