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International Journal of Pharmaceutics 323 (2006) 11–17
INTERNATIONAL JOURNAL OF PHARMACEUTICS
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Relationship between drug dissolution and leaching of plasticizer for pellets coated with an aqueous Eudragit® S100:L100 dispersion

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Received 26 September 2005; received in revised form 28 April 2006; accepted 23 May 2006
Available online 27 May 2006

Abstract

In order to investigate the relationship between drug dissolution and leaching of plasticizer, theophylline pellets coated with 30% (w/w) Eudragit® S100:L100 (1:1) plasticized with different levels of triethyl citrate (TEC) were prepared. The influence of storage conditions on the dissolution profile of theophylline and leaching of TEC was determined.

Theophylline was found to dissolve completely from pellets coated with Eudragit® S100:L100 (1:1) plasticized with 50% TEC at pH 6.0 after 2 h. The shape of the pellets was maintained during dissolution testing. Cracks due to the leaching of TEC were observed in the scanning electron micrographs (SEMs) following dissolution testing at pH 6.0. Both the dissolution of theophylline and the leaching of TEC decreased during storage due to further coalescence of the acrylic polymers. The dissolution profiles of theophylline showed a biphasic pattern and the lag times were estimated as the time points at which a second, rapid release of theophylline was initiated. Subsequently, the percent of TEC leached at the lag time was calculated. While the lag time was increased by storage time and humidity, the percent of TEC leached at the lag time was unchanged as a function of storage condition and was dependent on the initial TEC levels in the films.

In conclusion, the plasticizer content in the film coating influenced the dissolution profile of theophylline from pellets coated with Eudragit® S100:L100 (1:1). A large amount of the TEC was leached from the enteric films before drug release was initiated and a TEC level of approximately 30% in the films, based on the polymer weight, was the critical amount of TEC for initiating drug release during dissolution testing at pH 6.0. While enteric films are more soluble and dissolve faster at higher pH values, the kinetics of plasticizer release was one of the important factors controlling the dissolution of drugs at pH 6.0, at which pH the enteric polymers were insoluble.

Keywords: Theophylline; Aqueous film coating; Eudragit® S100; Eudragit® L100; Triethyl citrate

1. Introduction

Polymeric film coatings have been used to control drug release from solid pharmaceutical dosage forms (McGinity, 1997). In the coating process, plasticizers are often required to reduce the brittleness of the polymeric films. An aqueous polymeric dispersion is generally preferred over solvent based solutions because of safety and environmental concerns and these systems exhibit a lower viscosity than organic-based solutions at the same solids content. The incorporation of plasticizers into the coating formulation reduces the minimum film formation temperature (MFT) and promotes film formation. Various studies regarding the influence of plasticizer concentration on the physicochemical properties of polymeric films and the dissolution properties of drugs from coated products have been reported in the scientific literature (Saettone et al., 1995; Ocarter and Singla, 2000; Lecomte et al., 2004). For example, higher levels of plasticizers in polymeric films was shown to decrease metoprolol release from pellets coated with Eudragit® RS 30D (Ocarter and Singla, 2000) and to improve the stability of theophylline release after storage of coated pellets (Amighi and Moës, 1996). Furthermore, the types of plasticizers have also been shown to affect the drug release rate. For example, release of propranolol from pellets coated with the mixture of ethylcellulose and Eudragit® L100-55 was faster when a hydrophilic plasticizer, triethyl citrate (TEC), was incorporated into the coating compared with a hydrophobic plasticizer, dibutyl sebacate (Lecomte et al., 2004). Other researchers have demonstrated that plasticizers can be

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doi:10.1016/j.ijpharm.2006.05.043

leached from films during dissolution and this will influence both the mechanical and drug release properties (Bodmeier and Paeratakul, 1992, 1994a, 1994b; Frohoff-Hülsmann et al., 1999). Few reports on the relationship between drug release and leaching of the plasticizers during dissolution have been published for enteric polymers systems.

The methacrylic acid–methyl methacrylic acid copolymers including Eudragit® L100 and Eudragit® S100, which begin to dissolve at pH 6.0 and 7.0, respectively, are commonly used enteric polymers. Recent studies have focused on the combination of these acrylic enteric polymers to target drug delivery to the colon (Khan et al., 1999; Lecomte et al., 2004; Bando and McGinity, 2006). Since the MFT of these polymers is higher than normal coating temperatures (Lehmann, 1997), TEC levels of 50% and higher are recommended for aqueous dispersions. Despite the requirement of such high levels of TEC, few reports on leaching of the plasticizers from aqueous Eudragit® S100 and L100 films have been published. In our previous study (Bando and McGinity, 2006), leaching of TEC from cast films composed of Eudragit® S100:L100 (1:1) was reported to be dependent on the casting solvents, where the plasticizer diffused from aqueous based films more rapidly than from films prepared from organic solutions. In the current study, in order to investigate the relationship between drug dissolution and leaching of the plasticizer, theophylline pellets coated with 30% (w/w) Eudragit® S100:L100 (1:1) plasticized with different levels of TEC were prepared and the dissolution properties of theophylline and leaching of TEC from the film coating were simultaneously determined as a function of storage conditions.

2. Materials and methods

2.1. Materials

Theophylline as a model drug and lactose monohydrate as a diluent were purchased from Spectrum Chemical MFG. Corp. (Gardena, CA, USA). Nu-Pareil® (25/30) core pellets were supplied by CHR Hansen Inc. (Mahwah, NJ, USA) and Avicel® PH101 was donated by FMC Corp. (Newark, DE, USA). KLUCEL® (hydroxypropylcellulose, HPC-L) was supplied by Hercules Inc. (Wilmington, DE, USA). Eudragit® S100 (poly (methacrylic acid–methyl methacrylic acid) (MA-MMA) 1:2 copolymer) and Eudragit® L100 (MA-MMA 1:1 copolymer) were donated by Degussa Röhm America LLC (Piscataway, NJ, USA). Triethyl citrate (TEC) was donated by Morflex Inc. (Greensboro, NC, USA) and Altalc®500 USP (talc) as anti-tacking agent was supplied by Luzenac America (Englewood, CO, USA). Pharmacoat® 603 (hydroxypropylmethylcellulose, HPMC) was donated by Shin-Etsu Chemical Corp. Ltd. (Tokyo, Japan).

2.2. Preparation of theophylline core pellets

A 200 g batch of Nu-Pareil® (25/30) was transferred into a fluidized bed coater (Strea-1 Aeromatic-Fielder, Niro Inc., MD, USA) and theophylline pellets were prepared by layering a drug-binder dispersion (6.0% (w/w) theophylline, 6.0% (w/w) lactose monohydrate, 6.0% (w/w) Avicel® PH101, 2.0% (w/w) HPC-L, 80% (w/w) water). The inlet and outlet temperatures were 55 ± 2 °C and 35 ± 2 °C, respectively. The coating dispersion was applied at a rate of 2.0–2.5 g/min, and the pneumatic spray pressure was 1.5 bar. The coating dispersion was stirred continuously throughout the coating process to prevent sedimentation. Pellets were sieved after drying at 40 °C for 12 h, and the 16–20 mesh pellets were selected for further study.

2.3. Preparation of enteric coating dispersions

The dispersions of Eudragit® S100 and Eudragit® L100 were prepared separately and each acrylic polymer was partially neutralized by the addition of ammonia solution. The degree of neutralization was 15 mol% and 6 mol% for Eudragit® S100 and Eudragit® L100, respectively. The dispersions were stirred for 60 min prior to plasticization. After adding 50%, 70% or 100% TEC based on the polymer weight, polymer dispersions were stirred for an additional 60 min. Talc (50% based on dry polymeric weight) was previously dispersed in purified water using a POLYTRON (Brinkmann Instruments, Westbury, NY, USA) and the talc suspension was poured into the polymer dispersions. The final dispersions were prepared by adding the Eudragit® S100 slowly into the Eudragit® L100 dispersion.

2.4. Film coating

A 250 g batch of pellets (16–20 mesh) was transferred into a fluidized bed coater (Strea-1 Aeromatic-Fielder, Niro Inc., MD, USA), and the acrylic dispersions were applied until 30% (based on dry polymer weight) weight gain was achieved. The inlet and outlet temperatures were 55 ± 2 °C and 35 ± 2 °C, respectively. The coating dispersion was applied at a rate of 2.0–2.5 g/min, and the pneumatic spray pressure was 1.5 bar. The aqueous dispersion was stirred continuously throughout the coating process to prevent sedimentation. After application of the coating dispersion, the pellets were dried for an additional 10 min at 35 ± 2 °C in the fluidized bed unit, and then removed. An overcoat was added to prevent sticking of the pellets during storage. A HPMC solution including 50% talc based on HPMC weight (15% (w/w) solid) was used for this purpose (Harris and Ghebre-Sellassie, 1986) and was then applied to the pellets, resulting in an up to 5 wt.% gain as HPMC weight. Pellets were sieved after drying at 40 °C for 12 h, and the 12–16 mesh pellets were selected for further study. The coated pellets were stored at 40 °C in closed HDPE containers and 40 °C/75% RH in open containers for two months.

2.5. Dissolution of theophylline pellets

Dissolution testing of theophylline pellets was conducted using the USP 27 Apparatus II dissolution method (Paddle method, VanKel VK 6010; Cary, NC, USA) in 900 mL of media maintained at 37 °C with a paddle agitation rate of 50 rpm. The dissolution media included 0.1 N HCl or 50 mM phosphate buffered solutions (pH 6.0, 6.5 and 7.0). The pellets (ca. 400 mg)

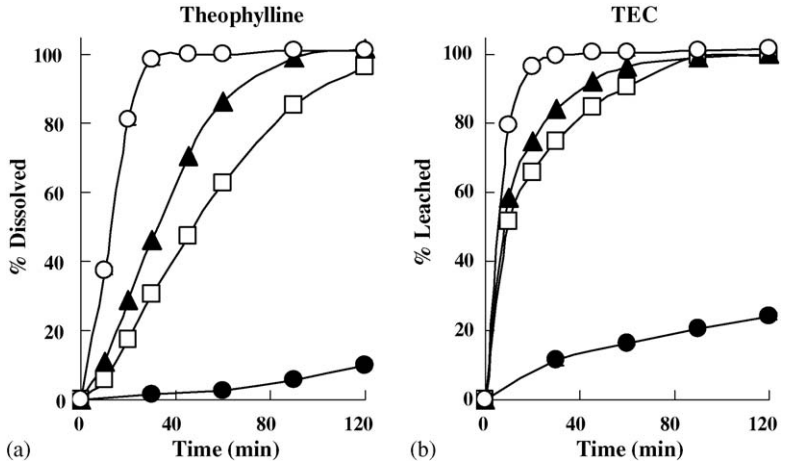

Fig. 1. Influence of media pH on (a) dissolution of theophylline and (b) leaching of TEC from pellets coated with 30% (w/w) Eudragit® S100:L100 (1:1) plasticized with 50% TEC (USP27 Apparatus II, 900 mL, 0.1 N HCl or 50 mM phosphate buffer (pH 5.5, 6.0 and 6.5), 50 rpm, 37 °C). The error bar shows the standard deviation ($n = 3$) (●) 0.1 N HCl; (□) pH 5.5; (▲) pH 6.0; (◯) pH 6.5.

were introduced into the dissolution medium, and 3 mL samples were withdrawn by an autosampler (VanKel VK 8000; Cary, NC, USA) at predetermined time points ($n = 3$). The concentration of theophylline and TEC in the dissolution media was determined using a Waters (Milford, MA, USA) high performance liquid chromatography (HPLC) system with a photodiode array detector (model 996) extracting at 270 nm for theophylline and at 210 nm for TEC. Samples were prefiltered through a 0.45 μm membrane (Whatman Inc., Clifton, NJ, USA) before injection of 50 μL by an autosampler (model 717plus). The column was a Capcell Pak C18 3 mm, 100 mm × 3.0 mm i.d. (SHISEIDO, Kyoto, Japan). The mobile phase for theophylline contained 10 mM acetate buffered solution: acetonitrile in volume ratios of 91:9 while a mixture of 25 mM pH 2.5 phosphate buffered solution: acetonitrile in volume ratios of 55:45 was used as the mobile phase for TEC. The solvents were filtered through a 0.45 μm nylon membrane and degassed by sonication. The flow rate was 0.5 mL/min. The retention times of the theophylline and TEC were approximately 4.5 and 3.5 min, respectively. The data were collected and integrated using Empower® Version 5.0 software (Des Plaines, IL, USA).

2.6. Data analysis of dissolution testing

Two parameters were determined in order to investigate the relationship between the rate of dissolution of theophylline and the leaching of TEC from the coating. The lag time was the time point at which a second, rapid release of theophylline was started and was calculated from the intersection of the linear parts of the second, rapid release phase with the *x*-axis, which represents the time scale. Subsequently, the percent of TEC leached from the polymeric films at the lag time was calculated from the leaching profiles of TEC.

2.7. Scanning electron microscopy

The surface morphology of the coated pellets before and after dissolution testing was observed with a Hitachi S-4500 field emission scanning electron microscope (Rolling Meadow, IL, USA). A gold–palladium layer was applied to the coated pellets for 50 s under an argon atmosphere using a Pelco model 3 cold sputter modules (TED Pella Inc., Tustin, CA, USA).

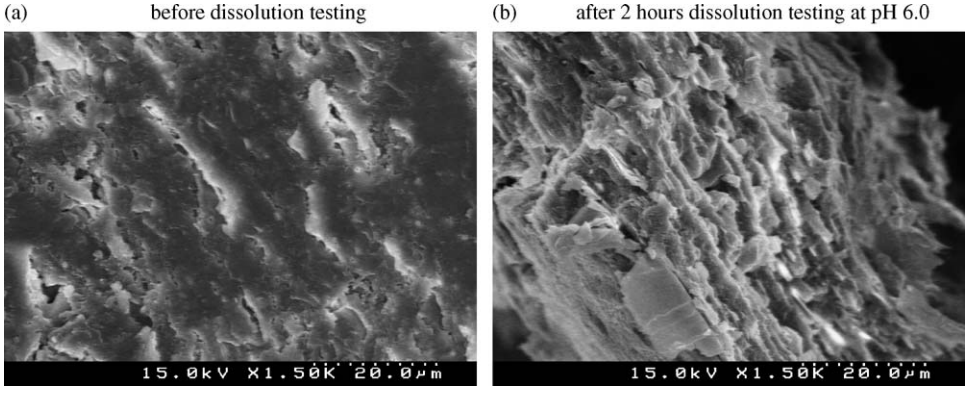

Fig. 2. SEM micrographs of theophylline pellet cross-section coated with 30% (w/w) Eudragit® S100:L100 (1:1) plasticized with 50% TEC before and after dissolution testing at pH 6.0: (a) before dissolution testing; (b) after 2 h dissolution testing at pH 6.0.

3. Results and discussion

3.1. Preparation of theophylline pellets

While overcoating with HPMC reduced pellet agglomeration, the pellets coated with the 100% TEC plasticized polymer continued to stick to each other during storage at 40 °C/75% RH, presumably due to the plasticizing effect of water absorbed into the film from the atmosphere (Nagakami et al., 1991), and thus were unsuitable for subsequent dissolution studies.

3.2. Influence of media pH on theophylline dissolution and leaching of TEC

The dissolution properties of theophylline pellets coated with 30% (w/w) Eudragit® S100:L100 (1:1) plasticized with 50% TEC were determined in acidic medium (0.1 N HCl) and in phosphate buffer (pH 5.5, 6.0 and 6.5). The concentration of TEC in the dissolution media was simultaneously determined. The results are displayed in Fig. 1. While the release of theophylline was less than 10%, approximately 25% of TEC had diffused from the acrylic coating after 2 h in acidic media. The carboxyl groups of the repeat units of Eudragit® S100 and Eudragit® L100 are unionized in 0.1 N HCl and the polymeric films have a closely packed structure, therefore dissolution of theophylline as well as the leaching of TEC in this medium was slow. These results demonstrate that the coating exhibited acid resistant properties even when approximately 25% of TEC had leached from the polymeric films. The percent of TEC leached from the film coating was higher than reported previously for cast films, where only 10% of the TEC had leached from aqueous cast films after 2 h in the acidic medium (Bando and McGinity, 2006). This difference is presumably a function of the different preparation methods (casting versus spraying). The results are consistent with an earlier report where the mechanical properties of films prepared from aqueous polymers were different for films prepared from the casting and spraying technique (Obara and MacGinity, 1994).

The release of theophylline and the leaching of TEC from the coated pellets were both a function of the pH of the dissolution media and increased with increasing pH. Theophylline was released completely within 2 h at pH 6.0 and the physical integrity of the pellets was maintained at the conclusion of the dissolution experiments. To investigate the morphological changes before and after dissolution testing at pH 6.0, theophylline pellets were observed by SEM and micrographs of the surface and cross-sections are shown in Fig. 2. While Eudragit® S100/L100 films showed a very dense structure prior to dissolution testing (Fig. 2a), some cavities were observed in the films following dissolution testing (Fig. 2b). Since both Eudragit® S100 and L100 are insoluble at pH 6.0, the formation of the cavities was attributed to the leaching of TEC from films during dissolution testing. A similar phenomenon has been reported for films composed of Eudragit® RS 30D and 40% TEC, where a porous structure was observed due to the plasticizer leaching after exposure to 0.1 M NaCl solution (Bodmeier and Paeratakul, 1992). The results from our study demonstrated that the structure of films composed of Eudragit® S100: L100 (1:1) plasticized with 50% TEC was changed during dissolution testing due to the rapid removal of the TEC at pH 6.0, in which both Eudragit® S100 and Eudragit® L100 are insoluble.

3.3. Influence of storage conditions on leaching of TEC as well as theophylline dissolution

The coated pellets were maintained in closed HDPE vials at 40 °C and in open vials at 40 °C/75% RH for two months and the influence of storage conditions on the leaching of TEC from the film coating as well as the dissolution properties of theophylline from pellets coated with 50% TEC plasticized polymer, was investigated.

The influence of two storage conditions on the dissolution properties of theophylline from film-coated pellets is shown in Fig. 3. The lag time of theophylline release became longer during storage at 40 °C in closed HDPE containers and at 40 °C/75%

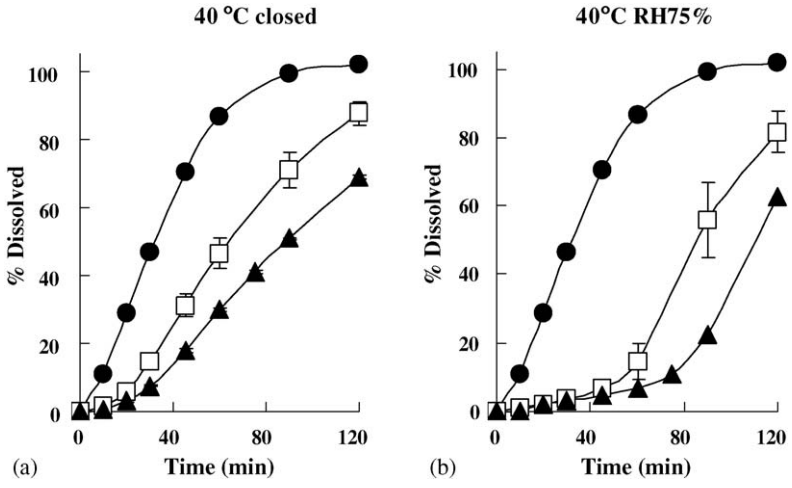

Fig. 3. Influence of storage time on dissolution of theophylline from pellets coated with 30% (w/w) Eudragit® S100:L100 (1:1) plasticized with 50% TEC at pH 6.0 (USP27 Apparatus II, 900 mL, 50 mM phosphate buffer (pH 6.0), 50 rpm, 37 °C). The error bar shows the standard deviation ($n = 3$): (●) initial; (□) one month; (▲) two months.

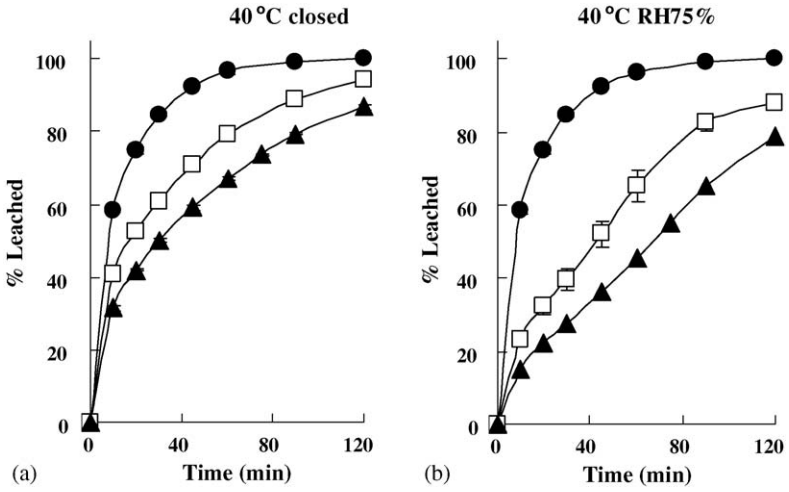

Fig. 4. Influence of storage time on leaching of TEC from pellets coated with 30% (w/w) Eudragit® S100:L100 (1:1) plasticized with 50% TEC at pH 6.0 (USP27 Apparatus II, 900 mL, 50 mM phosphate buffer (pH 6.0), 50 rpm, 37 °C). The error bar shows the standard deviation ($n = 3$): (●) initial; (□) one month; (▲) two months.

RH in open containers, due to further coalescence of the colloidal particles of the acrylic polymers. At the 40 °C/75% RH condition, longer lag time of theophylline release was observed compared with pellets stored in a closed container at 40 °C. This result demonstrated the plasticizing effect of water on the polymeric films. An increase in the water content of polymeric films (storage at 40 °C/75% RH) was reported to lower the glass transition temperature of cast films and to increase the polymer chain mobility (Nagakami et al., 1991), thereby promoting the coalescence of the latex particles at a given temperature.

The leaching profiles of TEC from pellets stored at elevated temperature are displayed in Fig. 4. Interestingly, the leaching of TEC also decreased when stored at 40 °C (closed container) and 40 °C/75% RH (open container). These results indicated that the kinetics of TEC leaching were also influenced by the degree of coalescence of the acrylic particles. The leaching of TEC has been reported to influence the mechanical properties of polymeric films and the permeability of films to water (Lecomte et al., 2004). Since the leaching of TEC also affected the dissolution properties of theophylline, the relationship between the dissolution properties of theophylline and the leaching of TEC was further investigated.

3.4. Influence of TEC level in the films on leaching of TEC as well as theophylline dissolution

To investigate the influence of TEC concentration in the films on its leaching as well as dissolution of theophylline, theophylline pellets coated with 30% (w/w) Eudragit® S100:L100 (1:1) containing different TEC levels (50%, 70% and 100% based on polymer weight) were prepared and the release rates were determined in pH 6.0 buffered media. The data from pellets stored at 40 °C in closed HDPE containers are summarized in Fig. 5. The higher TEC level in the films decreased the release rates of both theophylline and TEC from the coated pellets. The result demonstrates that the degree of coalescence of polymeric

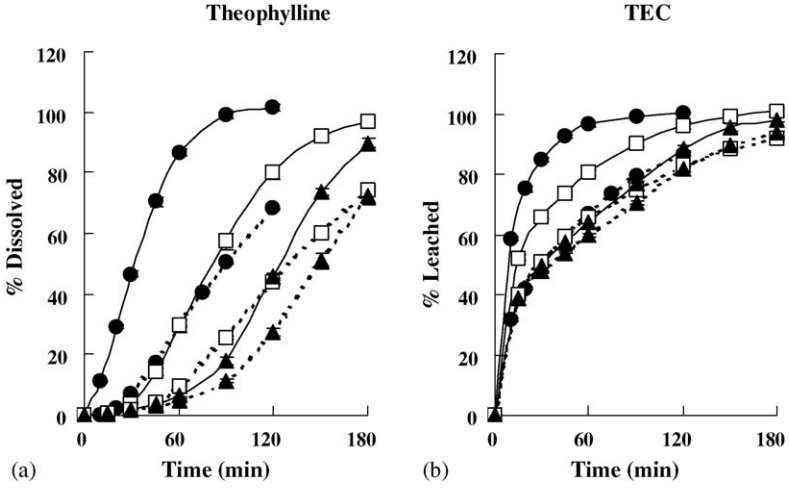

Fig. 5. Influence of TEC levels in the film on (a) dissolution of theophylline and (b) leaching of TEC from pellets coated with 30% (w/w) Eudragit® S100:L100 (1:1) at pH 6.0 (USP27 Apparatus II, 900 mL, 50 mM phosphate buffer (pH 6.0), 50 rpm, 37 °C). The error bar shows the standard deviation ($n = 3$): (-●-) 50% TEC (initial); (-□-) 70% TEC (initial); (-▲-) 100% TEC (initial); (···●···) 50% TEC (two months); (···□···) 70% TEC (two months); (···▲···) 100% TEC (two months).

particles is higher, when increased levels of TEC are present in the latex dispersions. Indeed, the initial theophylline dissolution profiles from pellets coated with the aqueous dispersion containing 100% TEC was similar to that for pellets stored in the closed vials at 40 °C for two months, indicating that an almost completely coalesced film was already formed at the end of the coating process. This gradual coalescence seemed to be much more pronounced for the pellets coated with polymeric aqueous dispersions containing lower TEC levels. Similar results were reported on chlorpheniramine maleate pellets coated with Aquacoat® (Bodmeier and Paeratakul, 1994b) and on theophylline pellets coated with Eudragit® RS30D (Amighi and Moës, 1996). No curing step was necessary to obtain good film formation when more than 25% TEC based on polymer weight was added to Aquacoat® dispersions and more than 35% TEC based on polymer weight was added to Eudragit® RS30D dispersions whereas an appropriate curing process was required to stabilize the film properties when lower plasticizer levels were selected (Bodmeier and Paeratakul, 1994b; Amighi and Moës, 1996). Since the MFTs of Eudragit® S100 (>95 °C) and L100 (>85 °C) are much higher than that of Eudragit® RS (ca. 47 °C) (Lehmann, 1997), higher amounts of TEC (approximately 100% and above based on polymer weight) were needed to form an almost totally coalesced film at the end of this coating process.

3.5. Relationship between theophylline dissolution and leaching of TEC

Since the dissolution profiles of theophylline from pellets coated with Eudragit® S100:L100 (1:1) showed a biphasic pattern, the lag times were defined as the time points at which the second, rapid release of theophylline was initiated. In this study, the lag times of the second, rapid release were calculated from the intersection of the linear portion of the dissolution profiles with the *x*-axis which represents the time scale. These biphasic dissolution profiles attributed to the leaching of TEC have been reported for propranolol HCl pellets coated with ethylcellulose:Eudragit® L30D-55 (1:1) plasticized with 25% TEC (Lecomte et al., 2004). In order to clarify the relationship between the dissolution of theophylline and the leaching of TEC, the percent of TEC leached from the films at the lag times were estimated. Since the lag time of theophylline release from fresh pellets plasticized with 50% TEC is too short, the percent of TEC leached from the pellets could not be accurately estimated. The lag times and the percent of TEC leached at the lag times are plotted in Fig. 6, for stability samples of theophylline pellets coated with Eudragit® S100:L100 (1:1) plasticized with 50% TEC except for the fresh pellets. The lag times increased with increasing storage time and humidity due to further gradual coalescence of the acrylic polymer. In contrast, the percent of TEC leached from pellets at the lag time was similar, irrespective of the storage time and humidity. For the pellets including 70% TEC and 100% TEC, the same analyses were conducted and the results are shown in Figs. 7 and 8, respectively. The lag times for the pellets including higher TEC levels were longer than that of the pellets coated with 50% TEC plasticized poly-

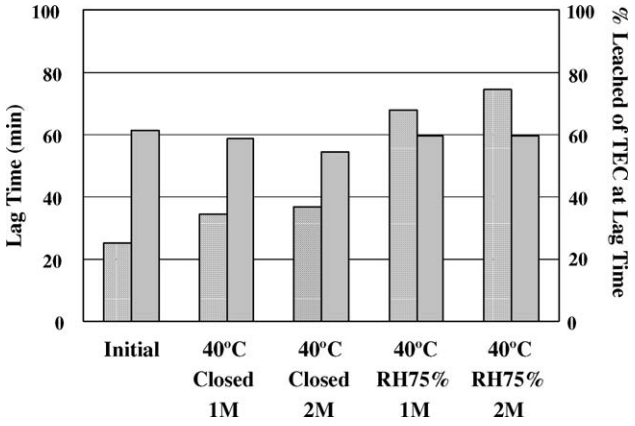

Fig. 7. Lag times of second rapid release of theophylline and percent of TEC leached at lag time from pellets coated with 30% (w/w) Eudragit® S100:L100 (1:1) plasticized with 70% TEC at pH 6.0. (▨) Lag time of second rapid release of theophylline; (■) percent TEC leached at lag time.

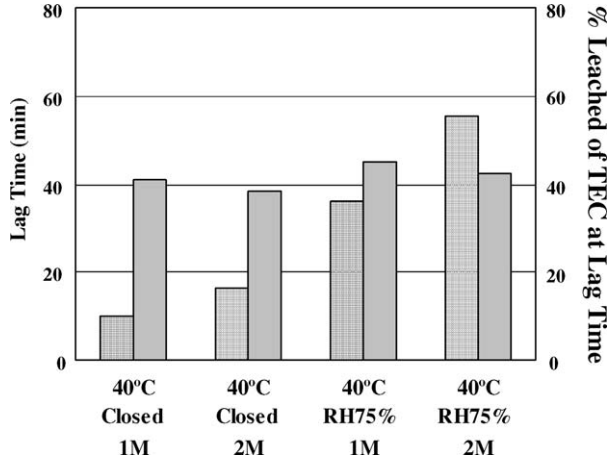

Fig. 6. Lag times of second rapid release of theophylline and percent of TEC leached at lag time from pellets coated with 30% (w/w) Eudragit® S100:L100 (1:1) plasticized with 50% TEC at pH 6.0. (▨) Lag time of second rapid release of theophylline; (■) percent TEC leached at lag time.

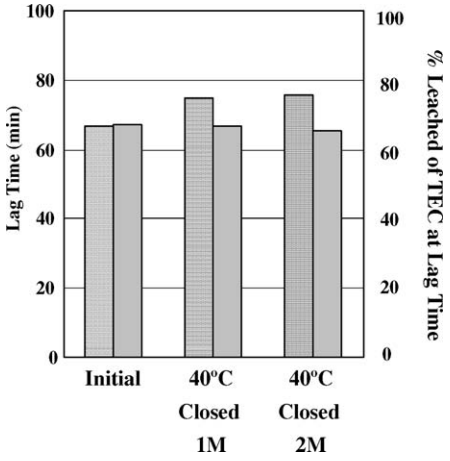

Fig. 8. Lag times of second rapid release of theophylline and percent of TEC leached at lag time from pellets coated with 30% (w/w) Eudragit® S100:L100 (1:1) plasticized with 100% TEC at pH 6.0. (▨) Lag time of second rapid release of theophylline; (■) percent TEC leached at lag time.

Table 1
Relationship between percent of TEC leached and percent TEC remaining in the films at lag times of second rapid release of theophylline

Percent of initial TEC in the films based on a polymer weight *A*	Percent leached of TEC *B*	Percent TEC remaining in the films *C*[a]
50	41.76 ± 2.85	29.1
70	57.99 ± 2.47	28.9
100	66.33 ± 0.84	33.7

[a] $C = A \times (1 - B/100)$.

mer and were also increased with increasing storage time and humidity. Interestingly, the percent of TEC leached from pellets at the lag times was also unchanged by storage conditions and the percent of TEC leached was dependent on the initial TEC levels. The amount of TEC remaining in the films at the lag times was calculated from initial TEC levels and these results as well as the percent of TEC leached from the films, are summarized in Table 1. The remaining amount of TEC in the films at the lag times was approximately 30% based on the polymer weight despite the initial TEC levels in the films.

In conclusion, the plasticizer content in the film coating influenced the dissolution properties of theophylline from pellets coated with Eudragit® S100:L100 (1:1). A large amount of the TEC was leached from the enteric films before drug release was initiated and a TEC level of approximately 30% in the films, based on the polymer weight, was the critical amount of TEC for initiating drug release during dissolution testing at pH 6.0. While the dissolution rate and solubility of enteric films will increase with an increase in the pH, the kinetics of plasticizer release was one of the principal factors controlling the dissolution of drugs in the media in which the enteric polymers were insoluble.

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