Influence of process parameters on the preparation of pharmaceutical films by electrostatic powder deposition

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Abstract

Electrostatic powder deposition (ESPD) has been developed as a solvent-free method to prepare pharmaceutical films. The aim of this work was to investigate the influence of process parameters during (1) electrostatic powder deposition, (2) curing, and (3) removal of the film from the substrate on the properties of the film. Polyethylene oxide (PEO) was used as the model polymer and stainless steel 316 as the substrate. Deposition efficiency (*i.e.* deposited weight) was measured with varying charging voltage, gun tip to substrate distance, and environmental humidity. Scanning electron microscopy was utilized to assess film formation, and adhesive and mechanical strength of films were measured with varying cure temperature and time. Adhesive strength was measured for films prepared on substrates of varying surface roughness. When deposition was performed at low humidity conditions, 25 %RH, process parameters did not significantly affect deposition behavior. At 40 %RH,

increasing deposition efficiency with decreasing gun tip to substrate distance and increasing voltage (up to 60kV) was observed. Complete film formation was seen by 30 minutes at 80°C, compared to lower curing temperatures and times. All films were readily removed from the substrates. The results show the ESPD process can be modified to produce films with good
25 mechanical properties (e.g. tensile strength > 0.06 MPa), suggesting it is a promising dry powder process for preparing pharmaceutical films.

Introduction

Oral solid dosage forms, specifically tablets and capsules, remain the most preferred dosage form and route of administration for drug delivery (Sastry et al., 2000). However,
30 difficulty in swallowing or dysphagia can significantly limit the use of tablets and capsules, particularly in pediatric and geriatric populations, as well as patients with central nervous system or musculoskeletal disorders (Stegemann et al., 2010; Stegemann et al., 2012). Due to these potential problems, oral films are emerging as a promising dosage form for oral drug
35 delivery (Borges et al., 2015; Dixit and Puthli, 2009). One of the advantages of oral films is the ability to either rapidly dissolve or adhere to the oral mucosa, allowing for rapid or controlled drug release for local and/or systemic absorption. A mucoadhesive film also provides a distinct advantage of enabling transmucosal absorption and thus bypassing hepatic first-pass
40 metabolism and the harsh and variable pH conditions in GI tract (Patel et al., 2011; Shakya et al., 2011; Sudhakar et al., 2006; Zhang et al., 2002).

Oral films are predominantly manufactured by solvent casting (2015; Borges et al.,
2015; Dixit and Puthli, 2009; Morales and McConville, 2011). Solvent casting involves the preparation of a solution of the active pharmaceutical ingredient (API), polymer carrier, and optionally a plasticizer and/or other excipients. The subsequent evaporation of the solvent

produces a film, which can then be cut into discrete shapes to produce the final unit doses.

45 Solvent casting is mainly limited by the need for a solvent, aqueous or organic. Given the high heat of vaporization of water, aqueous solutions can require long drying times, up to 24 hours (Kianfar et al., 2012; Shen et al., 2013; Sievens-Figueroa et al., 2012; Visser et al., 2015). The use of organic solvents is particularly undesirable from an environmental perspective and requires the manufacturing facility to incorporate solvent handling (i.e. explosion proof
50 equipment and rooms) and collection capabilities (Constable et al., 2007; Grodowska and Parczewski, 2010). Additionally, testing is required on the final drug product to ensure residual solvent levels are below ICH requirements. Formulation development activities for solvent casting, with both aqueous and organic solvent systems, involve optimizing solution rheology for casting (Preis et al., 2014) and ensuring physical stability upon storage (Gutierrez-Rocca
55 and McGinity, 1993).

More recently, electrostatic powder deposition (ESPD) has been shown as an alternative, solvent-free method to prepare free films for drug delivery (Prasad et al., 2015). ESPD involves the (1) charging, (2) spraying or transport, and (3) deposition of the charged particles onto a grounded substrate; this is typically done using a corona electrostatic gun. The
60 deposited powder is then cured using heat and subsequently removed from the substrate. Prasad et al. showed that an active physical mixture or co-processed composite-particles could be electrostatically charged and deposited onto a stainless steel substrate and subsequently cured to prepare a drug-loaded film. The films were readily removed from the substrate, as they were only adhered by weak electrostatic and/or Van der Waals forces. The
65 results of this study also illustrated that composite particles of acetaminophen (APAP): polyethylene oxide (PEO) (10:90) prepared by extrusion in this study, produced films of significantly less variability of APAP content (1.8% versus 11.9% RSD in films from composite

particles versus from physical mixture, respectively) (Prasad et al., 2015). This finding correlates well with typical manufacturing methods for dry powder coating compositions which consists of pre-mixing the polymer, pigments and/or other additives, melt extrusion (alternatively spray-drying, granulation, or co-grinding techniques have also been utilized), followed by milling/micronization to obtain composite particles of acceptable particle size for electrostatic powder coating (Harmuth, 1982; Hogan et al., 2002; Noonan, 1977; Wicks et al., 2007). These composite particles yield more efficient and uniform deposition, particularly for the deposition of components that may not exhibit ideal resistivity for processing. Additionally, uniform distribution of additives such as liquid plasticizers can be critical to film-forming properties of the coating material. Sauer et al. showed this to be advantageous for dry powder coating of tablets using pre-plasticized Eudragit L100-55 to promote film formation and obtain a functional, delayed-release tablet coating (Sauer et al., 2007).

The aim of this current work was to investigate the influence of the process parameters of electrostatic powder deposition (ESPD) including: (1) the impact of applied voltage, distance from the substrate, and environmental humidity on the deposition efficiency and uniformity; (2) the impact of cure temperature and time on film formation, peel strength and mechanical properties; and (3) the impact of substrate properties on adhesion of the film to the substrate. Polyethylene oxide (PEO) was utilized as a model thermoplastic polymer and stainless steel 316 was utilized as the substrate.

Materials and Methods

Materials

90 POLYOX™ WSR N10 NF was generously donated by Colorcon® (West Point, PA, USA). Bulk material was sieved and material between 25 µm (500 mesh) and 90 µm (170 mesh) was collected for use.

Sheets of stainless steel 316 (SS 316), 0.060" (1.524 mm) thickness, were used as received from McMaster Carr (McMaster Carr, Atlanta, GA, USA) in the following finishes:
95 unpolished, mirror finish #8, brush finish #4. Additional sheets of unpolished stainless steel 316 were subject to abrasive surface treatments as described below. The bulk composition of the unpolished SS 316 was reported as follows: (wt. %): C (0.28) Cr (16.58), Ni (10.08), Mo (2.04), Mn (1.46), Si (0.29), P (0.03), S ($\leq$ 0.01) and Fe (balance).

100 Substrate Abrasive Treatments

Sheets of unpolished SS316 were mechanically roughened by sand blasting using 70/100 (150-212 µm) beads. After abrasive treatment, samples were cleaned by isopropyl alcohol rinse, 10 minute sonication in a 1% Contrex® solution, followed by a thorough rinse using de-ionized water. After cleaning, the samples were passivated by soaking in a 50%
105 HNO₃ solution at 50°C for a minimum of 30 minutes [to reform the protective chromium oxide surface layer per ASTM A380/A380M Standard Practice for Cleaning, Descaling, and Passivation of Stainless Steel Parts, Equipment, and Systems \(ASTM, 2013\)](#). Immediately after removal from the passivating solution, the substrates were thoroughly rinsed using de-ionized water and allowed to dry overnight in a desiccator at 50°C. Substrates were wiped with
110 isopropyl alcohol prior to use or analysis, as needed. (ASTM, 2013)

Surface Analysis

Surface imaging and roughness calculations were conducted using a non-contact, optical profilometry using a Wyko NT9100 profiling system (Veeco, Plainview, NY, USA).

115 Imaging was conducted using the following settings: 20x objective lens, 2x field of view (FOV), scan size of 120 x 160 μm , and a vertical resolution of 4 μm (12 μm for the sandblasted substrate).. Surface roughness was calculated using WYKO Vision 4.2 software (Veeco, Plainview, NY, USA). The average roughness, R_a , root mean squared roughness, R_q , and the maximum height of the profile, R_t , were calculated as shown in Equations 1, 2, and 3, 120 respectively (per ASME B46.1-2009). Note that n=3 samples were analyzed; however, due to no discernable difference between the measurements, data and images from one representative sample is reported.

Equation 1. Average roughness

$$R_a = \frac{1}{L} \int_0^L |Z(x)| dx$$

125 Equation 2. Root mean squared (RMS) roughness

$$R_q = \sqrt{\frac{1}{L} \int_0^L Z(x)^2 dx}$$

Equation 3. Maximum height of roughness profile

$$R_t = R_p + R_v$$

where L is the evaluation length, $Z(x)$ is the distance from the reference mean line, R_p is the distance between the highest point of the profile from the mean reference line, and R_v is the 130 lowest point of the profile from the mean reference line.

XPS analyses were performed on an Axis Ultra DLD photoelectron spectrometer (Kratos, Manchester, U.K.) utilizing a monochromated Al K α anode X-ray source ($h\nu = 1486.5$ eV), hybrid optics (magnetic/electrostatic), and a multi-channel plate coupled to a hemispherical photoelectron kinetic analyzer. The spectrometer was calibrated by using Ag 3d 5/2 (368.3 eV) peak. All spectra were recorded in an analysis chamber at 10^{-9} Torr base pressure using an aperture slot of $300 \times 700 \mu\text{m}^2$ and pass energy of 80 eV. The photoelectrons takeoff angle was normal to the surface of the sample and 45° with respect to the X-ray beam. Casa XPS analysis software was used for peak analysis and the stoichiometry of samples was determined from corrected peak areas and employing Kratos sensitivity factors for each element of interest.

Surface energies were calculated based on contact angle measurements using water, formamide, and diiodomethane. Contact angles were measured using a FTA200 goniometer (First Ten Angstroms, Inc., Portsmouth, VA, USA). Solid surface energies were calculated using Equation 4, derived from Young's equation (Young, 1805), showing the relationship between contact angle, surface energy and interfacial energy, and the relationship of interfacial energy as a combination of dispersive and polar forces proposed by Owens and Wendt (Owens and Wendt, 1969).

Equation 4. Solid surface energy, including dispersive and polar components, as a function of surface energy and contact angle of liquid (Owens and Wendt, 1969)

$$\frac{1}{2}\gamma_l(1 + \cos \theta) = \sqrt{\gamma_s^d \gamma_l^d} + \sqrt{\gamma_s^p \gamma_l^p}$$

where γ_l represents the surface energy of the liquid, γ_s represents the surface energy of the solid, and the superscripts of d and p indicate the dispersive/apolar and polar components, respectively, of the total free energy. Values for surface energies, including dispersive and polar components, of test liquids were taken from Good (Good, 1992).

Electrostatic Powder Deposition

The ESPD process consists of the following steps: powder charging, spraying and deposition. The deposited material is then cured and the final film is removed from the metallic substrate. In this study, the substrate was covered with a stencil such that the powder deposited only on the exposed metal, a 25 x 63 mm strip along the center of the substrate. For each sample preparation, a fixed amount of powder was fed to a Nordson Vantage® Manual corona gun (Nordson Corporation, Westlake, OH, USA) using a volumetric feeder (Schenk AccuRate, Whitewater, WI, USA); thus, a fixed feed rate and spray time was utilized for each sample preparation. The powder was then sprayed using compressed air (0.5 bar pressure) through a conical deflector and charged by passing through the corona discharge produced by the high applied voltage (Prasad et al., 2016). After powder deposition, the substrate was then placed in an infrared oven. The resulting film was peeled from the substrate and film weight and thickness were measured. Thickness was measured using a Mitutoyo digital micrometer (Mitutoyo, Kawasaki, Japan) and the average of $n=3$ values was reported. Statistical analysis was conducted using JMP software (JMP Pro 12.0).

To study the impact of process parameters during ESPD on deposition efficiency, the charging voltage and gun tip to substrate distance were varied, as shown in Figure 1. Additionally, experiments were conducted at two environmental humidity conditions: 25 and 40 %RH. The humidity was controlled using humidifiers or dehumidifiers, as needed and

monitored using a Fisher Scientific Traceable™ Humidity/Temperature Pen (Pittsburgh, PA, USA). The samples from this study were prepared using unpolished SS 316 as the substrate and cured at 80°C for 60 minutes.

180 **Figure 1. Schematic of electrostatic powder deposition and process parameters including charging voltage, distance from substrate, and environmental relative humidity.**

To study the impact of process parameters during curing on film formation, the cure
185 temperature and time was varied as follows: 70, 80 and 90°C for 15, 30 and 60 minutes. These samples were prepared using 60 kV charging voltage, 20 cm gun tip to substrate distance, and using unpolished SS 316 as the substrate. Environmental humidity was measured at 40-44 %RH during these preparations. Films (n=3 for each condition) were removed from the substrate using the texture analyzer to measure peel energy for removal, characterized for film
190 formation using SEM, and tested for mechanical strength by puncture testing.

To study the impact of substrate properties on peel energy for film removal, substrates of varying surface finish including mirror finish #8, unpolished, brush finish #4, and sandblasted 70/100 were utilized as substrates for ESPD. Substrates were characterized by surface analysis techniques described above. Films (n=3 for each substrate) were prepared using
195 were 80 kV charging voltage, 30 cm gun tip to substrate distance, and cured at 80°C for 60 minutes. The resulting films were removed from the substrate using the texture analyzer to measure peel energy for removal.

Adhesive Strength Testing

200 Samples for adhesion testing were equilibrated for at least 24 hours at room temperature. Scotch tape was applied to substrates and equilibrated for at least 24 hours at room temperature as a positive control for adhesion testing. Adhesive testing was carried out using a 90° peel test fixture (TA-305A) on a Texture Analyzer (Stable Micro System TA-XTplus) equipped with a 5 kg load cell. The test was conducted with a crosshead speed of 0.2
205 mm/s. Exponent software (Stable Microsystems, Godalming, Surrey, UK) was used to process data. The peel energy was calculated by Equation 5.

Equation 5. Peel energy as a function of peel angle

$$G_a = \frac{F_{avg}}{b} (1 - \cos \theta)$$

where F_{avg} is the average force of removal, b is the width of the sample, and θ is the angle of
210 peel force; $\theta=90^\circ$ for the test fixture used in this study.

Mechanical Strength Testing

Mechanical properties of films were tested on a Texture Analyzer TA-XTplus (Stable Microsystems, Godalming, Surrey, UK) using 5 kg load cell. Samples were mounted on a TA-
215 108s-5 fixture (Texture Technologies, Hamilton, MA, USA) and were punctured using a ¼” spherical probe moving at 1 mm/s. Exponent software (Stable Microsystems, Godalming, Surrey, UK) was used to process data. Tensile strength was calculated as shown in Equation 6, as defined by Radebaugh et al. (Radebaugh et al., 1988).

220 **Equation 6. Tensile strength**

$$\sigma_{TS} = \frac{F}{A_{cs}}$$

where F is the force at rupture (N) and A_{cs} is the cross sectional area of the film in the film holder (mm^2).

Scanning Electron Microscopy (SEM)

225 Samples were mounted onto pin stubs using conductive carbon adhesive tape and sputter coated with a 12 nm thickness of palladium/platinum under argon using a Cressington 208HR sputter coater (Cressington, Watford, UK). The Zeiss Supra field emission SEM (Zeiss, Oberkochen, Germany) was operated at an accelerating voltage of 5 kV to obtain images.

230 Disintegration Testing

Disintegration time was determined using a petri dish method. A petri dish containing 25 mL of Sørensen's buffer, pH 6.8 at 37 °C was placed in an incubating shaker also held at 37 °C. The film sample, 25 x 25 mm, was gently placed on top of the media and the incubator shaker was set at 50 rpm to provide agitation. The time at which disintegration starts and the
235 time for complete disintegration were recorded for n=3 samples.

Results

Impact of applied voltage, distance from substrate, and environmental humidity on the deposition efficiency during ESPD

240 Films (n=3) were prepared using the conditions outlined in Figure 1. The weights of the film were used as an indicator of deposition efficiency, whereby higher weights indicate increased

deposition efficiency. The resulting film weights and corresponding standard deviations from these preparations are shown in Figure 2.

245 **Figure 2. Weights and standard deviations from films (n=3) prepared using varying voltage (40, 60 and 80kV), distance from substrate (10, 20, and 30 cm), and at different environmental humidity conditions (25 and 40% RH).**

The films prepared at 25 %RH showed less influence on deposition efficiency with
250 changing voltage and distance from substrate than seen with films prepared at 40 %RH. One-way ANOVA using Tukey-Kramer HSD ($\alpha = 0.05$) to compare means of film weights produced at 25 %RH indicated only the mean weights of films prepared at 20 vs. 30 cm distances showed a significant difference ($p = 0.0046$). Films prepared at 40 %RH exhibited a more significant impact from processing parameters, with one-way ANOVA using Tukey-Kramer
255 HSD ($\alpha = 0.05$) confirming significant differences in mean weights of films produced at 40 vs. 60 kV ($p=0.0042$), and 10 vs. 30 cm ($p<0.0001$) and vs. 20 cm ($p=0.0090$). The effect summary of the environmental humidity, applied voltage, and distance from substrate is shown in Figure 3; note that LogWorth is equal to $-\log_{10}(p \text{ value})$. This chart illustrates the significance of interactions of environmental humidity with voltage ($p<0.00001$), distance
260 ($p<0.0001$) and voltage*distance (0.0071). Distance was also classified as a significant factor ($p=0.0007$).

Figure 3. Summary of factors that significantly influenced deposition efficiency (shown in red) and factors that did not significantly affect deposition efficiency (shown in grey) and corresponding p-values.
265

At 40 %RH, the influence of the processing parameters on film weight was more marked than seen with the 25 %RH condition. A trend of decreasing deposition efficiency was seen with increasing distance from the substrate, illustrated in Figure 2. Additionally, deposition efficiency increased when charging voltage was increased from 40 to 60kV; however, a drop in weight was seen when voltage was increased from 60 to 80kV.

Impact of cure temperature and time on film formation, peel strength and mechanical properties

SEM micrographs obtained from the surface of the films cured at the varying temperature and time conditions are shown in Figure 4. After 15 minutes at 70°C particles were still undergoing deformation; however, after 60 minutes the particles edges and small voids can still be seen indicating incomplete coalescence. At 80 and 90°C after 15 minutes, much of the particle deformation and coalescence has taken place with some small voids visible and after 30 minutes complete coalescence is achieved.

Figure 4. SEM micrographs of surface of PEO N10 films cured at varying temperatures (70, 80, and 90°C) and times (15, 30, or 60 minutes). White bar (lower left) represents 100 µm.

The peel energies to remove the cured films from the unpolished SS316 substrate are shown in Figure 5. All films required low peel energy for removal, with mean values of 21 J/m² or lower, corresponding to mean peel forces of 0.36N or lower. Cure temperature exhibited the

most significant effect on peel energy ($p=0.0107$), with samples cured at 90°C for all time conditions requiring mean peel energies greater than 15 J/m².

Figure 5. Peel energies measured to remove PEO N10 films (n=3) prepared at varying cure temperatures (70, 80, and 90°C) and times (15, 30, or 60 minutes) from unpolished, SS316 substrate.

Puncture testing was conducted to determine the mechanical properties of the films prepared from the varying cure conditions. The calculated tensile strengths of these films are shown in Figure 6. Excluding the sample at the 70°C, 15 minute curing condition, the mean tensile strengths were similar between the curing conditions ranging between ~ 0.6 and 0.9 MPa.

Figure 6. Tensile strength of PEO N10 films (n=3) prepared with varying cure temperatures (70, 80, 90°C) and time (15, 30, 60 minutes).

With comparable mechanical properties and complete film formation seen with 80°C and 90°C samples by 30 minutes, films from the 80°C, 60 minute cure condition were chosen to evaluate disintegration behavior. Initial disintegration of the films was observed by 10 s, as shown in Figure 7. A very thin film edge can still be seen by 30 s and complete disintegration was observed by 40-55 s (not shown).

Figure 7. Images from disintegration testing of PEO N10 films (n=3) prepared at 80°C, 60 minute cure condition.

Impact of substrate properties on adhesion of the film to the substrate

Images of the surface topographies of the substrates of varying surface finish are shown in Figure 8 and the surface roughness values calculated for each of the as-received samples, as well as the sandblasted substrate, are summarized in Table 1. The mirror #8 and brush #4 topography revealed the striations from the polishing process used to obtain each finish. The topography of the unpolished sample revealed an irregular surface, typically seen with unpolished steel (Marshall, 1984). The sandblasted sample showed very distinct indentations from the abrasive treatment with relatively large beads (150-212 μm) producing a very coarse surface with high roughness value, $R_a = 1080 \text{ nm}$.

Figure 8. Images of surface topographies of (a) mirror #8, (b) unpolished, and (c) brush #4 finish as received, as well as (d) the sandblasted substrate prepared from abrasive treatment.

Table 1. Calculated substrate surface roughness values of as-received mirror, unpolished, and brush finish samples, as well as sandblasted substrate prepared from abrasive treatment. Values for average roughness, R_a , root mean squared roughness, R_q , and maximum height of roughness profile, R_t , reported, per equations 1, 2, and 3, respectively.

Substrate	R_a (nm)	R_q (nm)	R_t (μm)
Mirror #8	20.04	26.99	0.31

Unpolished	111.87	150.79	2.15
Brush #4	154.45	185.71	1.18
Sand 70/100	1080	1370	7.69

335 Figure 9 summarizes the XPS data reported as atomic percentages for the surface of each of the substrates. All samples consisted of a carbon (54-58%) and oxygen (32-37%) rich surface layer. The sandblasted sample exhibited slightly elevated levels of Ni (0.79%) and Cr (6.62%) and slightly reduced Fe (1.75%) when compared to the as-received samples.

340 **Figure 9. XPS data showing chemical composition in atomic % of substrate surfaces showing rich carbon (54-58%) and oxygen (32-37%) levels.**

The measured contact angle and calculated surface energy of each substrate are reported in Table 2. The contact angles of water on these substrates were relatively high, indicative of a hydrophobic surface. These subsequently correlated with relatively low surface energies for all substrate surfaces, ranging from 31 to 36 mJ/m².

345 **Table 2. Average contact angles (and standard deviations) measured using water (n=3) and calculated solid surface energies of substrates of varying roughness according to Equation 4.**

Substrate	Contact angle (°)	γ_s (mJ/m ²)
Mirror #8	79.9 (1.2)	35.39

Unpolished	88.9 (2.4)	31.05
Brush #4	77.3 (5.2)	36.26
Sand 70/100	91.8 (3.2)	31.78

The peel energies to remove the cured films and scotch tape controls from the various substrates are shown in Figure 10. All samples exhibited an increasing peel force required to remove films from substrates with increasing surface roughness, with the exception of the removal of scotch tape from the sandblasted substrate. The mean peel energies of the scotch tape were 112, 235 and 547 J/m² to remove the film from the mirror #8, unpolished, and brush #4 finish, respectively. The removal of the scotch tape from the sandblasted sample showed lower peel energy of 209 J/m², slightly lower than that required for the removal from the unpolished substrate. The peel energies required to remove the PEO N10 film from all substrates were substantially lower than those needed to remove the scotch tape, requiring means values of 7, 20, 21 and 31 J/m² to remove the film from the mirror #8, unpolished, brush #4 and sandblasted finish, respectively, corresponding to mean peel forces in the range of 0.1 - 0.5 N.

Figure 10. Peel energies measured to remove scotch tape (positive control, n=3) and PEO N10 films (n=3) from substrates of varying surface roughness

Discussion

Impact of applied voltage, distance from substrate, and environmental humidity on the
370 deposition efficiency during ESPD

The resistivity of powders used for ESPD is critical to their performance. Insulating powders, classified as volume resistivity $> 10^{10} \Omega\text{m}$, readily accumulate charge and exhibit slow charge dissipation or decay, allowing for strong adhesion to the grounded, conductive substrate (Bailey, 1998; Cazaux, 2007). However, excessive charge accumulation on the
375 deposited powder particles can induce back ionization. Back ionization, or back corona, is a phenomenon where oppositely charged ions are produced which can neutralize incoming particles, thus preventing further deposition of powder onto the substrate. In addition to limiting the powder layer thickness on the substrate, back ionization can also lead to surface defects, such as pitting, on the final film (Bailey, 1998; Cazaux, 2007; Prasad et al., 2016). Back
380 ionization can be mitigated by methods such as incorporating free ion traps when using corona charging to reduce excess ion deposition on the substrate or reducing the resistivity and thus enabling faster charge dissipation of the coating material by formulating with conductive or antistatic additives; however, process parameters including lower charging voltage or higher environmental humidity can also significantly aid in reducing charge accumulation on the
385 powder layer (Mazumder et al., 1997).

Given the dielectric properties of PEO, volume resistivity of $10^{10} - 10^{11} \Omega\text{m}$, it is a suitable powder for ESPD and has been previously utilized in this process to prepare drug-loaded films (Prasad et al., 2015). ESPD with PEO at 25 %RH appears to induce a self-limiting layer thickness, resulting in films of similar weights across all processing conditions, shown in
390 Figure 2. Without sufficient environmental humidity to facilitate charge dissipation, the particle resistivity becomes the driving factor influencing deposition behavior. At this low humidity

condition, the charged particles exhibit slow charge decay, leading to a high charge accumulation on the deposited powder layer. This charged powder layer then induces back ionization and prevents further powder deposition (Cazaux, 2007; Mazumder et al., 1997; Sims et al., 2000).

Increasing the environmental humidity can reduce particle resistivity. This effect is generally attributed to adsorbed moisture, which can reduce the particle surface resistivity and improve charge dissipation (Grosvenor and Staniforth, 1996; Karner and Urbanetz, 2011; Sharma et al., 2003). Increases in humidity can decrease resistivity by orders of magnitude; for example, Grosvenor et al. reported the resistivity of lactose and microcrystalline cellulose could be decreased from $10^{12} \Omega\text{m}$ at 22 %RH to $10^{10} \Omega\text{m}$ at 44 %RH (Grosvenor and Staniforth, 1996). With environmental humidity enabling reduced resistivity and faster charge dissipation, ESPD films produced at 40 %RH were not limited by the particle resistivity and were more influenced by other process parameters.

At each charging voltage, there was a decrease in the average film weight representing decreased deposition efficiency with increasing gun tip to substrate distance, shown in Figure 2. As the particles enter what is referred to as the transport region between the gun and the substrate, they are subject to several forces: aerodynamic forces from the compressed air used to spray the powder, the force on charged particles to follow the electric field produced by the electrode and grounded substrate, as well as the gravitational force of the particle itself. The smaller the distance between the gun tip and substrate, the more likely the particle will follow the electric field directed to the substrate and less material will be lost to overspray from the compressed air or to gravity. However, the gun tip to substrate distance affects the current flowing between the gun and the substrate; the closer the gun to the grounded substrate, the higher the current flow between the two, which corresponds to a higher number of free ions

directed to the substrate. Thus, although more powder particles are depositing on the substrate at the 10 cm gun tip to substrate distance, so are more free ions. This increased deposition of free ions increases the probability of inducing back ionization (Guskov, 2002). For the low humidity condition, this was the likely cause of lower deposition weight seen with the 10 cm samples prepared with 60 and 80kV charging voltage when compared to those prepared at 20 and 30 cm at the same charging voltage.

At 40 %RH, an increasing deposition efficiency was seen when charging voltage was increased from 40 to 60kV. Increasing charging voltage can produce particles with a higher charge to mass ratios that exhibit stronger adhesion to the substrate to be coated. This can in turn increase deposition efficiency (Meng et al., 2009). However, if the charging voltage is too high, back ionization can occur, leading to decreased deposition, as seen with the 80kV samples. This finding correlates well with other studies showing a loss of coating efficiency with higher charging voltage. Qiao et al. showed an increasing coating level achieved when electrostatically coating tablets with increasing charging voltage from 0 to 60kV; however, a decrease in levels were seen when using 80 to 100 kV (Qiao et al., 2010).

Impact of cure temperature and time on film formation, peel strength and mechanical properties

The mechanism of dry powder film formation, specifically with thermoplastic polymers, can be described by (1) deformation and coalescence of discrete powder particles, (2) spreading or leveling of the coalesced particles, and (3) the subsequent hardening of the film when removed from heat (Prasad et al., 2016; Sauer et al., 2013). The coalescence of discrete powder particles is a function of the viscosity and surface tension of the coating material at the cure temperature used, as well as the radius of the particles (Dillon et al., 1951). Curing

440 temperatures are typically selected near or above the glass transition temperature for amorphous polymer systems and near or above the melting point for crystalline or semi-crystalline polymers to promote viscous flow. The minimum film formation temperature (MFFT) is another value utilized in the coating industry. MFFT is defined as the minimum temperature at which a continuous film will form for a given material, typically this value is near the T_g for
445 many polymer systems (Jensen and Morgan, 1991; Keddie and Routh, 2010).

PEO N10 is a semi-crystalline polymer that exhibits a broad melt endotherm spanning 61-75°C (Prasad et al., 2015). When cured at 70°C, Figure 4 shows that after 15 minutes particles were still undergoing deformation and after 60 minutes the film exhibits incomplete coalescence with visible voids. Visual observations made of the films [cured at 70°C](#) correlate
450 with these findings, as films were still opaque upon removing at 15 minutes, whereas films cured for 30 and 60 minutes were translucent. Films prepared at 80 and 90°C were transparent [by 15 minutes](#), [suggesting a transparent film could be indicative of achieving sufficient melt for film formation](#). Thus, at 70°C there was sufficient melt flow to initiate particle deformation and coalescence, but not to facilitate complete coalescence and film formation by
455 60 minutes due to high melt viscosity (Uhlmann and Grundke). Higher temperatures, at both 80 and 90°C, enabled a further decrease in melt viscosity to decrease the time needed for deformation and coalescence, with minimal voids observed after 15 minutes and complete film formation after 30 minutes.

The peel energies for removing cured films from the unpolished SS316 substrate were
460 all relatively low, with mean values less than 21 J/m². Note that a good adhesive (i.e. tape) typically requires peel energies > 100 J/m² for removal (Gay, 2002). However, there was an increase in mean peel energies with values greater than 15 J/m² obtained for samples cured at 80°C for 60 minutes [and those cured at 90°C](#), [however these values were not statistically](#)

significant. Increases in peel energies have been observed by others with increased curing

465 temperatures and times, and this has been attributed to increased spreading of the molten polymer across the substrate at these conditions due to the reduced melt viscosities at these temperatures and contact time. Increased spreading or wetting of coating material onto the substrate has been directly linked to increased coating efficiency (Sauer and McGinity, 2009; Smikalla et al., 2011). The corresponding increase in interfacial contact area between the
470 coating and the substrate enhanced the adhesion between the two materials, leading to an increase, albeit a small increase, in adhesive strength (Kinloch, 1980).

The tensile strength of films cured at the varying conditions did not vary significantly, ranging from 0.6 to 0.9 MPa, with the exception of that of the 70°C, 15 minute condition.

Notably, these tensile strengths are greater than 0.06 MPa, which was defined as a lower limit
475 for oral films based on results obtained from analysis of commercial products (Pries, 2014).

The 70°C, 15 minute film exhibited a significantly higher tensile strength with a mean tensile strength around 1.6 MPa. In Figure 4, the 70°C, 15 minute sample showed a lesser degree of particle coalescence than the other time and temperature cure conditions and visual observations reported an opaque final film, indicating insufficient melt for film formation. Semi-
480 crystalline polymers consist of both crystalline and amorphous regions. The crystalline regions are dense, typically described as lamellar regions of folded chains, and are mechanically stronger than the amorphous regions. This strength is attributed to the density and the increased degree of bonding between the polymer chains (i.e. hydrogen, van der Waals, etc.) (Peterlin, 1975; Ward and Sweeney, 2012). With a reduced degree of melt and coalescence
485 seen with the films cured at 70°C for 15 minutes, the polymer retained a higher degree of crystallinity and thus exhibited a higher mechanical strength.

A disintegration test was conducted using films from the 80°C, 60 minute cure condition as this condition showed complete film formation and comparable mechanical properties as films from 80°C and 90°C samples at 30 and 60 minutes. Rapid initial disintegration was
490 observed by 10 s with complete disintegration in less than one minute, confirming satisfactory performance of PEO-based orodispersible films. The authors previously confirmed rapid drug release of acetaminophen (APAP) from APAP: PEO orodispersible films prepared by ESPD, showing greater than 85% drug release by 2 minutes (Prasad et al., 2015).

495 Impact of substrate properties on adhesion of the film to the substrate

Stainless steel 316 was chosen as a substrate for this study as it the primary material of choice for the construction of pharmaceutical equipment due to its resistance to corrosion (Cramer and Covino, 2006; Marshall, 1984). This characteristic is attributed to the formation of a dense, protective chromium oxide (Cr_2O_3) layer on the surface of the metal, preventing
500 oxidation of the bulk composition, specifically preventing rust formation (Fe_2O_3) (Adams, 1983; Detry et al., 2010). Paired with its electrical conductivity (Ho and Chu, 1977), SS 316 is a suitable substrate for the preparation of free films by ESPD. As shown in Figure 8, there were clear contrasts between the surface topographies of each finish. The mirror and brush finish exhibited unidirectional striations from the grit polishing process, while the unpolished surface
505 showed an irregular microstructure of a rolled or laminated stainless steel surface (Marshall, 1984). The sandblasted sample topography included circular depressions from the abrasive treatment beads. The roughness values reported in Table 2 quantify the increasing surface roughness with average roughness values, R_a , ranging from 20 to 154 nm for the as-received mirror #8 and the brush #4 finish, respectively, and jumping to 1080 nm with the sandblasted
510 surface. Notably, the maximum height profile of the unpolished sample was greater than that of

the brush #4 sample; this was due to the grit polishing process used to prepare the brush #4 finish.

While the bulk composition of SS316 chiefly consists of an iron alloy with Cr (16-18), Ni (10-14) Mo (2-3) and small amounts of other effective elements, the surface is comprised of a
515 dense chromium oxide (Cr_2O_3) layer that prevents iron oxidation or rusting (Adams, 1983).

When exposed to ambient air, the surface is further covered by carbon and oxygen. The carbon and oxygen content is due to physical adsorption of hydrocarbon contamination, such as alcohols or esters, onto the surface of the metal (Adams, 1983; Mazumder et al., 2006).

Carbon was measured at 54-58% and oxygen at 32-37% of the surface composition, shown in
520 Figure 9, confirming the presence of an adsorbed hydrocarbon layer. This hydrocarbon layer contributed to the hydrophobic nature of the surface, with contact angles ranging from 77-92° (Faille et al., 2002; Flint et al., 2000). The calculated surface energies for these surfaces were relatively low, ranging 31-36 mJ/m^2 . These low surface energy, hydrophobic substrates

facilitated a low degree of adhesion with the hydrophilic PEO N10 film. The Ni and Cr
525 enrichment and corresponding decrease in Fe seen with the sandblasted sample is characteristic of the sample undergoing mechanical abrasive treatments and the reformation of the chromium oxide layer during acid treatment (Adams, 1983; Haidopoulos et al., 2006; Rohly et al., 2003). Overall, the XPS analyses confirm that these substrates did not differ significantly in their chemical composition. Thus, the substrates only differ in their surface roughness and
530 topography.

The scotch tape, used as a reference for the peel test, showed a significant influence of substrate roughness on the mean peel energy, with $> 100 \text{ J/m}^2$ of peel force required for the mirror finish and around 550 J/m^2 required for removal from the brush finish. Notably, the force required for the removal of the scotch tape from the sandblasted substrate was slightly lower

535 than that for the unpolished substrate. This was attributed to the thin adhesive layer of the tape
and the deep indentations of the sandblasted sample. The thin adhesive layer was unable to
make contact with the surfaces along the inside of the deep indents. Thus, the tape was only
adhered to the top surface of the substrate with gaps in the interfacial contact area
corresponding to the indents. This resulted in a significantly lower interfacial contact area and
540 reduced adhesion.

The surface roughness of the substrate did not markedly affect the peel energy or
removal of the PEO films. Although a general trend was seen in that the peel energy increased
with increasing surface roughness, the average peel force from all substrates was less than 31
J/m². This signifies that the removal of the PEO film was robust and requires very little force,
545 confirming that there was no significant adhesion or bonding between the polymer and metal
substrate. This finding was consistent with the characterization of the SS316 substrate as a
low-energy, hydrophobic surface. Thus, with the absence of chemical bonding or mechanical
interlocking, the mechanism of adhesion between the PEO film and metal substrate is primarily
due to weak Van der Waals and/or electrostatic forces (Kinloch, 2012; Ramarathnam et al.,
550 1992). The incremental increases in adhesive peel energy with increasing roughness attributed
to an increase in surface area of the roughened metal, leading to increased interfacial contact
area between the film and substrate (Kinloch, 1980; Packham, 2003).

Conclusion

Here, we have demonstrated that a electrostatic dry powder coating process can be
555 adapted to produce non-adhering, free films by utilizing a substrate that does not readily bond,
mechanically or chemically, with the powder coating material. The effect of various processing
parameters was evaluated on (1) the deposition efficiency, (2) film formation, and (3) removal

of PEO N10 free films prepared using ESPD. At low humidity (25 %RH), the processing parameters studied showed little effect on overall deposition efficiency due to the onset of back ionization, whereas at increased humidity levels (40 %RH) trends of increasing deposition efficiency with decreasing gun tip to substrate distance and increasing voltage (up to 60kV) was observed. Back ionization was attributed to the self-limiting deposition efficiency at 25 %RH, as well as to the drop in deposition efficiency at 80 kV at 40 %RH. The PEO N10 films exhibited complete film formation by 30 minutes at 80 and 90°C. Peel testing of the films exhibited slightly increased adhesive strength ($> 15 \text{ J/m}^2$) for films cured at 80°C for 60 minutes or those cured at 90°C due to increased spreading and thus increased interfacial contact area for adhesion. Adhesive strength was also tested with substrates of varying finishes and exhibited a trend of increasing adhesive strength with increasing roughness. This finding was again attributed to greater interfacial contact with the substrate. All PEO films were readily removed from the SS316 substrates due to the hydrophobic nature and low surface energy of the surface. The ESPD process was able to produce films with good mechanical properties (tensile strength $> 0.06 \text{ MPa}$), demonstrating its application as an alternative to the traditional solvent-casting manufacturing process. This study also serves as guidance for the evaluation of additional pharmaceutical compositions and substrates.

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Factor	Low	Mid	High
Voltage (kV)	40	60	80
Distance (cm)	10	20	30
Humidity (%RH)	25	-	40

750

(a) Mirror #8

(b) Unpolished

(c) Brush #4

(d) Sand 70/100

(1) Electrostatic powder deposition

Finding: Higher humidity, 40 %RH, led to a greater influence of voltage and gun-to-substrate distance on deposition efficiency

(2) Curing

Finding: Appropriate cure temperature was critical for film formation

(3) Film removal

Finding: PEO films did not adhere (peel energy $< 100 \text{ J/m}^2$) to substrate, even with increasing surface roughness