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Novel use of Eudragit® NE 30D/Eudragit® L 30D-55 blends as functional coating materials in time-delayed drug release applications

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Abstract

The objectives of this study were to evaluate the mechanical and thermal properties of films prepared from Eudragit® NE 30D/Eudragit® L 30D-55 blends and to examine the dissolution behavior of beads coated with the polymer blends up to 120% weight gain. Eudragit® NE 30D and L 30D-55 dispersions were blended at 50:50, 67:33, 75:25, and 80:20 ratios. Cast films were evaluated by texture analysis and differential scanning calorimetry. Increasing Eudragit® NE 30D concentration increased miscibility, softness, and decreased stiffness of the films. At 80:20 ratio, the polymer blend was completely miscible whereby Eudragit® L 30D-55 was molecularly distributed in the mixture. This was confirmed by SEM analysis. The surface morphology of films and beads was evaluated before and after dissolution by scanning electron microscopy. SEM analysis demonstrated that the size of the pores formed after the dissolution of Eudragit® L 30D-55 at pH 6.8 was dependent on the miscibility of the Eudragit® blend. The implications of this effect were apparent in dissolution studies. For the 75:25 and 80:20 blends, a linear increase in lag time up to 7 h was observed with an increase in coat weight gain from 15 to 120%. At 60% weight gain, the 80:20 blend delayed drug release by approximately 7 h whereas the less miscible 75:25 blend delayed drug release by only 3.5 h. A lag time could therefore be controlled by manipulating both the theoretical weight gain of the beads and the concentration of Eudragit® NE 30D in the blend.

Keywords: Eudragit; Coating; Time-delayed release; Verapamil HCl; Dissolution; Beads

1. Introduction

Many physiological and biochemical processes such as body temperature, blood pressure, and potassium excretion depend on circadian rhythm, which is the activity cycle lasting 24 h (Waterhouse et al., 2003). These processes show daily rhythms that are in synchrony with the night–day cycle. Blood pressure and heart rate in normotensive and hypertensive patients, for example, have been shown to decrease at night and increase in the early morning hours (Lemmer, 1996; Carter, 1998). Consequently, the incidence of sudden cardiac death, stroke, ventricular arrhythmias, arterial embolism, and cardiovascular events like nonfatal and fatal myocardial infarction predominate in the early morning hours around 6.00 a.m. to 12.00 noon (Carter, 1998; Waterhouse et al., 2003). Therefore, early morning hours are considered as the hours of highest cardiovascular risk. These findings suggest that in order to improve compliance a dosage form should be administered at bedtime and release the drug at the early morning hours.

A delay in drug release can be achieved by a time programmed therapeutic scheme, which can deliver the drug of interest to a particular site of action at the right time and in the required amount. Several attempts have been made to develop time-delayed release dosage forms that release their payload after a predetermined time interval. The most common approach is to use a hydrophilic barrier that must be hydrated or eroded first before allowing water to reach to and release the drug from the core (Ayer et al., 1989; Gazzaniga and Giordano, 1993; Gazzaniga et al., 1993, 1994, 1995, 1997; Sangalli et al., 1998, 1999; Pozzi et al., 1994; Vandelli et al., 1996; Ross et al., 2000). Alternatively, a hydrophilic polymer can be incorporated inside a dosage form coated with a semi permeable membrane, which would swell with time and exert an internal pressure leading to the release of the drug after the rupture of the membrane (Ueda et al., 1989, 1994; Held et al., 1990; McNeill et al., 1993; Niwa et al., 1995). Using a different approach, time-delayed release

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beads containing diltiazem HCl were prepared by coating the beads with a thin film of ethylcellulose and Eudragit® RS 30D blend, which were capable of releasing the drug in what is called sigmoidal (S-shaped) profile (Stevens et al., 1992). Although this technique was specific for diltiazem HCl, it highlighted the potential of using polymer blends as coating materials to modulate the release profile of drugs. Similarly, Percel et al. (2003) prepared time-delayed release beads of H_2 histamine antagonist by using ethylcellulose and Eudragit® L 30D-55 polymer blend as a coating material to modulate drug release. While simple to fabricate, this technique had two drawbacks; first, it required a multi-step manufacturing process, and second, ethylcellulose blends had the capacity to delay drug release for a maximum of 2–4 h, which may not be long enough to release the drugs according to the circadian rhythm of some diseases. Therefore, developing an economic process with fewer steps to manufacture beads with considerably longer lag times remains a challenge.

The objective of the present study was to evaluate the suitability of Eudragit® NE 30D and Eudragit® L 30D-55 polymer blend as a coating material for use in delayed release applications. More specifically, the objectives were to (1) evaluate the thermal and mechanical properties of free films prepared from polymer blends consisting of Eudragit® NE 30D and Eudragit® L 30D-55 at different ratios, (2) investigate the dissolution behavior of verapamil HCl loaded beads and coated with the polymer blend in dissolution media of different pH, and (3) establish a relationship between the coat weight gain and the observed delay in drug release.

2. Materials and methods

2.1. Materials

The aqueous dispersions of Eudragit® RS 30D [poly(ethyl acrylate, methyl methacrylate) trimethylammonioethyl methacrylate chloride], Eudragit® NE 30D [poly(ethyl acrylate, methyl methacrylate), and Eudragit® L 30D-55 [poly(methacrylic acid, ethyl acrylate) were obtained from Evonic Industries (Piscataway, NJ). Triethyl citrate (TEC) was obtained from Vertellus Performance Materials (Greensboro, NC). Talc was purchased from Spectrum Quality Products (Gardena, CA). Verapamil HCl was supplied by BASF (Mount Olive, NJ). Nu-pareil sugar spheres (K) mesh size 14/18 (1400–1000 μm in diameter) was provided by CHR Hansen (Mahwah, NJ). Sodium hydroxide and sodium tribasic phosphate were purchased from Sigma Chemical Co. (St. Louis, MO). Hydrochloric acid was purchased from EMD Chemicals Inc. (Gibbstown, NJ). All chemicals and raw materials were used as received without further processing. Water used in this study was purified by Nanopure® Water System (Barnstead/Thermolyne, Dubuque, IA).

2.2. Free film preparation

The aqueous dispersions of Eudragit® L 30D-55 plasticized with 10% TEC (based on dry polymer weight) and Eudragit® NE 30D were diluted with an equal volume of purified water. Eudragit® NE 30D: L 30D-55 dispersions were then blended at ratios 50:50, 67:33, 75:25, and 80:20 and adjusted to a final weight of 291 g containing 11% of total solid polymer content. The dispersions were stirred for 6 h and then cast on Teflon plates (casting area: 28 cm × 28 cm; casting weigh: 261 g; total solid content: 28.7 g) and dried at 40 °C in an oven (VWR, Model 1350 GM, Bristol, CT) for 48 h. After drying, cast films were peeled from the Teflon surface, cut into dumb bell-shaped samples using standard metal template (ASTM D-638-IV, Benz Co., Inc., RI), and stored in a desiccator until analysis. The mean thickness ($n = 6$) of each film was measured using a digital gauge (Cole-Parmer Instrument Co., Vernon Hills, IL).

2.3. Mechanical properties of free films

The mechanical properties of the dried films were evaluated using a TA.XT Plus texture analyzer (Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK). Film specimens were held in place with grips, and the test procedure was performed in accordance with ASTM D882-75d method. The initial length of the film sample was 40 mm and the crosshead was raised at a constant speed of 5 mm/min. The test was carried out under ambient condition at 23 ± 2% relative humidity. Film specimens were visually inspected and those with physical damage were discarded. The obtained stress–strain profiles were used to calculate tensile strength, young's modulus, percent elongation at break, and the work required to break a film.

2.4. Thermal analysis of free films

Thermal analysis of free films was performed on film specimens using a modulated differential scanning calorimeter (MDSC model 2920, TA Instrument Co., New Castle, DE). Film samples (8–10 mg) were accurately weighed into aluminum pans and then hermetically sealed. Initially the samples were cooled to −40 °C, then they were heated at a constant rate of 10 °C/min up to 100 °C, followed by cooling to −40 °C. Samples were reheated for a second cycle in a modulation mode a ramp of 3 °C/min from −40 to 100 °C. The modulation temperature was ±1 °C and the modulation cycle was set at 60 s. The results were plotted as total heat flow, reversible heat flow (heat capacity component for enthalpic relaxation), and nonreversible heat flow (kinetic component for relaxation endotherm). Thermodiagrams were analyzed using TA Universal Analysis 2000 software (TA Instrument Co., New Castle, DE). The glass transition temperature (T_g) was recorded as the midpoint of the transition that appeared in the reversible heat flow.

2.5. Dissolution study of free films

Films prepared from Eudragit® NE 30D and Eudragit® L 30D-55 at 75:25 and 80:20 ratios were subjected to a dissolution study in 400 mL of pH 6.8 phosphate buffer using a USP Type II apparatus (VK 7000, Varian Inc., Cary, NC). Dissolution medium was maintained at 37 °C and stirred at a rate of 75 rpm. Samples, 16 cm^2 in size, were held at the bottom of the vessel

Table 1
Coating process parameters

Nozzle diameter	0.029 mm
Wurster insert	Bottom spray
Atomization air pressure	25 psi
Preheating temperature	32 °C
Preheating time	5 min
Batch size	20 g
Spray rate	0.6 mL/min
Inlet temperature	38 °C
Bed temperature	29–30 °C
Inlet air	220 LPM

using coiled stainless steel sinkers. After 4 h of immersion, the samples were withdrawn and dried at 40 °C in an oven for 12 h. Samples from the dried film were coated with 3.7 nm gold film and analyzed by scanning electron microscopy (SEM, Model 4800-S, Hitachi Technologies America Inc., Pleasanton, CA).

2.6. Preparation of coated beads

2.6.1. Coating beads with drug-layered matrix

Talc powder (3.25 g) was first homogenized with a blend of water and triethyl citrate (1.5 g) for 10 min. The mixture was then added to a Eudragit® RS 30D aqueous dispersions (25 g) under agitation. Verapamil HCl (3 g) was dissolved in purified water and then added to the coating dispersion. Final solid content was adjusted to 13% by adding purified water. Masterflex® Digi-Static® pump (Cole-Parmer Instrument Co., Vernon Hills, IL) was used to feed the formulations to the fluidized-bed coater (MFL.01, Vector Corp., Marion, IA). To ensure that only dry air is flowing into the system, a Hankison air trap and several in-line filters were placed between the fluid-bed and the compressor. Loading charge of 20 g Nu-pareil® sugar spheres, of mesh size 14/18, was used in this study. Coating process parameters are listed in Table 1. The coating dispersion was agitated during the coating process to maintain homogeneity in the formulation. At the end of the coating process, part of the coated beads was cured in an oven (VWR, Model 1350 GM, Bristol, CT) at 40 °C for 24 h, while the rest of the beads were further coated with a Eudragit® NE 30D and Eudragit® L 30D-55 blend.

2.6.2. Preparation of time-delayed beads

Charging load (20 g) of beads previously coated with verapamil HCl layered matrix was further coated with a delayed release film. The dispersions used to deposit a release-retarding film consisted of Eudragit® NE 30D and Eudragit® L 30D-55 at two ratios, 75:25 and 80:20. Eudragit® L 30D-55 was previously plasticized with 10% triethyl citrate based on dry polymer weight. Talc, at 50% of total polymer weight, was homogenized with purified water for 10 min and then added to the polymer blend. The solids content of the coating dispersion was adjusted to 9% by diluting with purified water. Masterflex® Digi-Static® pump was used to feed the coating dispersion to the fluidized-bed coater. The same processing parameters (Table 1) were used as in the application of the drug-layered matrix to the beads. Coating process was performed to the desired theoretical weight gain of 15, 30, 60, 90, or 120%. Theoretical weight gain, based on dry polymer blend weight, was determined using the following equation:

$$\text{Weight of dry polymer blend (g)} = \text{weight of charging load (g)} \times \frac{\text{theoretical weight gain}}{100}$$

The amount of applied coating dispersion that was used in each study was based on the required weight of dry polymer blend as given in the equation above. At the end of the coating process, the beads were collected and cured at 40 °C for 24 h. No sticking was observed at the end of this period.

2.7. Content uniformity

To determine the content of verapamil HCl in the beads, an accurately weighed sample (2 g), from each run, was ground and transferred to a 500 mL volumetric flask containing purified water. The flask was sonicated for 30 min and then stored at ambient temperature. After 24 h of storage, the aqueous dispersion was filtered and analyzed spectrophotometrically at 275 nm (Cary 50 probe UV spectrophotometer, Varian Inc., Cary, NC). All assays were carried out in triplicates and the mean value was reported.

2.8. Dissolution study of the coated beads

Dissolution studies on a fixed weight of 2 g of the beads were performed in triplicates using a USP type II (paddle) dissolution apparatus (VK 7000, Varian Inc., Cary, NC). Dissolution studies were performed in 900 mL of different media including purified water, 0.1N HCl, pH 6.8 buffer, and a step function pH media. In a step function medium the beads were initially immersed in 750 mL of 0.1N HCl for 2 h and then the pH was adjusted to 6.8 by adding 250 mL of 0.2 M sodium tribasic phosphate solution. A 0.1N HCl was prepared by adding 8.3 mL of concentrated (36.5–38%) HCl to sufficient amount of purified water to make 1000 mL. During dissolution studies the medium was maintained at 37 °C and agitated at 75 rpm. Samples (5 mL) were withdrawn at predetermined time intervals, filtered and analyzed spectro-photometrically at 275 nm. From the result, the cumulative percent of drug released was determined and plotted as a function of time.

3. Results and discussion

3.1. Thermal properties of free films

Compatibility or miscibility of a polymer blend can be evaluated either visually by optical appearance or instrumentally by determining the glass transition temperature (T_g) of the films. Compatible polymer blends give clear films upon casting and drying (Zheng and McGinity, 2003). The modulated differential scanning calorimetry (MDSC) thermogram of a clear film, prepared from compatible or miscible polymer blends yields a single intermediate T_g. On the other hand, if miscibility is

Table 2
Glass transition temperatures of films formed from different concentrations of Eudragit® NE 30D in blends with Eudragit® L 30D-55

% NE 30D in the blend	Observed T_g		Calculated T_g
0% (100% L 30D-55)[a]	78.67		N/A
50%	10.22	74.5	N/A
67%	−4.21	19.6	N/A
75%	−2.87	9.81	N/A
80%	7.93		8.93
100% NE 30D	−8.51		N/A

[a] Plasticized with 10% TEC based on dry polymer weight.

absent the obtained film will be translucent or opaque and would reveal two or more T_g values on the MDSC thermogram, depending on the number of constituents in the blend. Films obtained from the 50:50, 67:33 and 75:25 blends of Eudragit® NE 30D and Eudragit® L 30D-55 were translucent, whereas the film obtained from the 80:20 blend was transparent. Thermograms obtained from MDSC showed two T_g values for films made with Eudragit® NE 30D at concentrations up to 75% which indicates that the blend at these ratios were completely immiscible (heterogeneous). Film containing 80% Eudragit® NE 30D showed only an intermediate T_g value indicating that the blend is completely miscible (homogeneous) at this ratio. Table 2 lists the T_g values for all film samples. The T_g value of the film prepared from a Eudragit® NE 30D/Eudragit® L 30D-55 blend at a ratio of 80:20 was also calculated using the following equation (Coucman, 1978; Couchman and Karasz, 1978):

$$T_g = (T_{g1} \times W_1) + (T_{g2} \times W_2)$$

where T_g is the glass transition temperature of the polymer blend, T_{g1} and T_{g2} are the glass transition temperatures of the respective constituents, and W_1 and W_2 are the weight fractions. Using the above equation, the calculated T_g for a film containing 80% NE 30D was found to be 8.93 °C, which was in good agreement with the experimentally determined value (7.93 °C, Table 2). The results in this study corroborate with those reported by Zheng and McGinity (2003).

Increasing the concentration of Eudragit® NE 30D from 50 to 80% shifted the glass transition temperature of both polymers towards an intermediate value of a completely miscible blend. This is due to the increase in the degree of miscibility of the polymer blends until a completely miscible blend is obtained with 80% Eudragit® NE 30D. Heterogeneous blends consist mainly of Eudragit® NE 30D as a continuous phase containing Eudragit® L 30D-55 as embedded un-coalesced particles (Zheng and McGinity, 2003; Amighi and Moës, 1995).

3.2. Effect of polymer blend on the mechanical properties of free films

The mechanical properties of the Eudragit films were determined from their stress–strain profiles. A representative stress–strain profile is illustrated in Fig. 1. Evaluation of the mechanical properties of a polymeric film is very important as it determines the suitability of a polymer to be used in the coating process. Mechanical properties include tensile strength, percent

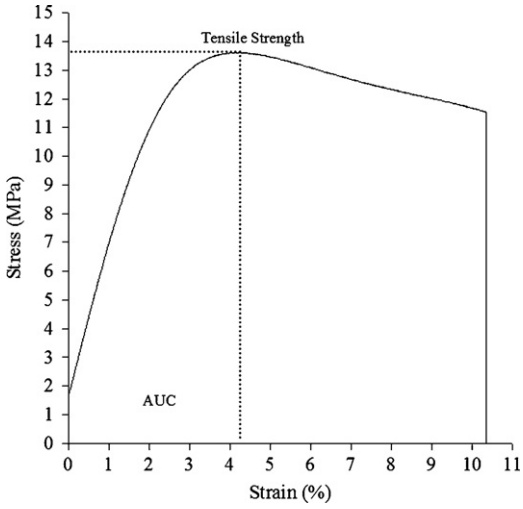

Fig. 1. A representative stress–strain profile of a free film obtained from texture analyzer.

elongation, elastic modulus, and work of failure. Tensile strength is the maximum stress (force/surface area) applied to a point at which the film specimen breaks. Percent elongation or strain is defined as the maximum elongation of the film specimen at tensile strength. Elastic modulus is an indication of the stiffness of the film and can be computed from the linear elastic deformation of the stress–strain profile. Work of failure is a function of work done in breaking the film specimen and is illustrative of the film toughness (O'Donnell and McGinity, 1997). Film coatings that exhibit high tensile strength and percent elongation are the most suitable for coating processes (Aulton, 2002).

The mechanical properties of films as a function of Eudragit® NE 30D concentrations in the blend are given in Fig. 2. Films prepared with 100% Eudragit® L 30D-55 were too brittle and therefore their mechanical properties were not measured. As seen in Fig. 2, increasing the ratio of Eudragit® NE 30D in the blend increased strain and decreased both stress and young's modulus. The change in the work of failure was erratic. Eudragit® NE 30D forms a soft, flexible film even at room temperature while Eudragit® L 30D-55 is a hard polymer and forms brittle films. Increasing the ratio of Eudragit® NE 30D in the polymer blend therefore increased softness, flexibility and decreased stiffness of the films. As illustrated in Fig. 2A and B, a blend of Eudragit® NE 30D and L 30D-55 at 80:20 ratio exhibited high percent elongation and a higher tensile strength than that of pure Eudragit® NE 30D. Therefore, an 80:20 blend of Eudragit® NE 30D and L 30D-55 is suitable for use in coating applications.

3.3. Dissolution study of free films

Due to its complete miscibility and suitable mechanical properties, the 80:20 blend of Eudragit® NE 30D and Eudragit® L 30D-55 was used in subsequent studies. The 75:25 blend, which is made of a partially miscible blend, was also used for comparison purposes. To demonstrate the difference between these blends, the dissolution behavior of the free films prepared

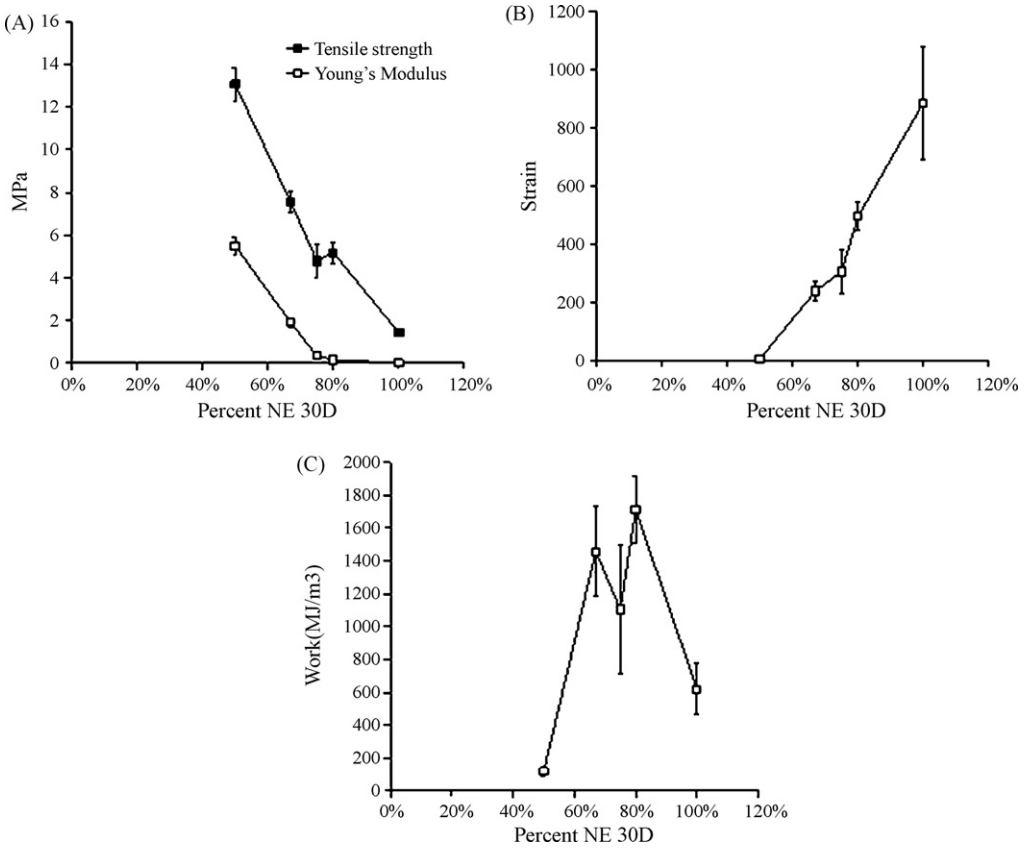

Fig. 2. (A) Stress and young's modulus, (B) strain, and (C) work of failure, of the Eudragit® NE 30D and Eudragit® L 30D-55 free films as a function of the Eudragit® NE 30D concentration in the blends.

from the 75:25 and 80:20 blends of Eudragit® NE 30D and Eudragit® L 30D-55 was performed in pH 6.8 phosphate buffer. After immersing the films in the buffer for 4 h, both films were placed in an oven at 40 °C and dried for 12 h. After drying film samples were analyzed by SEM.

SEM images of the film specimens are shown in Fig. 3. The miscibility of the Eudragit® NE 30D and Eudragit® L 30D-55 blend at 75:25 ratio is incomplete. At this ratio, Eudragit® L 30D-55 forms aggregated particles embedded in the continuous phase formed by Eudragit® NE 30D. Therefore, when a film at this ratio was immersed in the phosphate buffer, Eudragit® L 30D-55 dissolved in the medium creating large voids in the film. These pores were seen at low SEM magnification power (Fig. 3A). In the case of the completely miscible blend at 80:20 ratio, Eudragit® L 30D-55 is molecularly distributed in the blend and does not form aggregates. Therefore, after immersion and drying, the film of this miscible blend formed microscopic pores, which could only be seen at high SEM magnification (Fig. 3B).

3.4. Effect of the dissolution medium on drug release

To investigate the mechanism of drug release from beads coated with a blend of Eudragit® NE 30D and Eudragit® L 30D-55, the dissolution behavior of beads loaded with verapamil HCl and coated with the Eudragit blend to a theoretical weight gain of 30% at a 75:25 ratio was evaluated in dissolution media with different pH values. The dissolution profiles of the beads in water, 0.1N HCl, and pH 6.8 buffer, and in a step function pH medium are given in Fig. 4. Highest percent of drug release was obtained in phosphate buffer and a step function pH medium. In both media, >90% of the drug was released in 12 h. In contrast, less than 10% of verapamil HCl was released within 12 h when the dissolution study was performed in water and 0.1N HCl. These data indicate that the release of verapamil HCl from the beads is pH dependent. This could be explained by observing the chemical nature of the Eudragit® L 30D-55 polymer. Eudragit® NE [poly(ethyl acrylate methyl methacrylate] polymer is water insoluble and forms an insoluble film of medium permeability. At a 75:25 ratio, it also constitutes the bulk of the coating material. On the other hand, the solubility of Eudragit® L [poly(methacrylic acid ethyl acrylate] polymer, which forms 25% of the blend, is pH dependent. At pH $\geq$ 5.5, the carboxylic acid group of the methacrylic acid is transformed to carboxylate group by salt formation (Lehmann, 1997), which results in the dissolution of the polymer. This creates pores in the coat through which the drug diffuses into the dissolution medium. Therefore, the percent of the drug released within 12 h was high in both pH 6.8 phosphate buffer and step function pH dissolution medium. On the other hand, low percent of drug release was observed in both purified water and 0.1N HCl due to the insolubility of the Eudragit® L 30D-55 in these media. The release of verapamil

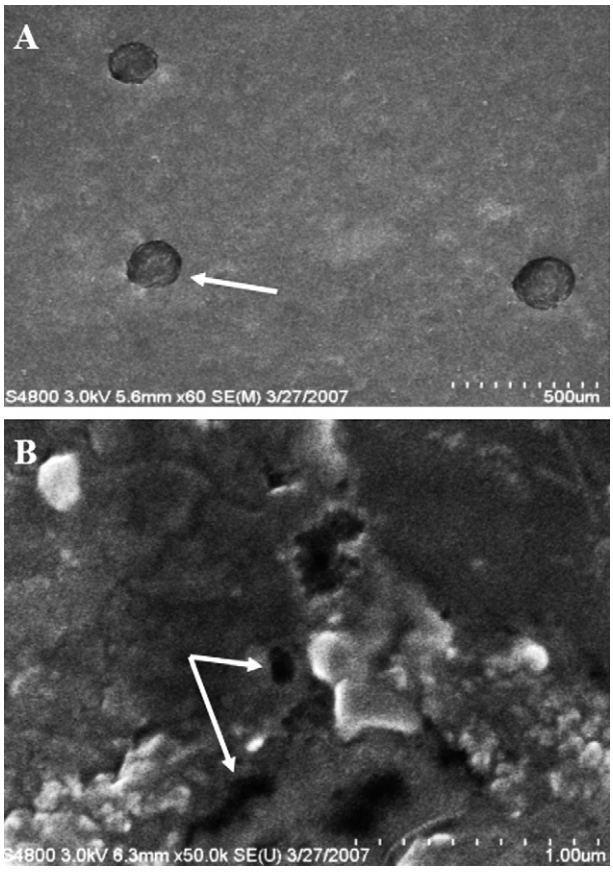

Fig. 3. SEM images of free films of Eudragit® NE 30D and Eudragit® L 30D-55 blends at (A) 75:25 ratio and (B) 80:20 ratio, after immersion in pH 6.8 buffer for 4 h (the arrows point to the pores formed from the dissolution of Eudragit® L 30D-55).

HCl from the beads could therefore be considered as a diffusion process through the polymeric film, which is further aided by Eudragit® L 30D-55 which acts as a pore former at high pH media. The impact of polymer weigh gain on drug release is further illustrated in subsequent sections.

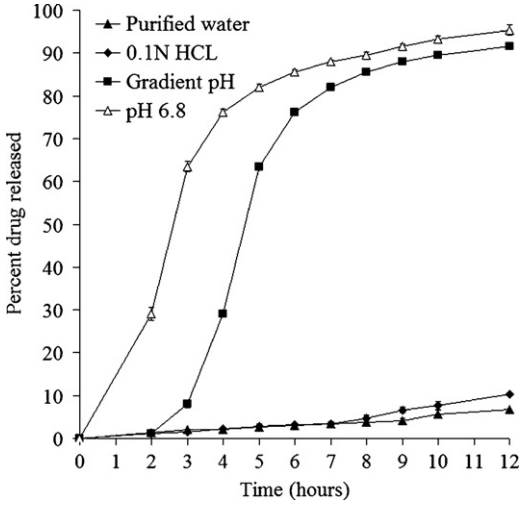

Fig. 4. Dissolution profiles of beads coated with a 75:25 Eudragit® NE 30D and Eudragit® L 30D-55 polymer blend in different dissolution media ($n = 3$).

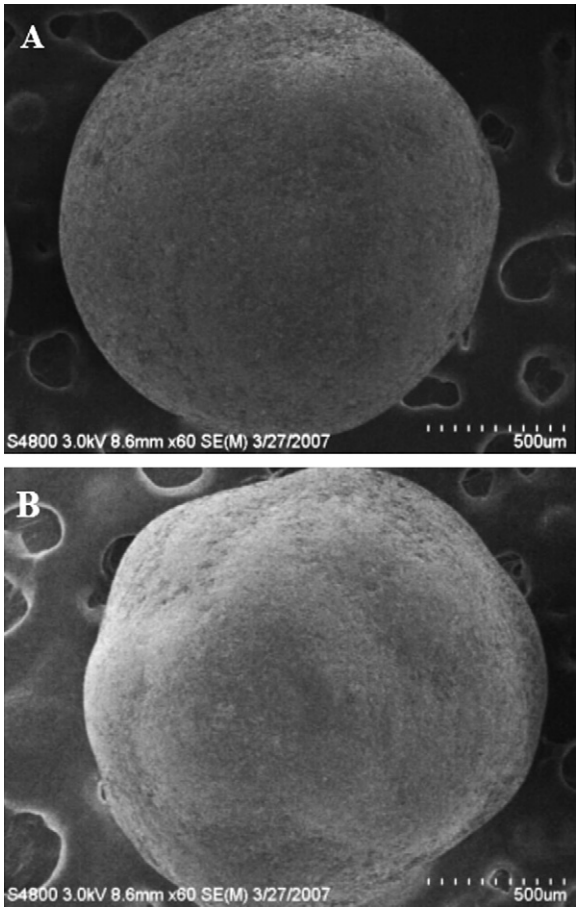

Fig. 5. SEM images of beads coated with Eudragit® NE 30D and Eudragit® L 30D-55 polymer blends at (A) 75:25 ratio and (B) 80:20 ratio.

3.5. Effect of polymer blend ratio on drug release

The ability of Eudragit® NE 30D and Eudragit® L 30D-55 blend at the two ratios, 75:25 and 80:20, to delay verapamil HCl release was investigated by testing the dissolution behavior of drug loaded beads with and without coating in a step function pH medium. No morphological differences were observed between the beads coated with either blends prior to the dissolution experiment as shown in the SEM images given in Fig. 5. Dissolution profiles of the verapamil HCl loaded beads without the Eudragit blend coat and those coated with either 100% Eudragit® NE 30D or Eudragit® L 30D-55 are given in Fig. 6. Also shown in the figure are the dissolution profiles of the beads coated with a blend of Eudragit® NE 30D and Eudragit® L 30D-55 at 75:25 and 80:20 ratios. All beads were coated to the same theoretical polymer weight gain of 60%.

Uncoated beads released 100% of verapamil HCl within 1 h whereas immediate release from beads coated with Eudragit® L 30D-55 was observed after 2 h, which is the time during which the pH of the medium was adjusted to 6.8. As discussed earlier, the solubility of the Eudragit® L 30D-55 polymer is pH dependent and is highest at pH $\geq$ 5.5. No release was observed within 12 h from beads coated with the insoluble Eudragit® NE 30D polymer. Beads coated with the polymer blend, however,

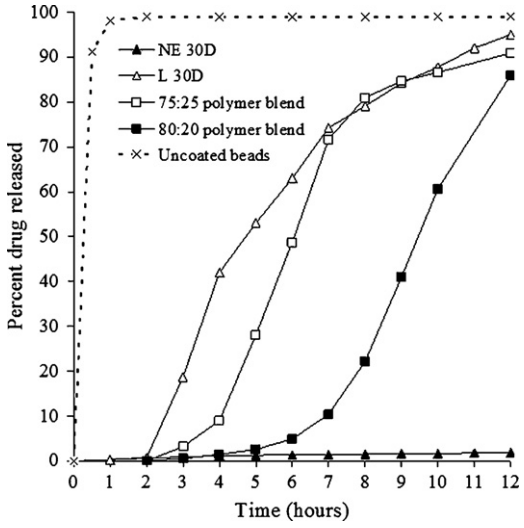

Fig. 6. Dissolution profiles of uncoated beads and beads coated with NE 30D, L 30D and blends thereof at ratios of 75:25 and 80:20 at 60% weight gain. Dissolution studies were performed in step function dissolution medium ($n = 3$).

revealed a true delay in drug release, as observed by the time required to release 10% of the drug. This finding indicates that the polymer blend is suitable as a functional film coating material for use in delayed drug release applications.

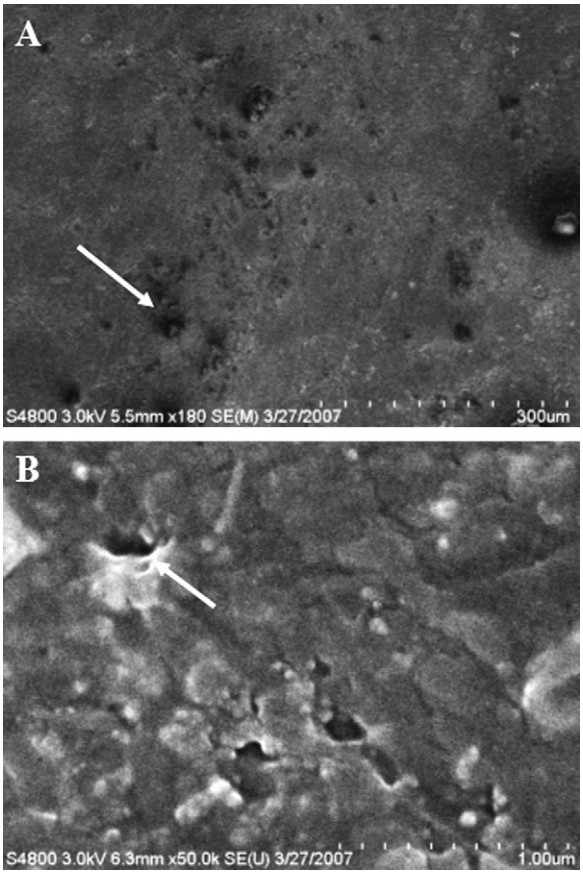

Fig. 7. SEM images of the surface of beads showing the pores formed after the dissolution of the beads coated with the (A) 75:25 and (B) 80:20, Eudragit® NE 30D and Eudragit® L 30D-55 polymer blends (the arrows point to the pores formed from the dissolution of Eudragit® L 30D-55).

The Eudragit® blend at 80:20 ratio delayed drug release by approximately 7 h whereas the 75:25 polymer blend delayed drug release by only 3.5 h. This could be explained by the fact that the 80:20 blend is a homogeneous mixture of the two polymers. This has implication on the molecular structure of the film and its ability to retard drug release. At this ratio and during the coating and curing processes, water evaporation generates surface tension effects and capillary forces between the polymer particles (Maejima and McGinity, 2001). This results in the coalescence of individual colloidal particles and the interdiffusion of polymeric particles to form a continuous film (Fukumori, 1994). Therefore, beads were cured at 40 °C for 24 h to produce a densely packed homogeneous film in which Eudragit® L 30D-55 was molecularly distributed. Curing leads to a complete fusion of polymer particles to form a continuous film, which is facilitated by the evaporation of the residual water. During the dissolution process in media with pH ≥ 5.5, Eudragit® L 30D-55

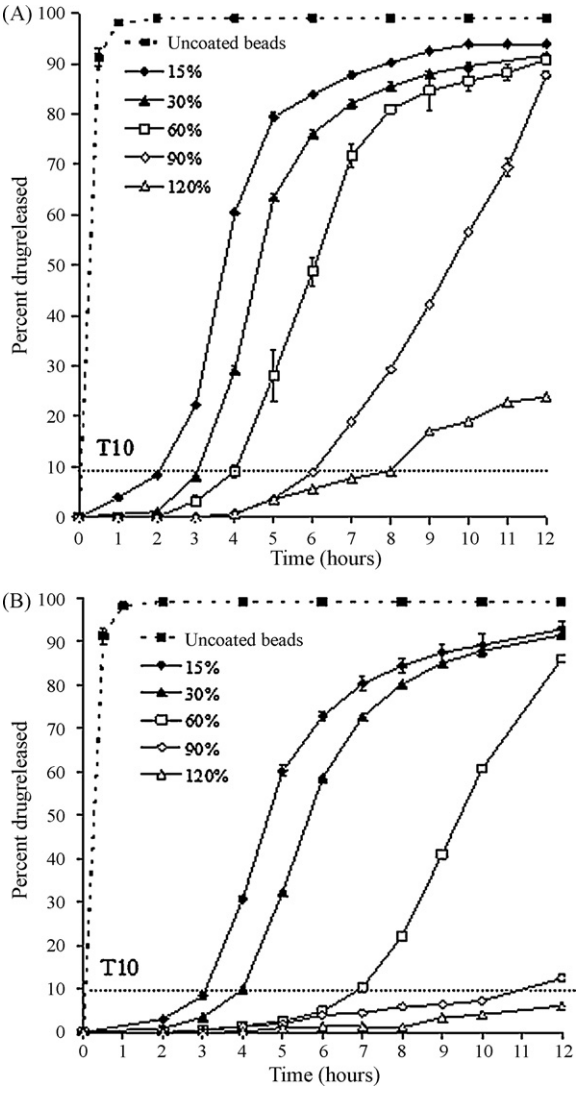

Fig. 8. Dissolution profiles of uncoated beads and beads coated to different theoretical weigh gain ranging from 15 to 120% with blends of Eudragit® NE 30D and Eudragit® L 30D-55 at (A) 75:25 ratio and (B) 80:20 ratio. Dissolution studies were performed in step function dissolution medium ($n = 3$).

dissolved slowly creating microscopic pores through which drug diffused into the dissolution medium. On the other hand, a blend of Eudragit® NE 30D and Eudragit® L 30D-55 at 75:25 ratio was less efficient in delaying drug release. This is because the blend was incompletely miscible. After coating and curing, the film consisted of Eudragit® NE 30D as a continuous phase containing Eudragit® L 30D-55 as embedded aggregated particles (Zheng and McGinity, 2003; Amighi and Moës, 1995). Therefore, during the dissolution process in media with pH ≥ 5.5, Eudragit® L 30D-55 rapidly dissolved creating large voids through which the drug diffused quickly into the dissolution medium. Differences in pore size between the two blends after dissolution are illustrated in the SEM images given in Fig. 7.

3.6. Effect of coating weight gain

Verapamil HCl loaded beads were coated with a 75:25 and 80:20 Eudragit blend to a theoretical weight gain ranging from 15 to 120%, based on dry polymer weight. The dissolution profiles of these beads are given in Fig. 8. A linear correlation was observed between lag time or T_{10}, which is the time required for 10% drug release, and theoretical polymer weight gain. Lag time increased with an increase in the theoretical weight gain of both polymer blends (Fig. 9). This is due to the time required for the drug to diffuse through the coating membrane. As shown in Fig. 9, the slope of the correlation between lag time and percent weight gain for the 80:20 blend was higher than that observed with the 75:25 blend. This indicates that the 80:20 blend is more efficient in delaying drug release. This could be attributed to the miscibility and impermeability of the 80:20 blend. Therefore, diffusion of the drug through this polymeric coat was the rate-controlling step, as opposed to the 75:25 blend, in which dissolution of the Eudragit® L 30D-55 aggregates enhance the release process.

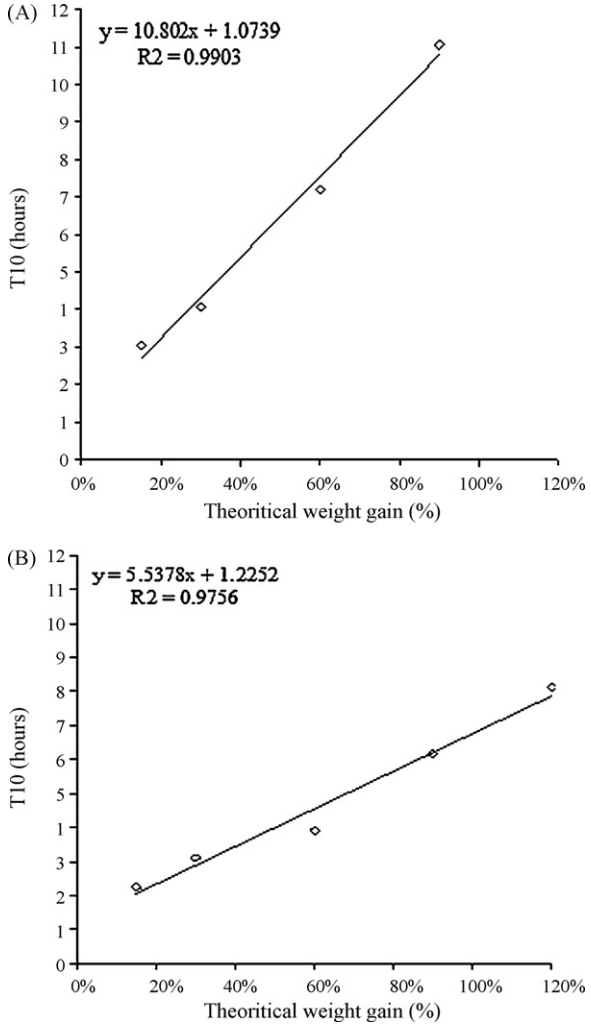

Fig. 9. Relationship between the theoretical weigh gain and T_{10} of beads coated with Eudragit® NE 30D and Eudragit® L 30D-55 polymer blends at (A) 75:25 ratio and (B) 80:20 ratio.

4. Conclusion

Blends of Eudragit® NE 30D and Eudragit® L 30D-55 polymers were successfully used as functional coating materials in delayed drug release applications. Free films prepared from these polymer blends exhibited mechanical properties that are suitable for coating. In order to obtain a miscible and homogenous blend, the concentration of Eudragit® NE 30D in the blend should be at least 80%. Miscibility of the polymer blends was shown to impact drug release. Faster release rates were observed with a heterogeneous blend. As shown by SEM images, the aggregation of Eudragit® L 30D-55 in an immiscible blend resulted in macroscopic voids that hastened drug release as opposed to microscopic pores formed during dissolution of a homogenous blend. In either case, upon contact with a dissolution medium of pH ≥ 5.5, the release rate of the drug from the beads was controlled by the size of the pores created by the dissolution of Eudragit® L 30D-55 and the theoretical weight gain, which impacted pore-length and the tortuosity of the diffusional path-length. The lag time (T_{10}) and drug release rate could therefore be controlled by manipulating both the theoretical weight gain of the beads and the concentration of Eudragit® NE 30D in the blend. These data suggest that Eudragit blends of NE 30D and L 30D-55 at 80% or greater NE 30D content could be used in chronotherapy, offering improvement to the previously reported polymer blends by extending drug release lag time to meet potential patient needs.

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