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Research Article

Influence of an Acrylic Polymer Blend on the Physical Stability of Film-Coated Theophylline Pellets

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Abstract. The purpose of this study was to investigate the physical stability of a coating system consisting of a blend of two sustained release acrylic polymers and its influence on the drug release rate of theophylline from coated pellets. The properties of both free films and theophylline pellets coated with the polymer blend were investigated, and the miscibility was determined *via* differential scanning calorimetry. Eudragit® RS 30 D was plasticized by the addition of Eudragit® NE 30 D, and the predicted glass transition temperature (T_g) of the blend was similar to the experimental values. Sprayed films composed of a blend of Eudragit® NE 30 D/Eudragit® RS 30 D (1:1) showed a water vapor permeability six times greater than films containing only Eudragit® NE 30 D. The presence of quaternary ammonium functional groups from the RS 30 D polymer increased the swellability of the films. The films prepared from the blend exhibited stable permeability values when stored for 1 month at both 25°C and 40°C, while the films which were composed of only Eudragit® NE 30 D showed a statistically significant decrease in this parameter when stored under the same conditions. Eudragit® NE 30 D/Eudragit® RS 30 D (1:1)-sprayed films decreased in elongation from 180% to 40% after storage at 40°C for 1 month, while those stored at 25°C showed no change in elongation. In coated pellets, the addition of Eudragit® RS 30 D to the Eudragit® NE 30 D increased the theophylline release rate, and the pellets were stable when stored at 25°C for a period of up to 3 months due to maintenance of the physico-mechanical properties of the film. Pellets stored at 40°C exhibited a decrease in drug release rate over time as a result of changes in film physico-mechanical properties which were attributed to further coalescence and densification of the polymer. When the storage temperature was above the T_g of the composite, instabilities in both drug release rate and physical properties were evident. Stabilization in drug release rate from coated pellets could be correlated with the physico-mechanical stability of the film formulation when stored at temperatures below the T_g of the polymer.

KEY WORDS: Eudragit® NE 30 D; Eudragit® RS 30 D; miscible polymers; physical stability; physico-mechanical properties; water vapor permeability.

INTRODUCTION

The coating of dosage forms with aqueous latex or pseudolatex dispersions is a common manufacturing process utilized in designing sustained release dosage forms. Both acrylic and cellulosic based polymer systems have been used as modified release coatings. While the use of these aqueous coating systems is advantageous in some respects, films formed by these polymers can undergo an aging process, resulting in physically unstable films as a function of time, temperature, and relative humidity (1–5).

The physical aging of polymeric films is a problem that both polymer scientists and chemical engineers have been aware of for many years. Struik (6) reported that the driving force for aging in amorphous polymers is the movement towards a thermodynamic equilibrium. As a result of being essentially "locked" in place at temperatures below the glass transition temperature (T_g) of the material, the polymer possesses an enthalpy and free volume that is much greater than at equilibrium. Since the molecular mobility of the polymer is not zero, the free volume of the material will continue to decrease slowly over time until equilibrium is reached. This densification of the polymer results in changes in the diffusivity of the membrane.

Drug release from pellets coated with insoluble polymers follows Fick's First Law of Diffusion, as seen in Eq. 1, where Q is the amount of drug that has diffused through the film as a function of time t, h is the thickness of the film, D is the diffusion coefficient of the API, S is the area available for diffusion, C_1 is the concentration of the drug in the dosage form, and C_2 is the concentration of the drug in the dissolution medium.

$$Q = \frac{DS(C_1 - C_2)t}{h} \quad (1)$$

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The changes in the film's porosity and tortuosity during aging have been related to D by Iyer and associates (7) through Eq. 2, where D_w is the diffusion coefficient of the drug in water and e and τ are the porosity and tortuosity of the film, respectively.

$$D = \frac{D_w(e)}{\tau} \quad (2)$$

Thus, during aging, the variation in diffusivity is a direct consequence of diminishing porosity and increasing tortuosity of the polymeric film coating.

Several strategies have been proposed to resolve the problem of physical aging in polymers employed for the coating of sustained release dosage forms. These include the addition of high levels of plasticizer (1) or talc (8), the inclusion of an immiscible, water-soluble non-ionic excipient (hydroxyethylcellulose) (5) or proteins (9), and the addition of silicon dioxide to the polymeric coating formulation (10). Another avenue of research that has been described in previous reports is the blending of high T_g polymers which are miscible with the functional coating. Wu and coworkers (11) found that a blend of Eudragit® RS 30 D and Eudragit® L 100-55 at a 3:1 ratio provided a stable release rate of theophylline from coated pellets when the dosage forms were stored at 40°C. The mechanism of stabilization was due to a decrease in the molecular mobility of polymer chains in the film. In a similar study (12), Zheng and coworkers investigated the influence of Eudragit® L 30 D-55 on the stability of Eudragit® NE 30 D films. They reported that films of a 5:1 blend of Eudragit® NE 30 D/L 30 D-55 equilibrated over a shorter period of time and that the release rate of phenylpropanolamine hydrochloride from pellets coated with the polymeric blend showed improved stability when compared to pellets coated with a formulation containing only Eudragit® NE 30 D.

The objective of the present study was to investigate the effect of blending Eudragit® NE 30 D with Eudragit® RS 30 D on the drug release rate and physical stability of coated theophylline pellets. The thermal properties of the components in the resulting mixture were examined, as were the physico-mechanical parameters (elongation) and water vapor permeability of sprayed films. It was hypothesized that the addition of Eudragit® RS 30 D would stabilize the drug release rate by raising the T_g of Eudragit® NE 30 D.

MATERIALS AND METHODS

Materials

Eudragit® NE 30 D and Eudragit® RS 30 D dispersions were donated by Evonik Degussa Corporation (Piscataway, NJ, USA). Anhydrous theophylline and lactose monohydrate were both purchased from Spectrum Chemical (Gardena, CA, USA). Polyvinylpyrrolidone (Kollidon® K-30) was donated by the BASF Corp. (Mount Olive, NJ, USA). FMC Corp. (Newark, DE, USA) provided the microcrystalline cellulose (Avicel® PH-101). Talc USP (Imperial 500) was donated by Luzenac America (Englewood, CO, USA).

Preparation of Core Pellets

Anhydrous theophylline (25%), lactose monohydrate (45%), and microcrystalline cellulose (25%) were passed through a 30-mesh sieve and then mixed 5 min. A 12.5% *w/v* aqueous solution of polyvinylpyrrolidone (equivalent to 5% in the final formulation) was used as a binder in the wet-massing process. The wet mass was extruded using an LCI Benchtop Granulator (Tokyo, Japan) at a rotation blade speed of 50 rpm. The extrudates were spheronized at 1,000 rpm for 2 min using a Caleva Model 120 Spheronizer (Dorset, UK). The pellets were sieved after drying for 24 h at 40°C, and the 16–20 mesh fraction was used for the coating trials.

Preparation of Coating Dispersions

An equal amount of Eudragit® NE 30 D and Eudragit® RS 30 D dispersions (45.83 g of each) was added to a beaker, placed on a magnetic stir plate, and mixed with slow agitation for a period of 1 h. A 13.75-g Imperial® 500 talc (equal to 50% of the total dry polymer weight) was added in a separate volume of water (170.0 g) and dispersed *via* high shear mixing with a Polytron®. The talc dispersion was then added to the acrylic blend. The resulting dispersion had a total solids content of 15% and was allowed to mix for a further 10 min prior to application to the theophylline pellets.

Eudragit® NE 30 D coating dispersions were prepared by first adding 68.75 g of the polymeric latex to a beaker. A Polytron® high shear mixer was used to disperse 10.31 g of Imperial® 500 talc (equal to 50% of the dry polymer weight) in 127.19 g of water. The talc dispersion was added to the acrylic latex with gentle stirring by a magnetic bar and stir plate and allowed to mix for 10 min prior to coating. The final dispersion had a total solids content of 15%.

Coating of Theophylline Cores

A 250-g batch of theophylline pellets was placed in a Strea-1 fluidized bed coater (Aeromatic-Fielder, Bubendorf, SW) and preheated for 10 min at 30°C before initiation of the coating process. The dispersion was delivered with a Watson-Marlow 520s peristaltic pump through marprene tubing. A 1.2-mm nozzle was used with an atomizing air pressure of 25 psi. The inlet temperature was maintained at 29–30°C and the outlet temperature was 25–27°C. The dispersion was applied at a rate of 1 g/min to avoid pellet agglomeration, until a theoretical weight gain of 2.5% had been reached. The application rate was then increased to 3 g/min. To prevent sedimentation of the dispersed solids, the polymeric dispersion was stirred continuously throughout the coating process. After coating, the pellets were dusted with 1.25 g of Imperial® 500 talc (0.5% based on the uncoated cores) and cured in a 60°C oven for 18 h.

Stability Testing and *In Vitro* Drug Release

After curing, the coated pellets were placed in aluminum induction-sealed high density polyethylene (HDPE) containers with 1.0 g MINIPAX molecular sieve sachets (Impak Corporation, Los Angeles, CA, USA) inside the container and stored at both 25°C/60% RH and 40°C/75% RH for a period of up to 3 months. Dissolution testing was performed according to the United States Pharmacopoeia (USP) 29 Apparatus II (Vankel VK 7000, Cary, NC, USA) over a 18-h period in 900 ml of pH 7.4 (50 mM) phosphate buffer.

The paddle speed was 50 rpm and the temperature of the media was maintained at 37±0.2°C.

Dissolution testing was performed in triplicate with 150 mg of coated pellets (containing 30±3 mg API) added to each dissolution vessel. A volume of 5-ml was removed by a Vankel 8000 Autosampler (Cary, NC, USA) at each sampling time point. Infinity samples were obtained by mixing with a high-shear homogenizer (Polytron®, Brinkmann Instruments, Westbury, NY, USA) for 1.5 min.

The theophylline content of each sample was analyzed using ultraviolet (UV) spectroscopy. After having been filtered, a volume of 150 µl was taken from each sample and placed in a corresponding well of a Falcon 96-well UV transparent plate (VWR International, West Chester, PA, USA). An equal volume of pH 7.4 dissolution media was added to each well to ensure that the concentrations were in the linear range of the analytical method. The tray was then loaded into a μQuant 96-Well Plate Reader (Bio-Tek Instruments, Inc., Winooski, VT, USA) and analyzed for theophylline at a wavelength of 273 nm. The amount of theophylline released was calculated by taking the analyte concentration, comparing this to the concentration of the infinity time point, and multiplying by 100 to obtain a percentage of theophylline released at each time point.

Free Film Preparation

Free films were sprayed using a 1:1 ratio of Eudragit® NE 30 D and Eudragit® RS 30 D, which was then diluted with an equal amount of water to achieve a total solids content of 15%. This dispersion was then allowed to mix with gentle agitation *via* a magnetic stir plate and stir bar for a period of 1 h prior to film spraying. For films containing only Eudragit® NE 30 D, the polymer dispersion was diluted with an equal amount of water to achieve a solids content of 15%.

The dispersion was sprayed onto a cylinder covered with Bytac® PTFE film rotating at 50 rpm *via* a Watson-Marlow 520s pump, marprene tubing, and a two fluid spray nozzle (Mini Hi-Coater, Vector Corporation, Marion, IA, USA). The atomizing air pressure was set at 0.3 kg/m^2 and the pump rate was 0.6 rpm (~1 g/min). The spray apparatus provided an oscillatory motion over a path of 5 cm at 28 rpm. The distance from the nozzle to the rotating cylinder was 12 cm. The temperature was controlled using two infrared heat lamps. The temperature was set such that the surface of the film was maintained at a temperature of 25–30°C as measured by an infrared thermometer. An amount of 100 g of the coating dispersion was used to create each composite film. After the spraying process was completed, the films were cured at a temperature of 60°C for a period of 18 h. The films were then removed from the oven and cut into specimens for either water vapor permeability (circular) or physical–mechanical testing (rectangular). These films were then placed in desiccators and stored at 25°C or 40°C for stability studies. The films were removed from the storage chambers and allowed to equilibrate at 25°C/50% RH for a period of 72 h prior to testing.

Table I. Pairwise Comparisons Performed by Tukey's HSD *Post Hoc* Analysis with 95% Simultaneous Confidence Interval of the Water Vapor Permeability of Eudragit® NE 30 D-Sprayed Films Stored at 25°C for a Period of up to 4 Weeks

	Initial	1 week	2 weeks
1 week	X		
2 weeks	X	O	
4 weeks	X	O	O

X significant difference, *O* no significant difference, *HSD* honestly significantly different

Water Vapor Permeability Testing

The water vapor permeability of the sprayed films was determined according to guidelines set forth in ASTM E 96/E 96-05 using the desiccant method (13). The thickness of each film was determined using a Mitutoyo Model ID-C1012EBS digital micrometer (Mitutoyo Corp., JP) by measuring four points along the circumference and one point at the center of a circular sample of film and averaging the values. The film specimen was secured to the open mouth of an aluminum permeability cup (4 cm inner diameter and 3 cm depth)

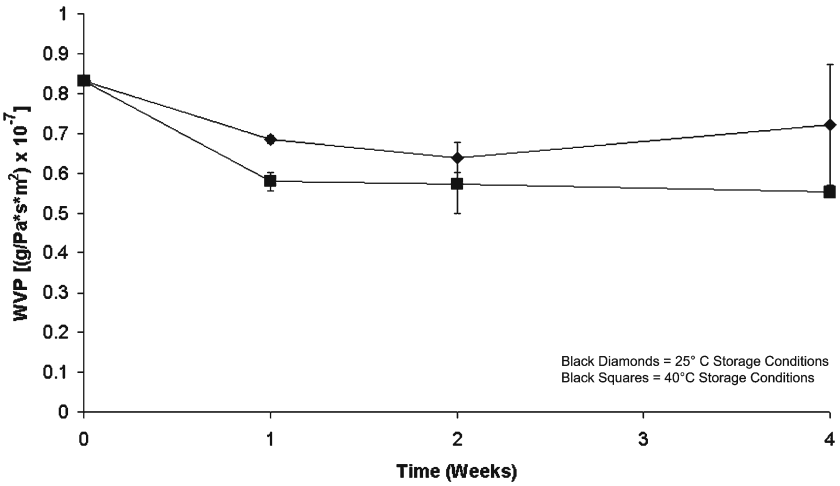

Fig. 1. The effect of storage conditions (temperature and time) on the water vapor permeability of Eudragit® NE 30 D-sprayed films stored at 0% RH (tested at 25°C/80% RH, n=3)

Table II. Pairwise Comparisons Performed by Tukey's HSD *Post Hoc* Analysis with 95% Simultaneous Confidence Interval of the Water Vapor Permeability of Eudragit® NE 30 D-Sprayed Films Stored at 40°C for a Period of up to 4 Weeks

	Initial	1 week	2 weeks
1 week	X		
2 weeks	X	O	
4 weeks	X	O	O

X significant difference, *O* no significant difference, *HSD* honestly significantly different

containing 20 g of Drierite® desiccant. The permeability cups (n =3) were accurately weighed, placed in a humidity chamber at 23°C/80% RH, and periodically reweighed over 96 h to determine the weight gain. The water vapor transmission rate (WVT) and permeability (P) were calculated using the following equations (13):

$$WVT = (G/t)/A \tag{3}$$

$$P = \frac{WVT}{S} \times (R_1 - R_2) \times d \tag{4}$$

where G is the weight change, t is the time during which G occurred, A is the test area (cup mouth area), S is the saturation vapor pressure at test temperature, R_1 and R_2 are the relative humidity in the test chamber and inside the cup (0% RH for the desiccant method), respectively, and d is the thickness of the film.

Physico-mechanical Testing

Stress–strain experiments with the sprayed films were performed using an Instron Model 4201 with a 1,000-N load cell. Prior to testing, films were cut into 70 mm×10 mm strips (n=5). The thickness was measured using a Mitutoyo Model ID-C1012EBS digital micrometer (Mitutoyo Corp., JP) and the average of five different measurements along the length of the film was determined. Stress–strain measurements were conducted on the cut films in accordance with ASTM guideline D 882-02 (14) using a gap distance of 50 mm, load range of 1 N, and crosshead speed of 25 mm/min. The elongation of the films was calculated using Bluehill v.2.5 software.

Determination of the Glass Transition Temperature

The thermal properties of sprayed films were determined using modulated differential scanning calorimetry (MDSC) with a DSC 2920 (TA Instruments, New Castle, DE, USA). Film samples of 5–10 mg were accurately weighed into aluminum pans and then hermetically sealed. The samples were analyzed over a range of −20–100°C with a nitrogen flow rate of 40 ml/min, a heating rate of 12°C/min, and a modulation rate of 0.5°C with a period of 40 s. The glass transition temperature (T_g) was determined as the midpoint of the transition using Modulated DSC Analysis V 1.1A software.

Statistical Analysis

Statistical analysis of *in vitro* dissolution data was conducted using the f_2 similarity factor treatment described by Shah and associates (15). Statistical evaluation of the physico-mechanical properties and water vapor permeability of sprayed films was conducted with Minitab Release 14 software using a one-way analysis of variance (ANOVA) with α=0.05 for a 95% confidence level and Tukey's honestly significantly different (HSD) *post hoc* test was used to compare the means of each population.

RESULTS AND DISCUSSION

Thermal Properties of the Acrylic Polymers

The lowering of the glass transition temperature (T_g) of a material from plasticization is due to the weakening of inter-polymeric bonds, resulting in an increase in the polymer chain flexibility. Acrylic polymers have been traditionally formulat-

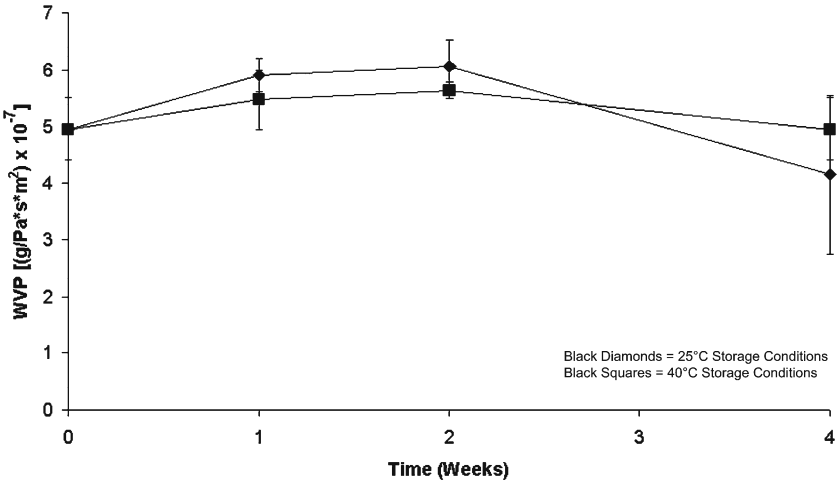

Fig. 2. The effect of storage conditions (temperature and time) on the water vapor permeability of Eudragit® NE 30 D/Eudragit® RS 30 D (1:1)-sprayed films stored at 0% RH (tested at 25°C/80% RH, n=3)

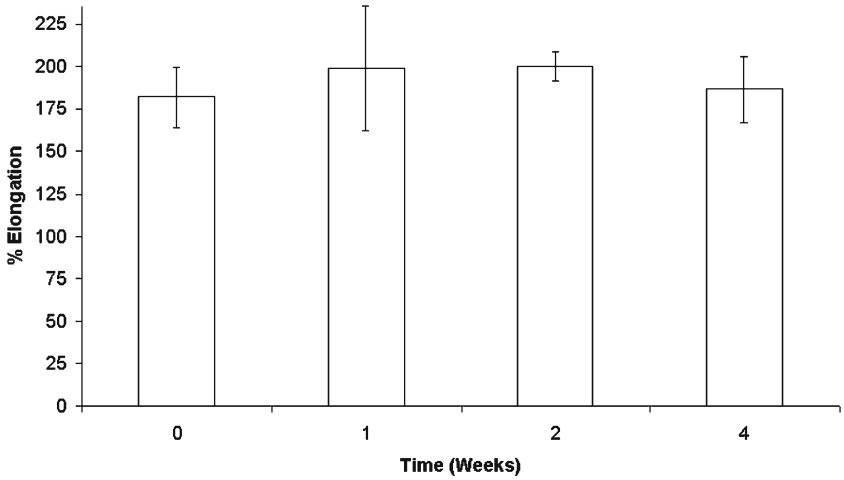

Fig. 3. The influence of temperature and time on the percent elongation properties of Eudragit® NE 30 D/Eudragit® RS 30 D (1:1)-sprayed films stored at 25°C (n=5)

ed with citrate esters (triethyl citrate, acetyl triethyl citrate, tributyl citrate, acetyl tributyl citrate), dibutyl sebacate, and triacetin to lower both the minimum film formation temperature and the T_g of the polymer. However, it has been reported that plasticizer loss during storage from polymeric systems used in both delayed and sustained release coating applications influenced the physico-mechanical stability of films (16, 17). Thus, the formulation of a polymeric blend for sustained release applications that did not employ volatile plasticizers, yet still formed coherent films at low processing temperatures, was of interest.

The plasticization of a high T_g material can also be achieved by blending with a miscible polymer that possesses a lower T_g (11, 12). Two materials have the potential for miscibility if the Hansen solubility parameters have a difference which is ≤ 7 $MPa^{1/2}$ (18). The Hansen solubility parameters of both Eudragit® NE 30 D and Eudragit® RS 30 D have been calculated at 17.1 $MPa^{1/2}$ (19), which indicated that the two polymers have the potential for miscibility. Equation 5, developed by Couchman (20), has been used (12) to predict the T_g of miscible polymer blends, where T_{g12} is the glass transition temperature of the composite, T_{g1} and w_1 are the T_g and the weight fraction of the lower T_g polymer, respectively, and T_{g2} and w_2 are the T_g and weight fraction of the higher T_g polymer, respectively.

$$T_{g12} = (T_{g1} \times w_1) + (T_{g2} \times w_2) \quad (5)$$

MDSC studies on films prepared from Eudragit® NE 30 D and Eudragit® RS 30 D separately showed the T_g to be 12.93°C and 67.03°C, respectively. These values corresponded well with those previously reported in the literature (19). MDSC revealed that 1:1 and 2:1 blends of Eudragit® NE 30D/Eudragit® RS 30 D were completely miscible at these ratios and showed single transitions of 38.09°C and 23.14°C, respectively. These values were close to the predicted values of 39.5°C for the 1:1 blend and 30°C for the 2:1 blend. Krajacic and Tucker (21) have shown that tablets comprising Eudragit® NE 30 D as a polymeric matrix-forming material would continue to cure in a dissolution medium heated to 37°C if the matrix was incompletely formed. To negate the effect of dissolution media temperature on drug

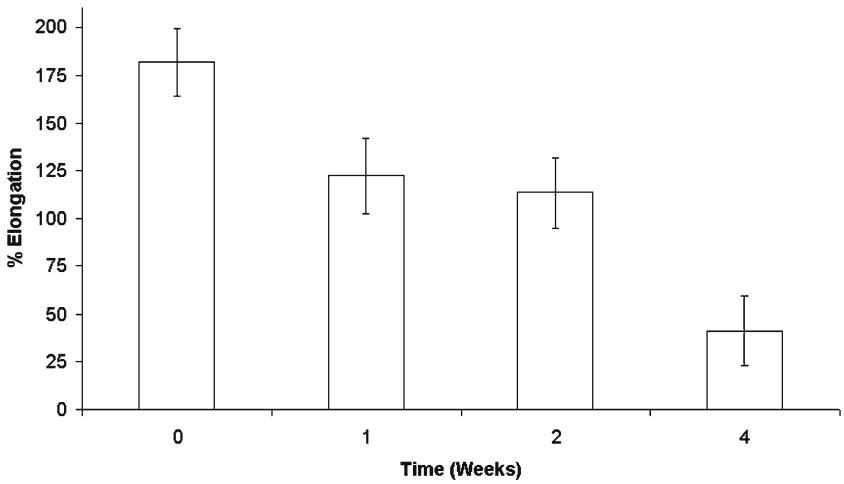

Fig. 4. The influence of temperature and time on the percent elongation properties of Eudragit® NE 30 D/Eudragit® RS 30 D (1:1)-sprayed films stored at 40°C (n=5)

Table III. Pairwise Comparisons Performed by Tukey's HSD *Post Hoc* Analysis with 95% Simultaneous Confidence Interval of the Percent Elongation of Eudragit® NE 30 D/Eudragit® RS 30 D (1:1)-Sprayed Films Stored at 40°C for a Period of up to 4 Weeks

	Initial	1 week	2 weeks
1 week	X		
2 weeks	X	O	
4 weeks	X	X	X

X significant difference, *O* no significant difference, *HSD* honestly significantly different

release, formulations composed of a 1:1 ratio of Eudragit® NE 30 D/RS 30 D with a T_g of 38.09°C were selected for further studies.

Water Vapor Permeability of Sprayed Acrylic Films

One method used in previous studies to investigate the physical aging of polymers is by following the water vapor permeability of thin films (5, 9, 10, 17, 22, 23). The water vapor permeability of sprayed Eudragit® NE 30 D films is shown in Fig. 1. These films were characterized by very low permeability values and exhibited statistically significant differences between the initial samples and those stored for 1 month at both 25°C (ANOVA, $p=0.004$) and 40°C (ANOVA, $p=0.001$). Tukey's HSD *post hoc* analysis (Tables I and II) indicated that the permeability at all time points was significantly lower than the permeability of the films initially tested. Physical aging of these systems was evident due to a densification and continuing coalescence of the low T_g polymer. The permeability of Eudragit® NE 30 D films could be enhanced by blending the polymer with an equal amount of Eudragit® RS 30 D as shown in Fig. 2. At the initial time point, the water vapor permeability of the blended acrylic polymer film was five times greater than the value for films comprising Eudragit® NE 30 D alone. This was attributed to the higher permeability of Eudragit® RS 30 D polymer. Stability studies showed no statistically significant difference in water vapor permeability between films stored at 25°C (ANOVA, $p=0.192$) or 40°C (ANOVA, $p=0.361$) at all time points.

Effect of Time and Temperature on the Physico-mechanical Properties of Sprayed Acrylic Films

The physical aging phenomenon can be monitored by determining elongation of polymeric films (3, 5, 9, 10, 17). Changes in this parameter are characterized by a relaxation of the polymer towards a state of equilibrium and can be influenced by factors such as the amount of plasticizer in the formulation, curing time, and the temperature and humidity of storage conditions.

The effect of time and temperature on the elongation of sprayed films consisting of a 1:1 blend of Eudragit® NE 30 D/RS 30 D are seen in Figs. 3 and 4. For films stored at 25°C for a period of up to 1 month (Fig. 3), no statistically significant difference was found (ANOVA, $p=0.690$), indicating that the films were physically stable at this temperature. However, films stored at 40°C (Fig. 4) exhibited a significant decrease (ANOVA, $p=0.001$) in elongation over the 1-month testing period. The results for the *post hoc* Tukey's HSD analysis are shown in Table III and indicate that the means of elongation at all time points showed a statistically significant decrease in elongation compared to that of films initially tested. While there was no significant change between the means of the 1- and 2-week time points, both were found to be significantly different at the 4-week time point which indicated that further coalescence and entanglement of the polymer chains occurred for films stored at higher temperature. This observation contradicted the water vapor permeability studies (Fig. 2), which showed no change in that parameter over the same time period under the same storage conditions and was attributed to the increased permeability of the polymeric film by the presence of the more permeable Eudragit® RS 30 D polymer.

The Influence of Storage Temperature on the Release Rate of Drug from Coated Pellets

The release properties of theophylline from Eudragit® NE 30 D-coated pellets are shown in Fig. 5. Coating of the

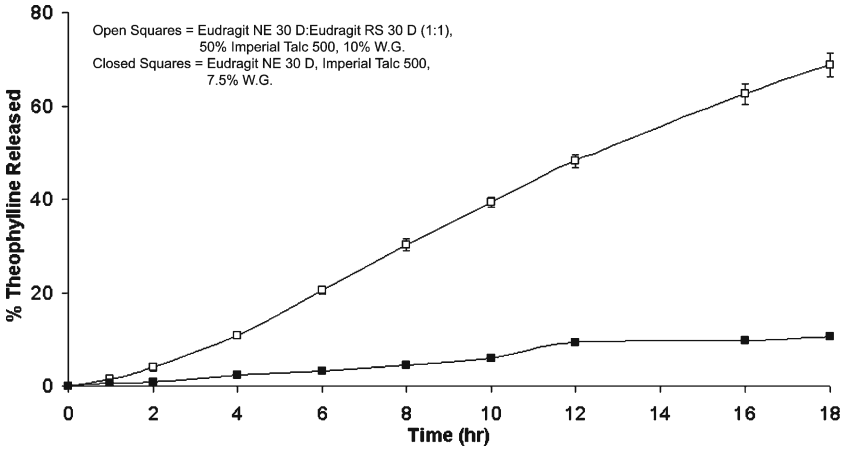

Fig. 5. The influence of the addition of Eudragit® RS 30 D on the release of theophylline from coated pellets (USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, $n=3$)

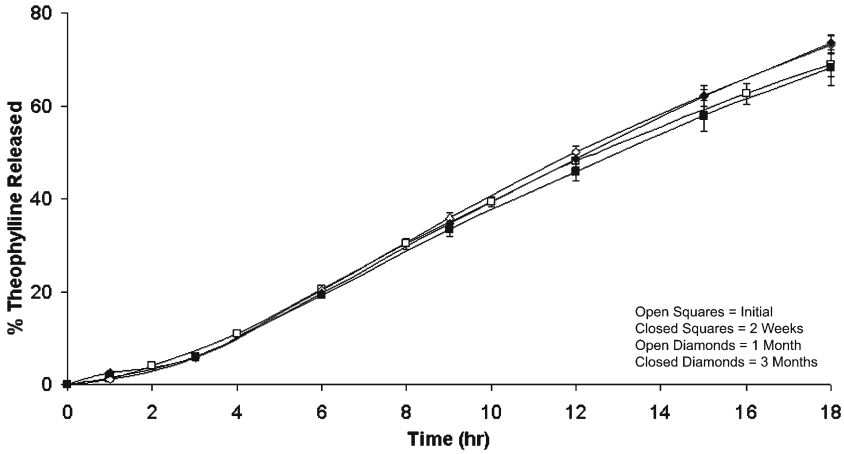

Fig. 6. The influence of storage time on the release of theophylline (30 mg) from pellets coated with Eudragit® NE 30 D/Eudragit® RS 30 D (1:1) and 50% Imperial® 500 talc coated to a 10% weight gain and stored in sealed HDPE containers with desiccant at 25°C/60% RH (USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, n=3)

pellets to a 7.5% weight gain with the poorly permeable polymer resulted in less than 20% of the drug being released after 18 h in pH 7.4 (50 mM phosphate) buffer. When a 1:1 blend of Eudragit® NE 30 D/RS 30 D was applied to the pellets at a 10% weight gain, the drug release rate increased and more than 60% theophylline was released after 18 h and a zero-order drug dissolution profile was observed after an initial lag time of 1–2 h. The increase in drug release could be explained by the difference in permeability of films formed by the polymers. The repeat unit of Eudragit® RS 30 D polymer possesses a quaternary ammonium functional group which promotes swelling and increases permeability of films comprising this material. Eudragit® NE 30 D lacks these functional groups and the drug release rate is controlled by the thickness of the film coating. These findings corresponded well to the difference in water vapor permeability of free films (Figs. 1 and 2).

The stability upon storage of theophylline pellets coated with the blend of acrylic polymers to a 10% weight gain is shown in Figs. 6 and 7. After coating and curing for 18 h at 60°C, the pellets were placed in aluminum induction sealed HDPE containers with desiccant at storage conditions of 25°C/60% RH and 40°C/75% RH for a period of up to 3 months. Coated pellets stored at the lower temperature (Fig. 6) were stable during the 3-month period, with an f_2 similarity factor of 78 between the initial dosage forms and those stored for 3 months. In contrast, those pellets stored at the higher temperature (Fig. 7) exhibited a decrease in the drug release rate during this time period and the f_2 similarity factor was 53. Though no change in water vapor permeability was seen for sprayed films stored at 40°C, the difference between this parameter and dissolution performance was confirmed by the results of the physico-mechanical properties of the sprayed films, in which there was a significant decrease

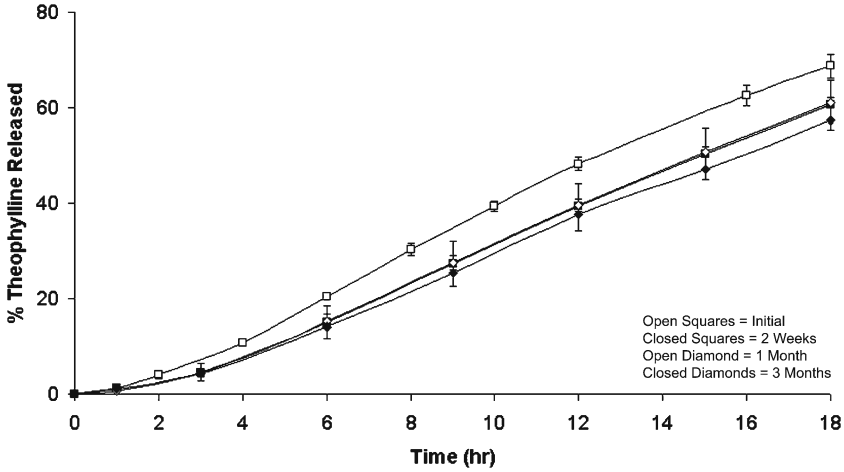

Fig. 7. The influence of storage time on the release of theophylline (30 mg) from pellets coated with Eudragit® NE 30 D/Eudragit® RS 30 D (1:1) and 50% Imperial® 500 talc coated to a 10% weight gain and stored in sealed HDPE containers with desiccant at 40°C/75% RH (USP 29 Apparatus II, 900 ml pH 7.4 buffered phosphate solution, 50 rpm, 37°C, n=3)

in elongation for these samples (Fig. 4). The films were stored at a temperature which was above the T_g of the polymeric blend where the molecular mobility of the polymer chains was high, and continuing coalescence and densification of the polymer occurred during storage. During dissolution, hydrodynamic effects were exerted on the coated pellets, including diffusion of water to the core. The increase in core volume due to osmotic effects causes the film to expand. Increased coalescence of the polymer during storage at temperatures above the T_g significantly affected the ability of the film to expand during dissolution, and the reduction in drug release rate was a direct result of the instability in the elasticity parameter of the film.

CONCLUSIONS

The combination of the miscible polymers Eudragit® NE and Eudragit® RS 30 D allowed film formation without the requirement of a plasticizer in the formulation. Films containing a 1:1 blend of Eudragit® NE30 D/RS 30 D possessed a glass transition temperature that was higher than those films consisting of a 2:1 blend and corresponded well to predicted values. Sprayed films composed of Eudragit® NE 30 D/RS 30 D (1:1) and theophylline pellets coated with the same formulation possessed higher water vapor permeability values and drug release rates, respectively, when compared to Eudragit® NE 30 D-sprayed films and film-coated dosage forms, which was attributed to the quaternary ammonium groups present in Eudragit® RS 30 D. Theophylline pellets coated with a blend of (1:1) Eudragit® NE 30 D/RS 30 D demonstrated a decrease in drug release rate when stored in aluminum induction-sealed HDPE containers at 40°C/75% RH. The release properties of coated pellets were correlated to instabilities in the physico-mechanical properties of sprayed films, which showed a decrease in percent elongation during a time period of 4 weeks when stored at 40°C. This reduced flexibility of the film coating during dissolution was due to increased coalescence and interdiffusion of the polymer chains when stored at temperatures above the T_g of the polymeric blend. However, when the same pellets were stored at 25°C/60% RH (below the glass transition temperature of the blend), the mechanical properties of the films were conserved and no change in drug release rate was observed over a 3-month period. The stability of Eudragit® NE 30 D films could be successfully enhanced at storage temperatures below the glass transition temperature by the addition of Eudragit® RS 30 D to the coating formulation.

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