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Research paper

A novel electrostatic dry powder coating process for pharmaceutical dosage forms: Immediate release coatings for tablets

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ABSTRACT

An electrostatic dry powder coating process for pharmaceutical solid dosage forms was developed for the first time by electrostatic dry powder coating in a pan coater system. Two immediate release coating compositions with Opadry® AMB and Eudragit® EPO were successfully applied using this process. A liquid plasticizer was sprayed onto the surface of the tablet cores to increase the conductivity of tablet cores to enhance particle deposition, electrical resistivity reduced from greater than $1 \times 10^{13}\ \Omega$ m to less than $1 \times 10^{9}\ \Omega$ m, and to lower the glass transition temperature (T_g) of the coating polymer for film forming in the pan coater. The application of liquid plasticizer was followed by spraying charged coating particles using an electrostatic charging gun to enhance the uniform deposition on tablet surface. The coating particles were coalesced into a thin film by curing at an acceptable processing temperature as formation was confirmed by SEM micrographs. The results also show that the optimized dry powder coating process produces tablets with smooth surface, good coating uniformity and release profile that are comparable to that of the tablet cores. The data also suggest that this novel electrostatic dry powder coating technique is an alternative to aqueous- or solvent-based coating process for pharmaceutical products.

1. Introduction

Polymer film coat is commonly applied in pharmaceutical dosage forms to achieve aesthetic quality, taste masking, enhancement of stability, and modification of drug release. The coating process is generally based on the dissolution or dispersion of polymeric materials in organic or aqueous solvents. The use of organic solvent suffers from the toxicological, environmental, cost- and safety-related issues [1]. These disadvantages have been largely eliminated by the introduction of aqueous-based coating technology. However, aqueous film coating requires a slower drying process and high energy input because of the high heat of evaporating water (539.4 cal/g). Other issues encountered with aqueous film coating are lower solid content in the coating solution and risk of microbial contamination [2]. The presence of water during the coating process and residual moisture in the film can affect stability of certain water sensitive drugs [3,4]. Thus, eliminating solvents in the pharmaceutical film coating is considered to be an effective way to reduce production cost, enhance process efficiency and improve product quality.

The trends toward "green" manufacturing and cost effectiveness have further spurred development of solvent-free coating techniques [2]. Several solvent-free coating processes such as compression coating [5,6], hot-melting coating [7], dry powder coating [8,9] and photocurable coating [10,11] have been investigated. These techniques offer many advantages such as shorter process time, eliminate solvent emission and reduce cost of good. Dry powder coating processes based on fluidized bed, pan coater and/or laboratory spheronizer have been tested for various coating polymers including Eudragit® RS [12], ethylcellulose [13], Eudragit® EPO [8], Eudragit L [14,15] and hydroxylpropyl methylcellulose acetate succinate [16–18]. In those processes, the coating materials were fed as free flowing dry powder, and their adhesion onto the surface was promoted by liquid bridges generated using a liquid plasticizer, a liquid binder and/or a low melting polymer [19,20]. Sometimes, a large amount of liquid plasticizer, binder and/or low temperature melting additives were used to promote powder adhesion. This method, however, most likely leads to the formation of sticky film because of the increase in molecular mobility as reflected by the decrease in glass transition temperature. For example, a large amount of liquid plasticizer (TEC) and low melting polymer PEG 3350 were used to promote adhesion of Eudragit® L100-55 on tablet cores [15]. Low melting additives such as cetyl alcohol was employed for Eudragit® RS/RL powder deposition on tablets [21]. Those dry powder coating approaches generally do not produce the smooth surface appearance required for commercial products.

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Electrostatic powder coating is a popular and mature technique for high quality powder deposition and film uniformity. It has been widely used in paint and automobile industries, primarily to coat metal workpieces due to their good conductivity and thermal stability. Deviating from the above-mentioned normal dry powder coating technique, electrostatic powder coating uses electrical field created by an electrostatic charging gun and grounded substrate to assist charged powder particle deposition. The first attempt to applying electrostatic dry powder coating to pharmaceutical tablets and medical devices was proposed by Phocus Ltd. [22,23]. The electrostatic powder coating process involved the deposition of charged powders on each side of the ground tablets separately and followed heating at 120 °C by IR radiation to allow for the film formation. However, the process required complex coating equipment, which significantly deviated from traditional pan coater [2,24]. Furthermore, heating at a high temperature may cause drug degradation.

In this study, a novel electrostatic dry powder coating process in a pan coater was developed. Pan coater is a standard equipment used for film coating in the pharmaceutical industry. Two immediate coating materials, Opadry® AMB and Eudragit® EPO, for immediate release tablets were employed in this research. Opadry® AMB has a moisture protection function, whereas Eudragit® EPO is useful for taste masking. The effects of various factors and operating conditions on the coating process were investigated. Opadry® AMB is a polyvinyl alcohol (PVA) polymer-based film coating system developed by Colorcon®. Eudragit® EPO is a copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters, developed by Evonik (formerly Rohm).

2. Materials and methods

2.1. Materials

Opadry® AMB and polyvinyl alcohol were provided by Colorcon (Pennsylvania, USA). Eudragit® EPO was donated by Evonik Degussa Corporation (Germany). Ibuprofen tablets and placebo tablets were prepared by Patheon Inc. (Mississauga, Canada). Glycerol was purchased from Caledon Laboratories Ltd. (Ontario, Canada). PEG 400 was purchased from EMD Chemicals Inc. (Ontario, Canada).

2.2. Particle size reduction and analysis

Particle size reduction of the coating material was performed by a combination of blade grind mill and ultrasonic sieving (HK Technologies Ultrasonics, Rugby, United Kingdom) prior to use. Particle size of the powder was determined by a Particle Size Distribution Analyzer (TSI Corporation, Model 3603, Shoreview, MN, USA). The particle size at 50% of total weight fraction was used as average particle size. The particle size test was conducted three times. The average of particle size was 26.6 μm and 10.0 μm for ground Opadry® AMB and Eudragit® EPO, respectively.

2.3. Thermal analysis of the polymer

The glass transition temperatures (T_gs) of the PVA polymer and Eudragit® EPO before and after blending with glycerol:water (1:1, v/v) and PEG 400 were obtained by differential scanning calorimetry (DSC) analysis (Mettler Toledo, DSC822, Mississauga, Canada), respectively. The samples (8–12 mg) were scanned under a nitrogen atmosphere at a heating rate of 5 °C/min over a temperature range of 20–150 °C and 0–100 °C for PVA and Eudragit® EPO, respectively. The T_g of each polymer was performed in duplicate.

2.4. Electrostatic dry powder coating process

The powder coating process was performed in a laboratory-scale electrostatic dry powder pan coating system. A 14-cm-diameter stainless steel coating pan was equipped with four aluminium baffles to promote smooth tumbling action. The equally spaced baffles (90° apart) extended from the inside of the pan rim to 5.0 cm from the bottom center. Both placebo tablets and ibuprofen tablets (approximately 60 g placebo tablets and 20 g ibuprofen tablets) were used in each experiment to conserve the usage of the active tablets. The coating level (%) was based on the weight gain of coated tablets relative the weight of uncoated tablets. The procedure and operating conditions of the experiments are key subjects of this study and will be detailed in Section 3.

2.5. Electrical resistivity test

A batch consisting of 60 g placebo tablets and 20 g ibuprofen tablets were loaded in the coating pan. The liquid plasticizer (glycerol:water (1:1, v/v), 0.4 g/min or PEG 400, 0.3 g/min) was sprayed onto tablet surface from a liquid spray gun. At 0, 1, 2, 3, 4 min, three tablets were sampled for electrical resistivity testing using an electrometer (Keithley 610B, Keithley instruments, Inc., USA). The electrical resistivity test of tablets was performed in duplicate.

2.6. Scanning electron microscopy

Powder coated tablets at different temperatures (40, 50 and 60 °C) and curing time intervals (0, 60, 120 min) were sputter coated with gold for 120 s under an argon atmosphere using EMITECH K550 sputter coater (Emitech Ltd., Ashford, UK). The surface morphologies of the samples were observed under a scanning electron microscopy (SEM, Hitachi S-2600 N, Ontario, Canada) operated at 5.0 kV.

2.7. Uniformity of coating

The coating weight and thickness uniformity within and between batches was determined using an analytical balance (Ohaus, Canada) and screw gauge according to previous study [25]. Ten tablets (10) per batch and three batches were tested. The coefficients of variation (CV) were calculated $(SD/m) \times 100$, where SD is standard deviations and m is average values.

2.8. In vitro drug release studies

In vitro dissolution of ibuprofen tablets before and after coating was carried out using the United States Pharmacopeia (USP) apparatus (Apparatus 2, paddle; Huanghai Rcz-6c2, Shanghai, China). Six tablets were dissolved in the dissolution vessels, each consisting of 900 ml medium at 37 °C at stirring speed of 50 rpm. Phosphate buffer (pH 7.2) and HCl (0.1 N) was chosen as the release medium for Opadry® AMB and Eudragit® EPO coated tablets, respectively. Samples were withdrawn from each vessel using a syringe (10 ml, replaced with fresh medium) at predetermined intervals and assayed using an 8453 UV–Visible Spectrophotometer (Agilent Technologies, Mississauga, Canada) at a wavelength of 222 nm.

3. Electrostatic powder coating process and apparatus

The new electrostatic powder coating process developed by us consists of three steps: plasticizer spraying, powder deposition and curing. First, a liquid plasticizer is sprayed onto the tablet surface primarily for decreasing the T_g of the coating polymer and

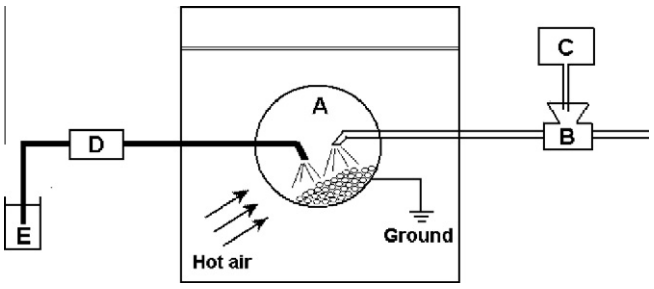

Fig. 1. Electrostatic powder coating system. (A) Coating pan, (B) electrostatic spray gun, (C) powder feeder, (D) liquid metering pump, and (E) liquid plasticizer.

facilitating the coalescence of polymeric particles into film. Secondly, coating particles are charged and sprayed by an electrostatic charging gun. The negatively charged particles will follow the direction of electrical field formed between the tip of the gun and the grounded coating pan and adhere to the tablet surface. The liquid plasticizer also plays another role in ensuring good adhesion of particles onto tablet surface by creating a temporary capillary force and increasing the surface electrical conductivity by wetting the tablet surface in powder deposition step. Thirdly, the deposited particles coalesce into a film at an elevated temperature suitable for the specific pharmaceutical products.

For the electrostatic powder coating process in liquid pan coater [24], two laboratory-scale research electrostatic powder coating systems (200 g and 2 kg maximum loadings) were designed and constructed in the laboratory of Powder Technology Research Centre (The University of Western Ontario). A schematic of the coating systems is shown in Fig. 1. The coating system is composed of an electrostatic spray gun, a coating pan, a liquid spray gun and a temperature control element. The coating pan is electrically grounded. The temperature of the coating apparatus is maintained by a heating element, and a digital thermoprobe is used to constantly monitor the system temperature. The liquid plasticizer (glycerol:water (1:1, v/v), 0.4 g/min or PEG 400, 0.3 g/min) was regulated by a fluid dispensing and metering pump (Fluid Metering Inc., USA) and sprayed onto the tablet surface through a liquid nozzle. The coating particles were quantitatively sprayed and negatively charged by the application of a high voltage (60 kV) at the tip of an electrostatic spray gun (Nordson Corporation, USA). Then, the tablets were cured at 40–60 °C for 2 h allowing for film formation.

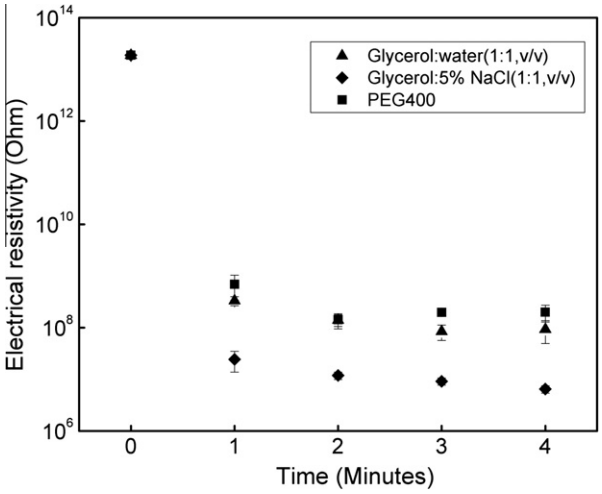

Fig. 3. Influence of liquid plasticizer on the electrical resistivity of tablets. Liquid flow rate: glycerol:water (1:1), 0.4 g/min, glycerol:5% NaCl (1:1), 0.4 g/min, PEG 400, 0.3 g/min; temperature: 60 °C.

4. Results and discussion

4.1. Mechanism of electrostatic powder deposition

The deposition of charged powder on pharmaceutical tablets is influenced by the electrical conductivity of the tablet cores and that of the grounded stainless steel coating pan (Fig. 2). For more conductive cores, the negative charge of the deposited particles will dissipate quickly due to grounding, allowing additional layers of powder to be attracted onto the tablet surface (Fig. 2 route (1)). If the tablet is less conductive, the electrical charge tends to build up on the tablet so as to impede further particle deposition (Fig. 2 route (2)). Although tablets with an electrical resistivity less than $10^9\ \Omega$ m are suitable for electrostatic powder coating [2], most pharmaceutical tablets have low electrical conductivity because they contain the excipients with high electrical resistivity [26]. Therefore, the electrical conductivity of tablets needs to be enhanced by liquid plasticizers to ensure satisfactory electrostatic powder deposition.

To understand the effect of liquid plasticizer on electrostatic powder deposition, the electrical resistivity of tablets were exam-

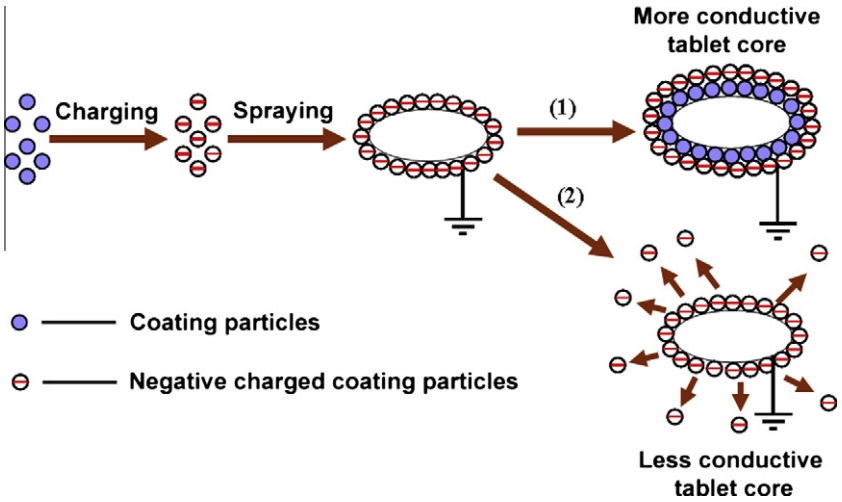

Fig. 2. Effect of electrical conductivity on powder deposition. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

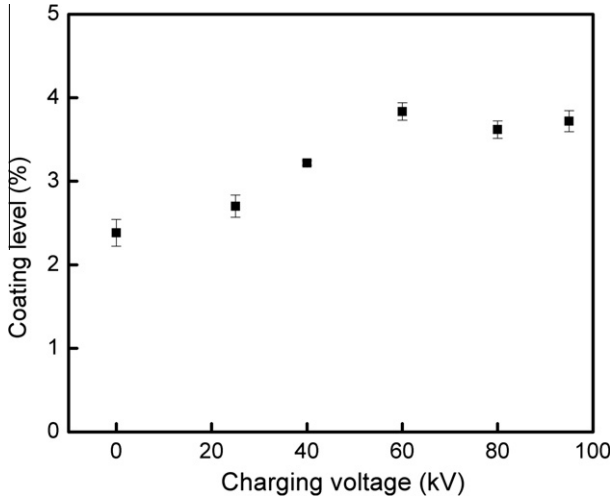

Fig. 4. The relationship between coating level and charging voltage. Liquid flow rate: 0.4 g/min, temperature: 60 °C.

ined under coating conditions. The electrical conductivity of tablet core was determined as a function of spraying time and different liquid plasticizers (glycerol and water, 1:1 (v/v); glycerol and 5% NaCl, 1:1 (v/v) and PEG 400). The results are presented in Fig. 3. Before a liquid plasticizer was applied, the tablets had resistivity above $1 \times 10^{13}\,\Omega\,m$. After spraying the liquid plasticizers, the resistivity of tablets was decreased, indicating the conductivity of the tablets was increased. In all cases, the resistivity of tablets dropped quickly within 1 min. The change in resistivity was much slower after 1 min and further reduction was not observed after 3 min. This phenomenon was in accordance with the hypothesis that solid-state electrical conduction occurs by a surface mechanism [26], and the conductivity does not further increase when the surface is well covered. As expected, adding a good conduct such as sodium chloride in the liquid plasticizer resulted in a further increase in conductivity. The coating level obtained by using the liquid plasticizer with and without salt (glycerol:water, 1:1 (v/v); glycerol:5% NaCl, 1:1 (v/v)) at 60 kV under same conditions was 3.84% and 3.77%, respectively. Further increasing the conductivity of tablet did not result in additional higher coating level ($p > 0.05$).

The influence of charging voltage on the coating level of Opadry® AMB is shown in Fig. 4. An increase in coating level was found with increasing charging voltage from 0 to 60 kV and reached highest value at 60 kV. Further increased charging voltage up to 90 kV produced slightly lower coating level than 60 kV. The coating levels of Eudragit® EPO coated tablets operated at 60 kV and 0 V were 3.16% and 2.13%, respectively. The coating level obtained at 0 V reflected the particle adhesion promoted by capillary force generated between the interface of liquid plasticizer and particles. Higher coating level obtained by coating at 60 kV than 0 V indicates that the adhesion of powder on tablet surface was enhanced by the introduction of electrical attractive force. Compared to relatively lower charging voltage, higher charging volt led to higher charging efficiency and subsequently higher coating level. However, the free ions are also proportional to the charging voltage. The free ions are attracted to the ground tablet surface and increase the cumulative charge of the coating layer, resulting in rapid development of back ionization and reduction in powder deposition. That's the reason that the coating level was not increased after the electrical charge reached a certain value.

4.2. Film formation

Film formation in dry powder coating mainly occurs in the curing step [27]. Unlike the aqueous-based coating process, where the evaporation of water was reported to provide the capillary force and temporarily plasticizing effect promoting the film formation, the film formation of dry powder coating process conforms to the dry sintering theory of polymers [28]. The dry sintering theory

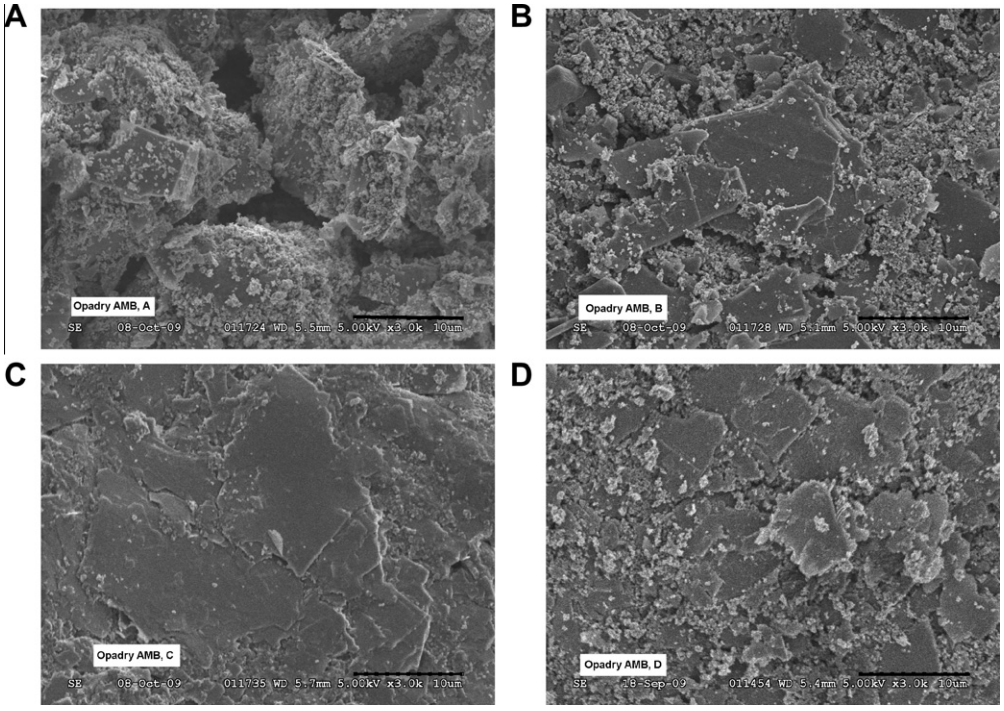

Fig. 5. Scanning electron micrographs of powder coated tablets with Opadry® AMB cured for (A) control no curing, (B) 60 min at 60 °C, (C) 120 min at 60 °C, and (D) 120 min at 50 °C.

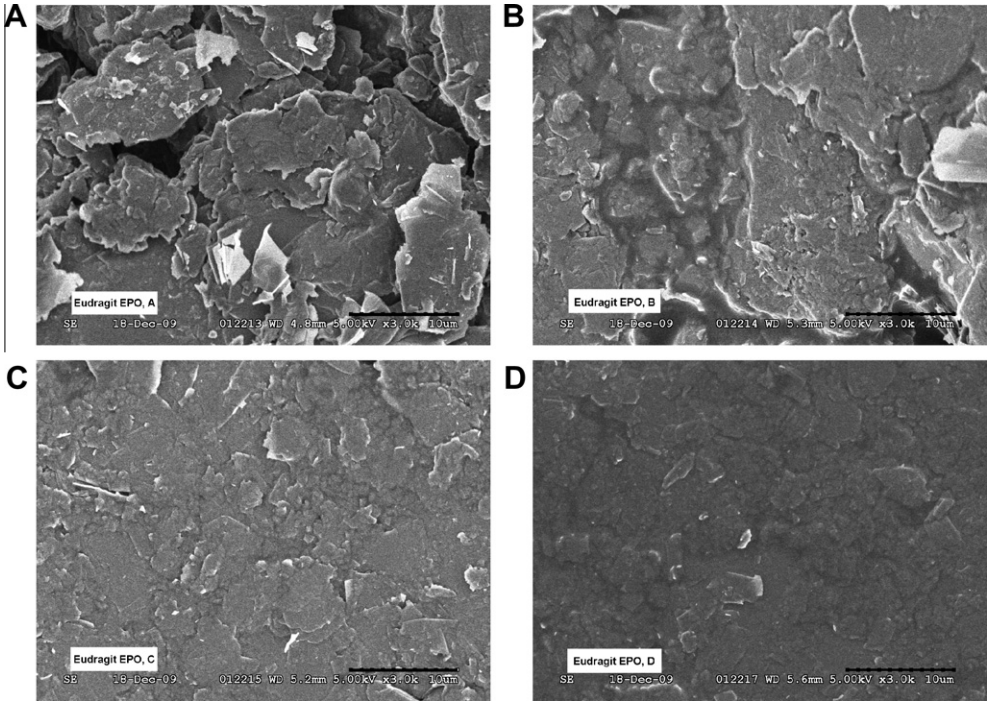

Fig. 6. Scanning electron micrographs of Eudragit® EPO powder coated tablets cured at 40 °C for (A) 0 (no curing), (B) 30, (C) 60, and (D) 90 min.

was first introduced by Dillon, where the film formation occurs because of particle deformation and viscous flow [29]. In order to induce the viscous flow of polymer particles and complete film formation, an additional curing step with an applied temperature close to or higher than the glass transition temperature (T_g) of the polymer is required to soften the coating polymers [28] and allow molecular movements to form a coating film. Common coating polymers have relatively high T_g relative to room temperature. This is necessary because low T_g polymers tend to be sticky. This will affect product integrity upon storage, packaging and product handling of health professionals and patients. On the other hand, the T_g needs to be sufficiently low (e.g. 50–60 °C) to allow curing at a slightly elevated temperature without causing drug degradation. Unlike metal substrates for powder coating in other industry, many drug substances and pharmaceutical excipients are relatively sensitive to heat, although they many of them can be exposed to an increased temperature such as 60 °C for a brief period of time (up to several hours) without affecting the degradation impurity content.

Plasticizer is well known to increase the flexibility and decrease the T_g of the polymer by interspersing themselves around the polymer and reducing inter-chain bonding strength. In this study, a target T_g of 40–60 °C was defined in consideration of the processing condition and product requirements. Glycerol, water and polyethylene glycols were used as plasticizers for PVA and Eudragit® EPO polymers [30–32]. A mixture of glycerol and water with a ratio of 1:1 and PEG 400 were tested as plasticizers for PVA and Eudragit® EPO. Based on the DSC results, a T_g of 79.6 °C and 53.1 °C for pure PVA and Eudragit® EPO polymers was lowered to 53.3 °C and 31.1 °C after mixing with plasticizers, respectively.

The main parameters affecting film formation in the curing step are temperature and time. To investigate their effects, the surface morphology of the coated tablets was observed under different temperatures through the curing period using a scanning electron microscope. Fig. 5 shows the SEM micrographs from the Opadry® AMB coated tablets at 60 °C for different curing time intervals, revealing the progress of film formation (Fig. 5). Before curing started, the uncured coated tablet showed porous layer with visible deposition of polymeric particles on the surface (Fig. 5A), indicating particle adhesion to the surface of the tablets, but did not coalescence into a smooth film during the powder deposition step. As curing progressed, particles coalesced partially into a smooth

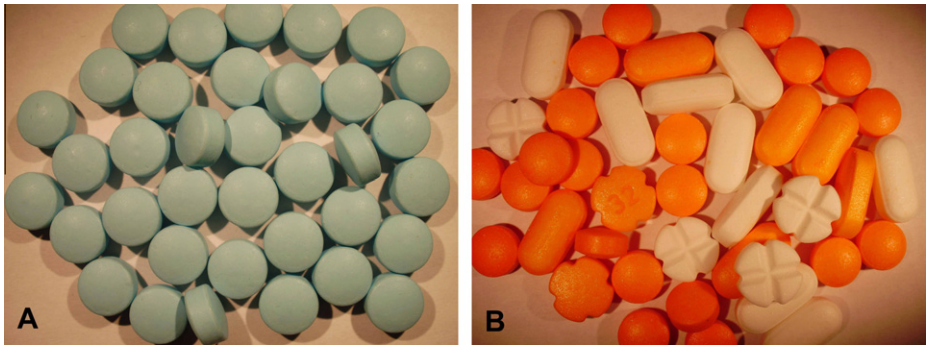

Fig. 7. Powder coated tablets with a film coating formulation containing (A) Opadry® AMB or (B) Eudragit® EPO. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Uniformity of film coat determined by percentage coefficient of variation (CV).

Main component of coating material	Run no.	CV by weight (%)		CV by thickness (%)		CV by diameter (%)		CV of coating weight
		Before coating	After coating	Before coating	After coating	Before coating	After coating	
Opadry® AMB	1	2.93	2.95	1.89	1.84	0.10	0.17	7.93
	2	1.98	1.93	1.53	1.49	0.11	0.09	5.33
	3	1.90	1.81	1.52	1.40	0.12	0.10	8.14
Eudragit® EPO	1	2.17	2.15	1.88	1.88	0.06	0.06	9.01
	2	1.68	1.70	1.24	1.23	0.06	0.05	7.04
	3	2.41	2.49	1.86	1.82	0.05	0.05	6.65

CV – percentage coefficient of variation (%).

film. At curing time of 60 min (Fig. 5B), the surface was seen to have formed some larger film pieces but was still characterized by the presence of small voids and some non-fused particles. After 120 min of curing time (Fig. 5C), the voids on the surface are barely visible, indicating that the particles were fused into a nearly complete film. When the curing temperature is lower, e.g. 50 °C, a relatively rough and incomplete film is seen (Fig. 5D). The SEM micrographs of Eudragit® EPO powder coated tablets showed similar film formation process as Opadry® AMB (Fig. 6A–D).

4.3. Evaluation of powder coated tablets

The Opadry® AMB and Eudragit® EPO coated tablets were evaluated by examining the appearance (visual, optical microscopy and SEM), uniformity and dissolution profiles. The dry powder coated tablets showed a high quality and smooth surface (Fig. 7A and B) that are comparable to acceptable film coated tablets manufactured by conventional coating methods. This satisfactory appearance was achieved by combining electrostatic charging of powders and the use of ultrafine powder coating in the coating process. The electrical repelling force between the charge particles facilitated a even distribution of particles on the tablet surface [33]. The use of ultrafine powder with mass median diameter (D_{50}) of approximately or less than 20 μm produces significant improvement in surface quality and comparable smoothness with that of liquid coating [34]. According to the reference that fine powder with particle size less than 30 μm is likely to become cohesive and form agglomerate and clumps. With the patented ultrafine powder coating technology, fine powder can still be used to achieve smooth coating surface [35].

Tablet weight, diameter and thickness uniformities before and after coating were used to examine the distribution of coating materials in coating process. The comparable CVs in these parameters and relatively small CVs in coating weight gain (Table 1) indicated a uniform coating particle distribution among the tablets within and between batches.

Dissolution testing is usually conducted to examine whether the film coat applied will affect the drug product release profile. A delay in dissolution suggests that bioavailability, i.e. the rate and extent of drug absorption *in vivo*, may be affected. The results indicated that dissolution profiles of ibuprofen tablets are essentially identical before and after coating for both coating compositions containing Opadry® AMB and Eudragit® EPO (Fig. 8A and B). Therefore, the data also showed that the electrostatic powder coating method and the coating formulations developed in this study can be applied in the coating of immediate release tablets. The release profile of the coating runs was found to be similar, indicating that the coating process is basically very reproducible and a commercial-scale process can be developed using the same procedures. Based on the content of the coating compositions, it is unlikely that the dissolution profile on product storage will be affected by the coating process or materials. Nevertheless, on going stability studies are being conducted to investigate the effect of storage on the dissolution profiles of coated tablets.

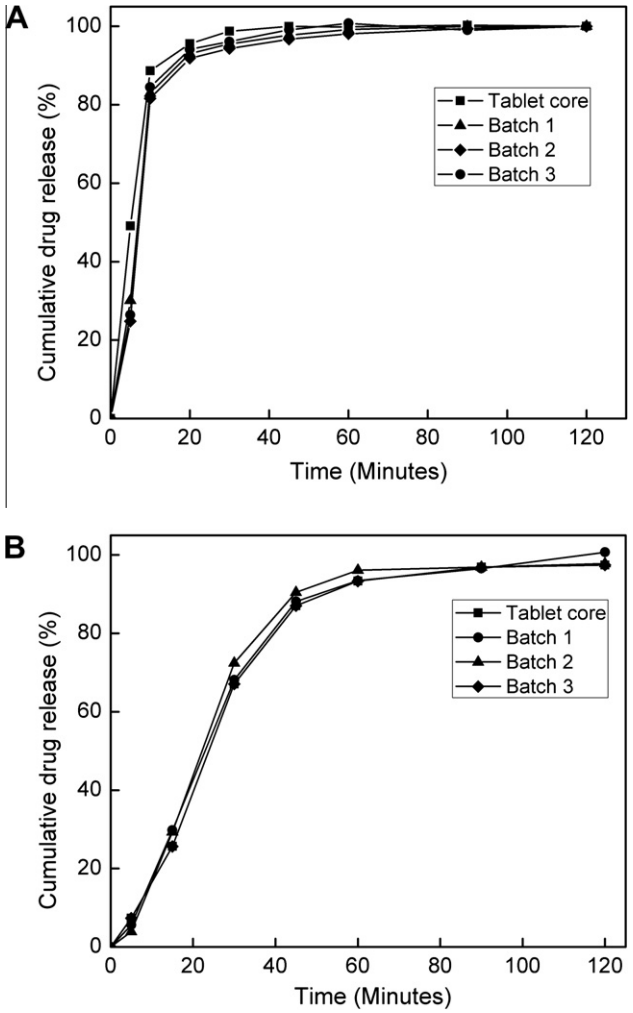

Fig. 8. Dissolution profiles ibuprofen from uncoated and coated tablets. The film coating formulation consists of (A) Opadry® AMB or (B) Eudragit® EPO.

5. Conclusion

A novel electrostatic dry powder coating technique based on liquid pan coater was developed and applied to form immediate release coatings with Opadry® AMB and Eudragit® EPO. Liquid plasticizer was used to decrease T_g of coating polymers and to promote powder deposition on the tablet surface by increasing electrical conductivity of tablets. Even though the enhanced electrical

conductivity of tablets met the requirements for electrostatic coating, it is still necessary to further improve the electrical conductivity in order to make full use of electrical attractive force. The dry coating particles fused into a complete film on the tablet surface after curing at elevated temperatures. The electrostatic powder coating technique is able to produce smooth and uniform coating film and has been demonstrated as a promising alternative to traditional aqueous-based coating process. However, the electrostatic dry powder coating process is still new and requires further validation through more experiments.

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