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RESEARCH PAPER

Influence of Eudragit® NE 30 D Blended with Eudragit® L 30 D-55 on the Release of Phenylpropanolamine Hydrochloride from Coated Pellets

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ABSTRACT

The objective of this study was to investigate the influence of Eudragit® NE 30 D blended with Eudragit® L 30 D-55 on the release of phenylpropanolamine hydrochloride (PPA·HCl) from coated pellets. The miscibility of Eudragit NE 30 D/L 30 D-55 blends at different ratios was studied by using differential scanning calorimetry. The release of PPA·HCl from pellets coated with Eudragit NE 30 D alone and a Eudragit NE 30 D/L 30 D-55 blend, when stored at 40°C and 60°C, was determined by UV spectroscopy. Eudragit NE 30 D and Eudragit L 30 D-55 were miscible in ratios greater than 4:1. The curing time that was required to reach an equilibrium state decreased with the addition of Eudragit L 30 D-55. The presence of Eudragit L 30 D-55 also produced a film coating that was less tacky, and a dispersion of Eudragit NE 30 D containing Eudragit L 30 D-55 (5:1) was shown to prevent agglomeration of the pellets during coating and storage.

Key Words: Eudragit® NE 30 D; Enteric polymer; Sticking; Aging; Physical stability.

INTRODUCTION

Eudragit® NE 30 D is a polymer composed of methyl methacrylate and ethyl acrylate monomers in a ratio of 2:1. Eudragit NE 30 D has a low glass transition temperature (T_g) of −8°C and a minimum film formation temperature of 5°C. Polymeric films prepared from Eudragit NE 30 D are soft and flexible; therefore, no plasticizer is required for film coating.[1] Because permeability of the film is pH-independent, Eudragit NE 30 D has been used widely in sustained-release film coatings,[2,3] granulations,[4,5] and as a component in transdermal films.[6] Eudragit L 30 D-55, a methacrylic acid copolymer, is an enteric polymer that is insoluble in acid and soluble above pH 5.5.

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The tackiness of some acrylic polymer-coated pellets that is experienced during film coating is primarily because of the thermal properties of the polymer. The order of tackiness of aqueous polymeric coatings, has been reported to be Eudragit NE 30 D > Eudragit® RS 30 D > Eudragit® RL 30 D > Aquacoat.[7] The sticking of pellets not only affects the appearance of the finished product, but it also influences the drug release rate because of structural changes in the surface morphology of the pellets during storage.

A gradual decrease in the drug release rate during storage for solid dosage forms coated with acrylic polymers has been reported by several authors to be the result of further coalescence of latex particles, which would significantly impact product stability.[8–11] When coalescence of latex particles in the film coating continues during product storage, changes in the drug release characteristics and the resultant blood level-time profile of the coated pellets are significant concerns. Pellets need to be cured for extended time period before stable drug release profiles are achieveds. The curing time required to obtain a stable film without further aging effects was found to depend on the storage condition, as well as the plasticizer level. A postcoating curing process is recommended for sustained-release acrylic coatings to achieve a stable film coating. Interestingly, few studies have been conducted to investigate the influence of a second polymer on the stability of drug release from polymer-coated dosage forms during storage. In the current study, the influence of Eudragit L 30 D-55 on the stability of drug release from Eudragit NE 30 D-coated pellets was investigated.

Blends of the acrylic polymeric have been successfully used to modify various film properties.[12–16] Eudragit NE 30 D, for example, was incorporated into other acrylic polymers to enhance the film formation and to adjust the permeability of the coating.[12] In another study, Eudragit L 30 D-55 was added to an Eudragit NE 30 D dispersion to achieve a higher drug release rate in the intestine because of the higher porosity and permeability of these films after the dissolution of the enteric polymer at intestinal pH values.[15] Amighi and Moës[8,9] investigated the influence of storage conditions on the properties of Eudragit NE 30 D and Eudragit RS 30 D sustained-release coating formulations containing a hydrophilic pore-forming agent, hydroxypropylmethylcellulose (Pharmacoat 606). The presence of hydroxypropylmethylcellulose at 10% (w/w) in the sustained-release film coating did not interfere with the coalescence of the polymer particles.

The objectives of the present study were to investigate the properties of pellets coated with Eudragit NE 30 D containing Eudragit L 30 D-55, and to determine the optimum composition of polymers that would eliminate both the sticking and adhesion problems seen with Eudragit NE 30 D, and also stabilize the release of phenylpropanolamine hydrochloride (PPA·HCl) from film-coated pellets. Thermal properties of the polymeric coatings were also studied.

MATERIALS AND METHODS

Materials

Eudragit NE 30 D (lot 1290912050) and Eudragit L 30 D-55 (lot 1210214049) dispersions were donated by Röhm American (Parsippany, NJ, USA). Phenylpropanolamine hydrochloride (lot LJ0098) was purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA, and New Brunswick, NJ, USA) and was used as the model drug substance. Kollidon® 30 (polyvinylpyrrolidone) (lot G983456P70) was supplied by BASF Corp. (Mount Olive, NJ, USA). Avicel® PH-101 (microcrystalline cellulose) (lot 1014) was donated by FMC Corp. (Newark, DE, USA). Talc (lot W001114-7) was supplied by Luzenac American, Inc. (Englewood, CO, USA).

Preparation of Core Pellets

Phenylpropanolamine hydrochloride (25%) and Avicel® PH-101 (73%) were mixed in a twin shell blender for 15 min and then wet-granulated with the addition of Kollidon 30 (2%) as a 20% w/w solution. The moistened mass was extruded using a LCI Benchtop Granulator (Tokyo, Japan). The rotation speed was controlled at 50 rpm. The extrudates were spheronized for 4 min using a Caleva model 120 Spheronizer (Dorset, UK). The spheronization speed was set at 1,000 rpm. Pellets were sieved after drying at 40°C for 12 hr, and the 16–20 mesh pellets were selected for further study.

Preparation of Coating Dispersions

Talc (100% based on dry polymer weight) was previously dispersed in purified water using a

POLYTRON® (Brinkmann Instruments, Westbury, NY, USA; Rexdale, Ontario, Canada) and then stirred continuously with the desired amount of Eudragit NE 30 D dispersion. To prevent agglomeration after mixing Eudragit NE 30 D and Eudragit L 30 D-55, the Eudragit NE 30 D and Eudragit L 30 D-55 dispersions were first diluted with an equal volume of purified water. The Eudragit dispersions were blended by stirring, and then the talc dispersion (100% of polymer weight, basis of dry polymer) was added. The concentration of acrylic polymers and the total solids content in the final dispersion were 7.5% and 15% w/w, respectively.

Film Coating

A 250 g batch of pellets (16–20 mesh) was transferred into a fluidized bed coater (Strea-1® Areomatic-Fielder), and the acrylic dispersions were applied until the desired film weight gain was achieved. The inlet and outlet temperatures were $33 \pm 2^{\circ}C$ and $30 \pm 2^{\circ}C$, respectively. The coating dispersion was applied at a rate of 2.5–3.0 g/min, and the pneumatic spray pressure was 2 bars. The aqueous dispersion was stirred continuously throughout the coating process to prevent sedimentation of the talc. The coating level of the pellets was 12% w/w (based on dry polymer weight). After application of the coating dispersion, the pellets were dried for an additional 10 min at $33 \pm 2^{\circ}C$ in the fluidized bed unit, then removed and stored at either $40^{\circ}C$ or $60^{\circ}C$.

Thermal Analysis of the Films

The thermal properties of cast films were determined by differential scanning calorimetry (Modulated DSC, TA Instruments, New Castle, DE, USA). The films were cast from aqueous dispersions containing 15% polymer content. The films were dried at $22^{\circ}C$ and 60% relative humidity followed by storage for 72 hr in desiccators containing desiccants (Drierite®) to remove residual water. Thickness of the dry films was approximately 300 μm. Film samples of 10 mg were accurately weighed into aluminum pans that were then sealed. Samples were analyzed under a nitrogen atmosphere at a heating rate of $3^{\circ}C$/min, over a temperature range of -50 to $160^{\circ}C$. The glass transition temperatures (T_gs) were determined as the midpoint of the transition using Modulated DSC Analysis V1.1A software.

Scanning Electron Microscopy

The surface morphology of the film-coated pellets was observed with a Hitachi S-4500 field emission scanning electron microscope (Rolling Meadows, IL, USA). A gold-palladium layer was applied to the pellets for 60 sec under an argon atmosphere using a Pelco model 3 cold sputter module (TED Pella, Inc., Tustin, CA, USA).

Drug Release Study

The U.S. Pharmacopeia (USP) 24, apparatus 2 (Vankel VK6010; Cary, NC, USA) was used to investigate the dissolution properties of coated pellets over an 8-hr period. The dissolution medium (500 mL) was 0.1 N hydrochloric acid solution, and was maintained at $37 \pm 0.2^{\circ}C$ and agitated at a paddle speed of 100 rpm.

Coated pellets containing 250 mg PPA·HCl were introduced into the dissolution medium, and 4-mL samples were withdrawn by an autosampler (Vankel VK 8000; Cary, NC, USA) at 0.5-, 1-, 2-, 4-, 6-, 8-hr time points. Sample concentrations were determined by UV spectroscopy (DU-65; Beckman instruments, Fullerton, CA, USA) at a wavelength of 255 nm. Dissolution tests were performed in triplicate.

RESULTS AND DISCUSSION

Film clarity is one criterion used to determine the miscibility of polymer blends. Films made from two mutually miscible or compatible polymers are optically clear, whereas those prepared from incompatible polymers are usually translucent or opaque. Eudragit NE 30 D/L 30 D-55 blends with different ratios (1:1, 2:1, 3:1, 4:1, and 5:1) were selected for the miscibility study. Films formed by combining Eudragit NE 30 D and Eudragit L 30 D-55 in ratios greater than 4:1 were clearer and more transparent than the films prepared using ratios less than 4:1.

Another accepted criterion of polymer miscibility is the detection of a single glass transition whose temperature is intermediate between those corresponding to the two polymer components. The T_g is the temperature at which a polymer changes during the heat cycle from a brittle substance (glass) to a rubbery mass. The presence of a single peak demonstrates that the polymers are miscible, and the blend is molecularly homogeneous within the limits of

Table 1. Glass transition temperatures (T_g's) of films formed from different ratios of Eudragit NE 30 D and Eudragit L 30 D-55 ($n = 3$).

Ratio (NE 30 D:L 30 D-55)	T_g (°C) (Observed)		T_g (°C) (Calculated)
NE 30 D	-0.34 ± 0.92		
L 30 D-55	115.70 ± 0.87		
1:1	-7.81 ± 1.07	92.74 ± 1.65	
2:1	-2.45 ± 0.31	79.00 ± 2.80	
3:1	-1.44 ± 0.91	69.436 ± 2.19	
4:1	25.72 ± 1.18		22.73
5:1	18.69 ± 0.68		18.88

detection of the technique used to measure the T_g. In general, if two polymers are miscible, then only one T_g is observed. The presence of two thermal transitions in the thermogram indicates that the polymers are not completely miscible or are immiscible. The T_gs of films containing different ratios of Eudragit NE 30 D and Eudragit L 30 D-55 are listed in Table 1. The T_g of Eudragit NE 30 D is approximately 0°C, and the T_g for Eudragit L 30 D-55 was shown to be 115°C. At ratios of Eudragit NE 30 D:Eudragit L 30 D-55, less than 4:1 (i.e., greater than 20% Eudragit L 30 D-55), two T_gs appeared in thermograms, indicating that the two polymers were not completely miscible at those ratios. However, only one T_g was seen when the film contained less than 20% of Eudragit L 30 D-55. The T_g of the film increased with an increasing level of Eudragit L 30 D-55, which was caused by a restriction in the mobility of the Eudragit NE 30 D polymer chains caused by the anionic polymer.

The T_gs of polymer blends were calculated using the following equation:[17–19]

$$T_g = (T_{g_1} * W_1) + (T_{g_2} * W_2) \quad (1)$$

where T_g is the glass transition temperature of the polymer combination, T_{g_1} and T_{g_2} are the glass transition temperatures of respective pure components, and W_1 and W_2 are the weight fractions. According to Eq. (1), the T_g of the polymer blends with the ratios 4:1 and 5:1 were calculated to be 22.73°C and 18.88°C, respectively. These results are in good agreement with the experimentally determined values, as shown in Table 1. Because Eudragit NE 30 D was shown to be miscible with Eudragit L 30 D-55 when the ratio was greater than 4:1, the 5:1 ratio was selected for further study.

The photographs in Fig. 1 show the physical appearance of pellets coated with Eudragit NE 30 D alone (Fig. 1A) and Eudragit NE 30 D/L 30 D blends (Fig. 1B) after storage for 50 days at 25°C and 60°C. Pellets were shown to adhere when stored at 25°C [Fig. 1A(1)], and sticking was more pronounced at the elevated temperature [Fig. 1A(2)]. Sticking problems were also experienced during the coating process. When 10% Eudragit L 30 D-55 or Eudragit L 100 was added to Eudragit NE 30 D, agglomeration of the pellets was still observed during storage. However, the sticking problem was eliminated by increasing the concentration of Eudragit L 30 D-55 in the polymeric coating formulation to 16.7%. These pellets coated with the Eudragit 5:1 polymer blend showed no adhesive effect when stored at either 25°C for 50 days [Fig. 1B(1)] or 60°C for 10 days [Fig. 1B(2)]. In addition, no agglomeration was observed during the coating process. For pellets coated with Eudragit NE 30 D, the addition of 1% talc to the pellets was necessary before storage at 60°C to prevent sticking. Furthermore, pellets coated with the blend of Eudragit NE 30 D/L 30 D-55 required no addition of antiadherents after the film-coating process.

The influence of storage at 40°C on the release of PPA HCl from Eudragit NE 30 D-coated pellets is shown in Fig. 2. At 40°C, the release rate of PPA·HCl decreased continuously over a 2-month period. When the storage temperature was increased to 60°C, the coalescence of the colloidal polymeric particles was accelerated, and a significant decrease in the drug release rate was seen after storage of the coated pellets for 72 hr at 60°C (Fig. 3).

Latex particles do not undergo complete coalescence during film formation. Film coalescence of latex particles occurs in two phases. The first phase that occurs during coalescence involves the evaporation of water. The formation of a transparent and continuous film occurs concurrently with the evaporation of water. The water initially evaporates at a constant rate, virtually unaffected by the presence

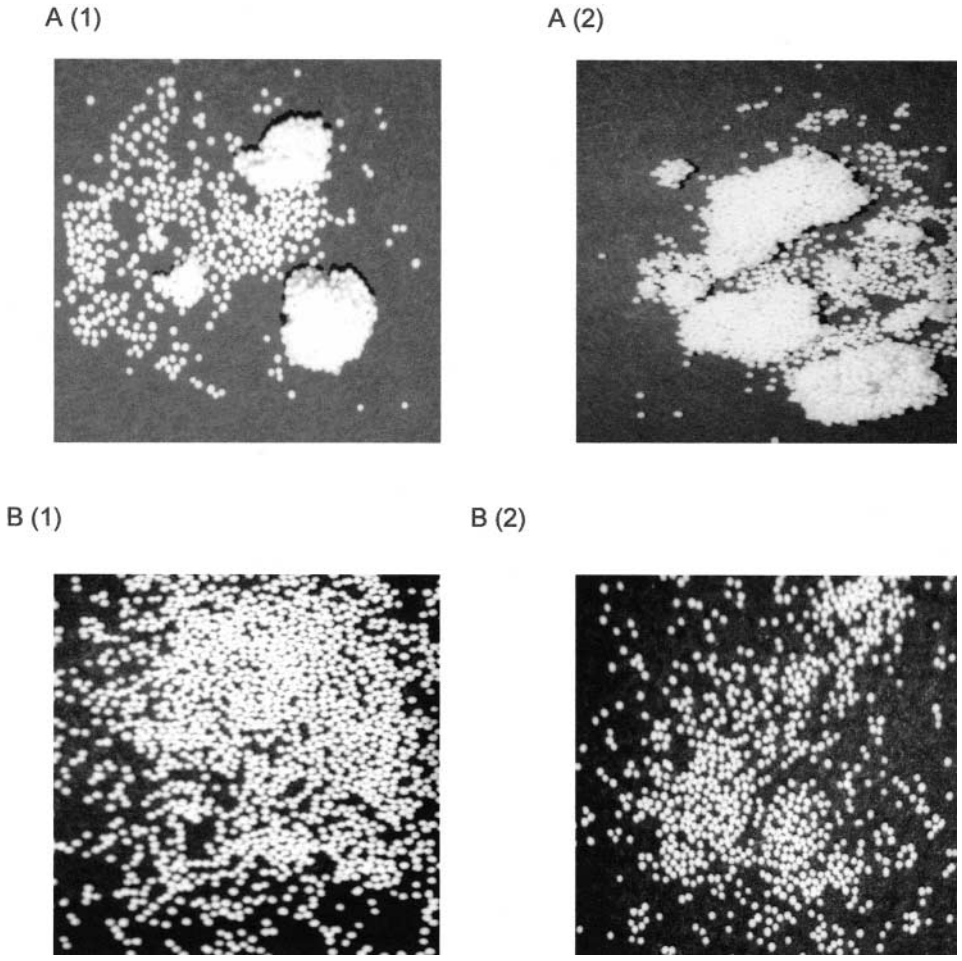

Figure 1. (A) Physical appearance of pellets coated with Eudragit NE 30 D after (4.7×): (1) 25°C for 50 days and (2) 2 hr at 60°C; (B) Appearance of the pellets coated with Eudragit NE 30 D and Eudragit L 30 D-55 (5:1) after storage (4.7×): (1) 25°C for 50 days and (2) 10 days at 60°C.

of particles, and then the rate of evaporation falls rapidly as the polymer particles come into irreversible contact. Evaporation occurs from a reduced air–water interfacial area during particle deformation and capillary channel closure.[20,21] The second phase of film coalescence involves the polymer molecules diffusing across the interparticle boundaries, which occurs during the aging of the film. The individual polymer particles then completely fuse into a homogeneous and continuous film.[22,23] In this final stage of film formation, there is a slow loss of residual water via diffusion through the polymer matrix to achieve an equilibrated state.

The degree of coalescence of the latex particles affects both the mechanical properties and the permeability of the film. This coalescence of the colloidal particles also results in a decrease in the free volume of the polymer during storage and physical aging. Because Eudragit NE 30 D is not soluble in the dissolution medium, the drug release rate is mainly controlled by diffusion. Diffusion is the mechanism of drug release both above and below the T_g, differing only in the frequency of motion of polymer segments and can be described by the "free volume theory," which states that molecules can only diffuse when the local free volume exceeds a critical value.[20,24] Therefore, permeability of the film decreased during storage, as a result of a decrease in the free volume from further coalescence.

The scanning electron micrographs of Eudragit NE 30 D-coated pellet surfaces showed that the film coating of uncured pellets was not uniform and complete. However, after storage at 40°C for 15 days, the film became smoother and more dense (Fig. 4),

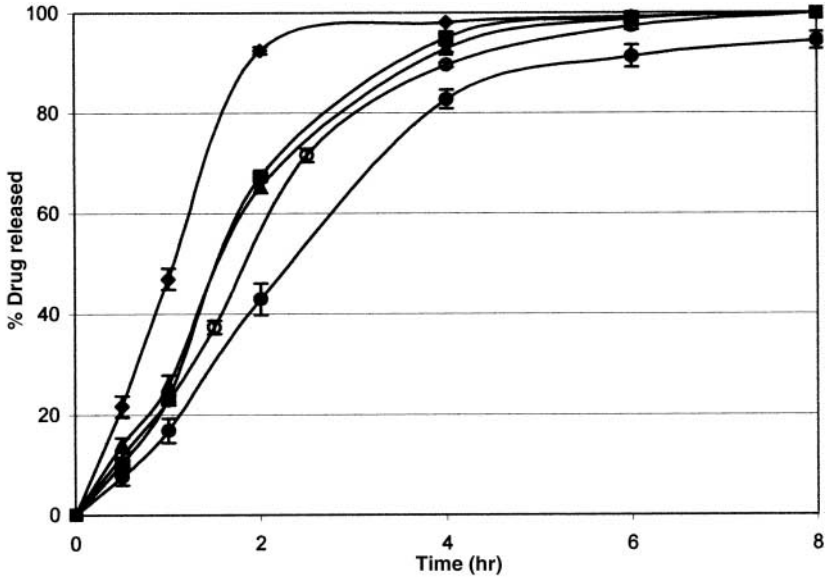

Figure 2. Influence of curing time on the release of PPA·HCl from pellets coated with Eudragit NE 30 D at 40°C (USP 24, apparatus 2, 500 mL of pH 1.2 HCl, 37°C, 100 rpm, $n = 3$). ◆, initial; ■, 3days; ▲,10 days; ○, 1 month; ●, 2 months.

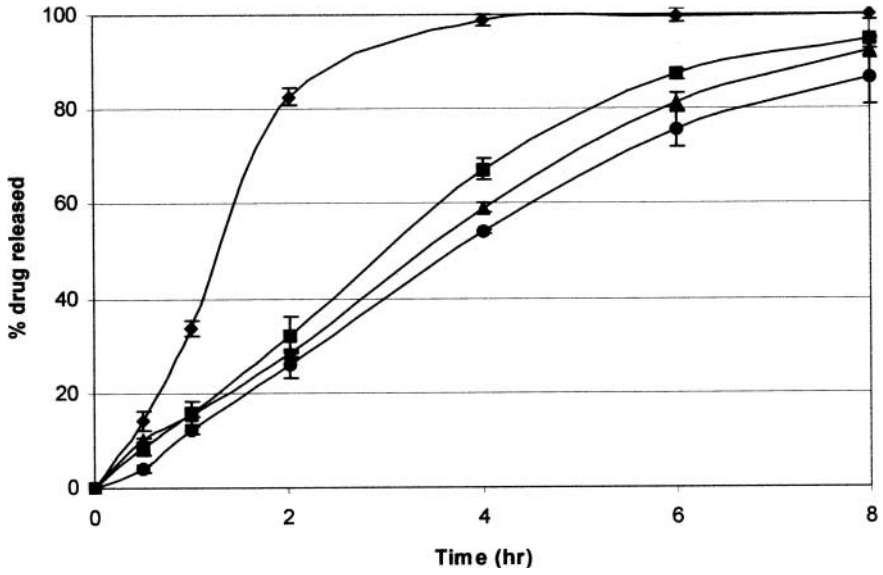

Figure 3. Influence of curing time on the release of PPA·HCl from pellets coated with Eudragit NE 30 D, stored at 60°C (USP 24, apparatus 2, 500 mL of pH 1.2 HCl, 37°C, 100 rpm, $n = 3$). ◆, initial; ■, 4 hr; ▲, 24 hr; ●, 72 hr.

which would explain the decrease in the drug release rate from the stored pellets.

Eudragit L 30 D-55 has a higher T_g (115°C) and forms tougher films than Eudragit NE 30 D. When Eudragit® L 30 D-55 was incorporated into the coating dispersion at a ratio of 5:1, the drug release profiles of the coated pellets were unchanged after 1 month of storage at 40°C (Fig. 5). When the curing temperature was increased, the drug release profile equilibrated after just 4 hr of curing at 60°C (Fig. 6). Thus, the time required to stabilize the drug release rate and equilibrate the drug release rate after storage at 60°C, was significantly decreased on the addition of Eudragit L 30 D-55 to the Eudragit

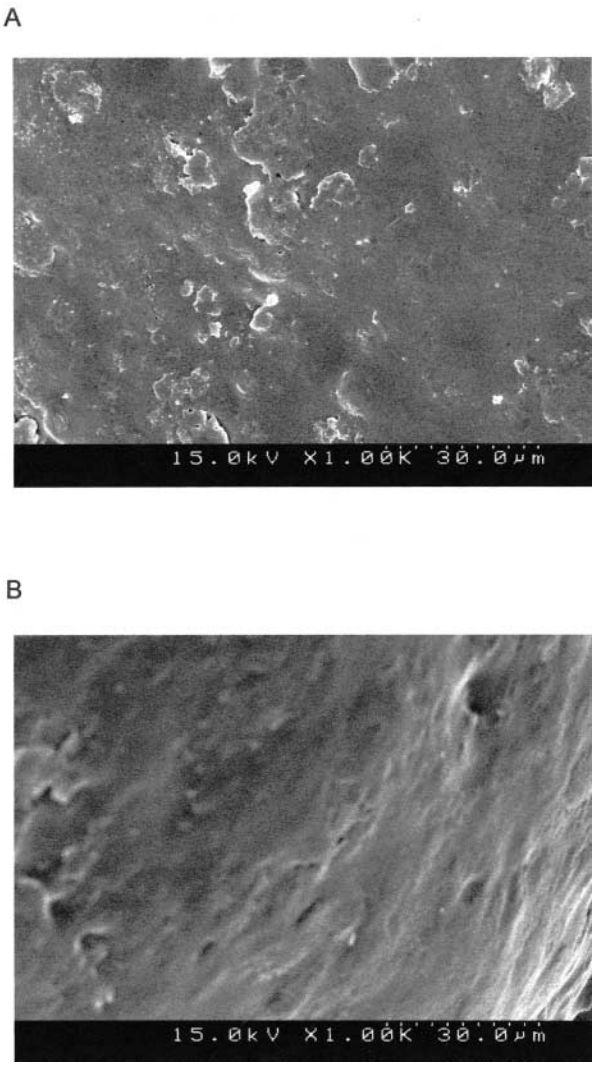

Figure 4. Surface morphology of pellets coated with Eudragit NE 30 D (1,000×). (A) Uncured; (B) 15 days at 40°C.

NE 30 D dispersion. No plasticizer was present in the acrylic blend.

The cumulative drug release percentage at 4 hr from PPA·HCl pellets coated with Eudragit NE 30 D alone and blended with Eudragit L 30 D-55 stored at 40°C is shown in Table 2. To study whether there is a significant difference between the cumulative drug release percentages when the product was stored for a specific storage time, Tukey's test ($\alpha = 0.05$) (comparing all pairs of cumulative drug release percentage means at each storage time) was conducted by using MINITAB software. The p values from Tukey's test are listed in Tables 3 and 4. The results indicated that, for the cumulative drug release percentage at 4 hr for pellets coated with Eudragit NE 30 D alone, all pairs of means (cumulative drug release percentage at 4 hr) at the different time points were significantly different (all p values < 0.05), indicating that the drug release rate changed continuously over the 2-month period. For the pellets coated with Eudragit NE 30 D blended with Eudragit L 30 D-55, the cumulative drug release percentages after 1 and 2 months were not significantly different ($p = 0.998$), indicating that the cumulative drug release percentage at 4 hr was stabilized after 1 month. The amount of drug released was found to decrease from approximately 98% to 82% after storage for 2 months for the Eudragit NE 30 D-coated pellets. However, the cumulative drug release percentage for pellets coated with Eudragit NE 30 D containing Eudragit L 30 D-55 decreased only slightly to approximately 98% and 94% after storage for 1 and 2 months, respectively. The presence of Eudragit L 30 D-55 in the film coating not only decreased the time required to obtain a stable drug release profile, but also the presence of the acrylic polymer stabilized the drug release rate, with a minimal decline after 2 months of storage.

The effect of Eudragit L 30 D-55 55 on the stabilization of drug release from the Eudragit NE 30 D- coated pellets is believed to be because of the high T_g of the enteric polymer. It is known that a strong driving force is necessary to overcome repulsive forces to deform particles and to cause the spheres to fuse.[22] Coalescence proceeds when the driving force is larger than the resistance of the latex particles to deform. Because Eudragit® L 30 D-55 has a significantly higher T_g, the structure of the polymer is more rigid than that of Eudragit NE 30 D. Therefore, the particles of Eudragit L 30 D-55 do not easily deform or fuse, serving as a framework structure to prevent further densification and coalescence of the Eudragit NE 30 D colloidal particles. Thus, the film permeability does not change dramatically during storage, and the drug release rate was not significantly influenced.

CONCLUSIONS

The drug release rate of PPA·HCl from pellets coated with Eudragit NE 30 D was found to decrease during storage, and was both a temperature- and a time-dependent process. Agglomeration of Eudragit NE 30 D-coated pellets was experienced in both the coating and curing processes, and sticking was more pronounced at elevated temperatures. When Eudragit NE 30 D was blended with Eudragit L 30 D-55,

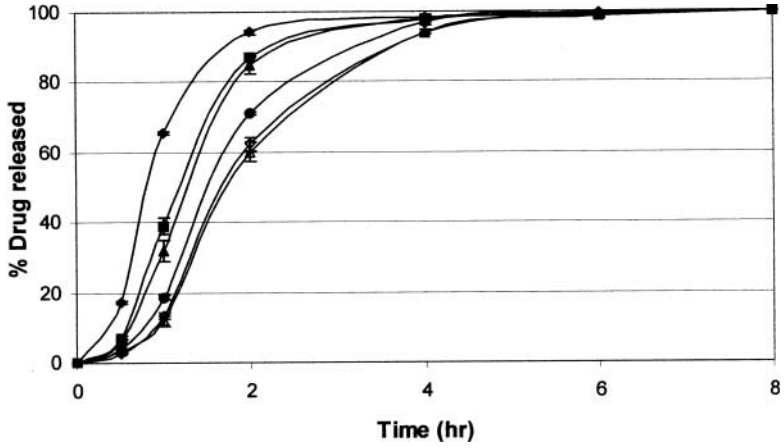

Figure 5. Influence of curing time on the release of PPA·HCl from pellets coated with Eudragit NE 30 D containing 16.7% Eudragit L 30 D-55, stored at 40°C (USP 24, apparatus 2, 500 mL of pH 1.2 HCl, 37°C, 100 rpm, $n = 3$). ◆, initial; ■, 24 hr; ▲, 48 hr; ●, 10 days; ◇, 1 month; △, 2 months.

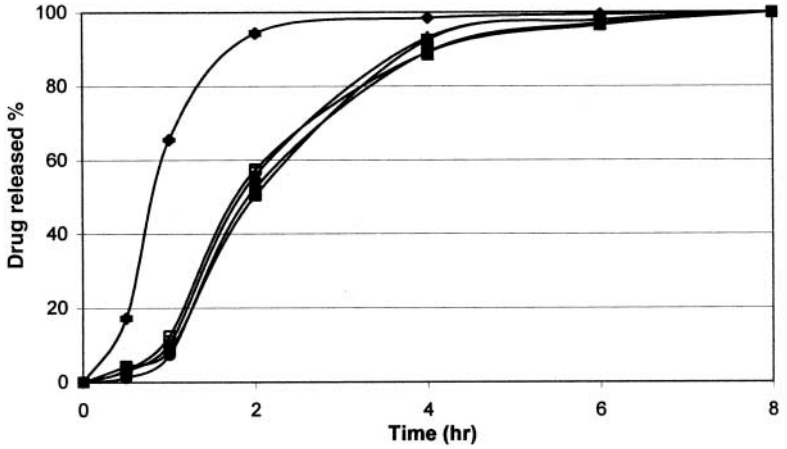

Figure 6. Influence of curing time on the release of PPA·HCl from pellets coated with Eudragit NE 30 D containing 16.7% Eudragit L 30 D-55, stored at 60°C (USP 24, apparatus 2, 500 mL of pH 1.2 HCl, 37°C, 100 rpm, $n = 3$). ◆, initial; ■, 4 hr; ▲, 10 hr; ●, 24 hr; □, 5 days.

Table 2. Influence of Eudragit L 30 D-55 on the 4-hr cumulative drug release percentage from Eudragit NE 30 D-coated pellets cured at 40°C (USP 24, apparatus 2, 500 mL of pH 1.2 HCl, 37°C, 100 rpm, $n = 3$).

Curing time	Pellets coated with Eudragit NE 30 D	Pellets coated with Eudragit NE 30 D containing 16.7% Eudragit L 30 D-55
Initial	98.11 ± 0.13	98.44 ± 0.14
10 days	92.84 ± 0.64	96.95 ± 0.61
1 month	89.05 ± 0.43	94.14 ± 0.53
2 months	82.76 ± 1.85	94.10 ± 0.76

Table 3. *p* values from Tukey's Test for pellets coated with Eudragit NE 30 D alone ($\alpha = 0.05$).

	Initial	10 Days	1 Month
Initial			
10 days	0.0009		
1 month	0.0000	0.0095	
2 months	0.0000	0.0000	0.0002

Table 4. *p* values from Tukey's Test for pellets coated with Eudragit NE 30 D blended with Eudragit L 30 D-55 ($\alpha = 0.05$).

	Initial	10 Days	1 Month
Initial			
10 days	0.0464		
1 month	0.0001	0.0013	
2 months	0.0001	0.0012	0.9998

the tackiness of the coating was reduced. No sticking of the pellets coated with Eudragit NE 30 D/Eudragit L 30 D-55 blend (5:1) was observed during the coating process or when stored at elevated temperatures. The decrease of the drug release rate from Eudragit NE 30 D-coated pellets during storage was reduced when Eudragit L 30 D was added to the coatings. The rate of drug release from the PPA·HCl pellets coated with Eudragit NE 30 D-55 and Eudragit L 30 D-55 (5:1) stabilized after 4 hr of storage at 60°C. The aqueous dispersions of Eudragit NE 30 D and Eudragit L 30 D-55 were shown to be completely miscible when the ratio of Eudragit NE 30 D and Eudragit L 30 D-55 exceeded 4:1.

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