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Research article

Influence of relative humidity on the mechanical and drug release properties of theophylline pellets coated with an acrylic polymer containing methylparaben as a non-traditional plasticizer

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Abstract

The purpose of this study was to investigate the influence of relative humidity (RH) on the mechanical and dissolution properties of theophylline pellets coated with Eudragit® RS 30 D/RL 30 D containing methylparaben (MP) as a non-traditional plasticizer. The coated beads were stored at 23°C and at different relative humidities (0, 29, 51, 75 and 84% RH). The effect of storage conditions on the rate of drug release from coated beads was determined in pH 7.4 phosphate buffer solution. The mechanical properties, including tensile strength and Young's modulus, of individual beads were determined by a diametral compression method with a Chatillon® tension/compression apparatus. The morphology of the intact and fractured beads was investigated using scanning electron microscopy (SEM). The moisture content of the polymeric films was determined using a Karl Fischer coulometric moisture analyzer. The results from the mechanical studies demonstrated that an increase in the relative humidity resulted in a decrease in the tensile strength and Young's modulus of the coated beads. SEM photographs showed that coated beads stored at 0% RH exhibited brittle fracture failure. The coated beads stored at 84% RH showed ductile behavior, which was attributed to the hydroplasticization effect on the acrylic polymer due to the uptake of moisture. The moisture content in the films was also shown to influence the rate of drug release from Eudragit® RS 30 D/RL 30 D coated beads containing MP as the plasticizer. The change in release profiles could be minimized when the relative humidity was reduced to zero. The dissolution rate of theophylline from the coated beads decreased when stored at high relative humidities. This trend was reversed when the coated beads that were stored at 84% RH for 5 weeks, were then equilibrated at 0% RH.

Keywords: Non-traditional plasticizer; Methylparaben; Relative humidity, Tensile strength; Young's modulus; Eudragit® RS 30 D; Coated beads

1. Introduction

The physical properties of polymers used for film coating are governed by several variables such as plasticization, temperature, and humidity. Many pharmaceutical polymers exhibit brittle properties and require the addition of a plasticizer to obtain an effective coating. Plasticizers function by weakening the intermolecular attractions between the polymer chains. The addition of plasticizers to film coating formulation generally results in an increase in the elongation and flexibility of films and a decrease in the tensile strength and Young's modulus [1]. Processing conditions and properties of film-coated dosage forms have also been shown to be influenced by the type and quantity of plasticizer. Currently, only a few plasticizers are approved for use in pharmaceutical film coatings due to their toxicity. Moreover, compatibility, leaching, evaporation, sticking and aging of film coated dosage forms have been reported with the traditional plasticizers in pharmaceutical aqueous film coatings [2–5].

The influence of preservatives, surfactants and drugs on the plasticization of proteins and polymers has been investigated [6–8]. The plasticizing properties of methylparaben and propylparaben in a pseudolatex dispersion of zein were reported by O'Donnell et al. [6]. Methyparaben, ibuprofen and chlorpheniramine maleate have previously been investigated for their influence on the thermal and mechanical properties of polymeric films of Eudragit® RS 30 D and on the rate of drug release from Eudragit® RS 30 D coated beads [8]. The addition of methylparaben to Eudragit® RS 30 D resulted in significant changes in the mechanical properties, making the polymer softer and more flexible. The glass transition temperature (T_g) of the polymer was significantly reduced and the elongation of the acrylic film

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containing 30% w/w methylparaben was found to increase by nearly 7-fold [8].

Water absorbed from the atmosphere can act as a plasticizer in polymeric films, altering the properties of the polymer to a considerable extent [9,10]. The presence of moisture in polymers has been reported to significantly influence drug release, stability, and the physico-chemical and mechanical properties of pharmaceutical dosage forms [11,12]. The effect of absorbed water on the properties of polymers has been studied by many workers [13,14]. The influence of storage humidity on the mechanical properties of films obtained from aqueous dispersions of acrylic and cellulosic polymers was reported by Bodmeier and Paeratakul [15]. Aulton et al. [16] found that exposing unplasticized films to high humidities resulted in significant changes in the mechanical properties and these results were consistent with a plasticizing action. Similar results were also reported by Masilungan and Lordi [17] who showed that the softening temperature of unplasticized HPMC films was reduced after 8 weeks of storage at 79% relative humidity.

The results in a previous study demonstrated that methylparaben was an effective plasticizer for Eudragit® RS 30 D [8]. The ubiquitous presence of moisture and the hydrophilic nature of the Eudragit® RS 30 D polymer is of considerable interest. During storage at different humidity conditions, a film-coated product may undergo changes in physicochemical characteristics that can affect the release property of the coated dosage forms. In order to retain the initial dissolution profiles of the Eudragit® RS 30 D coated beads throughout their shelf-life, the storage humidity conditions should be specified. In the current study, we have investigated the influence of relative humidity on the dissolution rate and mechanical properties of theophylline beads coated with Eudragit® RS30D containing methylparaben (MP) as a non-traditional plasticizer.

2. Materials

Eudragit® RS 30 D and RL 30 D were donated by Röhm America Inc. (Somerset, NJ). Methylparaben was purchased from Chemical Mfg. Corp. (Gardena, CA). Triethyl citrate (TEC) and dibutyl sebacate (DBS) were donated by Morflex Inc. (Greensboro, NC). Theophylline was purchased from Sigma Chemical Co. (St. Louis, MO). Microcrystalline cellulose (Avicel PH 101) was donated by FMC Corp (Princeton, NJ). Polyvinylpyrrolidone (*K* value 29–32) was obtained from ISP Technologies, Inc. (Wayne, NJ).

3. Methods

3.1. Bead preparation

Microcrystalline cellulose (MCC) (Avicel PH 101) and polyvinylpyrrolidone (PVP) were used as excipients and theophylline was used as the model drug in the bead formulations. The ratio of the three components in the pellet formulations was 65:10:25 (MCC:PVP:theophylline). A dry powder blend of microcrystalline cellulose and theophylline was mixed for 20 min using a twin-shell blender. The PVP aqueous dispersion (20%) was added as the granulating binder in the wet massing process. The moistened mass was extruded using a LCI Benchtop Granulator (LCI Corp., Charlotte, NC). The rotation speed of the impeller was controlled at 25 rev./min. The extrudates were spheronized using a Caleva Model 120 Spheronizer (G.B. Caleva Ltd., Dorset, UK) by setting the spheronization speed and residence time at 1000 rev./min and 15 min, respectively. The moistured spheronized beads were then dried at 40°C for 48 h.

3.2. Preparation of coated beads

The Eudragit® RS 30 D and Eudragit® RL 30 D were mixed in a ratio of 95:5. The acrylic coating suspensions were prepared by adding deionized water to the Eudragit® RS/RL polymeric dispersion to decrease the solids content to 15%. Methylparaben was added at the 15 or 20% level (based on the dry polymer weight) and stirred at room temperature with the acrylic dispersions for 24 h prior to film coating the pellets. Theophylline-containing beads, 14–18 mesh, were coated with 10% Eudragit® RS 30 D/RL 30 D (95:5) polymers in a fluid-bed coater (Uni-Glatt Laboratory Unit, Glatt Air Technique, NJ) using a method previously reported [8]. A 300-g batch of beads was placed in the fluid-bed coater and pre-warmed for 15 min prior to spraying. Inlet bed temperatures were held between 35 and 40°C. The atomizing air pressure was 2.0 kg/cm^2. The Eudragit® RS 30 D/RL 30 D polymer dispersions were applied at a rate of 2.0 g/min. The aqueous dispersion was stirred continuously throughout the coating process. To promote further coalescence of the polymeric film and to assure that the distribution of the non-traditional plasticizer was homogeneous, the coated beads were tray-dried at 40°C for 48 h in an air circulated oven. The dried beads were then stored at 0% RH and 23°C prior to further testing.

3.3. Thermal analysis of films

The glass transition temperature (T_g) of the polymeric films from coated beads was evaluated using a differential scanning calorimeter (Modulated DSC, TA Instruments, Inc., New Castle, DE). Polymeric films were carefully removed from the coated beads using a scalpel. Film samples (10-15 mg) were accurately weighed into aluminum pans and then sealed. The samples were tested under a nitrogen atmosphere at a heating rate of 10°C/min, over a temperature range of −20–100°C.

3.4. Moisture analysis of polymeric films

The moisture content of the polymeric films was determined using a Karl Fischer coulometric moisture analyzer

(Photovolt, Indianapolis, IN). The equipment was pre-calibrated and standardized with injections of 5 μl of pure double-distilled, deionized water. A calibration curve was constructed from injections of water ranging from 2 to 25 μl. Between each sample of polymeric film, a 5 μl injection of purified water was analyzed to ensure proper functioning of the coulometric moisture analyzer. Polymeric films were carefully removed from the coated beads using a scalpel. Approximately 10 mg of polymer was accurately weighed using a Mettler M3 microbalance (Mettler-Toledo Inc., Highstown, NJ) and immediately placed in the moisture analyzer. The time required for the dissolution of the film and the completion of the reaction was 1 min. A minimum of three samples from each lot was tested.

3.5. Mechanical analysis of coated beads

The stress-strain profiles and the mechanical properties of film coated beads, including tensile strength and Young's modulus, were determined for individual beads using a Chatillon® TCD-200 tension/compression tester (Chatillon, Greensboro, NC) equipped with a DFGS50 force gauge. A personal computer (Leading Edge, Westborough, MA) recorded the force (kg), measured by the gauge, and the displacement (mm) every 0.01 mm that the plate moved. The methods used to determine the tensile strength and Young's modulus of uncoated and coated individual beads have been described previously [18,19]. Coated beads with a particle size of 1.2 mm in diameter, were stored at different relative humidities for 5 weeks prior to mechanical testing. The force-deflection data ($n = 20$) were mathematically converted to stress–strain profiles. The Young's modulus was calculated from the linear portion of the stress–strain curve.

3.6. Scanning electron microscopy (SEM) of coated beads

SEM (JEOL microscope, model JSM-35C) was used to study the morphology of the intact and fractured film-coated beads after being compressed in a Chatillon® TCD-200 tension/compression tester. The samples were coated with gold–palladium using a Pelco Model 3 Sputter Coater under an argon atmosphere, and then examined with the scanning electron microscope.

3.7. Drug release studies

The USP XXIII Method II (paddle) was used to investigate the dissolution properties of theophylline from coated beads in 900 ml of medium, maintained at 37°C over a 12 h period. The media were agitated at 100 rev./min and samples were taken at specified time intervals and analyzed spectrophotometrically at 271 nm for theophylline content. The dissolution media consisted of 50 mM sodium phosphate buffer at pH 7.4. The cumulative percent drug release-time profiles were determined using 15 and 20% methylparaben (w/w, based on dry polymer weight) in the film coating.

3.8. Relative humidity

Saturated salt solutions were used to maintain a specific relative humidity in closed desiccators for the stability studies. The salts used in this study were of analytical grade and distilled water was used as the solvent. It has been reported that the RHs of saturated salts ($CaCl_2{\cdot}6H_2O$, $Ca(NO_3)_2{\cdot}4H_2O$, NaCl, KCl) were 29, 51, 75 and 84%, respectively, at 23°C [20]. A series of saturated salt solutions were prepared at 50°C and equilibrated for 1 week at 23°C prior to measurements. The RHs inside the desiccators were monitored using a digital hygrometer (VWR Scientific Products). The coated beads were exposed to different relative humidities at 23°C. The samples were removed at various time points and analyzed for drug release, moisture content, and mechanical properties.

4. Results and discussion

Both drug release and mechanical properties of coated beads are related to molecular chain mobility of the film-coating polymer which in turn is affected by parameters pertaining particularly to storage humidity conditions and composition of films. Glass transition temperature (T_g) is of great importance in both coating processing and the storage of the polymer coated dosage forms. The T_g is a specific measurement of the chain mobility of the polymer.

The results in Table 1 demonstrate the influence of relative humidity on the moisture content and T_g of the Eudragit® RS 30 D/RL 30 D (95:5) polymer containing 15% MP. The coated beads were equilibrated at 84% RH for 5 weeks,

Table 1
The moisture content and glass transition temperature of Eudragit® RS 30 D film containing 15% methylparaben stored at different relative humidity conditions

RH change from 84 to 0%	Moisture content (%)	Glass transition temperature (°C)	RH change from 0 to 84%	Moisture content (%)	Glass transition temperature (°C)
Initial beads	1.10	16.9	Initial beads	1.10	16.9
84% RH for 5 weeks	3.99	11.4	0% RH for 5 weeks	0.95	17.8
84% RH 5 weeks and 0% RH 2 weeks	2.89	13.2	0% RH 5 weeks and 84% RH 2 weeks	2.55	13.7
84% RH 5 weeks and 0% RH 5 weeks	1.45	15.2	0% RH 5 weeks and 84% RH 5 weeks	2.87	12.4

and then stored at 0% RH for either 2 or 5 weeks. The change in moisture content and T_g of the polymer was found to be similar to that of the initial film-coated beads, which demonstrated that the moisture content and thermal properties can be reversed after coated beads that were stored at a high humidity condition were equilibrated in a low humidity environment. When the coated beads were equilibrated at 0% RH for 5 weeks, and then moved to 84% RH for a further 2 or 5 weeks, the higher storage humidity led to a higher moisture content in the acrylic films and a lower T_g for the polymer. The T_g of a polymer can be significantly affected by the presence of moisture. This phenomenon may be explained by a mechanism that entails the replacement of inter-catenary hydrogen bonds by an interaction with water. Consistent with this explanation is the reversible change in mechanical properties of the polymer, since these properties have been considered to be related to the concentration of inter-catenary or inter-chain hydrogen bonds [24]. The polar nature of water and the chemical functionalities that are present in polymers, have often been the source of speculation with regard to the role of water–polymer interactions in the depression of T_g in these polymers [25–27].

The selection of a specific polymer for film-coated solid dosage forms is largely determined by its predominant drug release or failure mechanism. It is, therefore, very important to be able to predict the failure mechanism of polymeric film-coated beads as a function of the storage conditions. Compression testing of the coated beads was conducted using a Chatillon® digital force gauge and test stand. This equipment has previously been described in detail [8,18,19,21–23]. Typical stress–strain profiles of individual Eudragit® RS 30 D/RL 30 D (95:5) coated beads that were stored at 0–84% relative humidity, are shown in Fig. 1. The initial linear region in the curve suggests elastic deformation of the polymeric film. The slope of the linear portion of the curve was used to calculate the elastic or Young's modulus. An increase in the slope of the curve resulted from an increase in the elastic modulus, and as the stiffness and the strength of the polymeric film increased, then more stress would be required to produce a given amount of deformation. When stressed beyond the yield point, the coated beads either failed immediately (in the case of 0% RH) or continued to deform in a non-linear manner (as was the case for pellets stored at 84% RH). Based on theories of elasticity, ductile failure and brittle fracture occur when the shear stress and the tensile stress reach their maximum values, respectively. Increasing the relative humidity at which the coated beads were stored led to a reduction in the maximum force at fracture as seen in Fig. 1. These results demonstrated a significant increase in the flexibility of the polymeric films, presumably due to the plasticization effect of the absorbed moisture when the relative humidity was increased.

No significant plastic deformation prior to the yield point of the beads was found from the profiles in Fig. 1, irrespective of the relative humidity. However, the relative humidity had a significant influence on the fracture pattern of beads as seen in the post-peak regions of the stress–strain profiles. The fracture behavior of individual coated beads was also significantly changed by the storage humidity. The SEM photographs demonstrated a brittle fracture behavior for coated beads that were stored at 0% RH for 5 weeks, as shown in Fig. 2A. The beads stored at 0% RH generally demonstrated a sharp decline in stress after the coated beads were fractured. The beads split into several fragments at the stress of fracture and a few large fragments remained on the lower platen of the Chatillon® gauge. Thus, no residual stress was detected. However, the coated beads stored at 84% RH showed ductile behavior, as seen in Fig. 2B, where the beads flattened to a plate-like shape after fracturing. Since the mobility of molecules determines the ductility of a material, the moisture was shown to change the mobility of the polymeric chains due to the uptake of water into the polymeric film. The transition from a brittle fracture behavior to ductile behavior was found to take place at 51% RH (Fig. 2C). The brittle-to-ductile transition of the coated beads resulted from a hydroplasticization effect on the acrylic polymer due to the uptake of moisture by the plasticizer. When moisture was removed, the coated beads demonstrated a brittle fracture pattern.

The tensile strength of the coated beads decreased as the relative humidity increased for both 15 and 20% methylparaben levels in the polymer, as displayed in Fig. 3. The higher moisture content in polymeric films provided increased intermolecular freedom for the polymeric molecules to move, thereby lowering the tensile strength of the single bead. The Young's modulus of individual film-coated beads also decreased with an increase in the relative humidity, as seen in Fig. 4. The tensile strength and Young's modulus results demonstrated that the influence of storage relative humidity on polymer properties coincided with the changes in the mechanical properties of the coated beads. Young's modulus is a key indicator of the stiffness or rigidity of polymeric films and quantifies the resistance of the film to mechanical deformation. The moduli of a polymer generally increase with increasing chain stiffness and with increasing cohesive energy density. Moisture incorporated into the polymer matrix interposes itself between the polymer chains, resulting in a decrease in both chain stiffness and cohesive energy density. The network of non-bonded inter-chain interactions plays an especially crucial role in determining the magnitudes of the moduli of a polymer [28]. The presence of functional groups in a polymer determines the various types of interactions such as hydrophilic, van der Waals, and electrostatic. The inter-chain interaction between polymer and water results in the plasticization effect of moisture on the polymer, and therefore causes the changes in mechanical properties of the coated beads.

Fig. 5 shows the influence of relative humidity on the release rate of theophylline from beads coated with 10% Eudragit® RS 30 D/RL 30 D (95:5) polymer containing

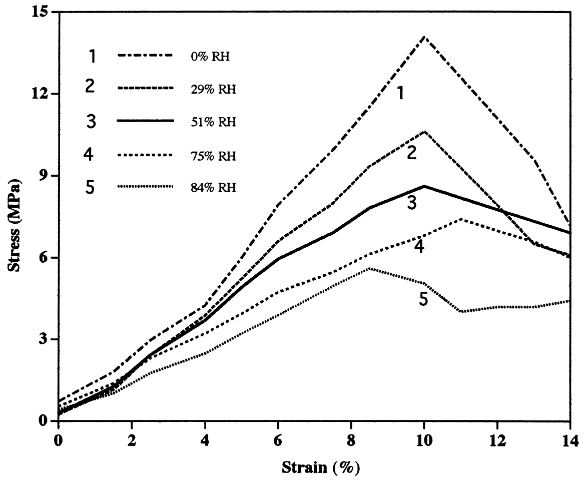

Fig. 1. Representative stress–stain curves of coated beads containing 20%

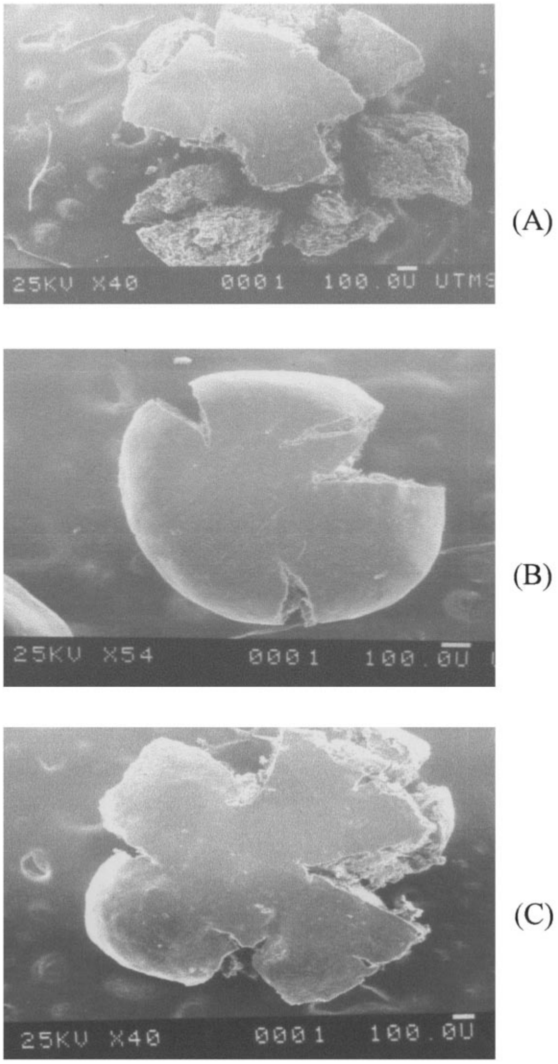

Fig. 2. Influence of relative humidity on the fracture behavior of beads coated with 10% Eudragit® RS 30 D/RL 30 D (95:5) containing 20% methylparaben (dry polymer weight). (A) 0% RH for 5 weeks, (B) 84% RH for 5 weeks, (C) 51% RH for 5 weeks.

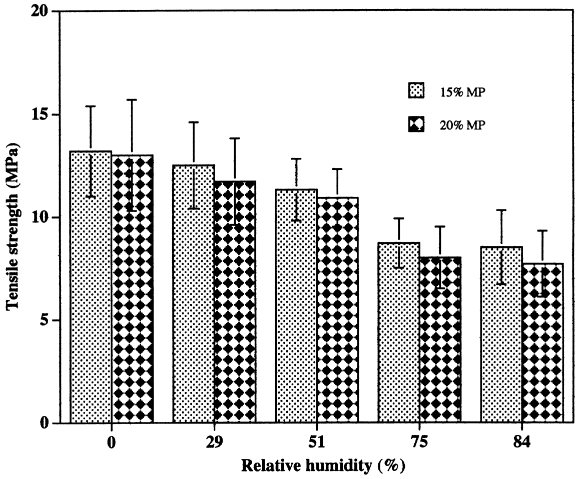

Fig. 3. Influence of relative humidity (5 weeks) on the tensile strength of theophylline beads coated with 10% Eudragit® RS 30 D/RL 30 D (95:5) containing 15 and 20% methylparaben as a non-traditional plasticizer ($n = 20$).

20% MP as the plasticizer. Drug release from coated beads was highly dependent on the relative humidity. A decrease in drug release rate was observed from coated beads stored at the higher relative humidity. These results are in agreement with the findings of Amigi and Moes who reported that drug release rates from beads coated with Eudragit® RS 30 D and plasticized with triethyl citrate were significantly reduced when the coated beads were stored at higher levels of relative humidity [3].

Coated beads equilibrated at 0% RH for 5 weeks were then stored at 84% RH and the data are presented in Fig. 6. The drug dissolution rate from the coated beads decreased as the storage time at 84% RH was increased. These findings were, as shown in Table 1, associated with a corresponding

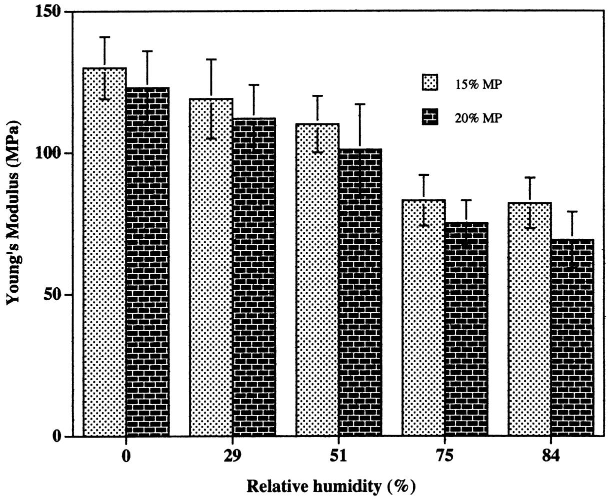

Fig. 4. Influence of storage relative humidity (5 weeks) on the Young's modulus of theophylline beads coated with 10% Eudragit® RS 30 D/RL 30 D (95:5) containing 15 and 20% methylparaben as the non-traditional plasticizer ($n = 20$).

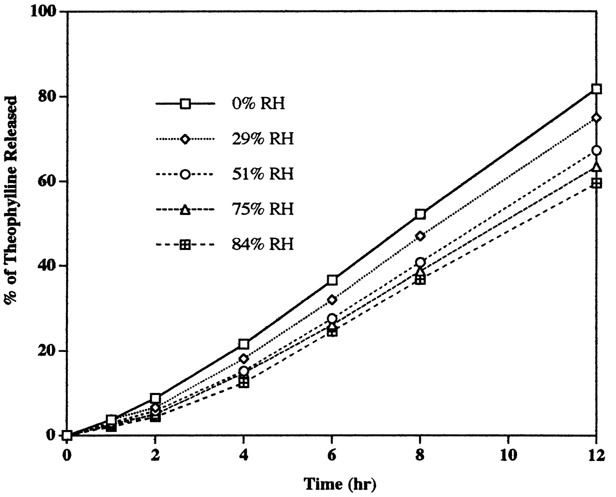

Fig. 5. Influence of relative humidity (5 weeks) on the release profiles of theopyhylline from beads coated with 10% Eudragit® RS 30 D/RL 30 D (95:5) containing 20% methylparaben as a non-traditional plasticizer.

change in the moisture content in the polymeric films due to a hydroplasticization of the polymer.

The coated theophylline beads that were stored at 84% RH for 5 weeks were then transferred to a 0% RH environmental condition. The dissolution profiles of the theophylline beads coated with Eudragit® RS 30 D/RL 30 D (95:5) containing 15 or 20% methylparaben as a non-traditional plasticizer are shown in Fig. 7. The dissolution rate of theophylline from beads that had been stored at 84% RH increased with increasing storage time at 0% relative humidity. Moreover, a more rapid reversion in the dissolution profile was found for the coated beads that were stored at 84% RH for 5 weeks and equilibrated at 0% RH for 5 weeks. These results demonstrated that the release profiles could be stabilized when the relative humidity was reduced to zero. The effect of storage time at 23°C on the dissolution rate of theophylline from coated beads is shown in Fig. 8. No significant differences were found in the dissolution profiles of theophylline from coated beads when stored for 6 months at 23°C and zero percent relative humidity.

In conclusion, an increase in the storage relative humidity resulted in a decrease in both the tensile strength and the Young's modulus of beads coated with Eudragit® RS 30 D/RL 30 D containing methylparaben as a non-traditional plasticizer. The coated beads exhibited a brittle fracture behavior when stored at 0% RH and were ductile following equilibration at 84% RH. This phenomenon is attributed to the hydroplasticization effect on the acrylic polymer due to the uptake of moisture by the plasticizer and the polymer. The dissolution rate of theophylline from the coated beads was found to decrease as relative humidity was increased. A reversion of the dissolution profiles was found when the coated beads that were initially stored at 84% RH for 5 weeks, were then stored at 0% RH for a further 5 week period. These findings were associated with the corresponding changes in the moisture content in the polymeric film coating. The results of this study suggest that the acrylic polymer coated beads containing methylparaben as the plas-

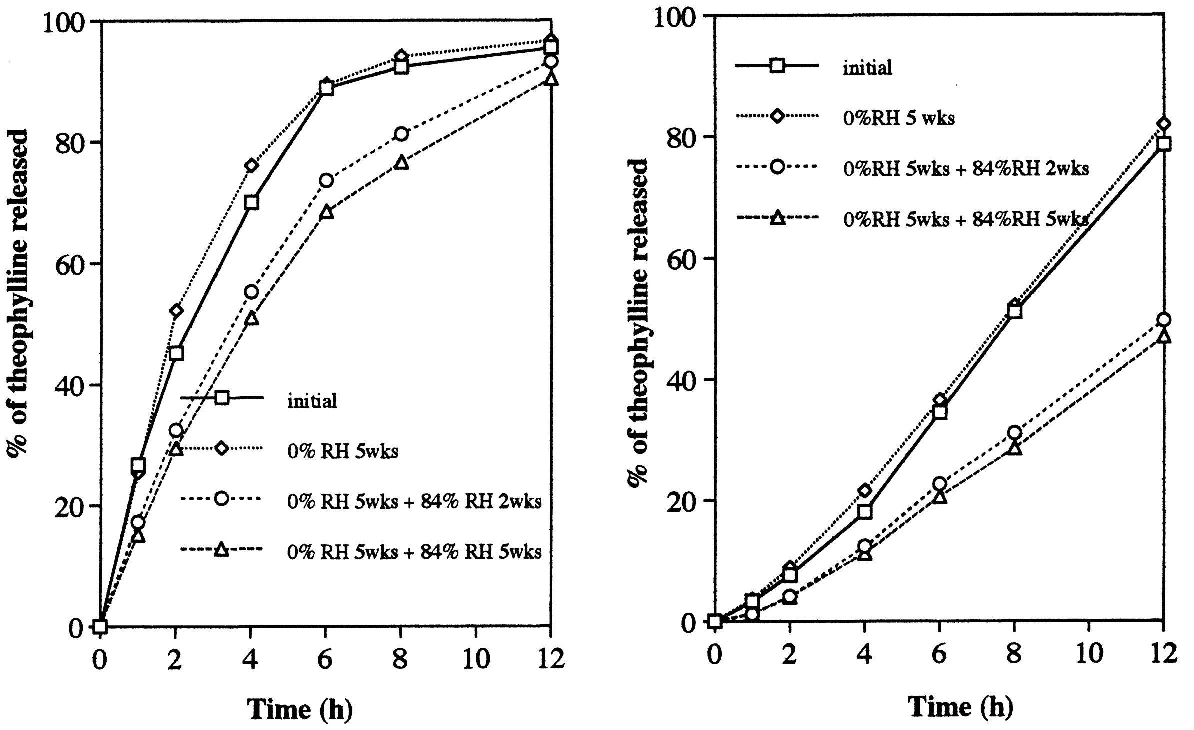

Fig. 6. Dissolution profiles of theophylline beads coated with 10% Eudragit® RS 30 D/RL 30 D (95:5) containing 15 (left) or 20% (right) methylparaben at a relative humidity change from 0 to 84% RH.

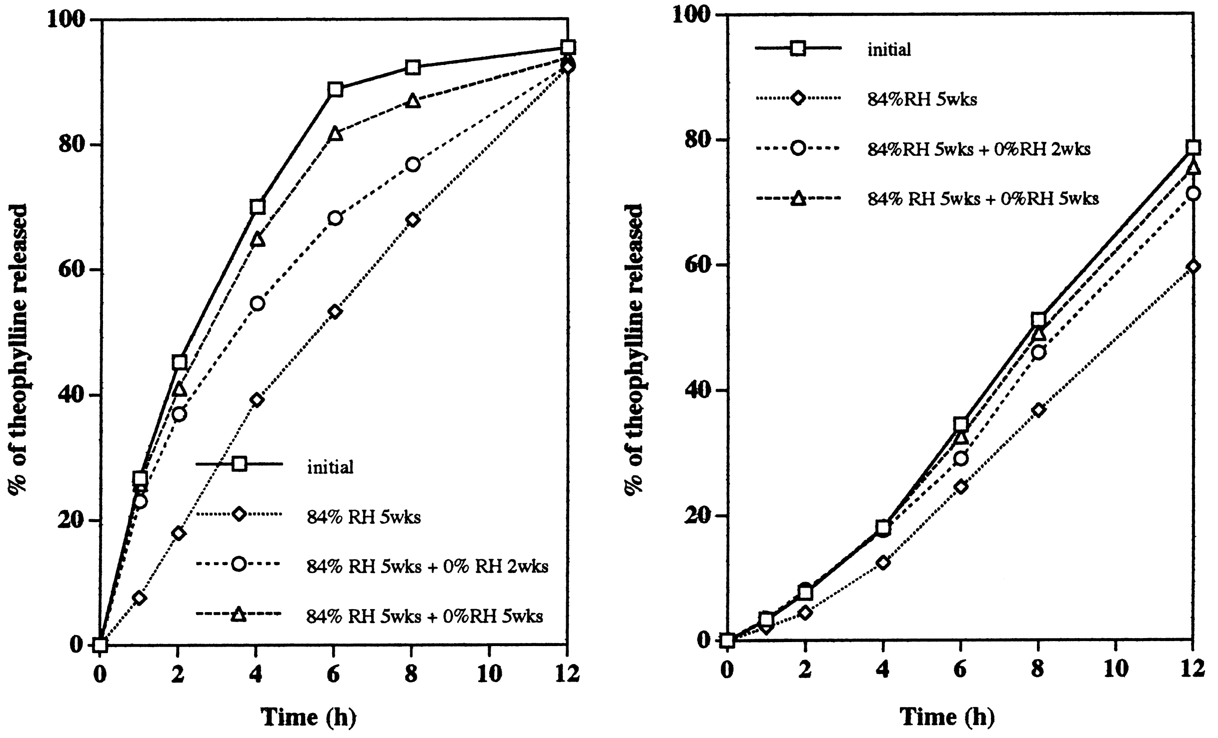

Fig. 7. Dissolution profiles of theophylline beads coated with 10% Eudragit® RS 30 D/RL 30 D (95:5) containing 15 (left) or 20% (right) methylparaben at a relative humidity change from 84 to 0% RH.

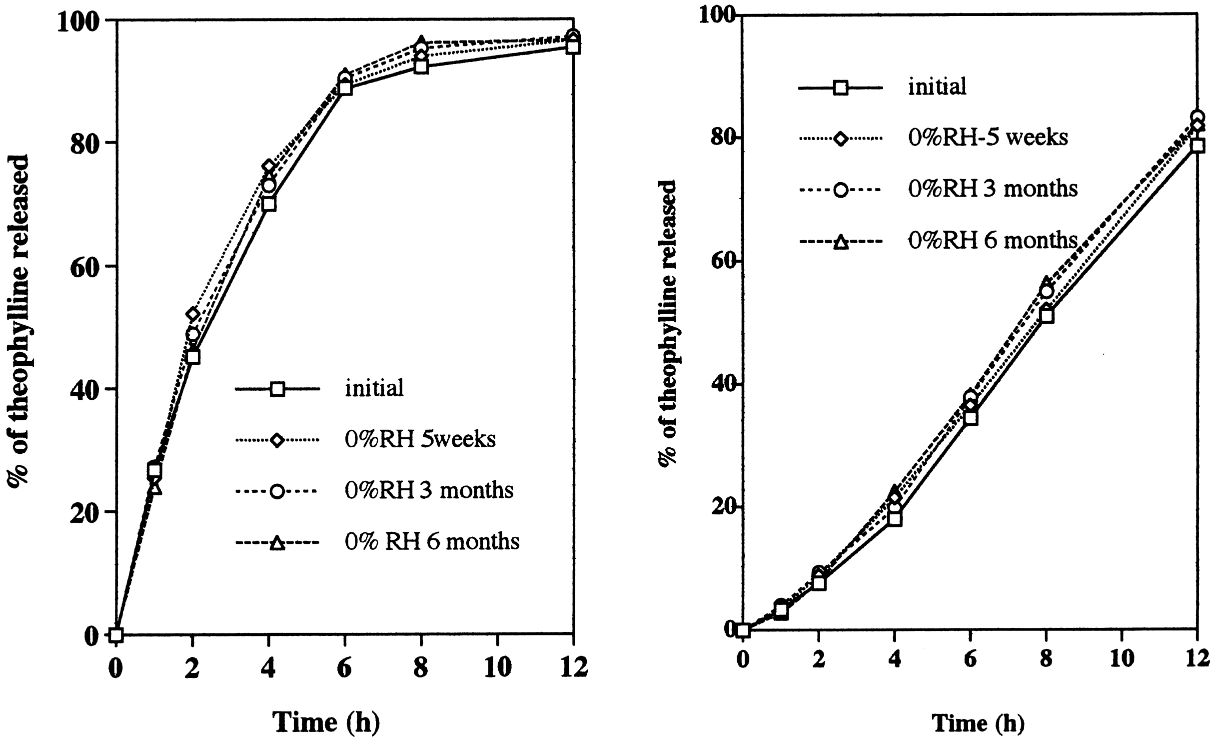

Fig. 8. Influence of storage time at 0% RH on the release profiles of theophlline from pellets coated with 10% Eudragit® RS 30 D/RL 30 D (95/5) containing 15 (left) or 20% (right) methylparaben as a non-traditional plasticizer using the USP paddle method.

ticizer should be stored at low relative humidity conditions in order to minimize the change in mechanical and drug release properties throughout the shelf-life of the coated dosage form.

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