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Effects of incorporated drugs on degradation of novel 2,2′-bis(2-oxazoline) linked poly(lactic acid) films

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Abstract

Earlier studies have indicated that the degradation rate of poly(lactic acid) (PDLLA) can be modified by using 2,2′-bis(2-oxazoline) as a chain extender in polymer synthesis to form a lactic acid-based poly(ester-amide) (PEA). In the present study, the effect of an incorporated drug on the degradation rate of the PEA was evaluated. The model drugs, neutral guaifenesin, acidic sodium salicylate (pK_a 3.0) and basic timolol (pK_a 9.2), were incorporated into solvent cast PDLLA and PEA films. The drug content in the films was 2% (w/w). The degradation studies were carried out in PBS (pH 7.4, 37 °C); the resulting decrease in molecular weight of polymers was determined by size exclusion chromatography and the weight loss of films was measured. In addition, the drug release from the films in PBS (pH 7.4, 37 °C) was studied. The model drugs were released from the PDLLA and PEA films in a biphasic or triphasic manner. The final fast release phase of the drugs from both PDLLA and PEA films started when the molecular weight (M_n) of the polymer had decreased close to 15,000 g/mol. The degradation rate of the PDLLA films was clearly enhanced by incorporated sodium salicylate or timolol. Whereas, the degradation rate of the PEA film was not enhanced by the incorporated drugs. The present results indicate that when compared to the PDLLA film, degradation rate of the PEA film in the presence of the drug is more predictable.

Keywords: Hydrolysis; Degradation; 2,2′-Bis(2-oxazoline) chain extender; Poly(lactic acid); Poly(ester-amide)

1. Introduction

The degradation characteristics of poly(lactic acid) (PLA) based polymers have been extensively studied during the last decades (Pitt et al., 1981; Vert et al., 1991, 1998; Li and McCarthy, 1999). Among many factors, such as molecular weight, and chemical composition of polymer, and shape and size of device, also physicochemical properties of incorporated drug affect the degradation rate of the PLA based polymers (Vert et al., 1991; Brannon-Peppas and Vert, 2000). The acidic drugs are expected to enhance the hydrolysis of ester bonds of PLA because of an acid catalysis (Vert et al., 1991; Brannon-Peppas and Vert, 2000). Whereas, a basic drug either accelerates the degradation rate of the PLA based polymer by behaving as a base catalyst acting on the ester bonds in polymer chains (Maulding et al., 1986; Cha and Pitt, 1989), or suppresses the degradation rate of the PLA based polymer by neutralizing the polymer terminal carboxyl residues, so that the autocatalytic effect of acidic chain ends on polymer degradation is minimized (Bodmeier and Chen, 1989; Mauduit et al., 1993; Miyajima et al., 1998). In case of a neutral drug, the hydrophilic drug typically enhances and a hydrophobic drug impedes the degradation rate of PLA (Vert et al., 1991).

In our earlier study, the novel lactic acid-based poly(ester-amide) for controlled drug delivery was introduced (Tarvainen et al., 2002). This polymer was synthesized in two steps that included a condensation polymerization of lactic acid to a low molecular weight prepolymer, and an increase in the molecular weight by utilizing 2,2′-bis(2-oxazoline) as a chain extender to form 2,2′-bis(2-oxazoline) linked poly(lactic acid) (PEA) (Tuominen and Seppälä, 2000; Tarvainen et al., 2002). The degradation rate of a drug-free PEA film is faster than that of a PDLLA film (Tarvainen et al., 2002). The aim of this study was

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to evaluate the effect of an incorporated drug on the degradation rate of PEA.

2. Materials and methods

2.1. Materials

Guaifenesin (M_w 198.2) was purchased from Sigma (St. Louis, MO, USA). Sodium salicylate (M_w 160.1) was purchased from Aldrich-Chemie (Steinheim, Germany). Timolol free base hemihydrate (M_w 332.4) was a gift from InterX Research (Lawrence, KS, USA). D,L-Lactide was purchased from Purac (Gorinchem, The Netherlands). L-Lactic acid was purchased from Archer Daniels Midland (Decatur, IL, USA). 2,2′-Bis(2-oxazoline) was purchased from Tokyo Kasei Organic Chemicals (Tokyo, Japan). Other materials were reagent grade.

2.2. Polymerization

Lactic acid-based poly(ester-amide) (PEA) was polymerized from a lactic acid-based carboxyl-terminated prepolymer and a chain extender, 2,2′-bis(2-oxazoline), by using a two-step synthesis. The synthesis of PEA and PDLLA have been described in more detail earlier (Tuominen and Seppälä, 2000; Tarvainen et al., 2002).

Before further processing PDLLA and PEA were purified by precipitation polymer/dichloromethane solutions (50%, w/v) with excess of ethanol, and dried for 24 h under reduced pressure at 40 °C.

2.3. Preparation of films

Drug-containing polymer films with 40 mg of a drug (guaifenesin, sodium salicylate or timolol) and 1.96 g of a polymer (PDLLA or PEA) were formed by casting from tetrahydrofuran (50 ml), using Teflon molds. Tetrahydrofuran was allowed to evaporate overnight at room temperature. Polymer films were kept two days in a vacuum desiccator, until circular films (diameter about 8 mm, weight 11.4–21.0 mg, and thickness 170–300 μm) were cut for investigation.

2.4. Degradation, weight loss and water uptake of films

The degradation (i.e. decrease in molecular weight), weight loss and water uptake of the PDLLA and PEA films were studied by shaking (100 strokes/min) the films in 10 ml of phosphate buffer solution pH 7.4 (PBS, USP XXIV) at 37 °C (Grant OLS200, Cambridge, UK). Fresh buffer was changed once a week. The films were removed from the medium at predetermined times and dried under vacuum at room temperature for 48 h.

Molecular weight (M_w, M_n) of the dried polymer film was determined at room temperature by size exclusion chromatography (SEC) (Waters SEC system; Interface module, 510 HPLC Pump, 410 Differential Refractometer, 700 Satellite Wisp, and four linear PL gel columns: 10^4, 10^5, 10^3 and 100 Å connected in series). Chloroform was used as solvent and eluent for the polymers. The samples were filtered through a 0.5 μm Millex SR filter. The injected volume was 200 μl and the flow rate was 1 ml/min. Monodispersed polystyrene standards were used in the calibration.

The percent of weight remaining was calculated as follows:

$$\text{weight remaining} = \frac{W_r}{W_i} \times 100\% \quad (1)$$

where W_r is the weight of the polymer in the film after incubation in the medium and W_i is the weight of the polymer in the film before incubation.

The percent of water uptake was calculated as follows:

$$\text{water uptake} = \frac{W_w - W_r}{W_r} \times 100\% \quad (2)$$

where W_w is the weight of the wet polymer film after wiping. In both equations the data were corrected for the weight losses due to released drug.

2.5. Drug release studies

Drug containing PDLLA and PEA films were incubated in 10 ml of PBS (pH 7.4, 37 °C) at a frequency of 100 strokes/min (Grant OLS200). At predetermined time intervals, 1 ml samples were collected, and each sample was replaced with fresh PBS. Fresh buffer (10 ml) was changed at 4-week periods. The amount of the released drug was assayed by a Gilson HPLC system, as described earlier (Tarvainen et al., 2002).

3. Results and discussion

To evaluate the degradation characteristics of the drug containing PEA and PDLLA films, 2% (w/w) of a model drug was incorporated into the solvent cast films. Neutral guaifenesin (M_w 198.2), acidic sodium salicylate (M_w 160.1, pK_a 3.0) and basic timolol (M_w 332.4, pK_a 9.2) were used as the model drugs.

3.1. Effect of an incorporated drug on the degradation of a film

Fig. 1 shows the degradation, weight loss and water uptake of the studied films in PBS (pH 7.4, 37 °C). Both basic timolol and acidic sodium salicylate enhanced the degradation rate of the PDLLA films (Fig. 1A). It must be noted that timolol clearly catalyzed the degradation of PDLLA films during the manufacturing process of the films, since the molecular weight of the timolol containing PDLLA films before incubation was substantially lower than the molecular weights of other PDLLA films (Fig. 1A). The weight loss of timolol and sodium salicylate containing PDLLA films after 26 weeks incubation was higher than that of drug-free films (Fig. 1B). Fig. 1A and B shows that the weight loss of the PDLLA film does not occur until the molecular weight of the film has decreased about to 15,000 g/mol or less, which is reported to be the limiting value for the weight loss of the PDLLA polymers (Pitt et al., 1981). The faster degradation rate of timolol and sodium salicylate PDLLA films cannot be explained by differences in water uptake as indicated in Fig. 1C.

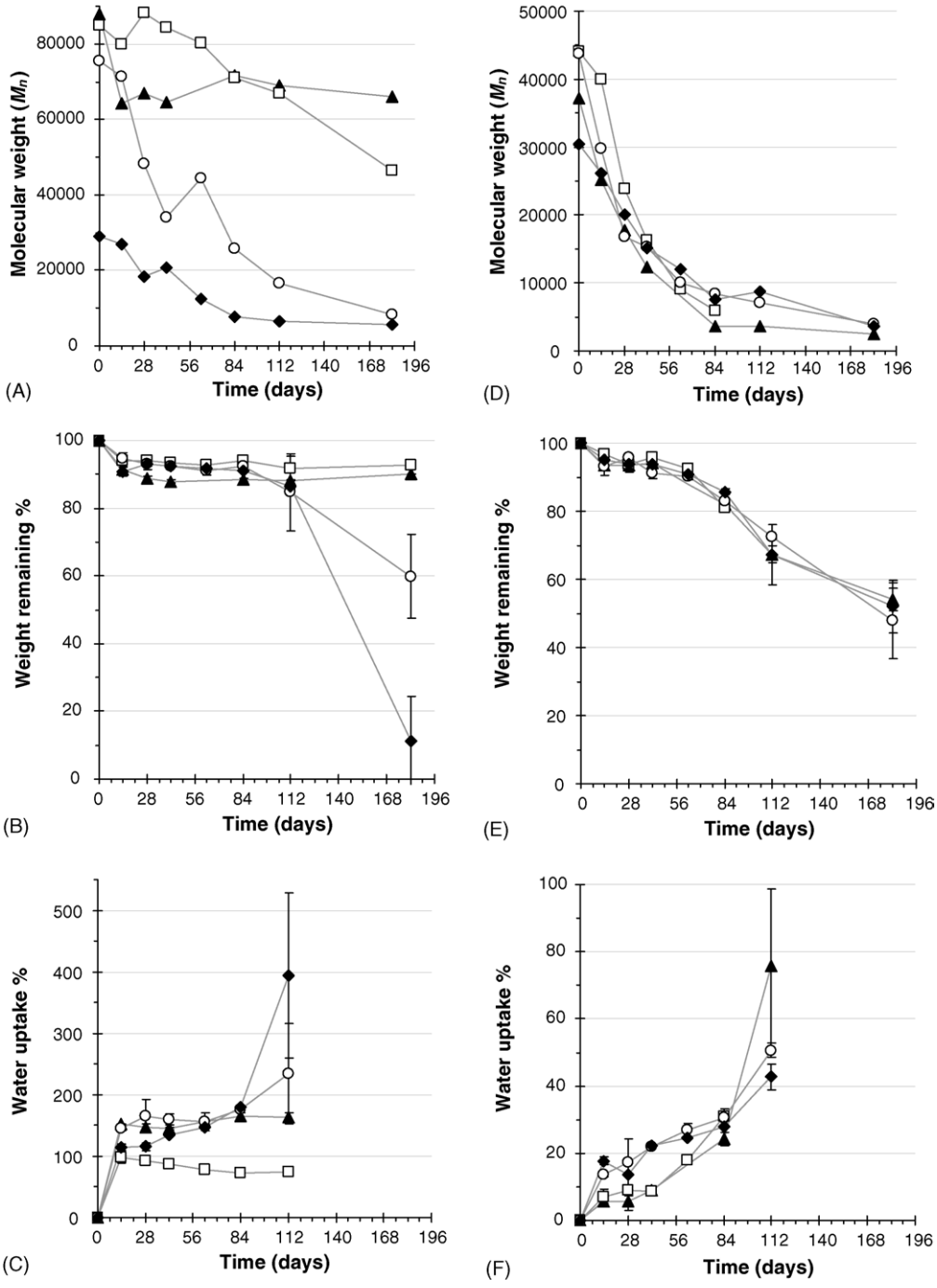

Fig. 1. Molecular weight (n = 1–2), percentage of remaining weight (n = 2) and percentage of water uptake (n = 2) of films. (A)–(C) The PDLLA films. (D)–(F) The PEA films. Symbols indicate drug-free films (▲), and guaifenesin (□), sodium salicylate (◯) and timolol (♦) containing films. Mean and S.D. are shown.

Thus, both the basic (Maulding et al., 1986; Cha and Pitt, 1989) and the acidic (Vert et al., 1991; Brannon-Peppas and Vert, 2000) drug behaved as catalyst acting on the ester bonds in polymer chains which enhanced the degradation rate of the PDLLA film.

The neutral guaifenesin had no notable effect on the degradation rate of PDLLA, as the molecular weights of drug-free and guaifenesin containing PDLLA films were close to each other after 112 days (Fig. 1A). The water uptake of guaifenesin containing PDLLA films was lower than that of drug-free PDLLA film (Fig. 1C), although guaifenesin is quite hydrophilic.

In contrast to PDLLA films, the model drugs did not enhance the degradation rate (Fig. 1D) and weight loss rate (Fig. 1E) of the PEA films. However, timolol slightly enhanced the degradation of PEA during the preparation process (Fig. 1D). One reason for the observed results might be the considerable faster degradation rate of drug-free PEA films when compared to the drug-free PDLLA films. Although, the exact degradation mechanisms of PEA are still unknown, earlier ^{1}H NMR studies have indicated that both the ester and oxamide groups are hydrolyzed during incubation, since the chemical shifts due to the oxamide groups

are dismissed after 8 days hydrolysis (Tarvainen et al., 2002). Fig. 1D and E shows that the weight loss of the PEA film does not occur until the molecular weight of the film has decreased about to 15,000 g/mol or less. When compared to the PDLLA films, the water absorption of PEA films occurred in markedly lower extent (Fig. 1C and F). The present results indicate that when compared to the PDLLA film, the degradation rate of the PEA film in the presence of the drug is more predictable.

3.2. Correlation between drug release from and degradation of the films

Overall, the release rates of studied model drugs were faster from PEA films than from PDLLA films (Fig. 2), although the water uptake of drug containing PDLLA films was substantially higher than that of drug containing PEA films (Fig. 1C and F). Typically, the release of model drugs from PDLLA and PEA films was found to occur in a biphasic or triphasic manner: (1) first an initial fast release phase, (2) followed by a slower release phase, and (3) finally a faster release phase (Fig. 3). The observed phasic release is typical for PLA based polymers (Gallagher and Corrigan, 2000; Jain et al., 2000; Lamprecht et al., 2000; Sturesson and Wikingsson, 2000). The initial fast release phase was due to the release of the drug incorporated at or near the surfaces of the polymer films. The second slower release phase was a result from the diffusion of the dissolved drug through the polymer films. The release during the final third phase, can be explained by the diffusion through the films and degradation of the films. The release characteristics of these model drugs from PDLLA and PEA preparations have been discussed in detail

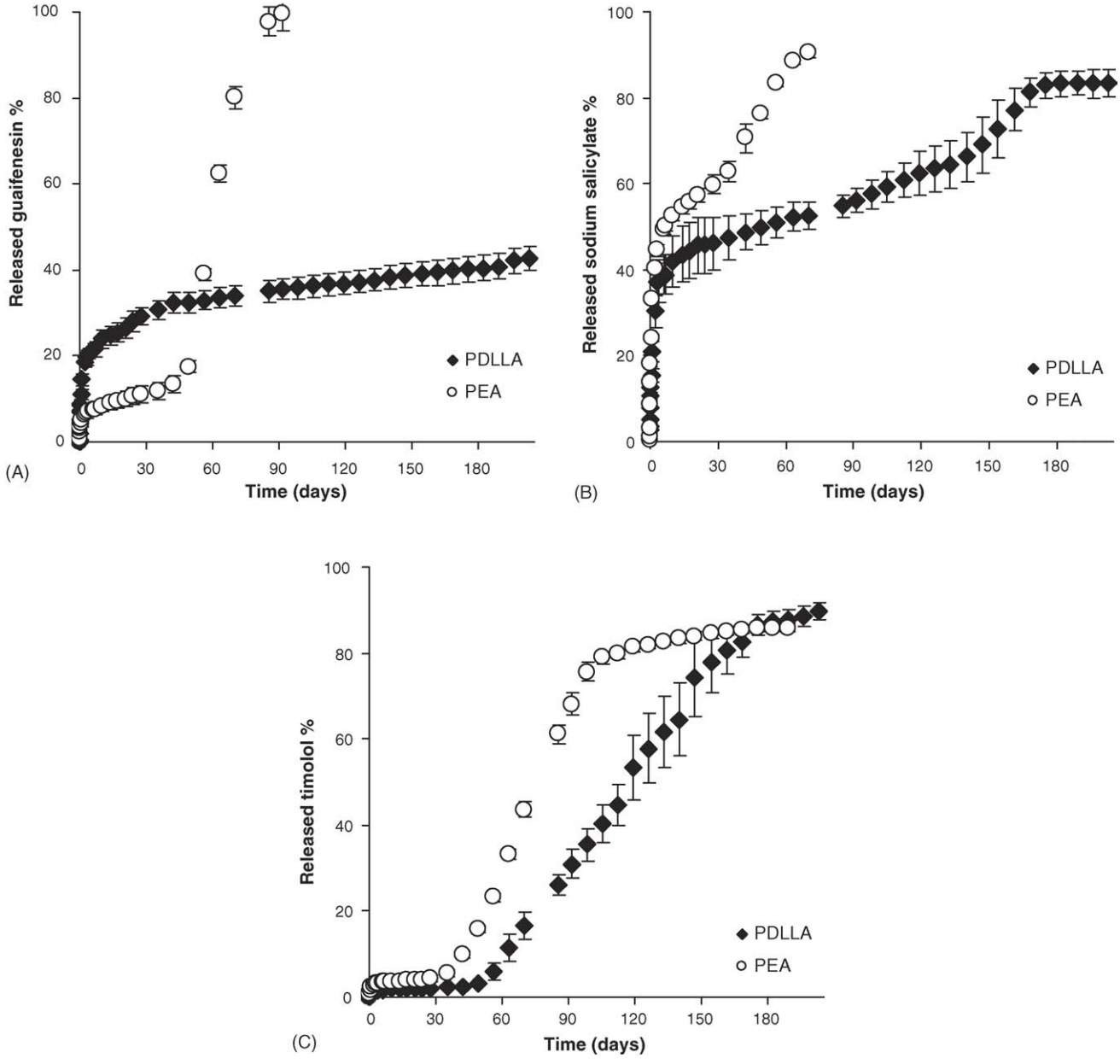

Fig. 2. Guaifenesin (A), sodium salicylate (B) and timolol (C) release from PDLLA and PEA films in PBS (pH 7.4). Mean and S.D. are shown ($n = 4$).

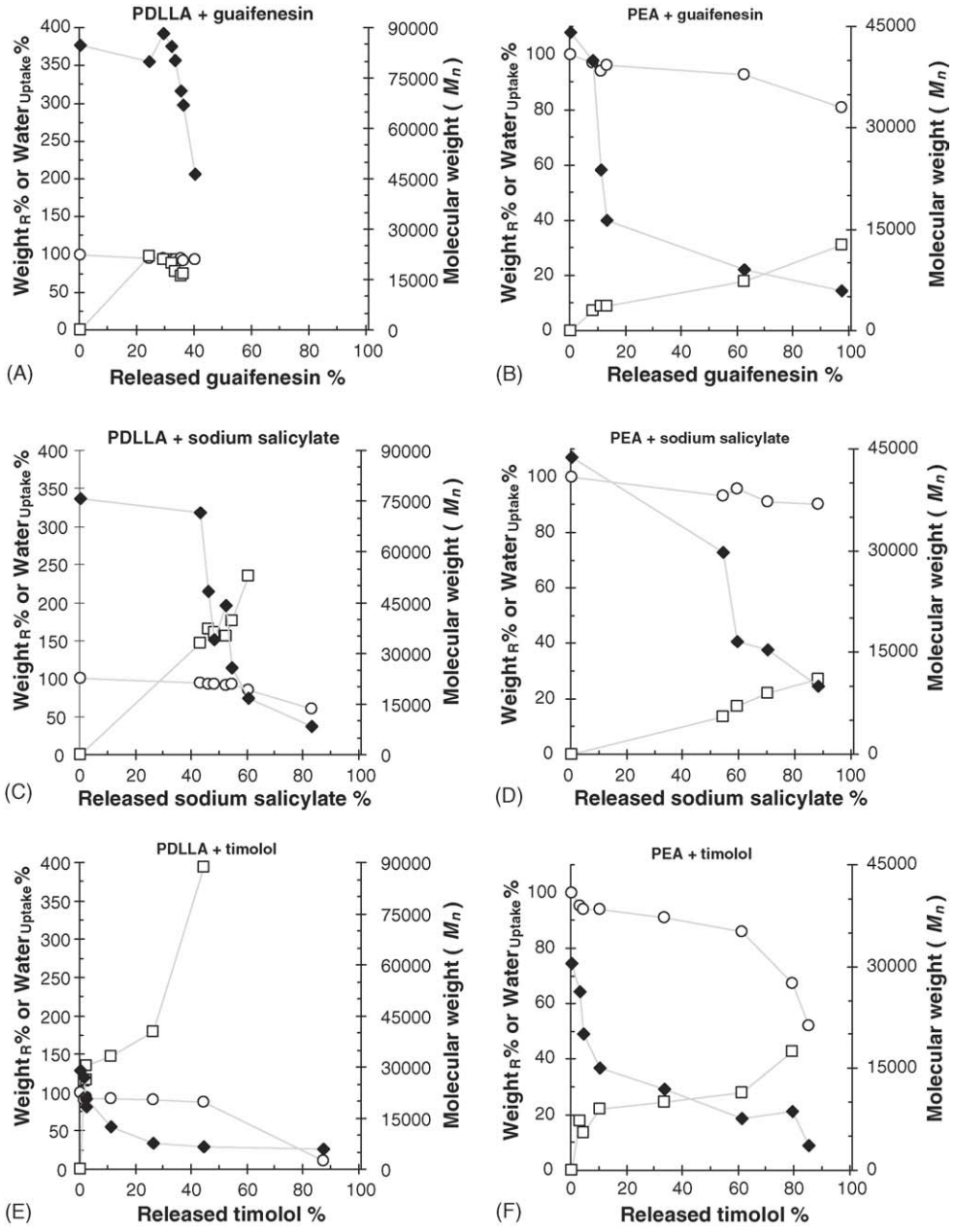

Fig. 3. Percentage of remaining weight (weight$_R$%, ○), percentage of water uptake (water$_{uptake}$%, □) and remaining molecular weight (♦) of studied polymer films vs. percentage of released drug; (A) PDLLA and guaifenesin, (B) PEA and guaifenesin, (C) PDLLA and sodium salicylate, (D) PEA and sodium salicylate, (E) PDLLA and timolol, and (F) PEA and timolol.

earlier (Tarvainen et al., 2002). It must be noted that the drug loadings in the present study (2%, w/w) are lower when compared to the earlier study (Tarvainen et al., 2002). Thus, the drug release rates are not similar in the earlier and present studies. It is well known that the drug loading affect degradation of and drug release from PDLLA based systems (Bodmeier and Chen, 1989; Mauduit et al., 1993; Li et al., 1996; Gallagher and Corrigan, 2000).

Fig. 3 demonstrates the weight loss of the film, the water uptake of the film and the decrease in molecular weight of the polymer as a function of drug release from PDLLA and PEA films. Interestingly, Fig. 3 shows that the final fast release phase of all three model drugs from both PDLLA and PEA films started when the molecular weight (M_n) of polymer had decreased close to 15,000 g/mol, indicating of molecular weight dependent drug release. When the molecular weight of lactide based polymer is about 15,000 g/mol, the erosion of the polymer starts (Pitt et al., 1981). At this point, the permeability and hydrophilicity of the polymer increases (Lemmouchi et al., 1998). Fig. 3 shows that the water uptake of films increases with a decrease in molecular weight. None of the model drugs was released either from the PDLLA or PEA films purely by erosion controlled manner as the drug release from the films was faster than the weight loss of the films (Fig. 3).

4. Conclusions

Sodium salicylate and timolol accelerated the degradation rate of the PDLLA film when compared to the drug-free PDLLA film. In contrast, the degradation rate of the PEA films was not enhanced by the drugs. These results indicate that the degradation rate of PEA films in the presence of the drug is more predictable than that of the PDLLA film. The drugs were released from the PDLLA and PEA films in a biphasic or triphasic manner. The final fast release phase of the drugs from both PDLLA and PEA films started when the molecular weight (M_n) of the polymer had decreased close to 15,000 g/mol.

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