Programmable Drug Delivery from an Erodible Association Polymer System

Xin Xu[1,3] and Ping I. Lee[1,2,4]

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An erodible association polymer system based on blends of cellulose acetate phthalate (CAP) and Pluronic F127, a block copolymer of poly(ethylene oxide) and poly(propylene oxide), has been investigated for its applicability to rate-programmed drug delivery. The compatibility and thermal properties were characterized by DSC and FTIR. Results from the thermal analysis indicate that the blends are compatible above 50% CAP, as revealed by a single composition-dependent glass transition temperature (T_g). The existence of molecular association through intermolecular hydrogen bonding between the carboxylic acid and the ether oxygen groups is supported by the observation of an upward shift in the IR carbonyl stretching frequency at increasing Pluronic F127 concentrations. Using theophylline as a model drug, the *in vitro* polymer erosion and drug release characteristics of the present polymer system were evaluated at different buffer pH's on a rotating-disk apparatus. The results show that the rates of both polymer erosion and drug release increase with the Pluronic F127 concentration in the blend. Further, at pH 4, the polymer erosion is minimal and the theophylline release appears to be governed mainly by diffusion through the polymer matrix. In contrast, at pH 7.4, the theophylline release is controlled primarily by the polymer surface erosion. To demonstrate the unique approach to programmed drug release based on the concept of nonuniform initial drug distribution, pulsatile patterns of drug release have been achieved successfully from the present surface-erodible polymer system using a multilaminate sample design with alternating drug-loaded layers. The results suggest that the pulsing frequency and peak rate of such pulsatile drug delivery are pH dependent; however, they can be modulated by varying the thickness, drug loading, and erosion rate of the constituent layers in the multilaminate.

KEY WORDS: cellulose acetate phthalate (CAP); Pluronic F127; association polymer; pulsatile drug delivery; programmable drug delivery; erodible polymer.

INTRODUCTION

To achieve optimum therapy, one has to deliver a drug to the body only when and where it is needed, and at the minimum dose level required to elicit the desired therapeutic effects. In reality, this requires a delivery system which provides a programmable concentration–time profile that produces optimum therapeutic responses. The conceptual basis for applying surface-erodible polymer matrices to achieve rate-programmed drug delivery has been established by Lee (1). It was shown that, by employing a novel nonuniform drug distribution approach, surface erosion-controlled systems can provide time-varying patterns of drug release not achievable by a diffusion-controlled mechanism alone. Other nonuniform initial concentration profiles capable of generating pulsatile and other programmed release patterns have also been identified (2,3).

Erodible polymers have played an increasingly important role in the design of controlled-release drug delivery systems (4,5). One of the major advantages associated with such delivery systems is the avoidance of surgical removal of implanted devices after the exhaustion of drug therapy. Erosion can occur as a result of polymer structural changes caused by a chemical reaction such as hydrolysis or enzymatic cleavage (6). It can also occur without chemical changes such as in the dissolution of glassy polymers (7). Most of the existing erodible polymers are suitable either for long-term delivery purposes (weeks or months; e.g., polylactides and polyglycolides) or for applications involving more rapid dissolution (minutes; e.g., gelatin and hydroxypropyl cellulose), erodible polymers suitable for intermediate-range delivery such as hours or days are mostly unavailable. Recently, we have reported the use of a new class of bioerodible polymers for general controlled-release applications, which is based on association polymers formed between a hydrogen-donating polymeric carboxylic acid and a hydrogen-accepting ethoxylated nonionic surfactant (8–10). Such association polymers are erodible at neutral or higher pH but totally insoluble at low pH. The rate of polymer erosion and the pH at the onset of erosion can be easily varied by the nature of the selected polymer components, thus making this system particularly suitable for a wide range of controlled release applications. The incorporation of a nonionic surfactant as a component increases the solubilizing power, thereby allowing a higher level of drug loading to be achieved.

In the present study, we investigate the thermal properties and the compatibility of such an association polymer system based on blends of cellulose acetate phthalate (CAP) and Pluronic F127, a poly(ethylene oxide) and poly(propylene oxide) block copolymer. The polymer erosion and drug release characteristics are examined in detail. The application of this polymer system to the design of laminated release devices to achieve a programmed pulsatile drug delivery is also demonstrated.

EXPERIMENTAL

Materials

Cellulose acetate phthalate (CAP) was obtained from Eastman Chemicals (Kingsport, TN). It was further purified by precipitation from an acetone solution followed by washing in deionized water to remove any low molecular weight extractables. After drying, the phthalyl content and free phthalic acid content were determined by the USP method. Purified CAP of this study had a phthalyl content of 32% (w/w) and contained less than 1% (w/w) free phthalic acid.

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[1] Faculty of Pharmacy, University of Toronto, Toronto, Ontario M5S 2S2, Canada.

[2] Department of Chemical Engineering and Applied Chemistry, University of Toronto, Toronto, Ontario M5S 1A4, Canada.

[3] Present address: Merck, Sharp & Dohme Research Laboratorie, West Point, Pennsylvania 19486.

[4] To whom correspondence should be addressed at Faculty of Pharmacy, University of Toronto, 19 Russell Street, Toronto, Ontario M5S 2S2, Canada.

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Pluronic F127 (MW 12,500), a nonionic surfactant, was obtained from BASF (Parsippany, NJ) and used without further purification. Theophylline, a xanthine derivative with MW 180.17 and pK_a 8.77, was purchased from Sigma (St. Louis, MO). It was employed as a model drug for the present study. All other reagents were analytical grade and obtained from Fisher (Toronto, Canada).

Sample Preparation

CAP and Pluronic F127 were dissolved in acetone separately and mixed at different ratios to form the desired association polymer blends. Film samples of the present association polymers were prepared by solvent casting on either Mylar or aluminum backing from 5–10% solutions in acetone. The resulting sample thickness was typically in the range of 0.3–0.5 mm. For drug-loaded film samples, a small but known amount of a 5% theophylline solution in 0.1 *M* NH_4OH was mixed with the above polymer solution before casting. These films were air-dried overnight under ambient condition and subsequently vacuum dried for 24 hr to ensure the removal of residual solvent before being stored in a desiccator prior to use.

For programmed drug release studies, trilaminates were prepared from films of a given association polymer composition having an individual film thickness of about 0.32–0.35 mm, with the outer layers containing 5% theophylline loading while the intermediate layer contained no theophylline. These alternating layers of films were placed on top of one another and laminated on a laboratory Carver press at 3000 lb for 1 min.

Infrared Spectroscopy

Infrared (IR) spectra of the present association polymers were measured with thin film samples and recorded on a Bio-Rad Model FTS-7 Fourier transform infrared (FTIR) spectrophotometer equipped with DTGS detector and a Model 3240 data station. These samples were scanned from 4000 to 500 cm^{-1} over 16 scans at a resolution of 2 cm^{-1}. Shifts in the carbonyl stretching bands were followed as a function of the blend composition at room temperature. Since pure Pluronic F127 does not form a free-standing film, a 3% solution of Pluronic F127 in CCl_4 was used for the FTIR measurement in a liquid cell. In this case, the IR spectrum of Pluronic F127 was subsequently obtained through spectra substraction on the data station.

Differential Scanning Calorimetry (DSC)

The association polymer films were analyzed for their glass transition (T_g) and melting (T_m) temperatures using a Perkin–Elmer differential scanning calorimeter Model DSC-2 equipped with a dual-stage cooler (Intracooler II) and a thermal analysis data station (TADS). The DSC thermograms were obtained for a range of blend compositions using a scan rate of 20°C/min over a temperature range of −70 to 200°C.

Erosion and Drug Release Studies

The polymer erosion and the corresponding theophylline release were investigated using a rotating-disk apparatus as shown in the schematic drawing in Fig. 1. It consists of three main parts, namely, the water-jacketed beaker maintained at a constant temperature by a circulating water bath (Haake D8-G; accurate to ±0.02°C), a removable sample holder, and a rotating shaft driven by a stepless stirring motor with digital speed control (Caframo RZR-2000). The polymer erosion and theophylline release were monitored continuously on a diode-array UV-Vis spectrophotometer (HP 8452A) using a peristaltic pump and a flow-through cell. The rotating-disk method was chosen because of its well-defined hydrodynamics based on the Levich model (11). As shown in Fig. 1, the present sample holder has a beveled edge toward the disk surface (total exposed sample area, 1.77 cm^2). This was designed to minimize the stagnant zone in the square corner formed between the holder and the sample surface.

To ensure the adherence to the Levich model, the system was first calibrated with a series of benzoic acid dissolution experiments using procedures similar to that of Mooney *et al.* (12). Sample disks of 300–500 mg were cast from molten benzoic acid. The rotating-disk experiments were carried out at 25°C in 200 mL of 0.01 *N* HCl, with the ionic strength adjusted to 0.5 *M* by the addition of KCl. The dissolution of benzoic acid was monitored continuously on the UV-Vis spectrophotometer. The rotational speed of the disk was varied from 60 to 300 rpm, corresponding to Reynolds numbers of 279 to 1402, well below the critical range for transition from laminar to turbulent flow at the sample surface (11,13). From the slope of the resulting Levich plot (dissolution rate vs square root of angular velocity), an aqueous diffusion coefficient for benzoic acid was evaluated to be 1.05×10^{-5} cm^2/sec, comparable to those reported by other investigators (12,14). This ensures the accuracy of the present experimental setup.

Subsequent erosion and release experiments for the present association polymer blends were carried out at 37°C and a rotating speed of 100 rpm. These experiments were conducted in 0.067 *M* Sørensen phosphate buffer at pH 7.4 unless otherwise noted. For the pH-dependence studies, 0.067 *M* Sørensen buffers of desired pH values were used. Both the CAP erosion and the theophylline release were followed by the UV method and analyzed on a HP89500 UV/Vis ChemStation using a multicomponent quantitation

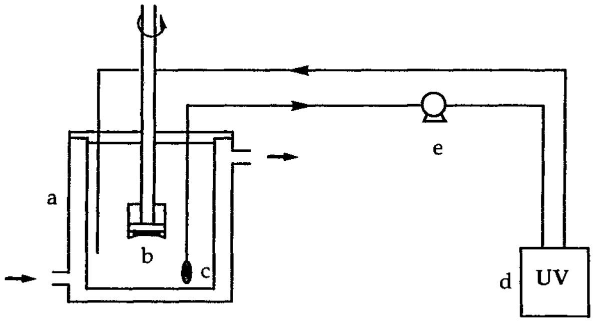

Fig. 1. Schematic representation of the rotating-disk apparatus for studying polymer erosion and drug release. a, Water-jacketed beaker; b, sample holder in cross-sectional view; c, filter; d, flow-through cell and UV-Vis spectrophotometer assembly; e, peristaltic pump.

Table I. Thermal Properties of CAP/Pluronic F127 Blends

		T_g (°C)		
CAP (wt%)	T_m (°C)	I	II	III
0	57	−60		
30	52	−59	−34	
50			−14	87
60				71
75				87
90				95
100				111

software. In all cases, duplicated runs were carried out and the results averaged.

RESULTS AND DISCUSSION

CAP is a widely used polymer for enteric coating which is insoluble at acidic pH but becoming soluble at neutral or alkaline pH. The commercial CAP used in this study contained 32% phthalyl groups as determined from our analysis, well within the 30–36% range specified by the USP. These phthalyl groups provide unreacted carboxylic acid groups as hydrogen donors. On the other hand, Pluronic F127 is a water-soluble ABA type of block copolymer consisting of poly(ethylene oxide) and poly(propylene oxide) segments with a reported MW of 12,500 and about 70% of the repeating units being ethylene oxide. The ether oxygen groups on the backbone of this block copolymer can serve as hydrogen acceptors. Upon mixing the acetone solutions of CAP and Pluronic F127, an appreciable increase in the solution viscosity was noted. This is attributed to the formation of an association polymer through intermolecular hydrogen bonding between these ether oxygen and carboxylic acid groups. The resulting film samples were transparent when the CAP content was more than 50%. However, translucent and opaque films have resulted when the Pluronic F127 content was increased above 50%. In all cases, these film samples appeared to be mechanically strong and resilient.

Thermal Properties

The results from the DSC analysis of the present CAP/Pluronic F127 blends are summarized in Table I. It is clear that, despite the distinctive T_g's of the CAP (111°C) and Pluronic F127 (−60°C), only one single T_g is observed in blends with a CAP content above 50% (w/w). This corresponds to the existence of a single miscible phase or, in other words, a compatible blend. On the other hand, below 50% CAP content, two T_g's emerge in the blend, suggesting the formation of a two-phase heterogeneous system. These findings are consistent with the observation that the physical appearance of these film samples changed from transparent to opaque when CAP content was reduced below 50%. Also evident from Table I is that, within the composition range of a compatible blend, i.e., above 50% CAP, the observed T_g increases with the CAP content. In addition, the melting peak characteristic to Pluronic F127 disappears as its concentration in the blend drops below 60–70%.

Intermolecular Hydrogen Bonding by FTIR

The sensitivity of FTIR spectroscopy to specific intermolecular interactions has made this analytical technique widely used in probing the hydrogen bonding and other intermolecular interactions in polymer blends (15–17). Free and hydrogen bonded groups can be readily identified based on their corresponding IR stretching modes. Figure 2 shows typical FTIR spectra of pure CAP, Pluronic F127, and a blend of 70/30 CAP/Pluronic F127. The FTIR spectrum for CAP is characterized by a strong carbonyl stretching band at 1735 cm^{-1}, whereas that of Pluronic F127 shows distinctive stretching bands at 2870 and 1110 cm^{-1} attributable to the hydroxyl and ether oxygen groups, respectively. All of these characteristic bands also appear in the IR spectrum of the blend.

To assess the effect of hydrogen bonding, representative spectra in the carbonyl stretching region (1630–1850 cm^{-1}) of various CAP/Pluronic F127 blends are shown in Fig. 3. The pure CAP is characterized by a major carbonyl band centred around 1735 cm^{-1} which develops a shoulder and shifts to a region of 1745–1750 cm^{-1} as the CAP concentration is reduced to 50%. Such a shift in the carbonyl stretching frequency reflects an increase in "free" $C=O$ groups due to the competition in intermolecular hydrogen bonding upon the addition of Pluronic F127. Since polycarboxylic acids are known to be strongly self-associating in the solid state through the formation of intermolecular carboxylic dimers (15,17), it is reasonable to expect that, in pure CAP, the primary intermolecular interaction also involves the hydrogen bonding between the $C=O$ group of one carboxylic acid moiety with the acid $O-H$ group of another. On the other hand, polyethoxylated polymers are inherently weakly self-associating, however they associate more strongly with polycarboxylic acids. Therefore, as the concentration of Pluronic F127 is increased in the blend, additional sites capable of hydrogen bonding are provided by the ether oxygen groups. As shown in the scheme in Fig. 4, the formation of each hydrogen bond between an acid $O-H$ and an ether oxygen group will liberate a "free" $C=O$ group, thus resulting in the observed upward shift in the characteristic stretching frequency. Similar shifts in carbonyl stretching band as a result of intermolecular hydrogen bonding have been reported in other miscible polymer blends (16,17). It is believed that such intermolecular hydrogen bonding also plays a key role in enhancing the compatibility of the present polymer blends.

Erosion and Drug Release Properties

Erosion profiles of the present CAP/Pluronic F127 blends with and without 5% theophylline loading are shown in Figs. 5a and 6a, respectively. An initial induction period with a slower rate of polymer erosion is evident in all cases. This is characteristic of the kinetics of dissolution in glassy polymers (7), where an initial swelling phase induced by the penetrating solvent is followed by a constant-rate, true dis-

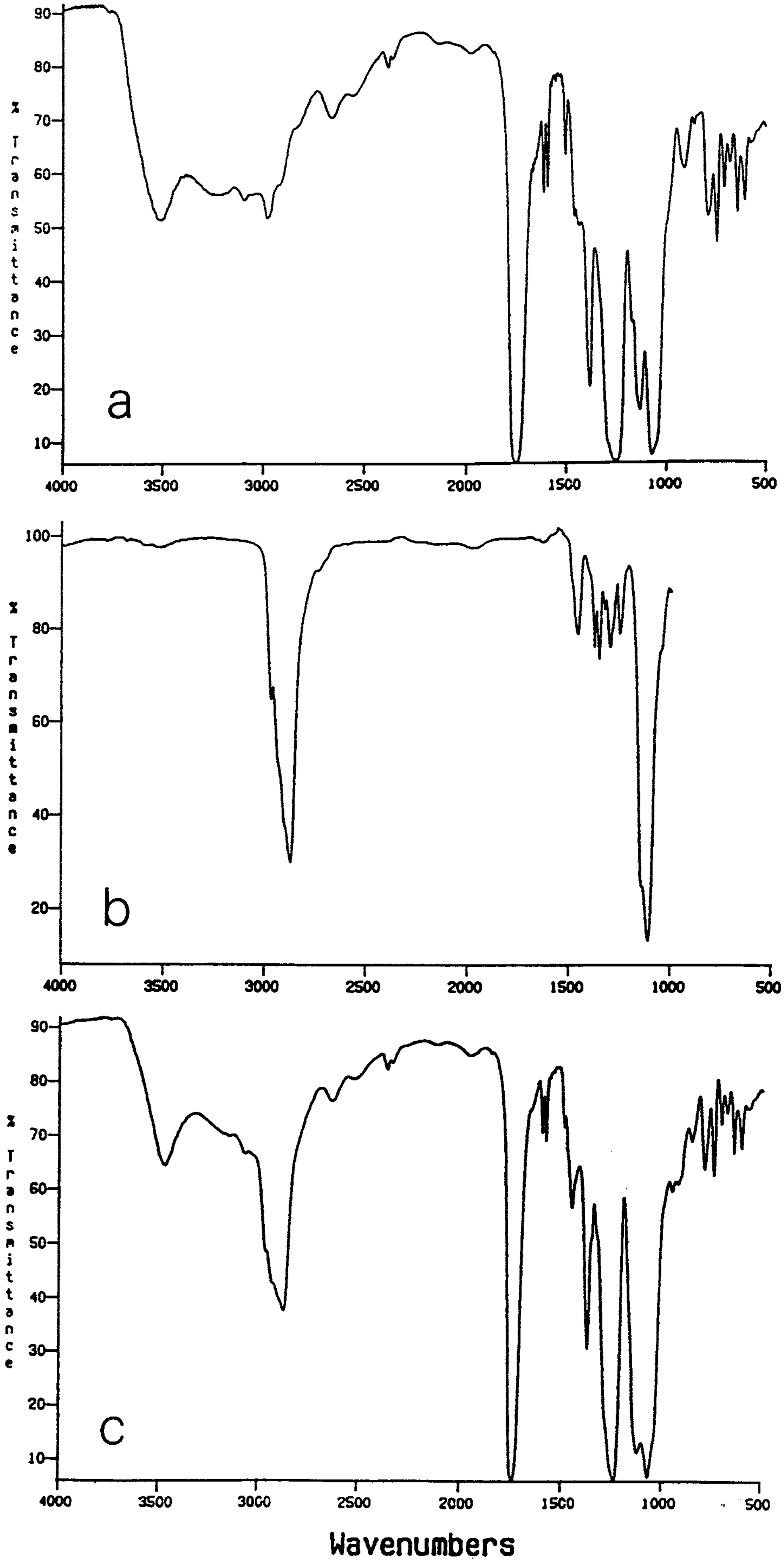

Fig. 2. Representative FTIR spectra. (a) CAP; (b) Pluronic F127; (c) 70/30 (w/w) CAP/Pluronic F127 blend.

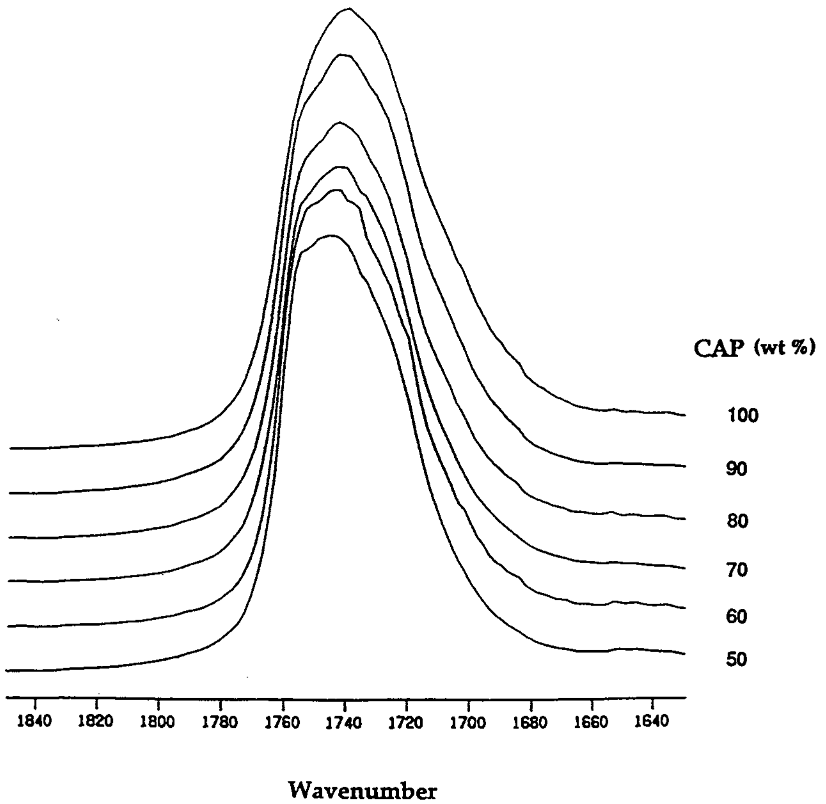

Fig. 3. Representative FTIR spectra in the carbonyl stretching region of CAP/Pluronic F127 blends as a function of CAP content.

solution step. The latter process occurs when the polymer concentration at the device surface decreases below a certain threshold level for polymer disentanglement to take place. In the present study, the rate of polymer erosion, calculated from the slope of the linear portion of an erosion curve, appears to increase almost linearly with the Pluronic F127 content (Fig. 5b). This is most likely due to the increasing hydrophilicity introduced by the addition of Pluronic F127. However, the presence of 5% theophylline loading does not seem to affect the rate of polymer erosion in any significant way.

The corresponding theophylline release profiles from blends with a 5% drug loading are presented in Fig. 6b. Similar to the trend in polymer erosion, the rate of theophylline release also increases with the Pluronic F127 content. However, unlike the polymer erosion, there are no apparent induction periods in the observed release profiles, suggesting the existence of some limited diffusional contributions to the initial drug release. Nevertheless, the fact that the extent of drug release follows closely that of the polymer erosion beyond the initial induction period (i.e., drug release/polymer erosion ~5% loading from Figs. 6a and b) supports a predominantly surface erosion-controlled release mechanism. This aspect was further explored by examining the pH dependence of polymer erosion and theophylline release from a compatible 70/30 CAP/Pluronic F127 blend. As shown in Fig. 7, the results of such a study indicate that the polymer erosion is minimal at pH 4 due to the lack of ionization of the pendant carboxylic acid groups below their pK_a. In this case, the accompanying theophylline release appears to be controlled primarily by diffusion through the polymer matrix as evident from the concave shape and prolonged duration of the release curve. In contrast, the fractional erosion and release curves are substantially linear and almost superimposable at pH 7.4, indicating a true surface erosion-controlled drug release. At pH 6, the polymer erosion curve is still mostly linear but lags behind the increasingly nonlinear drug release curve due to an increasing contribution from diffusion to the overall drug release. In this case, a combination of the mechanisms operating at both pH 7.4 and pH 4 is apparently at work. Thus, it is clear that the drug release from the present system can range from diffusion-controlled to surface erosion-controlled, depending on the pH and buffer conditions of the releasing medium.

Pulsatile Drug Delivery

Based on the novel concept of regulating drug release with a nonuniform initial drug distribution (1), the fractional drug release from a surface-erodible polymer matrix can be predicted from

$$\frac{M}{M_\infty} = \frac{\int_{a-Bt}^{a} f(x)x^n dx}{\int_0^a f(x)x^n dx} \tag{1}$$

with $n = 0$, 1, and 2 for flat sheet, cylinder, and sphere, respectively, where M is the amount released at time t, M_∞

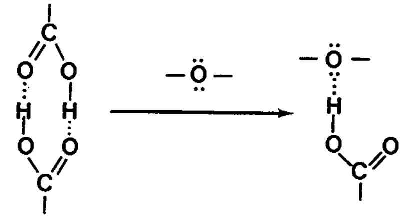

Fig. 4. Schematic diagram illustrating the carboxylic acid–ether oxygen interaction.

the total amount released, *a* the sample radius or half-thickness, *B* the surface erosion rate constant having the dimension of a velocity, and $f(x)$ the arbitrary initial drug distribution as a function of position x. To achieve a pulsatile drug delivery, Eq. (1) predicts that not only is an alternating pattern of drug-loaded and drug-free layers required, but also a drug loading decreasing toward the surface is needed for cylindrical or spherical samples in order to maintain the same peak rate as that in the sheet geometry (see Fig. 8). For a given polymer erosion rate, while the peak rate is adjustable by changing the loading level in each drug-loaded layer, the frequency and duration of the pulses can be further modulated by varying the thickness of individual layers.

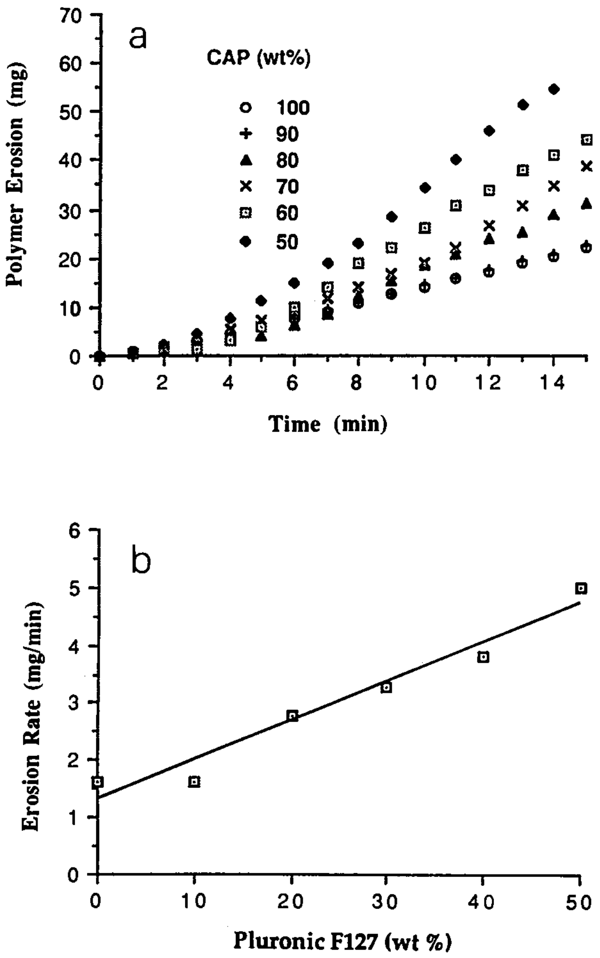

Fig. 5. Erosion characteristics of CAP/Pluronic F127 blends (without drug loading) in pH 7.4 buffer at 37°C. (a) Erosion profiles as a function of CAP content; (b) erosion rate as a function of Pluronic F127 content.

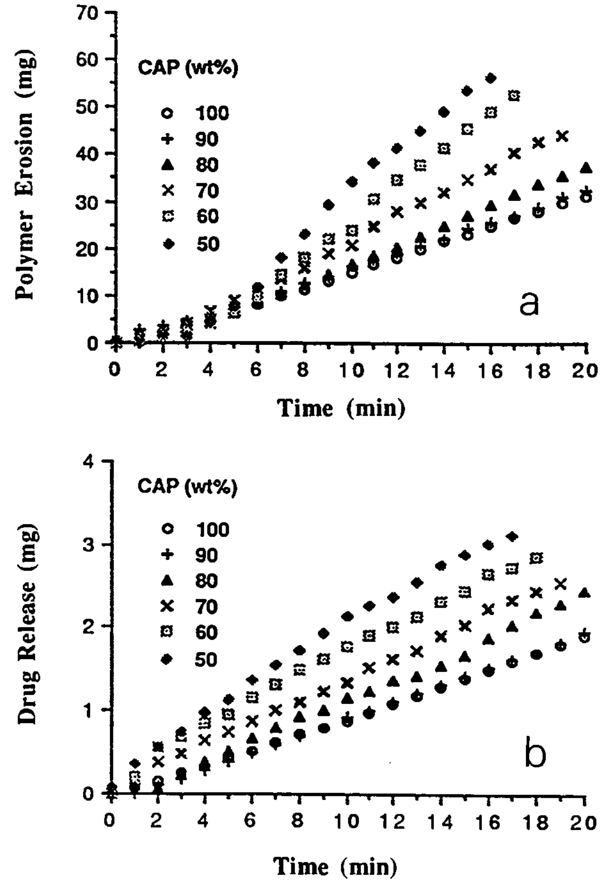

Fig. 6. Erosion and release characteristics of CAP/Pluronic F127 blends (with 5% loading of theophylline) in pH 7.4 buffer at 37°C, as a function of CAP content. (a) Polymer erosion profiles; (b) drug release profiles.

To illustrate the design of programmable delivery systems from surface-erodible polymers utilizing the concept of nonuniform drug loading (1,2), a laminated system based on the 70/30 CAP/Pluronic F127 blend has been studied. Trilaminates, with only the outer layers containing 5% theophylline and the intermediate layer drug-free, were studied for polymer erosion and drug release at pH 7.4. Since the erosion and diffusion processes are effectively restricted to one dimension from only one side of the sample in the rotating-disk apparatus, one would expect a pulsatile release pattern from such trilaminates when the surface erosion mechanism is dominating. As shown in Figs. 9a and 10a, a constant rate of polymer erosion is evident from the observed linear concentration–time curve, despite the discontinuity in drug distribution across the sample. In contrast, the corresponding cumulative drug release depicted in Fig. 9b exhibits stepwise changes, which translates to a pulsatile release behavior as shown in Fig. 10b. A theoretical pulsatile release rate pattern obtained from Eq. (1), based on the present alternating drug distribution, is also included in Fig. 10b for comparison. In this case, the linear increase in the initial and later segments of the release curve in Fig. 9b represents a constant-rate drug release resulting from the surface erosion of alternating

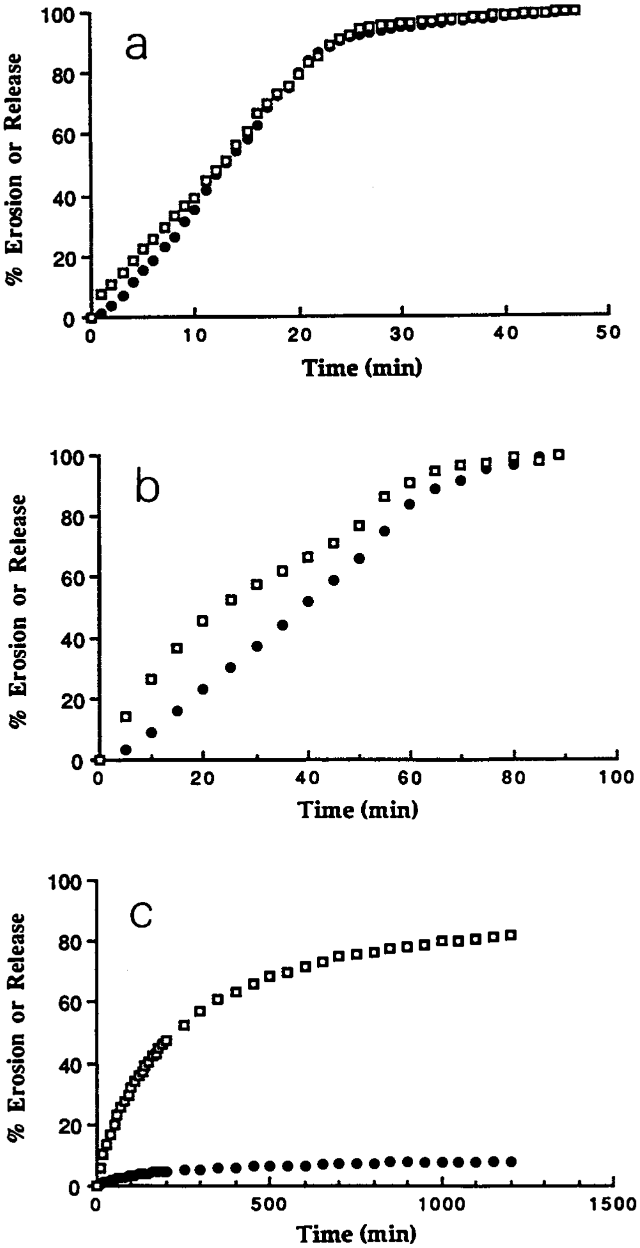

Fig. 7. Effect of buffer pH on the fractional polymer erosion (●) and theophylline release (□) from film samples of 70/30 (w/w) CAP/Pluronic F127 blend. (a) pH 7.4; (b) pH 6; (c) pH 4.

layers containing 5% theophylline, whereas the flat intermediate segment represents the lack of drug release during the erosion of the sandwiched drug-free layer. It is interesting to note that, in Fig. 10b, the agreement between the experimental and the theoretical pulsatile rate patterns is quite reasonable. This further substantiates the mechanism of a predominantly surface erosion-controlled drug release with a minimum contribution from the diffusion process at pH 7.4.

The significance of the surface erosion contribution to the achievement of pulsatile drug release was further investigated by studying the pH dependence of the polymer erosion and drug release from the present trilaminates at pH 6 and pH 4. Similar to the results of pH 7.4, a constant-rate and continuous polymer erosion was observed at both pH values despite the discontinuity of drug concentration profile across the trilaminates (data not shown). In this case, the polymer erosion behaved in a similar pH-dependent fashion as that of single-layered samples shown in Fig. 7, where the erosion rate is minimal at pH 4. However, as shown in Figs. 11a and b, the corresponding drug release rate profiles are quite different. For example, the pulsing frequency and peak rate in the resulting release rate profile have been significantly reduced at pH 6 compared with that at pH 7.4 (compare Fig. 11a with Fig. 10b), due primarily to the reduction of the polymer erosion rate. In this case, an increase in the diffusional contribution has resulted in a small but distinctive first-order decline in the initial release rate (Fig. 11a). At pH 4, however, the release rate profile is typically that of Fickian diffusion with no corresponding pulses (Fig. 11b). Since the erosion of the present polymer is minimal at pH 4, the resulting theophylline release is, therefore, controlled primarily by diffusion through the polymer matrix. Here, it may seem paradoxical that an alternating drug loading in the trilaminate did not result in a pulsatile release rate profile in Fig. 11b. However, it can be shown mathematically that discontinuities in the drug distribution will result in only smooth release rate profiles in *diffusion-controlled* matrix systems (1,2). Results in Figs. 10b and 11a further point to the fact that pulsatile drug delivery systems based on surface-erodible polymers can be designed to have different pulsing frequencies and peak rates by adjusting the thickness, drug loading, and erosion rate of the constituent layers in a multilaminate. In this case, the predictive Eq. (1) is useful in defining the required initial drug distribution in a given polymer matrix.

One may question the possibility of drug diffusion from the drug-loaded layer into the drug-free layer in the present system during storage. However, it has been shown previously that such migration of drug due to the nonuniform drug distribution can be substantially minimized in glassy polymers (2,3), since the drug diffusion coefficient in a glassy polymer generally can be more than 5–6 orders of magnitude smaller than that in a rubbery polymer. In the present case, the glass transition temperatures for the association polymers with more than 50% CAP content are well above room temperature (Table I). It is reasonable to expect that the glassy nature of these association polymers will also allow the preservation of the present alternating drug distribution.

CONCLUSIONS

An association polymer system based on blends of CAP and Pluronic F127 has been studied in terms of its physicochemical properties and its utility in rate-programmed drug delivery. Results from the thermal analysis indicate that these blends are compatible above 50% CAP with the formation of a single miscible phase. The observed shift in FTIR spectra in the carbonyl stretching region supports the existence of molecular association through intermolecular hydrogen bonding between the carboxylic acid and the ether oxygen groups. The polymer erosion and drug release properties have also been characterized using a rotating-disk apparatus. In this case, the rates of polymer erosion and theophylline release appear to increase with the concentration of Pluronic F127 in the blend. The associated drug release is

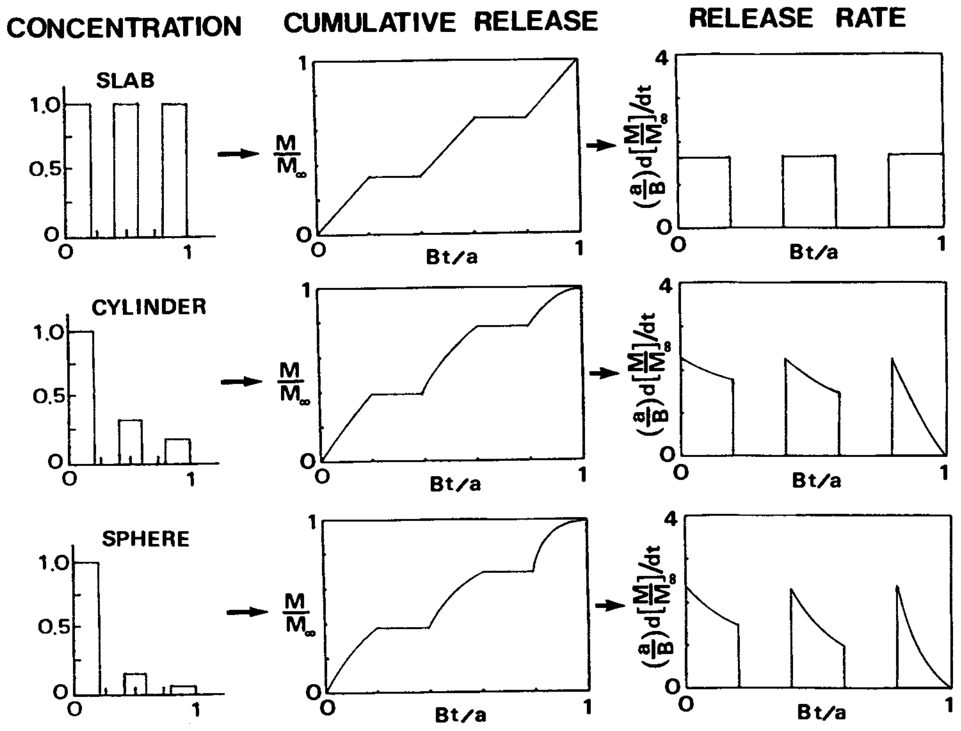

Fig. 8. Characteristics of pulsatile drug release from surface-erodible polymer laminates containing nonuniform drug distribution as predicted from Eq. (1).

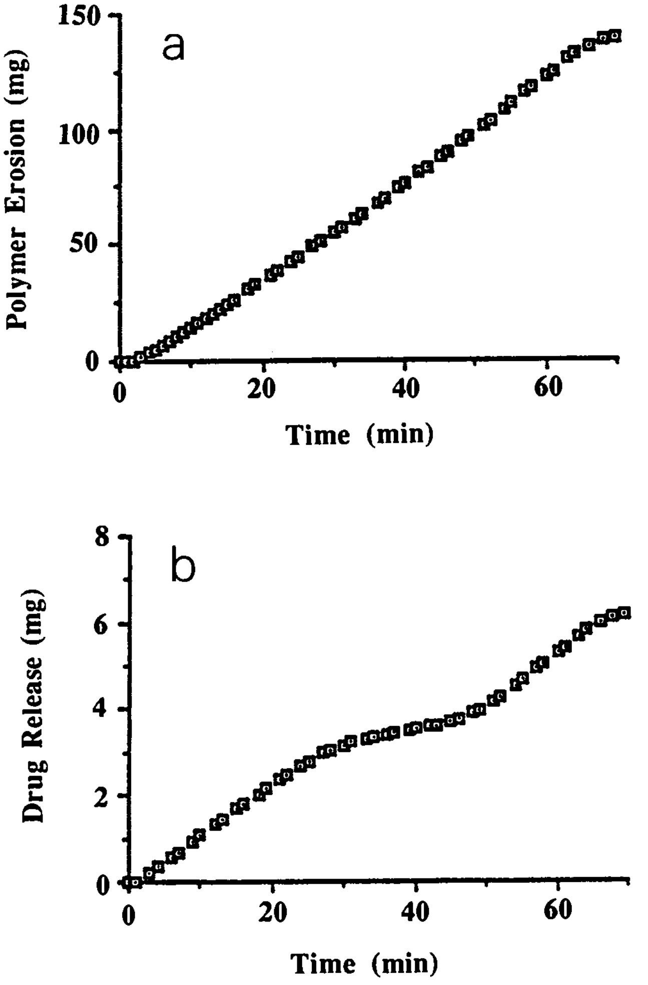

Fig. 9. Cumulative erosion and release profiles of trilaminates of 70/30 (w/w) CAP/Pluronic blend containing alternating theophylline-loaded layers (in pH 7.4 buffer at 37°C). (a) Polymer erosion; (b) drug release.

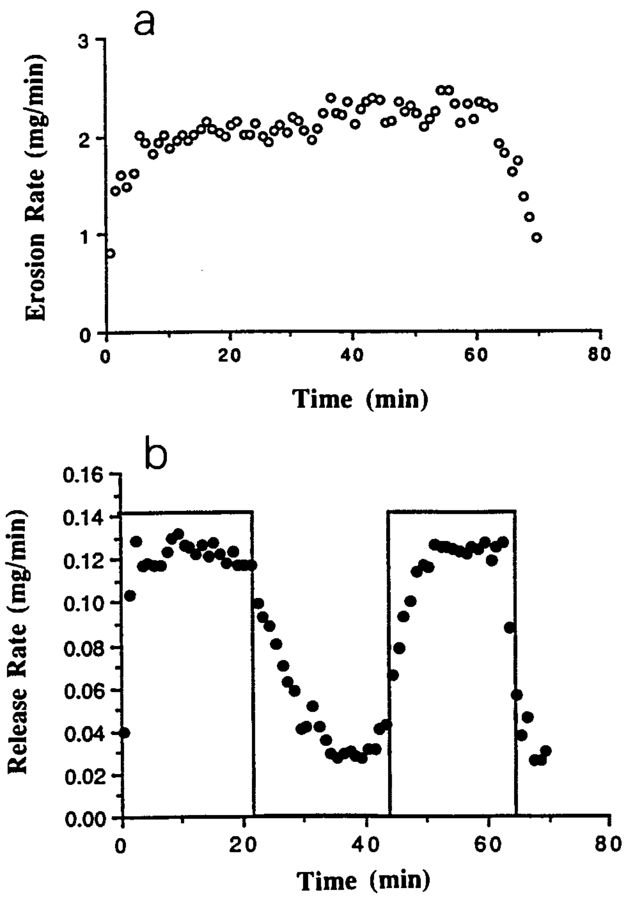

Fig. 10. Erosion and release rate profiles (in pH 7.4 buffer at 37°C) corresponding to the data in Fig. 9. (a) Rate of polymer erosion; (b) rate of theophylline release. (●) Data; (——) theoretical.

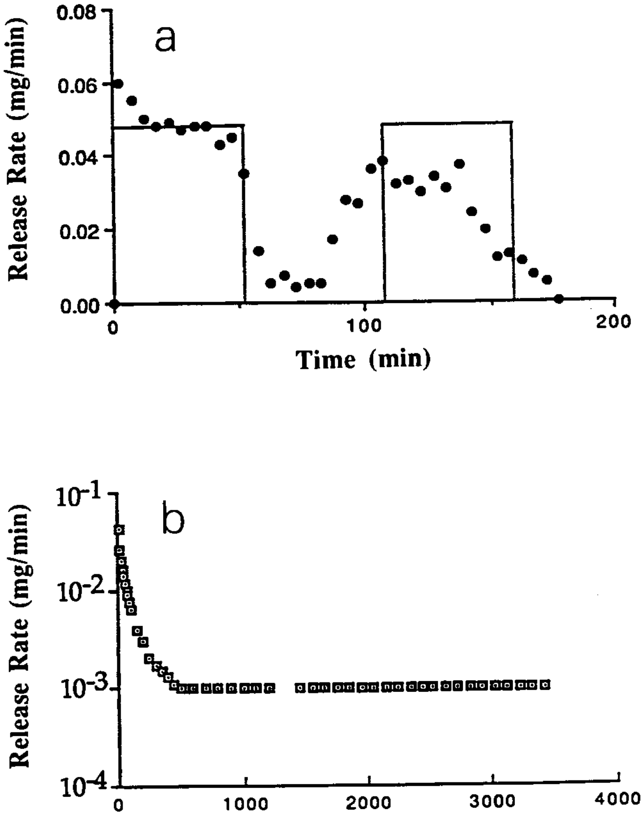

Fig. 11. Theophylline release rate profiles from the trilaminates in Fig. 9 as a function of the buffer pH. (a) pH 6: (●) data; (——) theoretical; (b) pH 4.

found to vary from diffusion-controlled at pH 4 to primarily surface erosion-controlled at pH 7.4. Such surface erosion characteristics of the present association polymers have been utilized to achieve pulsatile patterns of drug release from multilaminates containing alternating drug-loaded layers. Although the pulsatile release is demonstrated here only with a model drug, theophylline, similar systems can be designed for other bioactive compounds requiring pulsatile regimen. With the intermediate duration of erosion (e.g., hours) of the present association polymer system, an implantable system for the pulsatile delivery of gonadotropic hormones may be quite feasible. This aspect is currently being investigated in our laboratory. The results of this study not only demonstrate the flexibility in achieving programmed drug release employing nonuniform initial drug distribution as a mechanism, but also provide useful guidelines for the design and further development of pulsatile drug delivery systems based on erodible polymers.

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