

# Physicochemical properties of enteric films prepared from aqueous dispersions and organic solutions

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## Abstract

Cast films composed of mixtures of Eudragit® S100:L100 (1:1) and plasticized with triethyl citrate (TEC) were prepared from aqueous dispersions and organic solutions, and the physicochemical properties and the weight loss of cast films during dissolution testing were examined. The tensile strength of the organic cast films was significantly higher and the percent elongation was lower than that of the aqueous cast films. The weight loss of the organic films was also lower than that of the aqueous films. Furthermore, leaching of the TEC from the aqueous films was rapid and the TEC was found to diffuse from the films within one hour at pH 6.0, the pH at which the Eudragit® S100:L100 (1:1) films were insoluble. In contrast to the aqueous films, minimal levels of the TEC diffused from the organic cast films, and the disintegration of acrylic polymers occurred simultaneously with the release of TEC from the film during dissolution testing at pH 7.0. For Eudragit® L100-55, which could form films at lower TEC levels than Eudragit® S100:L100, both the organic and aqueous films showed the same weight loss after four hours in pH 5.0 media. These results demonstrated that for Eudragit® S100:L100 cast films, the high levels of TEC needed for film formation from aqueous dispersions resulted in rapid dissolution and disintegration at pH 6.0 and above. While aqueous dispersions are preferred for the coating of solid substrates, for Eudragit® S100:L100 film coatings, a change from organic solutions to aqueous dispersions in the coating process will impact film properties and product performance.

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## 1. Introduction

Enteric coatings have been applied to solid oral dosage forms to improve the chemical stability of acid-sensitive drugs, to decrease gastric irritation and to target drug release to the colon (Khan et al., 1999; Ashford et al., 1993; Rijk et al., 1988). The enteric acrylic acid copolymers including Eudragit® L100-55, Eudragit® L100 and Eudragit® S100, are in widespread use today. Since dissolution is a function of the pH of the surrounding medium, mixtures of these polymers have been investigated for targeting drug delivery to the colon (Khan et al., 2000). These enteric polymers may be applied to solid substrates as both organic solutions and aqueous dispersions. Due to safety

and environmental concerns and a lower viscosity at the same solids content, aqueous dispersions have been preferred over organic solutions for film coating processes.

Film formation from organic polymer solutions results from the evaporation of the solvent, which initiates an increase in the polymer concentration and inter-diffusion of the polymeric chains. At higher polymer concentrations, an intermediate gel-like stage is reached and, upon further evaporation of the solvent, a solvent-free polymeric film is obtained. Film formation from aqueous polymer dispersions is more complex. During coating, the colloidal polymer particles coalesce into a film that occurs concurrently with the evaporation of water (Wheatley and Steuernagel, 1997). Irrespective of the solvent system, plasticizers play a key role in the mechanical, adhesive, and dissolution properties of films and film-coated products. A plasticizer is generally required for aqueous polymeric dispersions to reduce the minimum film formation temperature (MFT). While 10% TEC is a recommended level for organic solvent coating, more than 50% TEC based on dry polymer weight is recommended for

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aqueous latex dispersions due to the high MFTs for Eudragit<sup>®</sup> S100 and L100. Plasticizers have been reported to leach from polymeric films during dissolution testing and affect product performance (Bodmeier and Paeratakul, 1992, 1994).

Recent reports concerning the influence of coating solvents on product performance have appeared in the literature for ethylcellulose (Lecomte et al., 2004; Wesseling and Bodmeier, 1999), cellulose acetate phthalate (Wheatley and Steuernagel, 1997), Eudragit<sup>®</sup> L100-55 (Thoma and Bechtold, 1999) and Eudragit<sup>®</sup> RS/RL (Lorck et al., 1997). The dissolution rate of 5-aminosalicylic acid from pellets coated with an aqueous Eudragit<sup>®</sup> S100 dispersion was shown to be faster than from pellets coated with an organic solution due to the partial neutralization of the aqueous colloidal polymers (Rudolph et al., 2001). Results from an earlier study, however, suggested that the partial neutralizations of acrylic polymers in aqueous dispersions had a minimal effect on the dissolution properties of pellets (Lehmann, 1986). For Eudragit<sup>®</sup> S100 and L100, few studies have been conducted to investigate the effects of casting solvents on film properties. In the current study, cast films composed of mixtures of Eudragit<sup>®</sup> S100:L100 (1:1) and plasticized with TEC were prepared from aqueous dispersions and organic solutions, and the physicochemical properties and the weight loss of cast films during dissolution testing were examined.

## 2. Materials and methods

### 2.1. Materials

The following materials were employed as film-forming agents: poly(methacrylic acid–methyl methacrylic acid) (MA–MMA) 1:2 copolymer (Eudragit<sup>®</sup> S100), MA–MMA 1:1 copolymer (Eudragit<sup>®</sup> L100) and poly(methacrylic acid–ethyl acrylic acid) (MA–EA) (Eudragit<sup>®</sup> L100-55 and Eudragit<sup>®</sup> L30D-55). These polymers were donated by Degussa Röhm America LLC (Piscataway, NJ, USA). Triethyl citrate (TEC) was donated by Morflex Inc. (Greensboro, NC, USA). Ethyl alcohol was purchased from AAPER Alcohol and Chemical Co. (Shelbyville, KY, USA). Ammonium hydroxide was purchased from Fisher Scientific International Inc. (Fair Lawn, NJ, USA).

### 2.2. Preparation of cast films under aqueous conditions

Cast films were prepared from aqueous dispersions by mixing Eudragit<sup>®</sup> S100 and Eudragit<sup>®</sup> L100 in a 1:1 ratio. The aqueous dispersions were plasticized with TEC at the 50% level, based on dry polymer weight. The polymers were partially neutralized by the addition of a dilute ammonia solution. The degree of neutralization was 15 and 6 mol% for Eudragit<sup>®</sup> S100 and L100, respectively. The Eudragit<sup>®</sup> L30D-55 was plasticized with TEC at the 10% level, based on dry polymer weight. Aqueous dispersions containing 15% polymer were poured into Teflon<sup>®</sup> molds (15 cm × 15 cm × 1.0 cm) and then dried at 50 °C for 24 h to remove residual water. The molds were then placed in a 100% relative humidity chamber for 10 h to make the films flexible enough to be removed intact from the mold. Film thickness was approximately 300 μm. A surgical knife was used to cut the films

into 9 cm × 1.5 cm rectangular specimens for mechanical tests and 3 cm × 1.5 cm for the dissolution tests. The film specimens were then dried at 40 °C for 24 h and stored in a constant humidity chamber maintained at 50% relative humidity and 23 °C until the mechanical and dissolution tests were performed (Gutiérrez-Rocca and McGinity, 1993).

### 2.3. Preparation of cast films under organic conditions

The organic-based cast films were prepared from solutions of the polymers in an ethanol:water (9:1) mixture. Two levels of plasticizer were used to prepare the films: 10% and 50% TEC. Plasticizer level was based on dry polymer weight. Organic solutions containing 20% polymer (1:1 ratio of Eudragit<sup>®</sup> S100:L100 or Eudragit<sup>®</sup> L100-55) were poured into Teflon<sup>®</sup> molds (15 cm × 15 cm × 1.0 cm) and then dried at 40 °C for 24 h to remove residual ethanol/water. The molds were then placed in an ethanol vapor chamber for 3 h to make the films flexible enough to be removed intact from the mold and to be cut with a surgical knife into the same size as the aqueous cast films. The film specimens were dried at 40 °C for 24 h and stored in a constant humidity chamber maintained at 50% RH and 23 °C until the mechanical and dissolution tests were performed.

### 2.4. Thermal analysis of the films

The thermal properties of the cast films were investigated by modulated differential scanning calorimetry (MDSC model 2920, TA Instruments, New Castle, DE, USA). Film samples of 10 mg were accurately weighed into aluminum pans and then sealed. Samples were analyzed under a nitrogen atmosphere at a heating rate of 3 °C/min with 1 min modulation ramping over a temperature range from 0 to 200 °C. The glass transition temperatures were determined at the midpoint of the thermal transition using Modulated DSC Analysis V1.1A software. Three measurements were performed on each film sample. The MDSC was calibrated using an indium standard.

### 2.5. Mechanical testing of the films

The mechanical properties of the cast films were evaluated using an Instron Model 4201 universal testing apparatus. The rectangular film specimens (9 cm × 1.5 cm × 300 μm) were held in place with pneumatic grips, and the test procedure was based on the ASTM D882-75d method. Film specimens with physical defects were discarded. The initial length of the film between the grips was 4 cm, and the extension speed was 4.0 mm/min. All samples were subjected to mechanical testing following 1 week of storage. The stress–strain curves were recorded for each sample, and the tensile strength at break and the percent elongation were calculated 4 ( $n = 5$ ).

### 2.6. Dissolution testing of the film

Dissolution testing of the cast films was conducted over a 4 h period using the USP 27 Apparatus 1 (Basket Method, VanKel VK6010; Cary, NC) in 500 mL of media maintained at

37 °C with a basket rotation rate of 100 rpm ( $n = 3$ ). The dissolution media included either 0.1 N HCl or 50 mM phosphate buffered solutions (pH 5.0, 6.0, 6.5 and 7.0). The film specimens (3 cm × 1.5 cm × 300 μm) were placed in the basket, removed at predetermined time points, dried at 50 °C for 24 h, and weighed. The amount of dissolved or disintegrated films was calculated as the percent weight loss at each sampling time point.

### 2.7. Estimation of TEC remaining in the films

Dried polymer films from the dissolution test were cut into small pieces and dissolved in ethanol: pH 7.4 phosphate buffered solution (1:1). Then, 4 mL pH 2.5 phosphate buffered solution was added to 1 mL polymer solution to precipitate the polymer. The solution was centrifuged at 10,000 rpm for 10 min and the amount of TEC in the supernatant was determined using a Waters (Milford, MA) high performance liquid chromatography (HPLC) system with a photodiode array detector (Model 996) extracting at 210 nm. Samples were pre-filtered through a 0.45 μm membrane (Whatman Inc., Clifton, NJ, USA). An auto sampler (Model 717plus) was used to inject 20 mL samples. The data were collected and integrated using Empower<sup>®</sup> Version 5.0 software (Des Plaines, IL, USA). The column was a Capcell Pak C18 3 mm, 100 mm × 3.0 mm i.d. (SHISEIDO, Kyoto, Japan). The mobile phase contained a mixture of 25 mM pH 2.5 phosphate buffered solution: acetonitrile in volume ratios of 55:45. 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 time of the TEC was approximately 3.5 min.

### 2.8. Statistical data analysis

Average and standard deviations for tensile strength at break and % elongation were determined. The statistical differences among cast films were determined by a one-way ANOVA. A  $p < 0.05$  was considered statistically significant.

## 3. Results and discussion

### 3.1. Thermal properties of the cast films

The glass transition temperatures of cast films prepared from aqueous dispersions and organic solutions are summarized

Table 1  
Glass transition temperatures of cast films

Films	$T_g^a$ (°C)
Aqueous cast films	59.9 ± 1.5
Organic cast films plasticized with 10% TEC	110.0 ± 2.4
Organic cast films plasticized with 50% TEC	59.2 ± 1.6

<sup>a</sup> Mean ± S.D. ( $n = 3$ ).

in Table 1. The glass transition temperatures of unplasticized Eudragit<sup>®</sup> S100 and L100 are approximately 160 °C (Lehmann, 1997). The addition of TEC to the coating formulation resulted in a decrease in the glass transition temperatures of the cast films, the extent of which was dependent on the TEC concentration. The glass transition temperature of the organic cast film plasticized with 10% TEC was the highest due to the low TEC level while the glass transition temperatures of the aqueous and the organic cast films plasticized with 50% TEC showed similar values. Our results are in agreement with previously published reports that showed plasticizers decrease glass transition temperature of polymeric films and the extent of the decrease is dependent on the levels of plasticizer in the films (Gutiérrez-Rocca and McGinity, 1994; Amighi and Moës, 1996). Furthermore, our results demonstrate that the glass transition temperature of resulting films is influenced to a greater extent by the levels of plasticizer in the formulation than the casting solvent.

### 3.2. Mechanical properties of the cast films

Previous reports in the literature have shown that both plasticizer concentration and casting solvent can influence the mechanical properties of polymeric films (Gutiérrez-Rocca and McGinity, 1994; Bodmeier and Paeratakul, 1994). In the current study, the tensile strength and % elongation of organic and aqueous-based films were determined and the data are presented in Fig. 1. The tensile strength of the aqueous cast films was significantly lower than that of the organic cast films plasticized with 10% TEC ( $p < 0.01$ ), while the percent elongation of the aqueous cast films was significantly higher than that of the organic cast films plasticized with 10% TEC ( $p < 0.01$ ).

Addition of 50% TEC to the organic cast films significantly decreased tensile strength ( $p < 0.01$ ) and significantly increased percent elongation ( $p < 0.05$ ) compared to organic cast films con-

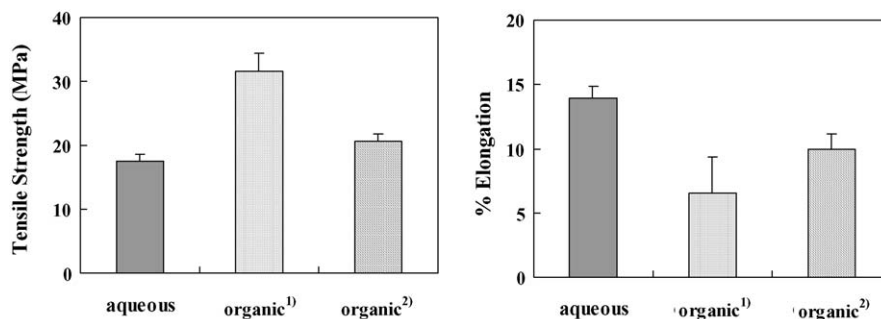


Fig. 1. Tensile strength at break and percent elongation of cast films composed of Eudragit<sup>®</sup> S100:L100 (1:1) ( $n = 5$ ). (1) Organic cast films plasticized with 10% TEC; (2) organic cast films plasticized with 50% TEC.

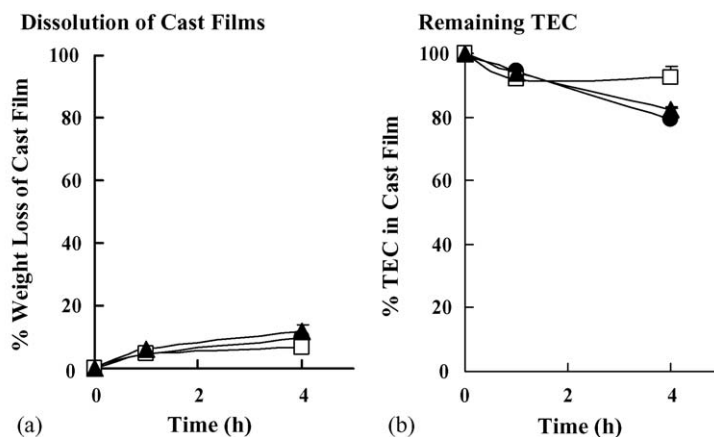


Fig. 2. Weight loss profiles of cast films composed of Eudragit<sup>®</sup> S100:L100 (1:1) (a) and percent TEC remaining in cast films profiles (b) under 0.1 N HCl (USP27 Apparatus I, 100 rpm, 500 mL, 37 °C,  $n=3$ ). (●) Aqueous cast film; (□) organic cast film plasticized with 10% TEC; (▲) organic cast film plasticized with 50% TEC.

taining 10% TEC. These effects of the TEC levels in the cast films on the mechanical properties were consistent with previous reports using Eudragit<sup>®</sup> L100-55 (Gutiérrez-Rocca and McGinity, 1994), Eudragit<sup>®</sup> L30D-55 (Gutiérrez-Rocca and McGinity, 1993), Eudragit<sup>®</sup> RS30D (Bodmeier and Paeratakul, 1993) and Aquacoat<sup>®</sup> (Bodmeier and Paeratakul, 1994).

### 3.3. Weight loss of cast films

#### 3.3.1. Dissolution tests at acidic condition

The dissolution tests of cast films prepared from aqueous dispersions and organic solutions were conducted in acidic medium (0.1 N HCl) and the results are shown in Fig. 2. The percent weight loss of the films ( $n=3$ ) was approximately 5% after 4 h and no significant differences between the three different formulations were noted. Approximately 80% of the TEC remained in the cast films after 4 h in the dissolution medium. Since the carboxyl groups of the repeat units of Eudragit<sup>®</sup> S100 and L100 are unionized in 0.1 N HCl, the cast films composed of the mixtures of these polymers have a close-packed structure and the weight loss in this medium due to leaching of the TEC was low. These results indicated that the acid resistant properties were not

influenced by the casting solvent or the concentration of TEC in the cast films.

#### 3.3.2. Dissolution tests at neutral pH

The dissolution tests of cast films prepared from aqueous dispersions and organic solutions were conducted in pH 6.0, 6.5 and 7.0 buffered media since Eudragit<sup>®</sup> L100 and Eudragit<sup>®</sup> S100 start to dissolve at pH 6.0 and 7.0, respectively. The percent weight loss and percent TEC remaining in the cast films are shown in Figs. 3 and 4, respectively.

At pH 6.0, the initial weight loss of the aqueous cast films was more rapid than that of the organic cast films plasticized with 10% TEC, with nearly 30% of the aqueous cast film having dissolved into the medium within 1 h and approximately 40% dissolved after 4 h. Nearly all the TEC was leached from the aqueous cast films within the first hour of dissolution testing. On the other hand, the percent weight loss of the organic cast films plasticized with 10% TEC was only 5% and about 80% of the TEC remained after 4 h in the dissolution medium.

At pH 6.5, about 50% of the aqueous cast films composed of Eudragit<sup>®</sup> S100:L100 (1:1) passed into solution within 1 h and the percent weight loss of the films achieved a plateau level at

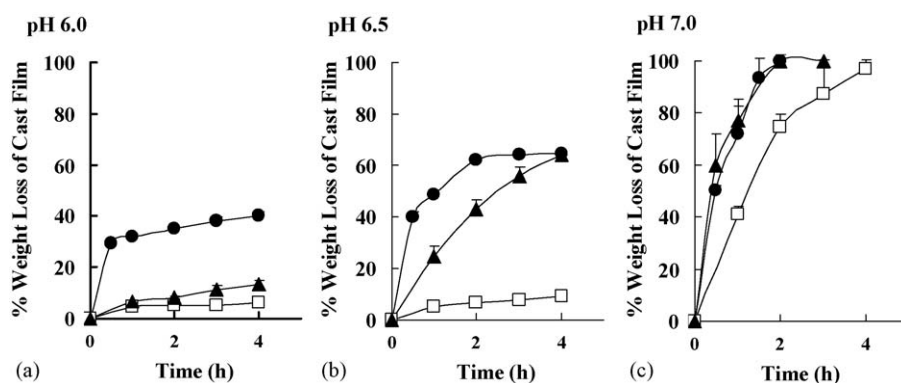


Fig. 3. Weight loss profiles of cast films composed of Eudragit<sup>®</sup> S100:L100 (1:1) as a function of media pH. (USP27 Apparatus I, 50 mM phosphate buffer (a) pH 6.0, (b) pH 6.5, and (c) pH 7.0, 500 mL, 100 rpm, 37 °C,  $n=3$ ). (●) Aqueous cast film; (□) organic cast film plasticized with 10% TEC; (▲) organic cast film plasticized with 50% TEC.



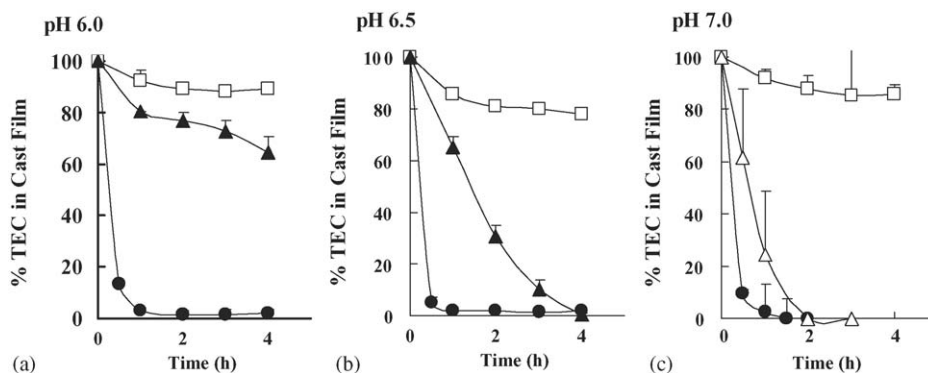


Fig. 4. Influence of media pH on the percent TEC remaining in cast films composed of Eudragit<sup>®</sup> S100:L100 (1:1). (USP27 Apparatus I, 50 mM phosphate buffer (a) pH 6.0, (b) pH 6.5, and (c) pH 7.0, 500 mL, 100 rpm, 37 °C,  $n=3$ .) (●) Aqueous cast film; (□) organic cast film plasticized with 10% TEC; (▲) organic cast film plasticized with 50% TEC.

65% within 2 h. Almost all of the TEC was released from the aqueous cast films within 30 min. These results demonstrated that Eudragit<sup>®</sup> L100 and TEC rapidly dissolved from the aqueous films during dissolution testing, since the theoretical weight of these materials in the film sample was approximately 66% and Eudragit<sup>®</sup> S100 is insoluble at pH 6.5. In contrast to the aqueous films, the percent weight loss of the organic cast films plasticized with 10% TEC was only 13% and about 80% of the TEC remained after 4 h.

The films cast from aqueous dispersions disintegrated in 2 h and the organic cast films plasticized with 10% TEC disintegrated in 4 h in pH 7.0 media. While almost all of the TEC was removed from the aqueous cast films within 30 min, the percent TEC remaining in the organic cast films plasticized with 10% TEC was maintained at approximately 80% during dissolution testing. These results indicated that the disintegration of the acrylic polymers occurred simultaneously with TEC release from the sample, during dissolution testing at pH 7.0.

Significant differences in the weight loss profiles between the aqueous and organic cast films plasticized with 10% TEC were observed at pH 6.0, rather than at pH 7.0. Using cellulose acetate phthalate (CAP) as an enteric polymer, similar results were reported by estimating disintegration times for aspirin tablets coated with Aquateric (CAP latex) and CAP/solvent (Wheatley and Steuernagel, 1997). These workers reported that at pH 6.4 and higher, there were no significant differences in disintegration time with either the aqueous latex or the organic solution. However, the disintegration time of tablets coated with an organic solution of CAP increased substantially as the pH decreased below 6.4, and a significant difference in disintegration time was observed between the films prepared from the aqueous latex and the organic solution.

### 3.3.3. Influence of casting solvents on weight loss of cast films

The film formation mechanism has been reported to be fundamentally different between aqueous dispersions and organic solutions (Wheatley and Steuernagel, 1997). For the purpose of clarifying the influence of the film formation mechanism for acrylic polymers attributed to casting solvents on dissolution

and disintegration of cast films, the organic cast films plasticized with 50% TEC, which included the same amount of TEC as aqueous cast films, were prepared and dissolution tests were conducted. The percent weight loss of cast films and percent TEC remaining in the organic cast films plasticized with 50% TEC are seen in Figs. 3 and 4, respectively.

At pH 7.0, the organic cast films plasticized with 50% TEC showed a similar weight loss profile to that of the aqueous cast films. The rate of weight loss of the aqueous cast films, however, was still faster than those of the organic cast films plasticized with 50% TEC at pH 6.5 and 6.0. Since these films contained the same amount of TEC, these results indicated that the film formation mechanisms due to casting solvents also affected dissolution and disintegration.

However, the weight loss of the organic cast films containing 50% TEC was much faster than that of the organic films containing 10% TEC at pH 6.5 and 7.0. Since TEC is a hydrophilic plasticizer, TEC partitions rapidly into the dissolution medium. The leaching of TEC would form pores in the films, increase the surface area for dissolution of the acrylic polymer and enhance the weight loss of cast films. These results demonstrated that the high levels of TEC in the organic cast films significantly increased the weight loss of cast films due to the rapid leaching of TEC from the sample.

### 3.3.4. Influence of casting solvents on weight loss of cast films composed of Eudragit<sup>®</sup> L100-55

While 10% TEC is recommended for organic solvent coating, more than 50% TEC based on dry polymer weight is recommended for aqueous latex coating because of the high MFTs for both Eudragit<sup>®</sup> S100 and L100. This rapid leaching of TEC due to the high TEC concentration will more rapidly disrupt the film structure. Alternatively, Eudragit<sup>®</sup> L100-55 can form films from aqueous latex plasticized with only 10% TEC due to its low MFT. In order to investigate the influence of casting solvents on weight loss of the cast films plasticized with the lower TEC level, aqueous and the organic cast films composed of Eudragit<sup>®</sup> L100-55 plasticized with 10% TEC were prepared and the weight loss of the cast films during dissolution testing was investigated. While the dissolution properties of cast films

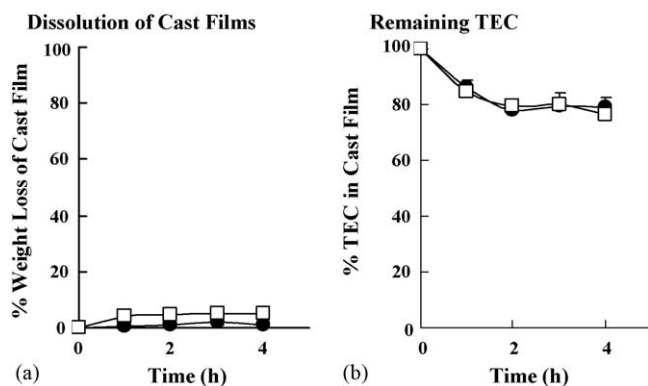


Fig. 5. Weight loss profiles of cast films composed of Eudragit<sup>®</sup> L30D-55 and Eudragit<sup>®</sup> L100-55 containing 10% TEC (a) and percent TEC remaining in cast film profiles (b) under pH 5.0. (USP27 Apparatus I, 50 mM phosphate buffer, 500 mL, 100 rpm, 37 °C,  $n=3$ .) (●) Aqueous cast film (Eudragit<sup>®</sup> L30D-55); (□) organic cast film (Eudragit<sup>®</sup> L100-55).

of Eudragit<sup>®</sup> S100:L100 (1:1) were estimated at a pH 6.0 and above, the dissolution tests for cast films of Eudragit<sup>®</sup> L100-55 were conducted in pH 5.0 medium since this polymer begins to dissolve at pH 5.5. The percent weight loss of the cast films and percent TEC remaining in the films at pH 5.0 are shown in Fig. 5 and were found to be similar between aqueous and organic films. These findings are in agreement with an earlier report that showed similar dissolution properties of drug from pellets coated with Eudragit<sup>®</sup> L100-55 under aqueous and organic conditions (Thoma and Bechtold, 1999).

Recently Lecomte et al. reported that the mechanism of film formation from aqueous and organic solvents influenced the film properties of ethylcellulose and Eudragit<sup>®</sup> L100-55 blends and the amount of TEC did not affect film properties (Lecomte et al., 2004). These authors compared the properties of film coatings containing between 10% and 25% TEC. Since weight loss of the aqueous film was more rapid than that of organic film containing 50% TEC, the mechanism of film formation between coating techniques would be one of the factors, which affect the physicochemical properties of the films. However, similar weight loss profiles were observed in the current study for lower TEC levels for cast films composed of Eudragit<sup>®</sup> L100-55. These results indicated that the higher amount of TEC was also a principal factor for the rapid weight loss of aqueous cast films composed of Eudragit<sup>®</sup> S100:L100 (1:1) compared with organic cast films plasticized with 10% TEC.

In conclusion, significant differences of mechanical properties between aqueous- and organic-based cast films were observed. Furthermore, the weight loss of the aqueous cast films composed of Eudragit<sup>®</sup> S100:L100 (1:1) plasticized with 50% TEC was rapid at a pH of 6.0 and above compared with those of organic cast films plasticized with 10% TEC. In contrast, in the cast films composed of Eudragit<sup>®</sup> L100-55 containing 10% TEC, a similar weight loss from aqueous cast films and organic cast films was shown. These results demonstrated that for Eudragit<sup>®</sup> S100:L100 cast films, in addition to the different film formation mechanism, the high levels of TEC needed for film formation from aqueous dispersions resulted in rapid

dissolution and disintegration of the aqueous cast films. While aqueous dispersions are preferred for the coating process, for Eudragit<sup>®</sup> S100:L100 film coatings, a change from organic solutions to aqueous dispersions in the coating process will clearly impact film properties and product performance.

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