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Use of Proteins to Minimize the Physical Aging of EUDRAGIT® Sustained Release Films

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ABSTRACT The objective of this study was to investigate the influence of two proteins, albumin and type B gelatin, on the physical aging of EUDRAGIT® RS 30 D and RL 30 D coated theophylline pellets. The physicomechanical properties of sprayed films, thermal properties of cast films, influence of proteins on the zeta potential and particle size of the dispersion, and the release of proteins from cast films under simulated dissolution conditions were investigated. The release rate of theophylline decreased significantly over time from pellets coated with an acrylic dispersion containing 10% albumin when there was no acidification of the acrylic dispersion; however, when pellets were coated with an acidified EUDRAGIT®/albumin dispersion, the theophylline release rate was stable for dosage forms stored in the absence of humidity. The drug release rate was faster for pellets coated with acrylic dispersions containing 10% gelatin compared to the albumin–containing formulations. When sprayed films were stored at 40°C/75% RH, the water vapor permeability decreased significantly for both EUDRAGIT® films and those containing EUDRAGIT® and albumin; however, there was no significant change in this parameter when 10% gelatin was present. Albumin was released from the acrylic films when the pH of the dissolution media was below the isoelectric point of the protein while no quantitative release of gelatin was observed in pH 1.2 or 7.4 media. The effect of gelatin to prevent the decrease in drug release rate was due to stabilization in water vapor permeability of the film. Acidification of the polymeric dispersion resulted in electrostatic repulsive forces between albumin and the acrylic polymer, which stabilized the drug release rate when the dosage forms were stored in aluminum induction sealed containers at both 40°C/75% RH and 25°C/60% RH.

KEYWORDS EUDRAGIT® RS 30 D, EUDRAGIT® RL 30 D, Aqueous film coating, Albumin, Type B gelatin, Physical aging, Stabilization, Pellets, Theophylline release

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INTRODUCTION

The use of aqueous polymeric dispersions for film coating solid dosage forms has gained in popularity due to increased government regulations, as well as the safety issues associated with the use of organic solvents in film coating

processes. The film formation mechanism, however, is more complex with latex and pseudolatex dispersions than with organic solvent systems. One problem prevalent in aqueous latex coating systems is physical aging of the polymeric film during storage. This results from the further coalescence of latex particles and a decrease in void volume of the polymeric film as the polymer relaxes towards an equilibrium state (Amighi & Moës, 1996; Frisbee et al., 1997; Wu & McGinity, 2003; Zheng & McGinity, 2003). Physical aging of film coatings will generally result in a decrease in the drug release rate from the coated dosage form (Amighi & Moës, 1996; Amighi & Moës, 1997; Frisbee et al., 1997; Maejima & McGinity, 2001; Zheng & McGinity, 2003; Zheng & McGinity, 2005).

Diffusion-controlled drug release can be described by Fick's Law, as seen in Eq. (1), where Q is the quantity of drug released in time t, D is the diffusion coefficient of the drug, S is the area of diffusion, C_1 is the drug concentration in the dosage form, C_2 is the drug concentration in the dissolution media, and h is the film thickness.

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

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

Fick's Law is related to physical aging by the Iyer equation, which is described by Eq. (2). Here, D is the diffusion coefficient of the drug, D_w is the diffusion coefficient of the drug in water, e is the film porosity, and τ is the film tortuosity. There is a decrease in film porosity and void volume and an increase in tortuosity as coalescence of the colloidal particles continues during storage, which results in a decrease in the diffusion coefficient. This decrease in the diffusion coefficient is responsible for the decrease in dissolution rate during storage of film coated dosage forms (Zheng et al., 2005).

There have been several approaches reported in the literature to prevent the physical aging of dosage forms coated with colloidal aqueous dispersions. Amighi and Moës (1996) reported that as the plasticizer concentration was increased, the degree of coalescence of the latex particles also increased and that pellets coated with a polymeric dispersion containing less plasticizer showed more pronounced aging effects. The time required to achieve a stabilized drug release rate was also dependent on the curing temperature, with stable films obtained faster when cured at higher temperatures. Maejima and McGinity (2003) showed that thermal treatment along with high concentrations of micronized talc stabilized drug release from pellets coated with EUDRAGIT® RS/RL 30 D plasticized with TEC. The addition of a high glass transition temperature polymer to an acrylic dispersion to stabilize drug release rates was reported by Wu and McGinity (2003). The addition of EUDRAGIT® L 100-55 to EUDRAGIT® RS 30 D resulted in a stable drug release rate in an acidic medium when coated pellets were stored under accelerated conditions. At a higher pH, an increase in drug release was seen due to pore formation as the enteric polymer dissolved. Similarly, EUDRAGIT® L 30 D-55 was shown to stabilize drug release from pellets coated with EUDRAGIT® NE 30 D (Zheng & McGinity, 2003). Inclusion of a hydrophilic polymer, hydroxyethylcellulose (HEC), to EUDRAGIT® RS 30 D dispersions stabilized the drug release rates during storage due to the formation of an immiscible secondary phase surrounding the colloidal particles which interfered with further coalescence of the colloidal acrylic particles (Zheng et al., 2005). Lastly, ionic electrostatic interactions have also been investigated to minimize physical aging effects in aqueous-based polymeric dispersions (Omari et al., 2004).

The objective of the present study was to investigate the influence of albumin and Type B gelatin on the physical aging of theophylline pellets coated with EUDRAGIT® RS/RL 30 D. The physicomechanical properties of sprayed films, thermal properties of cast films, protein influences on the zeta potential and particle size of the dispersions, and the release of proteins from cast films under simulated dissolution conditions were investigated. The effect of temperature and humidity during storage on drug release from coated pellets was studied as well as the influence of pH of the EUDRAGIT® polymeric dispersion on protein-polymer interactions.

MATERIALS AND METHODS

Materials

EUDRAGIT® RS 30 D and RL 30 D dispersions were donated by Degussa (Parsippany, NJ). Anhydrous theophylline, fraction V heat-shock bovine serum albumin (BSA), Type B gelatin, and lactose monohydrate

were all purchased from Spectrum Chemical (Gardena, CA). Polyvinylpyrrolidone (Kollidon® K-30) was donated by the BASF Corp. (Mount Olive, NJ). Microcrystalline cellulose (Avicel® PH-101) was donated by the FMC Corp. (Newark, DE). Altalc 500 V was supplied by Luzenac America, Inc. (Englewood, CO). Triethyl citrate (TEC) was donated by Morflex, Inc. (Greensboro, NC). Hypromellose (Pharmacoat® 603) was donated by Shin-Etsu Chemical Co. (Tokyo, JP).

Preparation of Core Pellets

Anhydrous theophylline (25%), lactose monohydrate (45%) and microcrystalline cellulose (25%) were passed through a 30-mesh sieve and then mixed in a twin-shell blender for 15 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 a LCI Benchtop Granulator (Tokyo, JP) at a rotation blade speed of 50 rpm. The extrudates were spheronized at 1000 rpm for 2 min using a Caleva Model 120 Spheronizer (Dorset, UK). The pellets were sieved after drying for 24 hr at 40°C, and the 16–20 mesh fraction was used for the coating trials.

Preparation of Coating Dispersions

EUDRAGIT® RS 30 D (95% dry polymer weight) and EUDRAGIT® RL 30 D (5% dry polymer weight) were combined with TEC (15%, based on the total dry polymer weight) and the protein solution (10%, based on the total dry polymer weight) and equilibrated with slow agitation for two hours under ambient conditions. Albumin was mixed with deionized water to yield a 3.75% solution prior to addition to the polymer dispersion. Gelatin was dissolved in deionized water (40°C) to yield a 1% solution and allowed to cool to room temperature before addition to the acrylic dispersion. Talc (50%, based on the total dry polymer weight) was dispersed in 150 mL of deionized water using a POLYTRON (Brinkmann Instruments, Westbury, NY) and then added to the acrylic dispersion for a further 15 min of agitation.

Film Coating

A 250-g batch containing 50% theophylline pellets and 50% nonpareils of the same size fraction was placed in a Strea-1 fluidized-bed coater (Aeromatic-Fielder, Bubendorf, SW), and the polymeric dispersion was applied with a peristaltic pump through a 1.2 mm nozzle until the film weight gain of the pellets was 15% theoretical gain. The inlet temperature was 40–42°C and the outlet temperature was 32–35°C. To avoid pellet agglomeration, the dispersion was applied at a rate of 1 g/min until a weight gain of 2.5% had been reached and then increased to 3 g/min. The atomizing air pressure of the unit was 25 psi. The polymeric dispersion was stirred continuously throughout the coating process to prevent the sedimentation of the dispersed solids.

To prevent agglomeration and sticking of the pellets during storage, a 2% total weight gain of hypromellose (Pharmacoat® 603) was applied to the coated pellets from a 5% w/w aqueous solution. The inlet temperature was 45°C, the outlet temperature 40°C, and the spray rate was 2 g/min. The pellets were then placed in a 40°C oven for 12 hr to remove residual moisture.

Free Film Preparation

Films were prepared by either a cast or spray method. For the cast method, the coating dispersion without talc was cast onto a Teflon plate and dried for 72 hr under ambient conditions. These films were used in experiments to study protein release from films as well as for thermal experiments. The second method to prepare the free films was a spray technique that was similar to a previously described method used by Obara and McGinity (1994). Films were sprayed onto a Teflon sheet attached to a cylinder rotating at 44 rpm. An infrared lamp was used to maintain the sprayed film in the temperature range of 22–28°C. The atomizing air pressure was 0.50 kg/cm^2. The spray rate was maintained at 2 g/min and delivered through the 1.2 mm nozzle. Formulations for the sprayed films were the same as those used in the coating trials.

Thermal Analysis of Films

The thermal properties of the cast films were determined by modulated differential scanning calorimetry (MDSC) (TA Instruments, New Castle, DE). The films were cast from aqueous dispersions in the same ratios that were used for the film-coating trials.

Film samples of 10–15 mg were weighed into aluminum pans and then sealed. The samples were analyzed in a nitrogen atmosphere with a heating rate of 3°C/min over a temperature range of –20–110°C with a modulation rate of 1°C/min. The glass transition temperature was determined as the midpoint of the transition using Modulated DSC Analysis V1.1A software.

Physico-Mechanical Testing

Stress-strain experiments with films prepared by the spray method were performed using an Instron Model 4201 according to ASTM guideline D 883-02 (2002). Films were cut into 100×10 mm strips. Thickness was measured using a Starrett® No. 723 digital micrometer (L.S. Starrett, Athol, MA) and the average of seven different measurements along the length of the film was determined. A 1000 N load cell was mounted on the instrument. The distance between the grips was 60 mm, the load range was 50 N, and the crosshead speed was set at 10 mm/min. The tensile strength at break was determined. This parameter wA calculated using the following formula:

$$Tensile\ Strength\ at\ Break = \frac{Load\ at\ Break}{Minimum\ Cross\text{-}sectional\ Area} \quad (3)$$

Water Vapor Transmission Rate

The water vapor transmission rate of the sprayed films was determined according to guidelines set forth in ASTM E 96-00 (2000) using the desiccant method, as previously described by Zheng and McGinity (2005). The thickness of each film was determined using a Starrett® No. 723 digital micrometer (L.S. Starrett, Athol, MA) by measuring eight points along the circumference of a circular sample of sprayed film and averaging the values. The film sample was secured to the open mouth of an aluminum permeability cup (4 cm inner diameter and 3 cm depth) containing 20 g of Drierite® desiccant. The permeability cups were accurately weighed, placed in a humidity chamber at 23°C/80% RH, and periodically reweighed over seven days to determine the weight gain. The water vapor transmission rate (WVT) and permeability (P) were calculated using the following equations (ASTM, 2000):

$$WVT = \frac{G \times A}{t} \quad (4)$$

$$P = \frac{WVT}{S} \times (R_1 - R_2) \times d \quad (5)$$

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, respectively, and d is the thickness of the film.

Particle Size and Zeta Potential Analysis

The particle size and zeta potential of the colloidal particles in the latex dispersion following the addition of either albumin or gelatin were determined using a Zeta Plus Zeta Potential Analyzer (Brookhaven Instruments Corp.). The dispersion samples were diluted with deionized water, added to a cuvette, and allowed to stabilize at 25°C. A refractive index of 1.59 was used for particle size studies.

Viscosity Measurements

The viscosity of the dispersions was measured using a Brookfield DV-I+ viscometer (Brookfield Engineering) with an H1 spindle size at 30 ± 1°C and 100 rpm ($n = 3$). The viscosity of a 30% w/v EUDRAGIT® RS/RL 30 D blend (95:5) was used as a control. For measurements of albumin-containing dispersions, 10% protein (based on the dry polymer weight of the acrylic) was added as a solution while being stirred with a magnetic stir bar. After all of the protein solution had been added, viscosity measurements proceeded and data was collected after 3 min.

Protein Release from Free Films

The dissolution rate of the protein from cast films containing either albumin or type B gelatin was studied. A 500 mg sample of cast film (containing approximately 40 mg of protein) was placed in scintillation

vials containing 20 mL of either pH 1.2 (0.1 N HCl) or pH 7.4 (50 mM) phosphate buffer previously heated to a temperature of 37°C. The vials were placed in an enclosed, temperature controlled (37°C) orbital shaker and agitated at a rate of 100 rpm. Samples of 1 ml were removed at 1-, 3-, and 6-hr intervals. The protein assay was performed using a DC Protein Assay kit (BIO-RAD) with a reaction time of 15 min and a λ_{max} of 750 nm using a μQuant 96-Well Plate Reader (Bio-Tek Instruments, Inc.).

Stability Testing and In Vitro Drug Release

Coated pellets were placed in polyethylene bottles and kept either open to the environment or hermetically sealed with aluminum induction seals with desiccant inside and then stored at 25°C/60% RH and 40°C/75% RH for up to 3 months. The percent water absorbed from the coated pellets was analyzed by heating the pellets to 110°C for a period of 30 min using an AND MF-50 moisture analyzer (DSC, Inc., Encino, CA). Dissolution was performed according to the United States Pharmacopeia (USP) 27 Apparatus II (Vankel VK 7000, Cary, NC) over a 12-hr 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.

A total of 300 mg of coated pellets was added to each dissolution vessel and 5-mL samples were removed by a Vankel 8000 Autosampler (Cary, NC) at 1-, 2-, 3-, 4-, 5-, 6-, 8-, 10-, and 12-hr intervals. An infinity sample was obtained by mixing with a high-shear homogenizer (POLYTRON, Brinkmann Instruments, Westbury, NY) and then analyzed for drug content. All dissolution tests were performed in triplicate.

The theophylline content of each sample was analyzed using high performance liquid chromatography (HPLC). The samples were filtered through a 0.45 μm nylon filter. A volume of 4 mL was allowed to pass through the filter with the remaining 1 mL being used for analysis after filtration. Analysis was performed using a Waters® 717 Plus Autosampler, two 515 HPLC pumps, a column heater set to 30°C, and 996 PDA. Results were calculated using Empower Pro software. A Metachem® Intertsil ODS-3 3 μm column (150×4.6 mm) was used for separation with an analyte retention time of 2.8 min. The amount of theophylline released was computed by taking the analyte peak area, comparing this to the peak area of the infinity time point sample, and multiplying by 100 to obtain a percentage of theophylline released at each time point.

RESULTS AND DISCUSSION

The water vapor permeability of EUDRAGIT® RS/RL 30 D sprayed films containing 15% TEC and either 10% albumin or gelatin is shown in Table 1. The films were stored at 40°C/75% RH in open containers. When comparing initial values between the albumin and gelatin formulations, no significant difference was observed; however, there was a significant difference (single factor ANOVA, $p < 0.05$) between the two protein-containing formulations and the EUDRAGIT® RS/RL 30 D films. This difference was due to the hydrophilicity of the proteins. During storage, a significant decrease in this parameter was seen in the EUDRAGIT® RS/RL 30 D films as well as those containing albumin which was attributed to a decrease in void space and further densification of the film. The films containing gelatin exhibited no significant change in water vapor permeability after storage and the significance of these results will become clear during the discussion of the results from the dissolution studies.

The tensile strength of sprayed films stored for 1 month at 40°C/75% RH is also shown in Table 1. Changes in tensile strength help explain the physical aging phenomenon in polymeric systems. The further coalescence of polymeric latex particles causes an increase in tensile strength, which was reported in previous studies (Zheng et al., 2005). All films exhibited significant increases in tensile strength during storage.

Plasticizers weaken polymeric intermolecular interactions and increase the flexibility of the polymer (Gutiérrez-Rocca & McGinity, 1994; Wu & McGinity, 1999), resulting in an increase in free-film elongation and a decrease in tensile strength. A common method used to evaluate plasticizer effectiveness is by determination of the glass transition temperature (T_g). The T_g was investigated to determine if plasticization would account for the mechanical changes observed in the protein-containing films. The presence of either protein in the acrylic film showed no significant impact on the glass transition temperature in the presence or

TABLE 1 **Effect of time on water vapor permeability (WVP) and tensile strength at break (TSB) of EUDRAGIT® RS/RL 30 D films containing 15% TEC as a plasticizer either 10% BSA or Type B Gelatin stored at 40°C/75% RH in open containers**

Formulation	WVP $(g/Pa \cdot s \cdot m^2) \times 10^{-7}$	TSB $(10^6$ Pa)
EUDRAGIT® RS/RL 30 D with 15% TEC, t_0	2.28 ± 0.06	7.49 ± 0.31
EUDRAGIT® RS/RL 30 D with 15% TEC, $t_{1\ mo}$	1.95 ± 0.06	7.95 ± 0.35
EUDRAGIT® RS/RL 30 D, 15% TEC, 10% albumin, t_0	2.76 ± 0.19	4.91 ± 0.53
EUDRAGIT® RS/RL 30 D, 15% TEC, 10% albumin, $t_{1\ mo}$	1.99 ± 0.19	9.09 ± 1.11
EUDRAGIT® RS/RL 30 D, 15% TEC, 10% gelatin, t_0	**2.74 ± 0.17**	5.40 ± 0.77
EUDRAGIT® RS/RL 30 D, 15% TEC, 10% gelatin, $t_{1\ mo}$	**2.47 ± 0.17**	14.12 ± 1.20

Note: Bolded values indicate no significant change when analyzed by single factor ANOVA with a p value of 0.05.

absence of triethyl citrate, indicating that neither protein plasticized the acrylic polymer and that both proteins were immiscible with the polymer (Table 2).

Monodisperse latex particles have previously been used to bind and separate albumin in biological applications (Yoon et al, 1996). This attraction was found to be due to the presence of hydrogen bonding between the latex particles and the albumin molecules. Since albumin is an amphoteric protein, the pH of the environment will determine the charge on the molecule. At a pH above the isoelectric point of the protein, the molecule carries a net negative charge, while at a pH below the isoelectric point, albumin will carry a net positive charge. Since the pH of the acrylic dispersion is in the range of 5.0–5.2 and the isoelectric point of albumin is 4.7 (Friedli, 1996), EUDRAGIT® RS/RL 30 D, which contains positively charged quaternary ammonium functional groups, will interact with the negatively charged albumin molecules and affect the film formation mechanism.

TABLE 2 **The effect of protein addition on the glass transition of EUDRAGIT® RS/RL 30 D cast films**

Formulation	T_g (°C)
EUDRAGIT® RS/RL	52.08
EUDRAGIT® RS/RL 30D, 10% albumin	54.12
EUDRAGIT® RS/RL 30D, 10% type B gelatin	51.87
EUDRAGIT® RS/RL 30D, 15% TEC	29.88
EUDRAGIT® RS/RL 30D, 15% TEC, 10% albumin	31.17
EUDRAGIT® RS/RL 30D, 15% TEC, 10% type B gelatin	28.01

During preparation of the coating dispersion, the acrylic dispersion exhibited a significant increase (single factor ANOVA, $p < 0.05$) in viscosity from 16.57 (±1.07) cps to 56.67 (±1.62) cps when the albumin solution was added. These findings were attributed to the agglomeration or binding between albumin and acrylic particles. These results are supported by Omari and colleagues (2004) who demonstrated that quaternary ammonium groups coupled with a chloride exhibit 100% dissociation of the chloride ion in the pH range of 1–8. As these functional groups are positively charged, they are free to interact with negatively charged molecules in solution. Particle size analysis was performed on an EUDRAGIT® RS/RL 30 D dispersion adjusted to pH 2.5 by the addition of 0.1 N HCl (Nyamweya et al., 2001a) and also at the pH of the dispersion as received (pH ≈ 5.0). An increase in mean particle size of 40 nm (initial size 125 nm) was seen when albumin was added to the dispersion (pH ≈ 5.0) while no increase in particle size was observed when albumin was placed in the pH 2.5 dispersion.

The effect of protein addition on the zeta potential of the latex dispersion can be seen in Table 3. The zeta potential is useful for determining how particles interact with one another and for predicting the stability of dispersed colloid systems. Inter-particle reactions are likely to occur when the particles are of a different

TABLE 3 The effect of protein addition on the ζ potential (in mV) of EUDRAGIT® RS/RL 30 D dispersions

	pH 5.2	pH 2.5
Formulation	ζ Potential (SE)	ζ Potential (SE)
EUDRAGIT® RS/RL 30 D	48.35 (3.25)	49.70 (2.97)
EUDRAGIT® RS/RL 30 D containing 10% albumin	32.47 (2.51)	49.83 (1.93)
EUDRAGIT® RS/RL 30 D containing 10% type B gelatin	49.63 (3.45)	46.75 (3.15)

charge, with these reactions mostly being coagulation (Nyamweya et al., 2001b). The zeta potential of the EUDRAGIT® dispersion in the current study was comparable to results reported by others (Nyamweya et al., 2001a). When an albumin solution was added to the acrylic dispersion, however, a significant decrease in zeta potential was noted, indicating a decrease in colloidal stability. At the lower pH, below the isoelectric point of albumin, colloidal stability was maintained as evidenced by no change in the zeta potential. These findings were attributed to an electrostatic repulsion between the positively charged protein and the polymer.

The influence of albumin on the theophylline release rate from coated pellets was studied. When stored at 40°C and 75% relative humidity in open containers over 3 months, there was a significant decrease in drug release from pellets coated with an acrylic dispersion (pH ≈ 5.0) containing albumin (Fig. 1). The drug release rate from the coated pellets had not equilibrated after three months of storage,

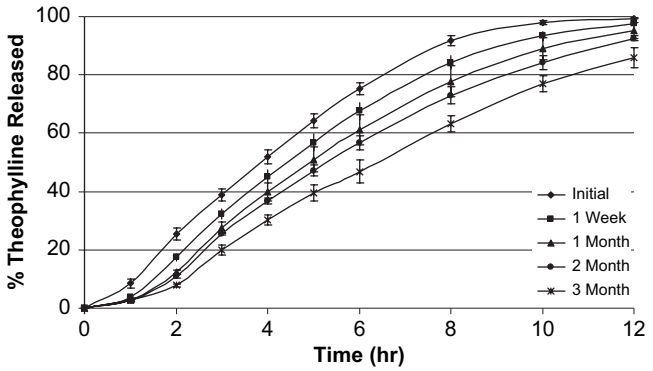

FIGURE 2 The influence of dispersion pH (2.5) on the release of theophylline from pellets coated with EUDRAGIT® RS/RL 30 D (15% WG) containing 10% albumin and stored at 40°C/75% RH in open containers (n = 3).

and only 42% of the total theophylline was released after a period of 12 hr. This decrease was in agreement with the changes observed in the physicomechanical and water vapor permeability properties of the sprayed films as noted in Table 1. When the pH of the EUDRAGIT® dispersion was adjusted to 2.5 by the addition of 0.1 N HCl, a smaller decrease in drug release rate was observed during storage, but physical aging was still evident (Fig. 2). Albumin, being negatively charged at a pH above its isoelectric point, interacted with the acrylic polymer and depressed the drug release rate when compared with an acidified dispersion.

When theophylline pellets coated with the acrylic-albumin dispersion were stored in hermetically sealed HDPE containers with desiccant, the coated pellets stored at 40°C/75% RH (Fig. 3) and 25°C/60% RH (Fig. 4) showed no change in drug release over time.

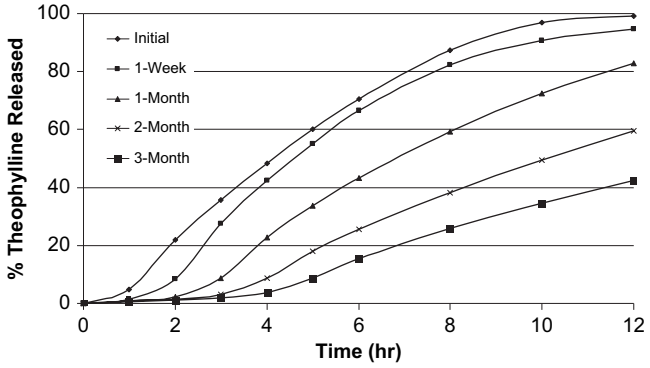

FIGURE 1 The influence of albumin on the release of theophylline from pellets coated with EUDRAGIT® RS/RL 30 D (15% WG) containing 10% albumin and stored at 40°C/75% RH in open containers (n = 3).

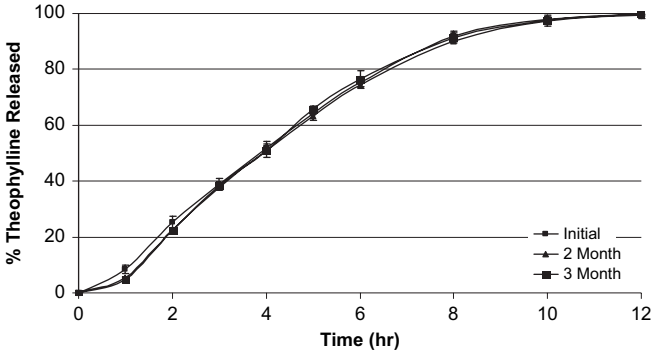

FIGURE 3 The influence of dispersion pH (2.5) on the release of theophylline from pellets coated with EUDRAGIT® RS/RL 30 D (15% WG) containing 10% albumin and stored at 40°C/75% RH in hermetically sealed HDPE containers with desiccant (n = 3).

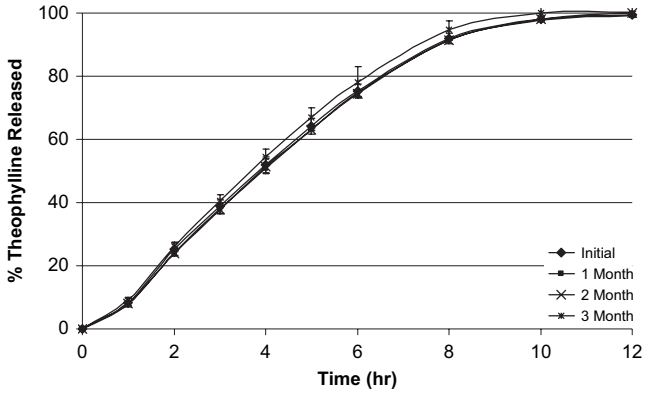

FIGURE 4 **The influence of dispersion pH (2.5) on the release of theophylline from pellets coated with EUDRAGIT® RS/RL 30 D (15% WG) containing 10% albumin and stored at 25°C/60% RH in hermetically sealed HDPE containers with desiccant (*n* = 3).**

The decrease in drug release rate seen in Figs. 1 and 2 was due to a combination of protein-polymer interaction and humidity causing a decrease in the permeability of the film, rather than the temperature at which the dosage forms were stored. The absorption of water due to highly humid storage environments has been shown to increase the physical aging of films (Amighi & Moës, 1996; Amighi & Moës, 1997; Wu & McGinity, 2000; Wu & McGinity, 2003). Water acts as a plasticizer and can cause further coalescence of the film during storage, leading to a decrease in drug release. Both formulations containing 10% albumin and gelatin showed an increase in water content of 4.35% and 3.55%, respectively, during storage over 1 month at 40°C and 75% relative humidity in open containers.

The addition of gelatin to the acrylic dispersion produced an opposite effect on drug release when compared to albumin. As seen in Figs. 5 and 6, film-coated dosage forms showed no change in the dissolution rate at 40°C and 75% relative humidity when stored in open containers and closed containers. The complete coalescence of latex particles can only be achieved when polymeric molecules located at the interface between adjacent particles interpenetrate as a result of viscous flow. The addition of an immiscible hydrophilic polymer resulted in the formation of an incompatible phase around the colloidal latex particles, which prevented complete coalescence and interdiffusion of polymer chains (Zheng et al., 2005). Stabilization of drug release in the gelatin containing formulations can be explained by the water vapor permeability results which showed no change during storage after 1 month at 40°C/75% RH.

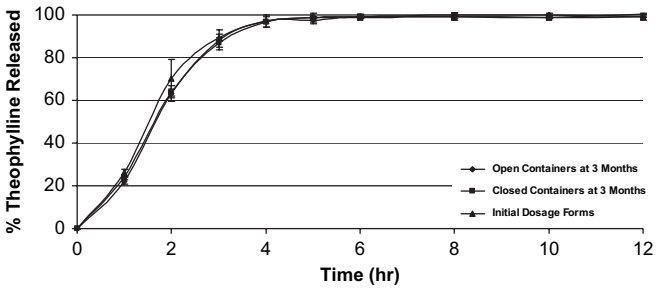

FIGURE 5 **The effect of gelatin on the release of theophylline from pellets coated with EUDRAGIT® RS/RL 30 D containing 10% gelatin and stored at 40°C/75% RH in open and closed containers (*n* = 3).**

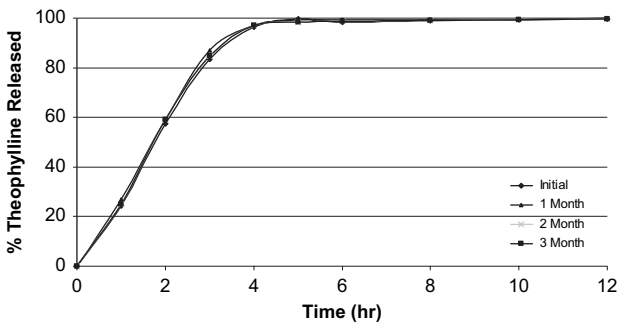

FIGURE 6 **The influence of dispersion pH (2.5) on the release of theophylline from pellets coated with EUDRAGIT® RS/RL 30 D (15% WG) containing 10% gelatin and stored at 40°C/75% RH in hermetically sealed HDPE containers with desiccant (*n* = 3).**

The theophylline release was faster from pellets coated with an acrylic-gelatin dispersion in comparison to those coated with an acrylic-albumin dispersion. One potential reason for these results may be related to pore formation in the film due to solvation of the protein during dissolution. This was studied indirectly by investigating the amount of protein released in the media from cast films of EUDRAGIT® RS/RL 30 D (95:5), 15% TEC, and either 10% albumin or type B gelatin. The release of albumin in the dissolution media was found to be a function of pH, as seen in Fig. 7. At a media pH of 1.2, albumin was released into the dissolution media. The acidic environment changed the net charge of the albumin molecule to positive, resulting in albumin release from the film due to charge-charge repulsion with the quaternary ammonium group of the acrylic polymer. The drug release in 0.1 N HCl was faster with 100% of theophylline being released within 2–3 hr (data not shown). At pH 7.4, a detectable amount of albumin was released in the dissolution media; however, this

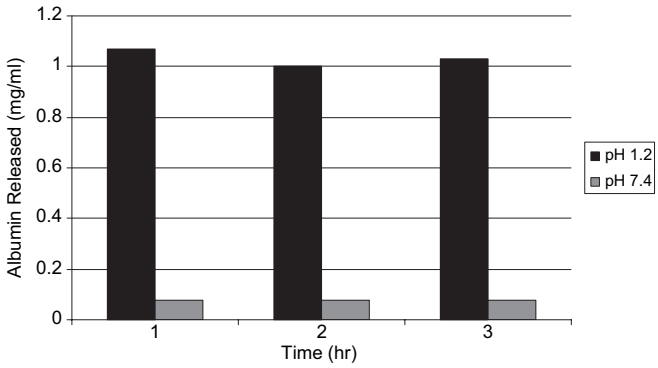

FIGURE 7 **The effect of dissolution media pH on the release of albumin from EUDRAGIT® RS/RL 30 D films plasticized with TEC (*n* = 5).**

amount was below the limits of quantification in the assay used. At this pH, the film was in an environment above the isoelectric point of the albumin, retaining the net negative charge and thus keeping the albumin bound to the acrylic polymer. When latex films containing gelatin were investigated, the amount of gelatin free in solution was below the limits of detection at both pH 1.2 and 7.4. These data show that gelatin did not dissolve to create pores through which theophylline would diffuse, but rather formed diffusional domains due to entanglement of the high molecular weight polypeptide with the acrylic polymer which altered the rate of diffusion of the drug through the membrane. This is further supported by the lag time in drug release rate seen in Figs. 1–4 and the increased rate of theophylline release seen in Figs. 5 and 6. The acrylic latex is a copolymer of acrylic and methacrylic acid esters with hydrophilic quaternary ammonium groups, which are responsible for the polymer's ability to swell when exposed to aqueous media (Zheng & McGinity, 2005). The initial delay of drug release in formulations coated with acrylic-albumin dispersions shows that the polymer was the rate controlling membrane for drug release. Conversely, the faster release of theophylline from gelatin-containing formulations was due to the gelatin phase of the coating being responsible for the increase in the drug release rate.

CONCLUSION

The addition of 10% Type B gelatin to EUDRAGIT® RS/RL 30 D films plasticized with 15% TEC stabilized theophylline release profiles, with no change in the release rate for pellets stored at 40°C and 75% relative humidity in both open and closed containers, with the mechanism being due to the stabilization of the water vapor permeability parameter. The hydrophilic gelatin molecule resulted in films which exhibited a steady water vapor transmission rate and faster release of the model drug from the coated dosage forms compared to those containing albumin. The absence of gelatin in the dissolution media during protein release studies confirmed that the increase in drug release rate resulted from gel domains which facilitated diffusion of theophylline rather than the formation of pores in the film. Complexation between albumin and the colloidal latex particles was due to changes in pH of both dispersion and dissolution media. Humidity was a factor in the stability of theophylline pellets coated with albumin-containing acrylic dispersions. A decrease in both the physicomechanical properties and water vapor permeability of these films led to a decrease in theophylline release when stored in open containers at high humidity.

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