MCGRATH, M. G., VRDOLJAK, A., O'MAHONY, C., OLIVEIRA, J. C., MOORE, A. C. & CREAN, A. M. 2011. Determination of parameters for successful spray coating of silicon microneedle arrays. *International Journal of Pharmaceutics,* In Press, Corrected Proof.
doi:10.1016/j.ijpharm.2011.05.064

DETERMINATION OF PARAMETERS FOR SUCCESSFUL SPRAY COATING OF SILICON MICRONEEDLE ARRAYS

Marie G. McGrath [a], Anto Vrdoljak [a], Conor O'Mahony [b], Jorge C. Oliveira [c], Anne C. Moore[a,d], Abina M. Crean [a,*]

[a] School of Pharmacy, University College Cork, Cork, Ireland

[b] Tyndall National Institute, Lee Maltings, University College Cork, Cork, Ireland

[c] Department of Process and Chemical Engineering, University College Cork, Ireland

[d] Department of Pharmacology, University College Cork, Cork, Ireland

Email address of each author:

Marie G. MCGRATH: marie_mc_grath@hotmail.com

Anto VRDOLJAK: a.vrdoljak@ucc.ie

Conor O'MAHONY: conor.omahony@tyndall.ie

Jorge C. OLIVEIRA: j.oliveira@ucc.ie

Anne C. MOORE: anne.moore@ucc.ie

Abina M. CREAN: a.crean@ucc.ie

[*] Corresponding author: School of Pharmacy, University College Cork, Cork, Ireland.

Tel.: +353 21 490 1667; fax: +353 21 490 1656.

E-mail address: a.crean@ucc.ie (A.M. Crean).

Abstract

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

Keywords: microneedle, spray coat, silicon, hydroxypropylmethylcellulose, carboxymethylcellulose.

Introduction

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

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

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

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

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

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

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

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

Materials and methods

Materials

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

Characterisation of the coating solutions

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

Spray coating process

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

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

Identification of suitable processing parameters

HPMC film-coating was investigated in the HPMC study and CMC film-coating was investigated in the CMC study. Both experimental designs consisted of a six factor, two level, fractional factorial design applied to a L_8 orthogonal array to define the experimental conditions, as described in **Table 1** and **2.** Each set of experiments was carried out in triplicate. Two way analysis of variance (ANOVA) was used to assess the impact of the various processing parameters on the coating weight response factor. The average experimental response for each factor at each level was calculated. These values indicate the relative impact of using a high or low level of each factor on the coating weight. The statistical significance of each factor at each level was determined by calculating the sum of squares using all individual data points. From the sum of squares data, variance (mean square) values for each factor and the variance due to the error term were then calculated. From these values, the F statistic, the ratio of variance due to the effect of a factor and variance due to the error term, was determined. The F factor measures the significance of the factor under investigation with respect to variance of all the factors included in the error term (Roy, 1990).

Assessment of film-coating coalescence and weight

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

Results

Characterisation of coating solutions

It is hypothesised that properties of the substrate to be coated and the physicochemical properties of the coating solution would affect the formation of an intact film. In advance of coating trials a number of relevant physicochemical properties were determined. All HPMC and CMC coating solutions used in this study were aqueous based. The contact angle of water on flat silicon patches was determined to be 32.5° +/- 2.0° at ambient temperature. A surface is considered hydrophilic when the contact angle of water on its surface is < 90 ^{o}. The contact angle measured suggests that silicon is a hydrophilic material and will be wetted by aqueous based formulations employed in this investigation, thereby facilitating coating of the silicon substrates investigated. The surface tension of HPMC and CMC coating solutions employed are detailed in **Table 4.** HPMC exhibited surfactant properties and these values correlated well with those previously described (Twitchell, 1990). The surface tension of 1 %w/v CMC coating solutions, were significantly higher than those determined for the 5 %w/v CMC and both HPMC coating solutions ($p \leq 0.01$). As increased surface tension can adversely affect coating coalescence, a surfactant Tween 80 was incorporated as a formulation variable within the CMC study. The addition of 1 % w/v Tween 80 to CMC solutions reduced surface tension to values comparable to the HPMC solutions. The viscosity of HPMC and CMC coating solutions employed are also detailed in **Table 4.** There was a disproportionate increase in the viscosity of HPMC solutions with increase in concentration. This increase in viscosity is thought to be the result of an increased resistance to flow due to the large hydrodynamic volume of the randomly coiled polymer chains and their associated hydrogen-bonded water molecules (Clasen and Kulicke, 2001). The viscosity of CMC solutions also increased disproportionately with increased concentration. The addition of 1% w/v Tween 80 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 that 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 μm and a Ra (roughness) value of 0.16 μm, 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 μm) and relatively high Ra
267 value of 0.74 μm. Coalescence of the droplets on the surface was incomplete with areas

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

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

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

Spray coating microneedles with HPMC

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

Assessment of CMC film-coat coalescence and weight

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

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

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

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

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

Spray coating microneedles with CMC

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

Discussion

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

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

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

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

As a wide range of processing parameters highlighted in the introduction can influence film-coat formation, the number of processing parameters identified for investigation in studies 1 and 2 was relatively large (6 factors). A full factorial design of experiment would have required 64 individual runs for each study. The Taguchi method of experimental design 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

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

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

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

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

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

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

Conclusions

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

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

Acknowledgements

The authors would like to thank Enterprise Ireland (Commercialisation Fund), Higher Education Authority (Programme for Research in Third-Level Institutions) and Science Foundation Ireland (National Access Programme) for funding this work. Scanning Electron Microscopy was conducted at the Electron Microscopy facility at the Biosciences Institute, UCC, Ireland. Colorcon®, U.K. kindly donated the HPMC (Methocel) used in this study.

References

Ameri, M., Daddona, P.E., Maa, Y.F., 2009. Demonstrated Solid-State Stability of Parathyroid Hormone PTH(1-34) Coated on a Novel Transdermal Microprojection Delivery System. Pharmaceutical Research 26, 2454-2463.

Aulton, M.E., Twitchell, A.M., 1995. Solution properties and atomization in film coating, in: G.Cole., J.H., M.Aulton (Ed.), Pharmaceutical Coating technology. Taylor & Francis, London, pp. 64-117.

Aulton, M.E., Twitchell, A.M., Hogan, J.E., 1986. Proc. 4th Int. Conf. Pharm. Tech, APGI, Paris, France V, pp. 133-140.

Behzadi, S.S., Toegel,S.,Viernstein,H., 2008. Innovations in Coating Technology. Recent Patents on Drug Delivery & Formulation, 209-230.

Chen, X., Prow, T.W., Crichton, M.L., Jenkins, D.W.K., Roberts, M.S., Frazer, I.H., Fernando, G.J.P., Kendall, M.A.F., 2009. Dry-coated microprojection array patches for targeted delivery of immunotherapeutics to the skin. Journal of Controlled Release 139, 212-220.

548 Clasen, C., Kulicke, W.M., 2001. Determination of viscoelastic and rheo-optical material
549 functions of water-soluble cellulose derivatives. Progress in Polymer Science 26, 1839-1919.
550 Cormier, M., Johnson, B., Ameri, M., Nyam, K., Libiran, L., Zhang, D.D., Daddona, P.,
551 2004. Transdermal delivery of desmopressin using a coated microneedle array patch system.
552 Journal of Controlled Release 97, 503-511.
553 Dalton, C., Easeman, R., Garcon, N., 2007. Needles coating with vaccine, in: Agency, E.P.
554 (Ed.), http://www.europatentbox.com/inventors/DALTON-COLIN-CLIVE/232152.html.
555 Gill, H.S., Prausnitz, M.R., 2007. Coated microneedles for transdermal delivery. Journal of
556 Controlled Release 117, 227-237.
557 Kim, Y.C., Quan, F.S., Compans, R.W., Kang, S.M., Prausnitz, M.R., 2010. Formulation and
558 coating of microneedles with inactivated influenza virus to improve vaccine stability and
559 immunogenicity. Journal of Controlled Release 142, 187-195.
560 Maa, Y.F., 2005. Apparatus and method for transdermal delivery of influenza vaccine, in:
561 application, U.S.P. (Ed.), http://www.freepatentsonline.com/y2005/0220854.html.
562 Matriano, J.A., Cormier, M., Johnson, J., Young, W.A., Buttery, M., Nyam, K., Daddona,
563 P.E., 2002. Macroflux (R) microprojection array patch technology: A new and efficient
564 approach for intracutaneous immunization. Pharmaceutical Research 19, 63-70.
565 Mehta, A.M., 2008. Processing and Equipment Considerations for Aqueous coatings, in:
566 McGinity, J., Felton, L.A. (Eds.), Aqueous Polymeric Coatings for Pharmaceutical Dosage
567 Forms, 3rd ed. Informa Heathcare USA, New York, pp. 67-104.
568 Missaghi, S., Fassihi, R., 2004. A novel approach in the assessment of polymeric film
569 formation and film adhesion on different pharmaceutical solid substrates. AAPS
570 Pharmscitech 5, 1-8.
571 Mueller, R., Kleinebudde, P., 2007. Comparison of a laboratory and a production coating
572 spray gun with respect to scale-up. AAPS Pharmscitech 8, Article 3,E1.
573 Muller, R., Kleinebudde, P., 2006. Comparison study of laboratory and production spray
574 guns in film coating: Effect of pattern air and nozzle diameter. Pharmaceutical Development
575 and Technology 11, 425-433.
576 Prausnitz, M.R., 2004. Microneedles for transdermal drug delivery. Adv Drug Deliver Rev
577 56, 581-587.
578 Rowe, R.C., 2003. Handbook of Pharmaceutical Excipients, 4th ed. Pharmaceutical Press and
579 American Pharmaceutical Association, Bath.
580 Roy, R.K., 1990. A Primer on the Taguchi Method, Society of Manufacturing Engineers.

Sathyan, S., Gayatri.,G, 2005. Thin Film Coating Systems, in: Agency, U.S.P. (Ed.), http://www.patentstorm.us/applications-by-date/2009/0611/1.html, US 20060093658.

Tobiska, S., Kleinebudde, P., 2003. Coating uniformity and coating efficiency in a Bohle Lab-Coater using oval tablets. Eur J Pharm Biopharm 56, 3-9.

Twitchell, A.M., 1990. title., De Montfort University, Leicester.

Wilke, N., Reed, M.L., Morrissey, A., 2006. The evolution from convex corner undercut towards microneedle formation: theory and experimental verification. J Micromech Microeng 16, 808-814.

Yang, M.R., Zahn, J.D., 2004. Microneedle insertion force reduction using vibratory actuation. Biomedical Microdevices 6, 177-182.

Zhu, Q.Y., Zarnitsyn, V.G., Ye, L., Wen, Z.Y., Gao, Y.L., Pan, L., Skountzou, I., Gill, H.S., Prausnitz, M.R., Yang, C.L., Compans, R.W., 2009. Immunization by vaccine-coated microneedle arrays protects against lethal influenza virus challenge. P Natl Acad Sci USA 106, 7968-7973.

Figure Legends

Figure 1. Schematic diagram of spray coating apparatus.

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

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

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

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

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

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
1	0.5	3.1	5	5	30	1
2	0.5	3.1	5	12	90	3
3	0.5	4.5	10	5	30	3
4	0.5	4.5	10	12	90	1
5	1.0	3.1	10	5	90	1
6	1.0	3.1	10	12	30	3
7	1.0	4.5	5	5	90	3
8	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.

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

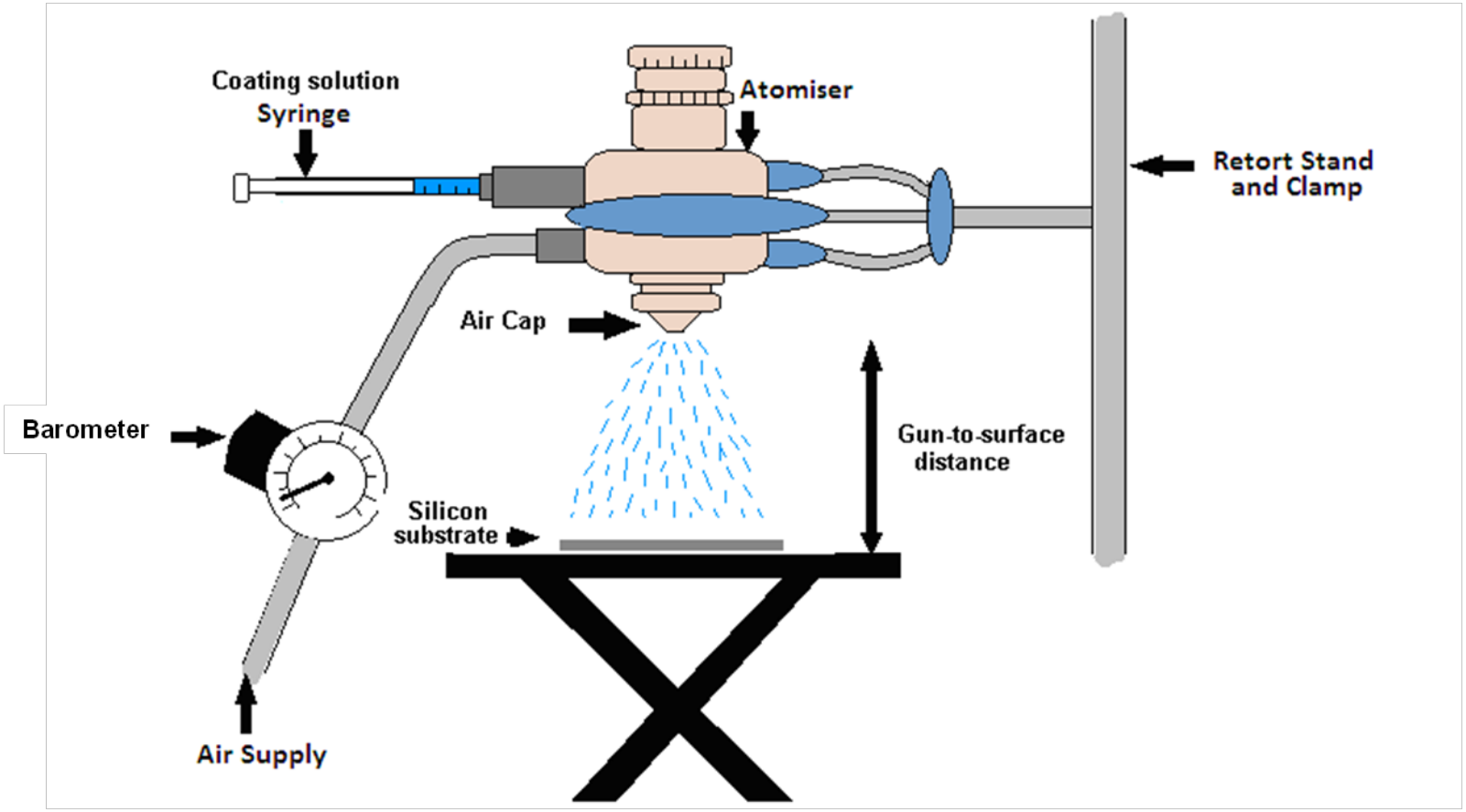
Coating solution
Syringe
Atomiser
Retort Stand
and Clamp
Air Cap
Barometer
Gun-to-surface
distance
Silicon
substrate
Air Supply

Figure 1

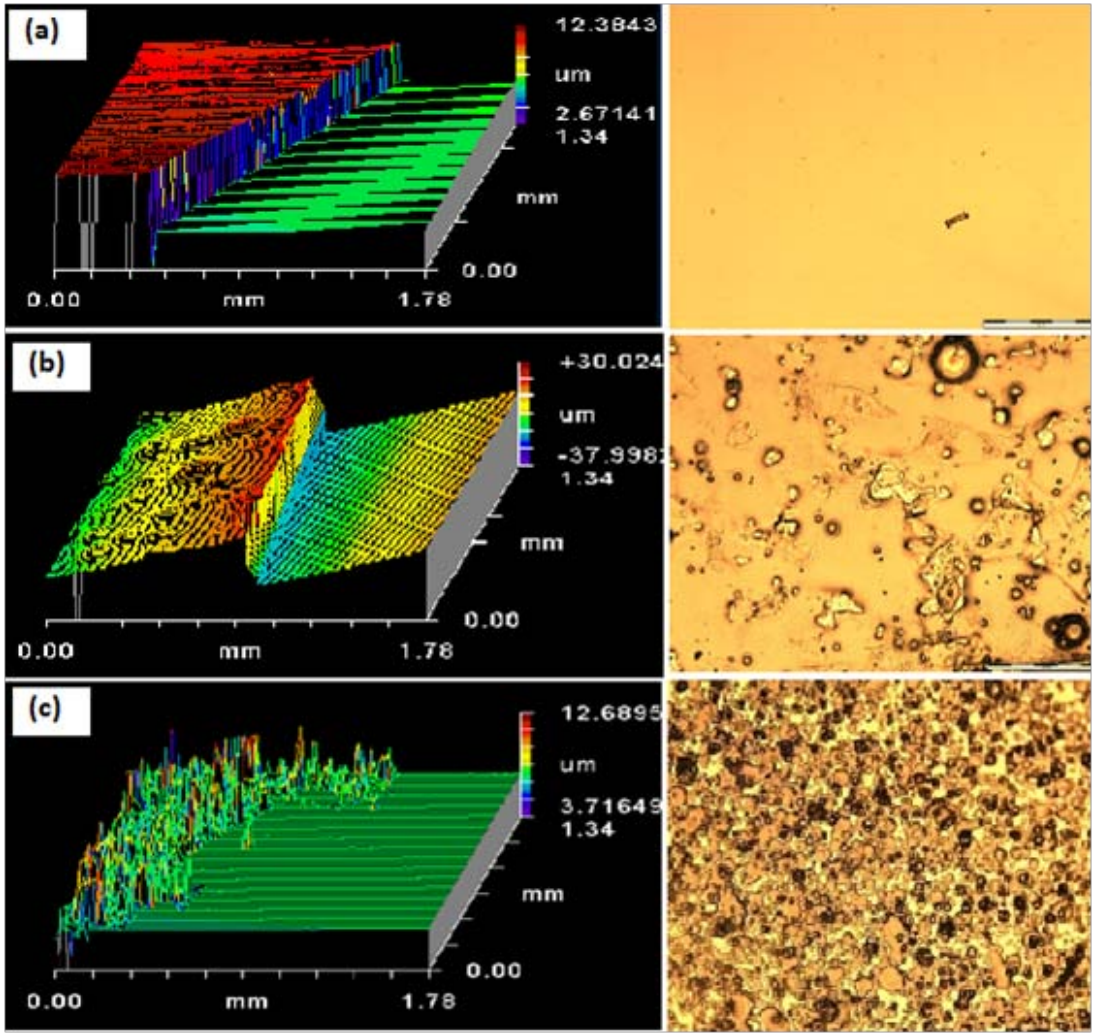
(a)
12.3843
um
2.67141
1.34
mm
0.00
0.00
mm
1.78
(b)
+30.024
um
-37.998
1.34
mm
0.00
0.00
mm
1.78
(c)
12.6895
um
3.71649
1.34
mm
0.00
0.00
mm
1.78

Figure 2.

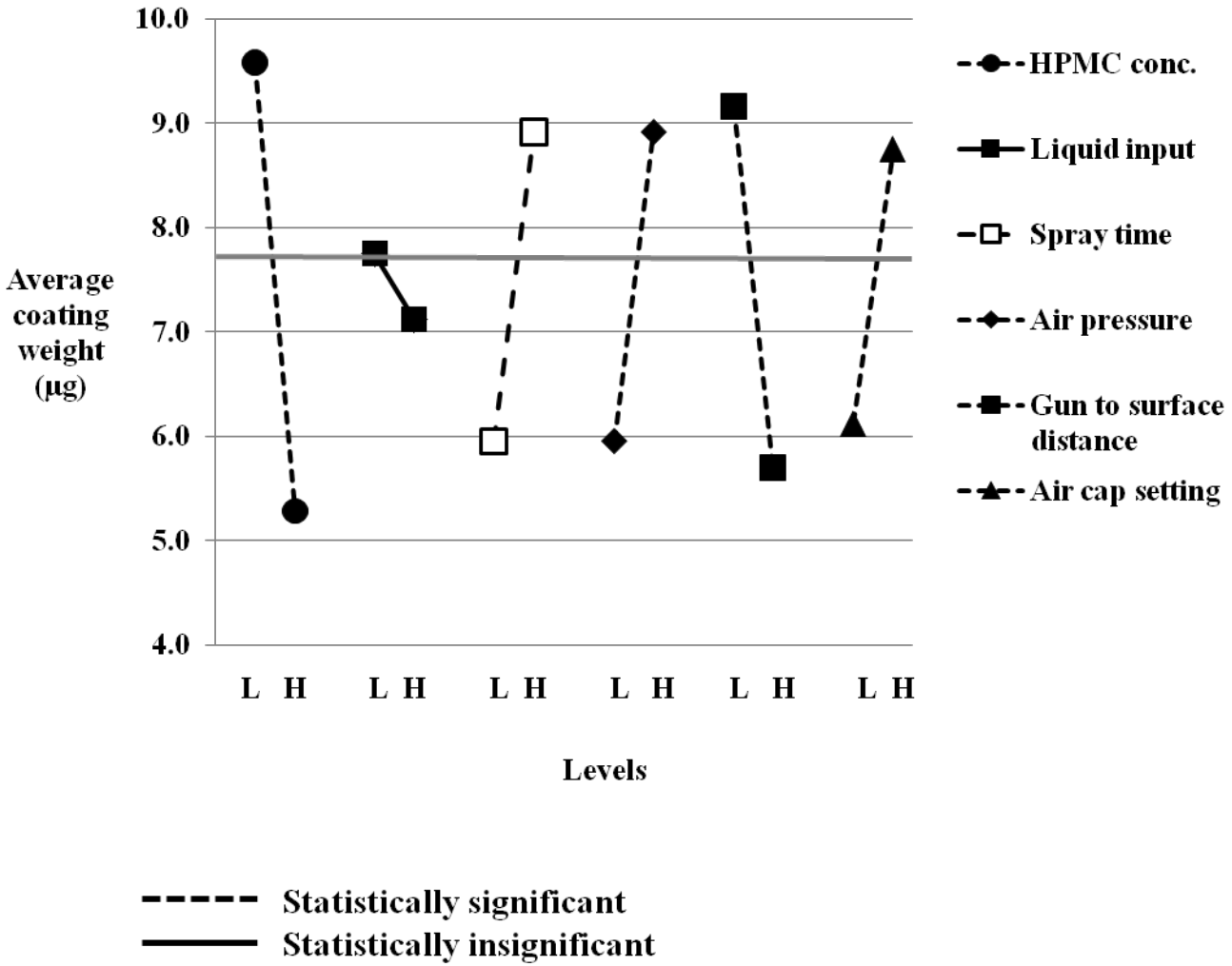
10.0
9.0
8.0
7.0
6.0
5.0
4.0
Average coating weight (µg)
L H L H L H L H L H L H
Levels
HPMC conc.
Liquid input
Spray time
Air pressure
Gun to surface distance
Air cap setting
Statistically significant
Statistically insignificant

Figure 3.

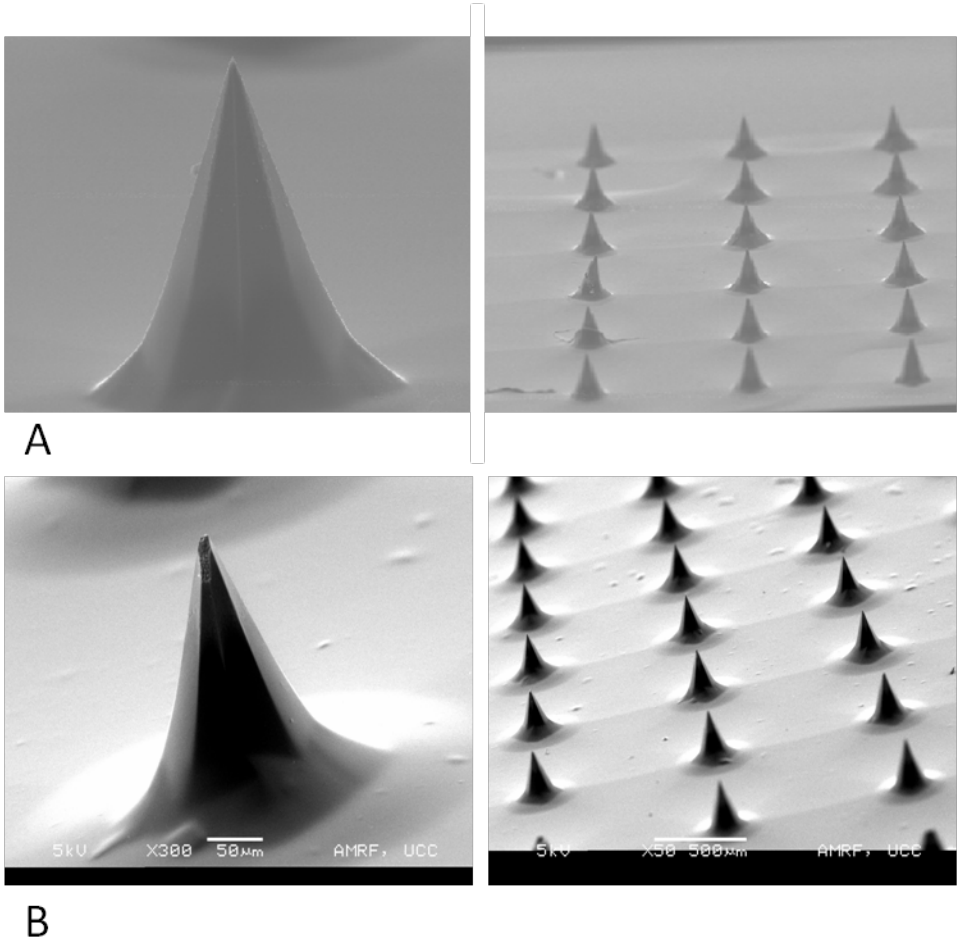

Figure 4.

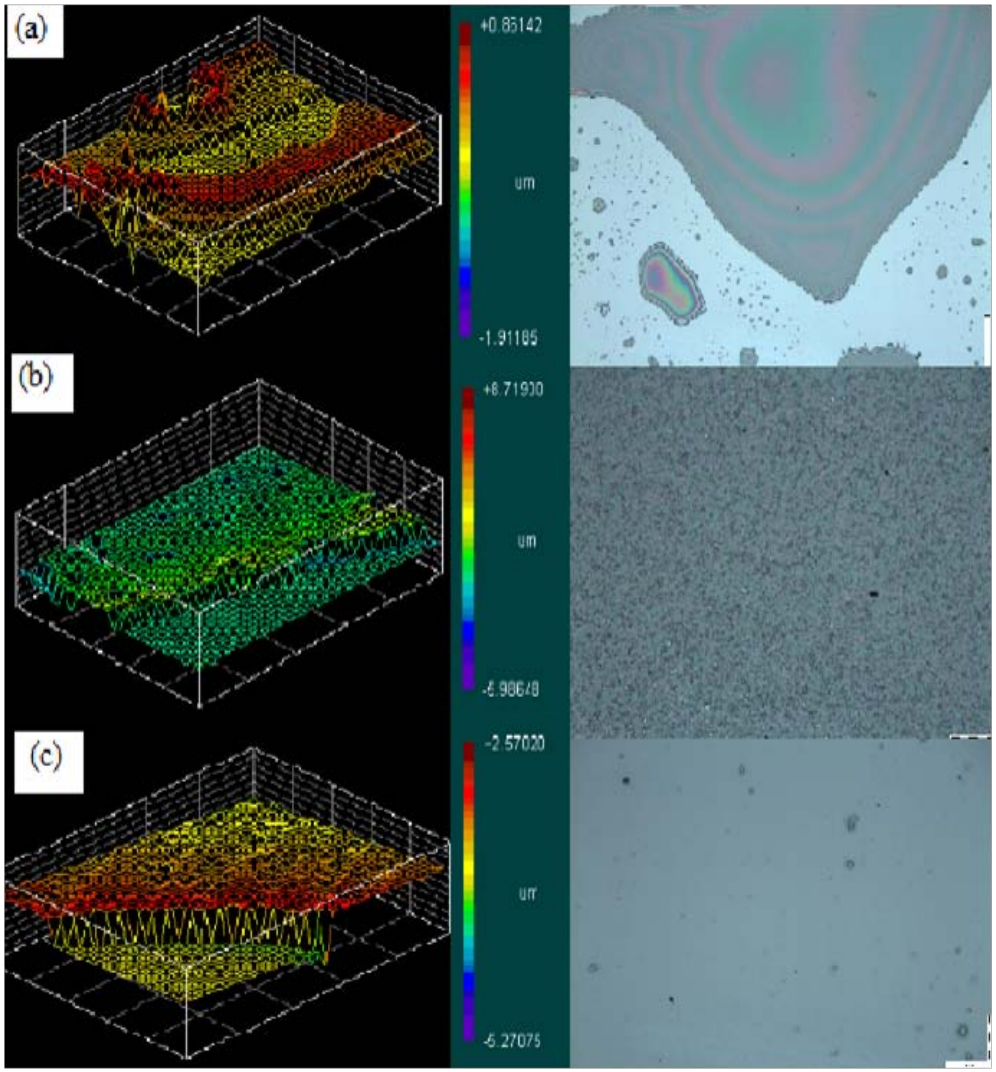

Figure 5

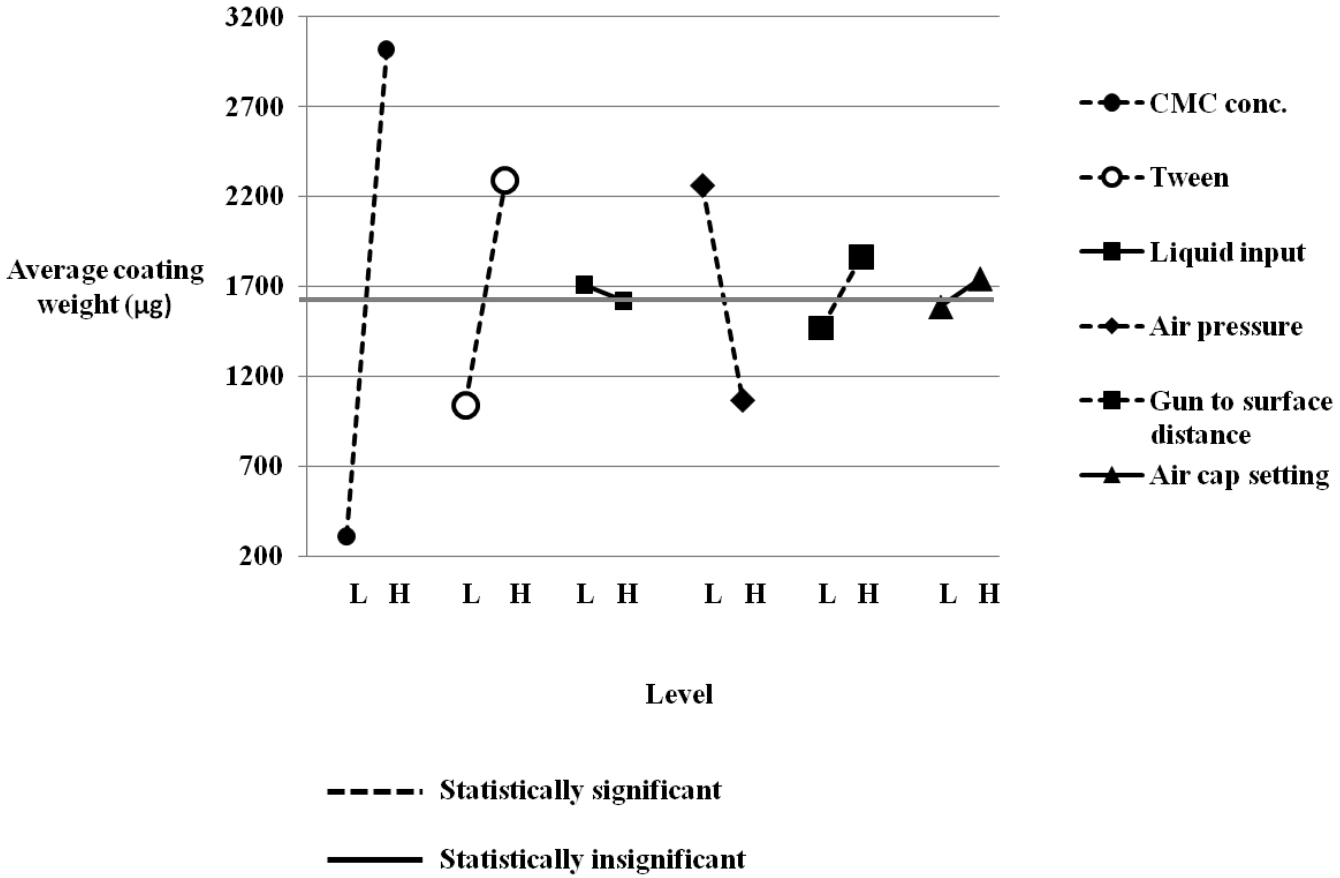
3200
2700
2200
1700
1200
700
200
Average coating weight (µg)
L H L H L H L H L H L H
Level
CMC conc.
Tween
Liquid input
Air pressure
Gun to surface distance
Air cap setting
Statistically significant
Statistically insignificant

Figure 6