A novel electrostatic dry coating process for enteric coating of tablets with Eudragit® L100-55

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A B S T R A C T

An electrostatic dry coating process based on a liquid pan coater was developed for enteric coating of tablets with Eudragit® L100-55. Two different liquid plasticizers of triethyl citrate (TEC) and PEG400 were used in the coating process. In contrast to TEC, PEG400 produced good powder adhesion and successful coating. DSC results showed that PEG400 lowered the glass transition temperature (Tg) of Eudragit® L100-55 to a greater extent than TEC at the same blend ratio, indicating that PEG400 was more effective in plasticizing the polymer. PEG400 showed higher contact angle on both surfaces of tablet cores and coating powders as well as lower absorption into the tablet cores than TEC, suggesting that more PEG400 existed at the interface between tablet core and coating powders. The combination effects of higher plasticizing efficiency and more PEG400 available at the tablet surface produced higher plasticization of Eudragit® L100-55, leading to the successfully initial powder adhesion. The powder adhesion was further enhanced by the electrostatically assisted coating process, as confirmed by the higher coating level and coating efficiency with electrical charging (60 kV) than the ones without it (0 kV). The micrographs of scanning electron microscopy and in vitro drug release tests of the coated tablets showed that higher curing temperature and longer curing time led to enhanced film formation and acid resistance. The electrostatic dry coating process has been demonstrated to be a promising process for enteric coating of tablets.

1. Introduction

Dry coating, has been recognized to be an environmentally-friendly and a promising coating technology to overcome the limitations associated with organic and aqueous coating systems [1]. Organic solvent coating suffers from toxicological, environmental, cost and safety-related concerns [2]. The reported problems with aqueous coating include slow drying rate and high energy input [1], limited applicability for water-sensitive drugs [3] and film aging [4].

The concept of dry coating originates from the fact that most of problems with liquid coating are associated with the solvents used to dissolve or disperse the coating materials. By eliminating the solvents in the coating process, dry coating overcomes most of the above-mentioned limitations. A variety of dry coating processes based on fluidized bed, pan coater and/or laboratory spheronizer have been tested to coat various polymers including Eudragit® RS L100-55, ethyl cellulose [6], hydroxypropyl methylcellulose acetate succinate [7–9]. The reported dry coating processes involved directly layering powder particles onto the surface of substrates with a liquid plasticizer being sprayed simultaneously and a following curing step at elevated temperatures to allow for film formation. Some other dry coating processes that completely removed liquid from coating process were also reported to coat Eudragit® EPO[10,11], Eudragit® L100-55 [11] and Eudragit® RS PO/Eudragit® RL PO [12]. In these complete solvent-free processes, polymers with high glass transition temperature (Tg) needed to be pre-plasticized with liquid plasticizer prior to coating. Even though much effort has been made, there still exist some difficulties for the various developed dry coating processes such as relative complicate operation process, unsatisfied film appearance and sticky film.

Electrostatic dry coating is an alternative approach for the current pharmaceutical coating techniques. The coating process involves charging coating particles with high voltage by an electrostatic spray gun, spraying the charged particles onto the grounded substrates under the combination of electric attractive force and compressed air, and curing the substrates at elevated temperature for film formation. The electrostatic dry coating was introduced for pharmaceutical tablet coating by Phoqus Ltd. [13,14]. In Phoqus’ process, the charged particles were attracted and deposited on each side of the tablets separately with the appli-
cation of electrical field. Then radiant heat was used to fuse the particles at 120 °C for less than 1 min. However, the diffusion of the technology has been compromised by a complicated operation and complex coating apparatus. Prior to Phoqus, an analogous technology taking advantage of electrostatic attraction has been presented for layering of drug or excipient onto pellet cores in the field of pellet manufacturing [15].

A novel electrostatic dry coating process has been developed for pharmaceutical applications by the authors [16,17]. A liquid pan coater was combined with an electrostatic dry powder spray gun and powder delivery feeder. The main benefits of the process are: (1) The coating process is easy to control due to the resembling liquid coating process; (2) The coating apparatus is simple because the commercial liquid pan coater can be retrofitted for the dry coating process by simply combining a powder feeder and an electrostatic spray gun.

The objective of the study was to develop an electrostatic dry coating process for enteric coating of tablets with Eudragit® L100-55. The effect of liquid plasticizer and electrical charging on powder adhesion as well as the effect of curing conditions on the film formation and acid resistance were also investigated.

2. Materials and methods

2.1. Materials

Eudragit® L100-55 was provided by Evonik Degussa Corporation (Germany). Round shaped ibuprofen tablets (diameter: 8.0 mm, thickness: 4.8 mm, weight: 0.32 g, hardness: 64 N) and placebo tablets (diameter: 7.0 mm, thickness: 3.8 mm, weight: 0.16 g, hardness: 66 N) were obtained from Patehon (Ontario, Canada).

Purchased from Caledon Laboratories Ltd. (Ontario, Canada).

The formulation of ibuprofen tablet consists of 90% ibuprofen, 9.5% microcrystalline cellulose and 0.5% magnesium stearate. The formulation of placebo tablet consists of 99.5% microcrystalline cellulose and 0.5% magnesium stearate. Triethyl citrate (TEC) was purchased from EMD Chemicals Inc. (Ontario, Canada).

Colloidal silicon dioxide (AEROSIL® 200 Pharma) was donated by Evonik Degussa Corporation (Germany). Talc was purchased from Mallinckrodt Baker Inc. (Canada).

2.2. Particle size reduction and analysis

Eudragit® L100-55 and talc coarse powders were ground to fine powders separately by a homemade jet mill with a 150 mm diameter grinding chamber. The grinding pressure for the powders was 100 psi. The feed rate of the powders was 5 g/min. The particle size of the ground powder was tested by Particle Size Distribution Analyzer (PSD 3603, TSI Corporation, Shoreview, MN, USA). The single-particle-counting technique was used by the PSD 3603 to determine aerodynamic particle size with time-of-flight (TOF) and time-in-beam (TIB) technologies. The value of the particle diameter at 50% in the cumulative distribution was designated as median diameter (D50). The D50 of the Eudragit® L100-55 and talc ground powders were 21.7 ± 1.87 μm and 28.9 ± 2.54 μm (mean ± SD, n = 3), respectively.

2.3. Modulated differential scanning calorimetry (MDSC)

Modulated differential scanning calorimetry (MDSC) was employed to investigate the thermal properties of Eudragit® L100-55 and the plasticized Eudragit® L100-55 using a METTLER-TOLEDO DSC 1 calorimeter equipped with STAR® system (Mettler Toledo, Switzerland). The plasticized Eudragit® L100-55 was prepared by mixing the polymer with TEC and PEG400 using a mortar and pestle for 15–30 min, respectively. The samples containing different ratios of a plasticizer (10%, 25%, 50%, and 100%) based on the polymer weight were obtained. Prior to analysis, the samples (3–4 mg) were weighed and sealed into aluminum pans. The temperature ramp rate was 2 °C/min at a modulation rate of ±1.00 °C every 60 s over the temperature range from 0 to 150 °C under nitrogen atmosphere. The Tg was determined as the temperature at midpoint of the change in the reverse heat flow of the second heating cycle. The Tg of each sample was performed in triplicate.

2.4. Contact angle measurements

The contact angles of the liquid plasticizers (TEC and PEG400) on the tablet cores and compacts of coating powders (Formulation A in Table 2) were determined by the sessile drop method. The coating powders were compressed into flat-faced compacts with a hardness of 4.9 N at the same compression force using a single punch tablet press (First Pharmacy Machine, Shanghai, China).

The samples were placed on an adjustable platform. Droplets of liquid plasticizers (1 μl) were dropped on the surface with a micrometer syringe. The contact angle was determined by measuring the tangent to the curve of the droplet on the surface of the sample after 1 min (n = 6).

2.5. Viscosity measurements

The viscosity of the liquid plasticizers (PEG400 and TEC) was determined using a rotational rheometer (Rheometer AR2000ex, TA Instruments Ltd., USA) at 25 °C.

2.6. Coating process

The coating process was performed in a laboratory scale electrostatic dry powder pan coater system with an electrostatically grounded stainless steel coating pan (Fig. 1). The cylindrical coating pan dimensions were 12.7 cm in diameter × 12.7 cm in height. Four aluminum baffles were mounted inside (90° apart) the pan to promote a good tumbling movement of the tablets. The tablets (60 g of placebo tablets and 20 g of ibuprofen tablets) were loaded in the coating pan and preheated to a certain temperature of 40 °C, 50 °C, or 60 °C for different runs of coating. Placebo tablets were added to maintain the volume of substrates. The process parameters are shown in Table 1. The liquid plasticizer (PEG400 or TEC) was regulated by a fluid dispensing and metering pump (Fluid Metering Inc., USA) and sprayed onto the tablet surface when the pan was rotating. Afterward, the coating powders were sprayed though an electrostatic spray gun (Nordson Corporation, USA) inserted into the coating pan from the opening of the front door. The powder coated tablets were further cured for film formation in the same coating pan with lowered rotating speed (13–29 rpm) to allow film formation and acid resistance to occur. The temperature of the heating cycle. The Tg was determined as the temperature at midpoint of the change in the reverse heat flow of the second heating cycle. The Tg of each sample was performed in triplicate.

Table 1

<table>
<thead>
<tr>
<th>Process parameters of the electrostatic dry coating.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet loading</td>
</tr>
<tr>
<td>Charging voltage</td>
</tr>
<tr>
<td>Inlet air temperature</td>
</tr>
<tr>
<td>Liquid plasticizer feed rate</td>
</tr>
<tr>
<td>Liquid plasticizer feed time</td>
</tr>
<tr>
<td>Atomizing air pressure</td>
</tr>
<tr>
<td>Nozzle diameter</td>
</tr>
<tr>
<td>Powder feed rate</td>
</tr>
<tr>
<td>Powder feed time</td>
</tr>
<tr>
<td>Pan speed during coating</td>
</tr>
<tr>
<td>Pan speed during curing</td>
</tr>
<tr>
<td>Curing temperature</td>
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<tr>
<td>Curing time interval</td>
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</tbody>
</table>
The coating level (%) was calculated from the weight gain of coated tablets divided by the weight of uncoated tablets. The coating efficiency (%) was calculated from the weight gain of the coated tablets divided by the mass of feeding powders.

2.7. Absorption of liquid plasticizers into tablet core

To measure the absorption of liquid plasticizers into the tablet core, the operation was as same as coating process except that the tablets were taken out from the coating pan after spraying liquid plasticizers. The tablets \((n=5)\) were carefully wiped with a filter paper to remove the surface adherent liquid. The absorption of liquid into tablet core (%) was calculated from weight gain of tablets and divided by the weight of tablets before spraying liquid. The operation was repeated for three times to obtain a mean value.

2.8. Scanning electron microscopy (SEM)

The powder coated tablets cured at various conditions were sputter coated with gold for 120 s under an argon atmosphere using EMITECH K550 sputter coater (Emitech Ltd., Ashford, UK). The surface morphology of the powder coated tablets was examined by a scanning electron microscopy (SEM, Hitachi S-2600 N) operated at 5.0 kV.

2.9. Dissolution tests

The in vitro drug release from the dry coated tablets was tested using the USP apparatus 2 (Paddle Apparatus). Release experiments \((n=6)\) were performed in a dissolution apparatus at 37 °C with a paddle speed of 100 rpm (Huanghai Rcz-6c2, Shanghai, China). Dissolution tests were performed in 750 ml of HCl (0.1 N, pH 1) for the first 2 h and 1000 ml of phosphate buffer (pH 6.8) by adding 250 ml of 0.2 M tribasic sodium phosphate solution for additional 2 h. At predetermined time intervals, 10 ml of samples were withdrawn from each vessel and replaced with fresh release media. The samples were filtered and analyzed using an 8453 UV–Vis Spectrophotometer (Agilent Technologies, Mississauga, Canada) at a wavelength of 222 nm.

2.10. Stability test

One batch of the tablets coated according to the conditions shown in Table 1 and cured at 60 °C for 3 h were prepared for stability test. The coated tablets with 4.0% coating level were placed in HDPE vials (75 ml) and induction sealed with aluminum film. The HDPE vials were capped and stored at 40 °C/75% RH for 6 months and 25 °C/60% RH for 12 months, respectively. The coated tablets were withdrawn at regular intervals of 0, 3, 6, and 12 months and examined the dissolution profiles according to dissolution test method.

3. Results and discussion

3.1. Plasticizing effect of liquid plasticizers

The plasticizing effect of a liquid plasticizer with respect to reducing the glass transition temperature \((T_g)\) and increasing mobility of a coating polymer plays an important role in facilitating coalescence of the polymer into a continuous film in dry coating process. The plasticizing effect of liquid plasticizers (TEC and PEG400) on Eudragit \(\text{L} 100-55\) polymer was investigated by measuring the \(T_g\) variation after mixing with different ratios of either plasticizer. As shown in Fig. 2, the \(T_g\) of pure Eudragit \(\text{L} 100-55\) polymer was 125.7 °C and clearly decreased with the presence of either liquid plasticizer. The representative DSC thermograms of plasticizer/Eudragit \(\text{L} 100-55\) blends with different ratio are presented in Fig. 3A and B. Within all the investigated concentration ratios (10%, 25%, 50% and 100%, w/w, based on the polymer weight), PEG400/Eudragit \(\text{L} 100-55\) blend showed lower \(T_g\) than TEC/Eudragit \(\text{L} 100-55\) blends, indicating PEG400 was more

![Fig. 1. Schematic of the electrostatic powder coating system. (A) powder feeder; (B) electrostatic spray gun; (C) pan coater; (D) liquid plasticizer spraying nozzle. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)](image1)

![Fig. 2. Influence of triethyl citrate (TEC) and polyethylene glycol 400 (PEG400) concentration on the glass transition temperature of Eudragit \(\text{L} 100-55\).](image2)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation A</th>
<th>Formulation B</th>
<th>Formulation C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit (\text{L} 100-55)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Talc</td>
<td>98 (98%)</td>
<td>80 (80%)</td>
<td>40 (40%)</td>
</tr>
<tr>
<td>Yellow #6 lake pigment</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Coating level (%)</td>
<td>4.0 ± 0.25</td>
<td>4.3 ± 0.35</td>
<td>4.1 ± 0.30</td>
</tr>
<tr>
<td>Coating efficiency (%)</td>
<td>70 ± 4</td>
<td>72 ± 5</td>
<td>68 ± 5</td>
</tr>
</tbody>
</table>

\(a\) Based on the weight of Eudragit \(\text{L} 100-55\).

\(b\) Based on the weight of tablets.
efficient than TEC in plasticizing Eudragit® L100-55. The Tg of plasticized coating polymer was reported to be a key parameter in dry coating process, in which the curing temperature to achieve sufficient film formation was required to be close to or higher than the Tg of the plasticized polymer [18]. In this study, a target Tg of the plasticized Eudragit® L100-55 between 40 and 60°C was expected considering that most of the applied temperature in coating process fell into this temperature window. Addition of 100% of PEG400 was capable of decreasing the Tg of Eudragit® L100-55 below 60°C, ensuring the film formation at relatively low curing temperature in the dry coating process.

3.2. Electrostatic dry coating

The outline of the electrostatic dry coating is shown in Fig. 4. The coating process is simply composed of three steps: (1) Preheating, the tablets are preheated in the pan coater to a certain temperature. (2) Powder adhesion, the liquid plasticizer is sprayed onto the tablet surface followed by spraying coating powders with an electrostatic spray gun. (3) Film formation, the deposited powder particles on the tablet surface coalesce into a continuous film under curing.

The mechanism of the electrostatically assisted powder adhesion is shown in the inset of Fig. 1. The coating powders are negatively charged at the tip of an electrostatic corona charging spray gun by a high voltage. The charged powders will follow the electric field lines generated between the charging tip of the spray gun and the grounded pan coater, resulting in the adhesion onto the tablet surface. To achieve a successful powder adhesion, tablet cores are required to possess certain electrical conductivity in order to be properly grounded by contacting with the conductive pan coater. Our previous studies revealed that the electrical conductivity of tablet core was greatly increased after spraying PEG400 or TEC [16,19], which satisfied the recommended electrical resistance (less than 10^12 Ω m) for electrostatic dry coating [1].

3.2.1. Dry coating powder formulation

In a preliminary experiment, the dry coating was conducted using the pure Eudragit® L100-55 polymer, which was failed due to the severe tackiness of the coated tablets during the curing step. Talc has been widely used in the coating formulation to prevent the tackiness in coating. Therefore, blends of Eudragit® L100-55 and talc at different ratios of 100/40, 100/80, and 100/98 (w/w) were prepared and used for the dry coating process (Table 2). The increase of talc in the coating formulation had no significant influence on the powder adhesion (P > 0.05) and coating efficiency (P > 0.05), as determined by one-way ANOVA. The Eudragit® L100-55/talc ratio was fixed at 100/98 because the coated tablets tended to become sticky and compromised the film integrity during the curing step when the ratio was higher than 100/98. Therefore, formulation A is chosen as the final powder formulation for the dry coating process.

3.2.2. Powder adhesion

In dry coating process, adhesion of coating powders onto the substrate surface is much more difficult than that in liquid-borne coating process due to the absence of dispersion medium for the coating powders. The adhesion of coating powders occur via two steps in dry coating process: first, the substrate surface is wetted by a liquid plasticizer; second, the coating powders adhere to the substrate surface under the combination of capillary forces and increased stickiness of coating polymer in contact with liquid plasticizer [20,21]. The liquid plasticizer plays a role in facilitating the initial adhesion of coating powders because it generates the capillary forces at the interface between the coating powders and the substrate surface [21–23]. However, the capillary forces produced by the liquid plasticizer will disappear due to the penetration of the liquid plasticizer into the coating powders. Some liquid additives or low melting substances have been used to strengthen
and extend the capillary forces, resulting in enhanced adhesion of coating powders onto the substrate surface [21,23]. For example, the application of a molten layer of cetyl alcohol enhanced the adhesion of pre-plasticized Eudragit® L100-55 powders onto the tablet surface. TEC was firstly employed in the dry coating process because it was a recommended plasticizer for Eudragit® L100-55 in aqueous coating. However, the continuous layer of coating powders on tablets could not be achieved with TEC as liquid plasticizer. This was in agreement with the previous articles that the adhesion of Eudragit® L100-55 to tablets was only accomplished by pre-plasticizing of Eudragit® L100-55 with TEC and PEG 3350 and using of PEG 3350 or Eudragit® EPO as a subcoating [20,22]. In those studies, the spreading of the subcoating materials on the tablet surface was considered to be crucial for Eudragit® L100-55 powder adhesion. The adhesion of the Eudragit® L100-55 powders was facilitated by the combination of capillary forces, surface tension, and viscous resistance of the molten subcoating layer, which inhibited rapid separation of the coating powders from the tablet surface. In contrast to TEC, PEG400 showed good ability in facilitating adhesion of Eudragit® L100-55 coating powders on the tablet surface under the same coating conditions.

In order to gain an insight into the difference in facilitating powder adhesion between PEG400 and TEC, the viscosity of the two liquid plasticizers was first compared. As shown in Table 3, PEG400 has a higher viscosity than TEC. The effect of viscosity of liquid plasticizer on the coating efficiency in dry coating was investigated by Smikalla et al. [25]. The study demonstrated that as the viscosity of the liquid plasticizer increased, there was a decreasing trend in coating efficiency, indicating a lower powder adhesion, insufficient for generating strong adhesion forces, leading to the detachment of coating powders from the tablet surface and poor powder adhesion.

The spreading behavior of two liquid plasticizers on the surfaces of tablet and coating powders was further investigated by measuring the contact angles and liquid absorption (Table 3). TEC showed low contact angles on both surfaces of the tablet core (10 ± 1.7°, n = 6) and the compacts of coating powders (0.5 ± 0.5°, n = 6). Compared to TEC, PEG400 showed extremely significant increase (P < 0.001) in the contact angles on both surfaces of tablet cores (17.8 ± 1.0°) and compacts of coating powders (20.5 ± 0.89°). This indicated that PEG400 had less affinity to both surfaces of tablet cores and coating powders than TEC. The absorption of liquid plasticizer into tablet core was also determined by calculating the weight gain of the tablet cores after spraying plasticizer under the same coating conditions (Table 3). The tablet cores showed significantly lower weight gain after applying PEG400 than those applying TEC (0.16 ± 0.03% vs. 0.28 ± 0.05%, n = 3, P < 0.05), indicating that less PEG400 was absorbed into the tablet cores. Therefore, it could be presumed that more liquid would remain on the tablet surface after applying PEG400 because less PEG400 was absorbed into tablet cores and coating powders. In contrast to PEG400, TEC tended to penetrate into the tablet core and the bed of coating powders rather than existed at the interface between the tablet and coating powders.

Besides the difference in spreading behavior, the two liquid plasticizers exhibited different efficiency in plasticizing Eudragit® L100-55. DSC tests showed that the PEG400 lowered the Tg to a greater extent than TEC at the same blend ratio, indicating that PEG400 was more effective in plasticizing Eudragit® L100-55. The combination effect of higher plasticizing efficiency and more liquid PEG400 on the tablet surface resulted in a higher degree of plasticization and lower Tg of the polymer, as compared to TEC. This would lead to an increase in adhesive properties such as stickiness and contact area of the coating polymer, thus stronger powder adhesion [26]. In addition, the excess liquid PEG400 on the tablet surface might also exert extended capillary forces during the powder deposition step, further enhanced the powder adhesion. To achieve powder adhesion, it has to be ensured that the adhesion forces are strong enough to withstand the tumbling of the tablets and the gravity of the coating powders. The lower plasticizing efficiency and less liquid TEC on the tablet surface were probably insufficient for generating strong adhesion forces, leading to the detachment of coating powders from the tablet surface and poor powder adhesion.

Table 4 summarizes the coating level and coating efficiency of the different runs of dry coated tablets under different conditions. It could be noted that significantly higher coating level (4.0–4.5% vs. 2.1%, n = 3, P < 0.05) and coating efficiency (70–72% vs. 33%, n = 3, P < 0.05) were obtained by coating the tablets at the charging voltage of 60 kV than those coated at 0 kV. The coating powders were negatively charged by the high voltage (60 kV) at the electrode of the charging gun. The movement of the charged powders was mainly directed by the electric attraction force derived from the electric field between the electric charging gun and the grounded pan coater, resulting in enhanced powder deposition on the tablet surface. When the charging voltage was 0 kV, the flow direction of uncharged coating powders could not be manipulated by the electric field lines. The uncontrolled spray pattern of the coating powders compromised the powder deposition on the tablet surface, leading to lower coating level and coating efficiency.

3.2.3. Film formation

The film formation of dry coating process mostly occurred in the curing step by heating the tablets at a temperature higher than or close to the Tg of the coating polymer [18,27]. The most important parameters affecting the coalescence of coating powders into a

<table>
<thead>
<tr>
<th>Liquid plasticizer</th>
<th>Viscosity (mPa s)</th>
<th>Contact angle (°)</th>
<th>Amount of absorption (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tablet core (hardness, 64 N)</td>
<td>Compacts of coating powders (hardness, 4.9 N)</td>
</tr>
<tr>
<td>TEC</td>
<td>26 ± 0.30</td>
<td>10 ± 1.7</td>
<td>0.5 ± 0.5</td>
</tr>
<tr>
<td>PEG400</td>
<td>79 ± 0.34</td>
<td>17.8 ± 1.0</td>
<td>20.5 ± 0.89</td>
</tr>
</tbody>
</table>

* P < 0.001 compared with contact angles of TEC, performed with two-tailed student’s t test.
* P < 0.05 compared with the amount of TEC absorption, performed with two-tailed student’s t test.
* Based on the weight of tablet core.
film were curing temperature and curing time [18]. To investigate their effects, the surface morphology of the coated tablets under different curing conditions was examined using a scanning electron microscope (SEM). The coated tablets with 4.0% weight gain were used for the examination due to the sufficient acid resistance in the dissolution test. The SEM micrographs of the coated tablet cured at different temperatures (40°C, 50°C and 60°C) for 2 h are shown in Fig. 5. When the tablets were cured at 40°C, the coalesced film showed more voids and cracks than that cured at higher temperatures. This was in agreement with the fact that higher curing temperature could promote the coalescence of coating powders into a film. The SEM micrographs of the coated tablets cured at 60°C for different time intervals (0 h, 1 h, 2 h, and 3 h) revealed the progression of the film formation, which was characterized by the diminishing voids and non-fused particles as time extended (Fig. 6).

3.3. In vitro dissolution studies

The dry coated tablets were tested in the release medium (0.1 N HCl) to reveal the effect of curing temperature and curing time on the acid resistance of the film. For the enteric coated formulations, acid resistance is the most important quality in dissolution tests. Acid resistance is characterized by the percent of drug release in 0.1 N HCl during 2 h. The United States Pharmacopoeia (USP) requires less than 10% of the drug is released after the first 2 h in acid medium. The coating level of 4.0% (2.9 mg/cm² polymer weight gain) for the ibuprofen tablets was determined as target weight gain because of the sufficient and consistent acid resistance characterized by the low ibuprofen release in acid medium (1.89% ± 0.29%, n = 6). The influence of curing temperature and curing time on the acid resistance of the Eudragit® L100-55 enteric film was investigated using the coated tablets with a coating level of 4.0% (2.9 mg/cm² polymer weight gain). As shown in Fig. 7, increasing curing temperature and curing time led to decreased drug release in the acid medium. The enhancement of acid resistance was attributed to the increased completeness of the coated film at higher curing temperature and longer curing time. The results of acid resistance indicated that coating and curing at 60°C produced the best enteric film and acid resistance, which was in agreement with the SEM micrographs.

It could be noted that the required coating level to achieve sufficient acid resistance was relatively low (2.9 mg/cm² polymer weight gain) for the dry coating process. To achieve enteric protection of a tablet core, 3–4 mg/cm² polymer weight gain is usually recommended to be applied to the dosage form with organic coating [28]. However, the thickness of enteric coat required to ensure acid resistance depends on a variety of variables and varies with individual formulations. Drug release during the acid phase is a result of swelling of the film coating, water penetration into the core, drug dissolution, and subsequent diffusion through the hydrated polymeric film [29]. The solubility of an active pharmaceutical ingredient (API) in the acid medium is one of the predominant factors affecting the acid resistance of the enteric coat. APIs with lower solubility have been known to require less enteric coat than the ones with higher solubility [22]. In this study, the relatively low polymer weight gain capable of providing enteric protection was probably attributed to the extremely low solubility (0.038 mg/ml) of ibuprofen in acid medium at 37°C [30] and limited diffusion through the hydrated polymeric film [22].

3.4. Storage stability of powder coated tablets

Most of dry powder coated tablets have been reported to exhibit good physical stability during storage. For example, dry powder coated pellets with ethyl cellulose and Eudragit® RS showed an unchanged release profiles within a 3-year storage [5,6]. However, Eudragit® L100-55 powder coated tablets showed discrepancy in

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### Table 4

Coating level (n = 3, mean value ± standard deviation) and coating efficiency (n = 3, mean value ± standard deviation) of the electrostatic dry coated tablets.

<table>
<thead>
<tr>
<th>Plasticizer</th>
<th>Charging voltage (kV)</th>
<th>Coating level (%)</th>
<th>Polymer weight gain (mg/cm²)</th>
<th>Coating efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG400</td>
<td>60</td>
<td>4.5 ± 0.26</td>
<td>3.3 ± 0.25</td>
<td>72 ± 5</td>
</tr>
<tr>
<td>PEG400</td>
<td>60</td>
<td>4.0 ± 0.25</td>
<td>2.9 ± 0.15</td>
<td>70 ± 4</td>
</tr>
<tr>
<td>PEG400</td>
<td>0</td>
<td>2.1 ± 0.29</td>
<td>1.5 ± 0.20</td>
<td>33 ± 4</td>
</tr>
<tr>
<td>TEC</td>
<td>60</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
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</table>

Based on the weight of tablet core.

![Fig. 5. SEM micrographs of Eudragit® L100-55 powder coated tablets curing for 2 h at different temperatures: (A) 40°C, (B) 50°C, and (C) 60°C.](image-url)
drug release during storage at 25 °C/60% RH and 40 °C/75% RH for 12 weeks [20,22]. In comparison with the good storage stability at 25 °C/60% RH, the drug release decreased and became less consistent with a higher standard deviation at 40 °C/75% RH. This was attributed to the relative low \( T_g \) of the coating film and resulting in higher molecular mobility of the coating polymer under higher temperature and humidity storage conditions.

The coated tablets with 4.0% of coating level were chosen for conducting the physical stability test due to the sufficient acid resistance. The dissolution profiles of the coated tablets stored at either 40 °C/75% RH for 6 months or 25 °C/60% RH for 12 months were studied. Prior to dissolution testing, all samples were equilibrated to ambient temperature in the sealed container for 48 h to exclude the possible influence of the tablet temperature on dissolution. The drug release profiles of the coated tablets are shown in Fig. 8. The powder coated tablets exhibited excellent stability over 12 months at 25 °C/60% RH, which was characterized by no detectable difference in the drug release profiles. The powder coated tablets stored at 40 °C/75% over 6 months showed a slightly lower drug release (89% ± 15% vs. 99% ± 4.0%, \( n = 6 \)) at the first time point in pH 6.8 phosphate buffer, as compared to the initial coated tablets. However, no significant difference in drug release was found between the two groups (\( P > 0.05 \)). The aging phenomenon of the dry coated tablets stored at 40 °C/75% RH reported by the previous studies was circumvented by the developed electrostatic dry coating process.

4. Conclusions

A novel electrostatic dry coating process based on liquid pan coater for enteric coating of tablets with Eudragit® L100-55 was successfully developed. The adhesion of coating powders on the tablet surface was facilitated using PEG400 as liquid plasticizer rather than TEC. This was attributed to the higher degree of
plasticization of Eudragit® L100-55 produced by PEG400 due to the higher plasticizing efficiency and more amount of plasticizer available on the tablet surface. The adhesion of coating powders on the tablet surface was further enhanced by the electric attractive force. Curing temperature and curing time were the main factors affecting the acid resistance of the coated tablets. The dry coated tablets showed good physical stability stored at 25°C/60% RH over 12 months. The electrostatic dry coating technique has been proven to be successful for enteric coating of tablets with Eudragit® L100-55.

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